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PHARMACOLOGY *for* NURSING CARE

SEVENTH EDITION

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Contents

I. INTRODUCTION

1 Orientation to Pharmacology

If you are a typical nursing student, by now you've been hitting the books for 14 or so years and have probably asked yourself, “What's the purpose of all this education?” In the past your question may have lacked a satisfying answer. Happily, now you have one: The reason you've spent most of your life in school was to get ready to study pharmacology!

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

FOUR BASIC TERMS

At this point it will help to define four basic terms: *drug, pharmacology, clinical pharmacology,* and *therapeutics*. As we go through these definitions, we will also consider the kinds of drug-related information that this text does and does not address.

Drug.

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

Pharmacology.

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

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

Clinical Pharmacology.

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

Therapeutics.

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

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

PROPERTIES OF AN IDEAL DRUG

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

The Big Three: Effectiveness, Safety, and Selectivity

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

Effectiveness.

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

Safety.

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

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

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

Selectivity.

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

Additional Properties of an Ideal Drug

Reversible Action.

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

Predictability.

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

Ease of Administration.

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

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

Freedom from Drug Interactions.

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

Low Cost.

An ideal drug would be easy to afford. The cost of drugs can be a substantial financial burden. As an extreme example, 1 year of therapy with natalizumab [Tysabri], a new drug for multiple sclerosis, can cost $25,000 or more. More commonly, expense becomes a significant factor when a medication must be taken chronically. For example, people with hypertension, arthritis, or diabetes must take medications lifelong. The cumulative expense of such treatment can be huge—even for drugs of moderate price.

Chemical Stability.

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

Possession of a Simple Generic Name.

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

Because No Drug Is Ideal ...

From the preceding, we can see that available medications are not ideal. No drug is safe. All drugs produce side effects. Drug responses may be difficult to predict and may be altered by drug interactions. Drugs may be expensive, unstable, and hard to administer. Because medications are not ideal, all members of the healthcare team must exercise care to promote therapeutic effects and minimize drug-induced harm.

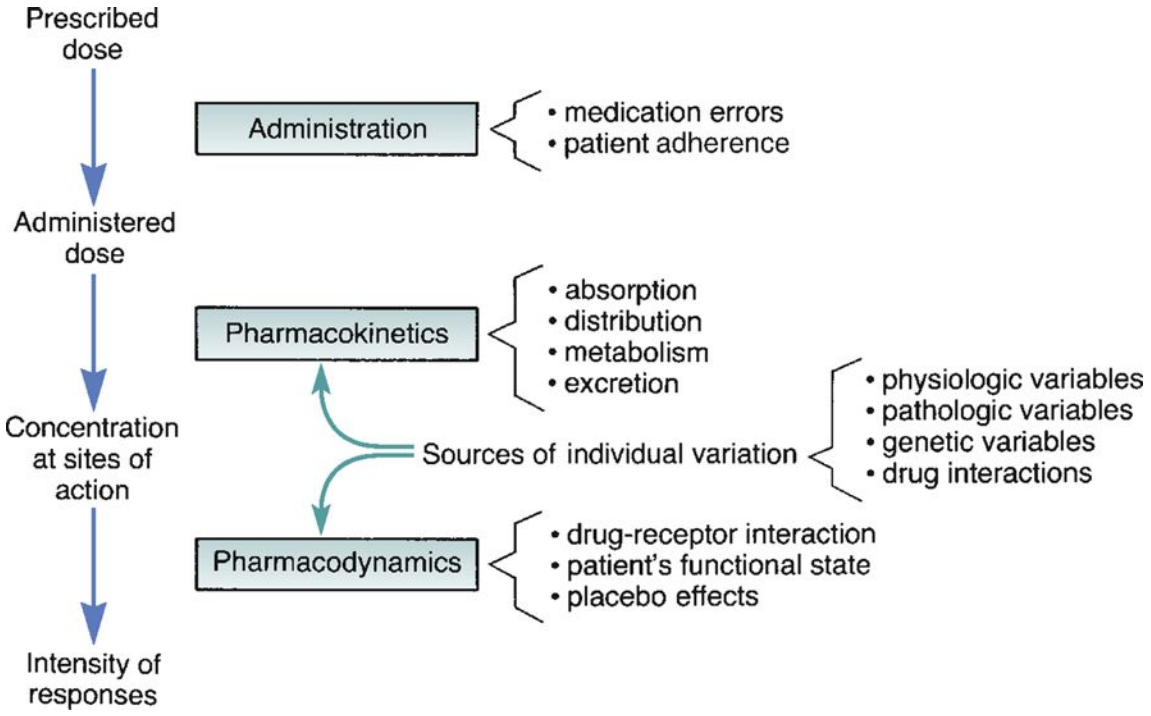


Figure 1-1 Factors that determine the intensity of drug responses.

THE THERAPEUTIC OBJECTIVE

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

FACTORS THAT DETERMINE THE INTENSITY OF DRUG RESPONSES

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

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

Administration

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

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

Pharmacokinetics

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

Pharmacodynamics

Once a drug has reached its sites of action, pharmacodynamic processes determine the nature and intensity of the response. Pharmacodynamics can be thought of as the *impact of drugs on the body*. In most cases, the initial step leading to a response is the binding of a drug to its receptor. This drug-receptor interaction is followed by a sequence of events that ultimately results in a response. As indicated in Figure 1-1, the patient's "functional state" can influence pharmacodynamic processes. For example, a patient who has developed tolerance to morphine will respond less intensely to a particular dose than will a patient who lacks tolerance. Placebo (psychologic) effects also help determine the responses that a drug elicits. Pharmacodynamics is discussed at length in Chapter 5.

Sources of Individual Variation

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

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

SUMMARY

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

KEY POINTS

- The most important properties of an ideal drug are effectiveness, safety, and selectivity.
- If a drug is not effective, it should not be used.
- There is no such thing as a safe drug: All drugs can cause harm.
- There is no such thing as a selective drug: All drugs can cause side effects.
- The objective of drug therapy is to provide maximum benefit with minimum harm.
- Because all patients are unique, drug therapy must be tailored to each individual.

2 Application of Pharmacology in Nursing Practice

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

EVOLUTION OF NURSING RESPONSIBILITIES REGARDING DRUGS

In the past, a nurse's responsibility regarding medications focused mainly on the *Five Rights of Drug Administration,* namely, give the *right drug* to the *right patient* in the *right dose* by the *right route* at the *right time*. More recently, a Sixth Right—right documentation—was added. Clearly, the Six Rights are important. However, although these basics are important, much more is required to achieve the therapeutic objective. The Six Rights guarantee only that a drug will be administered as prescribed. Correct administration, without additional interventions, cannot ensure that treatment will result in maximum benefit and minimum harm.

The limitations of the Six Rights can be illustrated with this analogy: The nurse who sees his or her responsibility as being done following correct drug administration would be like a major league baseball pitcher who felt that his responsibility was over once he had thrown the ball toward the batter. As the pitcher must be ready to respond to the consequences of the interaction between ball and bat, you must be ready to respond to the consequences of the interaction between drug and patient. Put another way, although both the nurse and the pitcher have a clear obligation to deliver their respective "pills"

in the most appropriate fashion, proper delivery is only the beginning of their responsibilities: *Important events will take place after the "pill" is delivered, and these must be responded to*. Like the pitcher, the nurse can respond rapidly and effectively only by anticipating (knowing in advance) what the possible reactions to the pill might be.

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

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

In drug therapy today, nurses, together with physicians and pharmacists, participate in a system of checks and balances designed to promote beneficial effects and minimize harm. Nurses are especially important in this system because it is the nurse—not the physician or pharmacist—who follows the patient's status most closely. As a result, you are likely to be the first member of the healthcare team to observe and evaluate drug responses, and to intervene if required. In order to observe and evaluate drug responses, and in order to intervene rapidly and appropriately, you must know *in advance* the responses that a medication is likely to elicit. Put another way, in order to provide professional care, you must understand drugs; the better your knowledge of pharmacology, the better you will be able to *anticipate* drug responses and not simply react to them after the fact.

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

APPLICATION OF PHARMACOLOGY IN PATIENT CARE

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

Preadministration Assessment

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

give. Preadministration assessment is discussed further under *Application of the Nursing Process in Drug Therapy*.

Collecting Baseline Data.

Baseline data are needed to evaluate drug responses, both therapeutic and adverse. For example, if we plan to give a drug to lower blood pressure, we must know the patient's blood pressure prior to treatment. Without these baseline data, we would have no way of determining the effectiveness of our drug. Similarly, if we are planning to give a drug that can damage the liver, we need to obtain baseline liver function test results in order to evaluate this potential toxicity. Obviously, in order to collect appropriate baseline data, we must first know the effects that our drug is likely to produce.

Identifying High-Risk Patients.

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

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

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

Dosage and Administration

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

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

The following basic guidelines can help ensure correct administration:

- Read the medication order carefully. If the order is unclear, verify it with the prescriber.
- Verify the identity of the patient by comparing the name on the wristband with the name on the drug order or medication administration record.
- Read the medication label carefully. Verify the identity of the drug, the amount of drug (per tablet, volume of liquid, etc.), and its suitability for administration by the intended route.

- Verify dosage calculations.
- Implement any special handling the drug may require.
- Don't administer any drug if you don't understand the reason for its use.

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

Evaluating and Promoting Therapeutic Effects

Evaluating Therapeutic Responses.

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

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

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

Promoting Patient Adherence.

Adherence—also known as compliance or concordance—may be defined as the extent to which a patient's behavior coincides with medical advice. If we are to achieve the therapeutic objective, adherence is essential. Drugs that are self-administered in the wrong dose, by the wrong route, or at the wrong time can-

not produce maximum benefit—and may even prove harmful. Obviously, successful therapy requires active and informed participation by the patient. By educating patients about the drugs they are taking, you can help elicit the required participation. Promoting adherence is discussed further below.

Implementing Nondrug Measures.

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

Minimizing Adverse Effects

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

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

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

Minimizing Adverse Interactions

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

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

Making PRN Decisions

A PRN medication order is one in which the nurse has discretion regarding how much drug to give and when to give it. (PRN stands for *pro re nata,* a Latin phrase meaning *as needed* or *as the occasion arises*.) PRN orders are most common for hypnotics (sleeping pills). In order to implement a PRN order rationally, you must know the reason for drug use and be able to assess the patient's medication needs. Clearly, the better your knowledge of pharmacology, the better your PRN decisions are likely to be.

Managing Toxicity

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

APPLICATION OF PHARMACOLOGY IN PATIENT EDUCATION

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

- Drug name and therapeutic category (eg, penicillin: antibiotic)
- Dosage size

- Dosing schedule
- Route and technique of administration
- Expected therapeutic response and when it should develop
- Nondrug measures to enhance therapeutic responses
- Duration of treatment
- Method of drug storage
- Symptoms of major adverse effects, and measures to minimize discomfort and harm
- Major adverse drug-drug and drug-food interactions
- Whom to contact in the event of therapeutic failure, severe adverse reactions, or severe adverse interactions

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

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

Dosage and Administration

Drug Name.

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

Dosage Size and Schedule of Administration.

Patients must be told how much drug to take and when to take it. For some medications, dosage must be adjusted by the patient. Insulin is a good example. For insulin therapy to be most beneficial, the patient must adjust doses

to accommodate changes in caloric intake. How to make this adjustment is taught by the nurse.

With PRN medications, the schedule of administration is not fixed. Rather, these drugs are taken as conditions require. For example, some people with asthma experience exercise-induced bronchospasm. To minimize such attacks, they can take supplementary medication prior to anticipated exertion. It is your responsibility to teach patients when PRN drugs should be taken.

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

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

Technique of Administration.

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

Duration of Drug Use.

Just as patients must know when to take their medicine, they must know when to stop. In some cases (eg, treatment of acute pain), patients should discontinue drug use as soon as symptoms subside. In other cases (eg, treatment of hypertension), patients should know that therapy will probably contin-

ue lifelong. For other conditions (eg, gastric ulcers), medication may be prescribed for a specific time interval, after which the patient should return for re-evaluation.

Drug Storage.

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

Promoting Therapeutic Effects

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

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

As noted, nondrug measures can complement drug therapy. For example, although drugs are useful in managing high cholesterol, exercise and diet are also important. Teaching the patient about nondrug measures can greatly increase the chances of success.

Minimizing Adverse Effects

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

- Insulin overdose can cause blood glucose levels to drop precipitously. Early signs of hypoglycemia include sweating and increased heart rate. The patient who has been taught to recognize these early signs can respond by ingesting

glucose-rich foods, thereby restoring blood sugar to a safe level. In contrast, the patient who fails to recognize evolving hypoglycemia and does not ingest glucose may become comatose, and may even die.

- Many anticancer drugs predispose patients to acquiring serious infections. The patient who is aware of this possibility can take steps to avoid contagion (eg, avoiding contact with people who have an infection; avoiding foods likely to contain pathogens). In addition, the informed patient is in a position to notify the prescriber at the first sign that an infection is developing, thereby allowing rapid treatment. In contrast, the patient who has not received adequate education is at increased risk of illness or death from an infectious disease.
- Some side effects, although benign, can be disturbing if they occur without warning. For example, rifampin (a drug for tuberculosis) imparts a harmless red-orange color to urine, sweat, saliva, and tears. Your patient will appreciate knowing about this in advance.

Minimizing Adverse Interactions

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

APPLICATION OF THE NURSING PROCESS IN DRUG THERAPY

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

Review of the Nursing Process

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

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

Assessment.

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

Analysis: Nursing Diagnoses.

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

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

Planning.

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

Implementation (Intervention).

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

Evaluation.

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

Applying the Nursing Process in Drug Therapy

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

Preadministration Assessment

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

- Collection of baseline data needed to evaluate therapeutic responses
- Collection of baseline data needed to evaluate adverse effects

- Identification of high-risk patients
- Assessment of the patient's capacity for self-care

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

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

Baseline Data Needed to Evaluate Therapeutic Effects.

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

Baseline Data Needed to Evaluate Adverse Effects.

All drugs have the ability to produce undesired effects. In most cases, the adverse effects that a particular drug can produce are known. In many cases, development of an adverse effect will be completely obvious in the absence of any baseline data. For example, we don't need special baseline data to know that hair loss following cancer chemotherapy was caused by the drug. However, in other cases, baseline data are needed to determine whether or

not an adverse effect has occurred. For example, some drugs can impair liver function. In order to know if a drug has compromised liver function, we need to know the state of liver function prior to drug use. Without this information, we can't tell from later measurements whether apparent liver dysfunction was pre-existing or caused by the drug. Clearly, in cases like this, baseline data are needed. As noted earlier, knowing what data to collect comes directly from your knowledge of the drug under consideration.

Identification of High-Risk Patients.

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

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

When identifying factors that put the patient at risk, you should distinguish between factors that put the patient at extremely high risk versus factors that put the patient at moderate or low risk. The terms *contraindication* and *precaution* can be used for this distinction. A *contraindication* is defined as a pre-existing condition that precludes use of a particular drug under all but the most desperate circumstances. For example, a previous severe allergic reaction to penicillin (which can be life threatening) would be a contraindication to us-

ing penicillin again—unless the patient has a life-threatening infection that cannot be controlled with another antibiotic. *A precaution,* by contrast, can be defined as a pre-existing condition that significantly increases the risk of an adverse reaction to a particular drug, but not to a degree that is life threatening. For example, a previous mild allergic reaction to penicillin would constitute a precaution to using this drug again. That is, the drug may be used, but greater than normal caution must be exercised. Preferably, an alternative drug would be selected.

Assessment of the Patient's Capacity for Self-Care.

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

Multiple factors can affect the capacity for self-care and the probability of adhering to the prescribed regimen. Patients with reduced visual acuity or limited manual dexterity may be unable to self-medicate, especially if the technique of administration is complex. Patients with limited intellectual ability may be incapable of understanding or remembering what they are supposed to do. Patients with severe mental illness (eg, depression, schizophrenia) may lack the understanding or motivation needed to self-medicate. Some patients may lack the money to pay for drugs. Others may fail to take medications as prescribed because of individual or cultural attitudes toward drugs. Among geriatric patients, a common cause for failed self-medication is a conviction that the drug was simply not needed in the dosage prescribed. A thorough assessment will identify all of these factors, thereby enabling you to account for them when formulating nursing diagnoses and the patient care plan.

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

CNS = central nervous system, GI = gastrointestinal.

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

Analysis and Nursing Diagnoses

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

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

Analysis must identify potential adverse effects and drug interactions. This is accomplished by synthesizing knowledge of the drug under consideration and the data collected during assessment. Knowledge of the drug itself will indicate adverse effects that practically all patients are likely to experience. Data on the individual patient will indicate additional adverse effects and interactions to which the particular patient is predisposed. Once potential adverse effects and interactions have been identified, pertinent nursing diagnoses can be easily formulated. For example, if treatment is likely to cause respiratory depression, an appropriate nursing diagnosis would be “impaired gas exchange related to drug therapy.” Table 2-1 presents additional examples of nursing diagnoses that can be readily derived from your knowledge of adverse effects and interactions that treatment may cause.

Analysis must characterize the patient's capacity for self-care. The analysis should indicate potential impediments to self-care (eg, visual impairment, re-

duced manual dexterity, impaired cognitive function, insufficient understanding of the prescribed regimen) so that these factors can be addressed in the care plan. To varying degrees, nearly all patients will be unfamiliar with self-medication and the drug regimen. Accordingly, a nursing diagnosis applicable to almost every patient is "deficient knowledge related to the drug regimen."

Planning

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

Defining Goals.

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

Setting Priorities.

This requires knowledge of the drug under consideration and the patient's unique characteristics—and even then, setting priorities can be difficult. Highest priority is given to life-threatening conditions (eg, anaphylactic shock, ventricular fibrillation). These may be drug induced or the result of disease. High priority is also given to reactions that cause severe, acute discomfort and to reactions that can result in long-term harm. Since we cannot manage all problems simultaneously, less severe problems must wait until the patient and care provider have the time and resources to address them.

Identifying Interventions.

The heart of planning is identification of nursing interventions. These interventions can be divided into four major groups: (1) drug administration, (2) interventions to enhance therapeutic effects, (3) interventions to minimize ad-

verse effects and interactions, and (4) patient education (which encompasses information in the first three groups).

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

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

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

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

Establishing Criteria for Evaluation.

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

Implementation

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

Evaluation

Over the course of drug therapy, the patient must be evaluated for (1) therapeutic responses, (2) adverse drug reactions and interactions, (3) adherence to the prescribed regimen, and (4) satisfaction with treatment. How frequently evaluations are performed depends on the expected time course of therapeutic and adverse effects. Like assessment, evaluation is based on laboratory tests, observation of the patient, physical examination, and patient interviews. The conclusions drawn during evaluation provide the basis for modifying nursing interventions and the drug regimen.

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

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

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

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

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

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

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

Preadministration Assessment.

This section summarizes the information you should have before giving a drug. Each section begins by stating the reason for drug use. This is followed by a summary of the baseline data needed to evaluate therapeutic and adverse effects. After this, contraindications and precautions are summarized, under the heading *Identifying High-Risk Patients*.

Implementation: Administration.

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

Preadministration Assessment

Therapeutic Goal

Baseline Data

Identifying High-Risk Patients

Implementation: Administration

Routes

Administration

Implementation: Measures to Enhance Therapeutic Effects

Ongoing Evaluation and Interventions

Summary of Monitoring

Evaluating Therapeutic Effects

Minimizing Adverse Effects

Minimizing Adverse Interactions

Managing Toxicity

TABLE 2-2 Modified Nursing Process Format for Summaries of Nursing Implications

Implementation: Measures to Enhance Therapeutic Effects.

This section addresses issues such as diet modification, measures to increase comfort, and ways to promote adherence to the prescribed regimen.

Ongoing Evaluation and Interventions.

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

Patient Education.

This topic does not have a section of its own. Rather, patient education is integrated into the other sections. That is, as we summarize the nursing implications that relate to a particular topic, such as drug administration or a specific adverse effect, patient education related to that topic is discussed concurrently. This integration is done to promote clarity and efficiency of communication. In order to make this important information stand out, it appears in colored type.

What About Diagnosis and Planning?

These headings are not used in the summaries. There are several reasons for the omission, the dominant one being efficiency of communication.

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

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

SUMMARY

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

KEY POINTS

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

3 Drug Regulation, Development, Names, and Information

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

LANDMARK DRUG LEGISLATION

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

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

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

In 1962, Congress passed the *Harris-Kefauver Amendments* to the Food, Drug and Cosmetic Act. This law was created in response to the thalidomide tragedy that occurred in Europe in the early 1960s. Thalidomide is a sedative now known to cause birth defects. Because the drug was used widely by pregnant women, thousands of infants were born with phocomelia, a rare birth defect characterized by the gross malformation or complete absence of arms or legs. This

tragedy was especially poignant in that it resulted from nonessential drug use: The women who took thalidomide could have done very well without it. Thalidomide was not a problem in the United States because the drug had been withheld by the FDA (see Chapter 106, Box 106-1).

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

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

In 1992, FDA regulations were changed to permit *accelerated approval* of drugs for acquired immunodeficiency syndrome (AIDS) and cancer. Under these guidelines, a drug could be approved for marketing prior to completion of Phase III trials (see below), provided that rigorous follow-up studies (Phase IV trials) were performed. The rationale for this change was that (1) medications are needed, even if their benefits may be marginal, and (2) the unknown risks associated with early approval are balanced by the need for more effective drugs. Although accelerated approval seems like a good idea, in actual practice, it has two significant drawbacks. First, manufacturers often fail to con-

duct or complete the required follow-up studies. Second, if the follow-up studies—which are more rigorous than the original—fail to confirm a clinical benefit, the guidelines have no clear mechanism for removing the drug from the market.

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

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

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

Two laws—the *Best Pharmaceuticals for Children Act* (BPCA), passed in 2002, and the *Pediatric Research Equity Act* (PREA) of 2003—were designed to promote much-needed research on drug efficacy and safety in children. The BPCA offers a 6-month patent extension to manufacturers who evaluate a drug

already on the market for its safety, efficacy, and dosage in children. The PREA gives the FDA the power, for the first time, to require drug companies to conduct pediatric clinical trials on new medications that might be used by children. (In the past, drugs were not tested in children. Hence, there is a general lack of reliable information upon which to base therapeutic decisions.)

In 2007, Congress passed the *FDA Amendments Act* (FDAAA), the most important legislation on drug safety since the Harris-Kefauver Amendments of 1962. The FDAAA expands the mission of the FDA to include rigorous oversight of drug safety *after* a drug has been approved. (Prior to this act, the FDA focused on drug efficacy and safety *prior* to approval, but had limited resources and authority to address drug safety after a drug was released for marketing.) Under the new law, the FDA has the legal authority to require postmarketing safety studies, to order changes in a drug's label to include new safety information, and to restrict distribution of a drug based on safety concerns. In addition, the FDA is required to establish an active postmarketing risk surveillance system, mandated to include 25 million patients by July 2010, and 100 million by July 2012. Because of the FDAAA, adverse effects that were not discovered prior to drug approval will come to light much sooner than in the past, and the FDA now has the authority to take action (eg, limit distribution of a drug) if postmarketing information shows a drug to be less safe than previously understood.

NEW DRUG DEVELOPMENT

The development and testing of new drugs is an expensive and lengthy process, requiring 6 to 12 years for completion. Of the thousands of compounds that undergo testing, only a few enter clinical trials, and of these, only 1 in 5 gains approval. Because of this high failure rate, the cost of developing a new drug can exceed $800 million.

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

The Randomized Controlled Trial

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

Use of Controls.

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

Randomization.

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

other out, leaving differences in the treatments as the best explanation for any differences in outcome.

Blinding.

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

Stages of New Drug Development

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

Preclinical Testing

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

Clinical Testing

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

Phase I.

Phase I trials are usually conducted in *healthy volunteers*. However, if a drug is likely to have severe side effects, as many anticancer drugs do, the trial is done in volunteer patients who have the disease under consideration. Phase I testing has three goals: evaluating drug metabolism, pharmacokinetics, and biologic effects.

Phases II and III.

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

Phase IV: Postmarketing Surveillance.

In Phase IV, the new drug is released for general use, permitting observation of its effects in a large population. Under the FDAAA of 2007, postmarketing surveillance will be much more effective than in the past.

TABLE 3-1 Steps in New Drug Development

Preclinical Testing (in animals)
- **Toxicity**
- **Pharmacokinetics**
- **Possible Useful Effects**

↓

Investigational New Drug (IND) Status

↓

Clinical Testing (in humans)

Phase I
- *Subjects:* healthy volunteers
- *Tests:* metabolism, pharmacokinetics, and biologic effects

Phase II
- *Subjects:* patients
- *Tests:* therapeutic utility and dosage range

Phase III
- *Subjects:* patients
- *Tests:* safety and effectiveness

Conditional Approval of New Drug Application (NDA)

↓

Phase IV: Postmarketing Surveillance

Limitations of the Testing Procedure

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

Limited Information in Women and Children

Women.

Until recently, very little drug testing was done in women. In almost all cases, women of child-bearing age were excluded from early clinical trials. The rationale for excluding women was concern for fetal safety. Unfortunately, FDA policy took this concern to an extreme, effectively barring *all* women of child-bearing age from Phase I and Phase II trials—even if the women were not pregnant and were using adequate birth control. The only women allowed to participate in early clinical trials were those with a life-threatening illness that might respond to the drug under study.

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

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

Children.

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

Drug	Indication	Year Introduced/ Year Withdrawn	Months on the Market	Reason for Withdrawal
Rotigotine[*] [Neupro]	Parkinson's disease	2007/2008	10	Patch formulation delivered erratic dosages
Tegaserod[‡] [Zelnorm]	Irritable bowel syndrome	2002/2007	56	Risk of cardiovascular events
Natalizumab[‡] [Tysabri]	Multiple sclerosis	2004/2005	3	Progressive multifocal leukoencephalopathy
Valdecoxib [Bextra]	Arthritis, pain	2001/2005	41	Myocardial infarction, stroke
Rofecoxib [Vioxx]	Arthritis, pain	1999/2004	64	Myocardial infarction, stroke
Rapacuronium [Raplon]	Neuromuscular blockade	1999/2001	19	Bronchospasm, unexplained fatalities
Alosetron[‡] [Lotronex]	Irritable bowel syndrome	2000/2000	9	Ischemic colitis, severe constipation; deaths have occurred
Troglitazone [Rezulin]	Type 2 diabetes	1999/2000	12	Fatal liver failure
Grepafloxacin [Raxar]	Infection	1997/1999	19	Severe cardiovascular events, including seven deaths
Bromfenac [Duract]	Acute pain	1997/1998	11	Severe hepatic failure
Mibefradil [Posicor]	Hypertension, angina pectoris	1997/1998	11	Inhibits drug metabolism, causing toxic accumulation of many drugs
Dexfenfluramine [Redux]	Obesity	1996/1997	16	Valvular heart disease

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

Failure to Detect All Adverse Effects

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

The hidden dangers in new drugs are illustrated by the data in Table 3-2. This table presents information on 14 drugs that were withdrawn from the U.S. market soon after receiving FDA approval. In all cases, the reason for withdrawal was a serious adverse effect that went undetected in clinical trials. Admittedly, only a few hidden adverse effects are as severe as the ones in the table. Hence, most do not necessitate drug withdrawal. Nonetheless, the drugs in the table should serve as a strong warning about the unknown dangers that a new drug may harbor.

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

Exercising Discretion Regarding New Drugs

When thinking about prescribing a new drug, clinicians would do well to follow this guideline: *Be neither the first to adopt the new nor the last to abandon the old.* Recall that the therapeutic objective is to produce maximum benefit with min-

imum harm. To achieve this objective, we must balance the potential benefits of a drug against its inherent risks. As a rule, new drugs have actions very similar to those of older agents. That is, it is rare for a new drug to be able to do something that an older drug can't do already. Consequently, the need to treat a particular disorder seldom constitutes a compelling reason to select a new drug over an agent that has been available for years. Furthermore, new drugs generally present greater risks than the old ones. As noted, at the time of its introduction, a new drug is likely to have adverse effects that have not yet been reported, and these effects may prove very bad for some patients. In contrast, older, more familiar drugs are less likely to cause unpleasant surprises. Consequently, when we weigh the benefits of a new drug against its risks, it is likely that the benefits will be insufficient to justify the risks—especially when an older drug, whose properties are well known, would probably provide adequate treatment. Accordingly, when it comes to the use of new drugs, it is usually better to adopt a wait-and-see policy, letting more adventurous prescribers discover the hidden dangers that a new drug may hold.

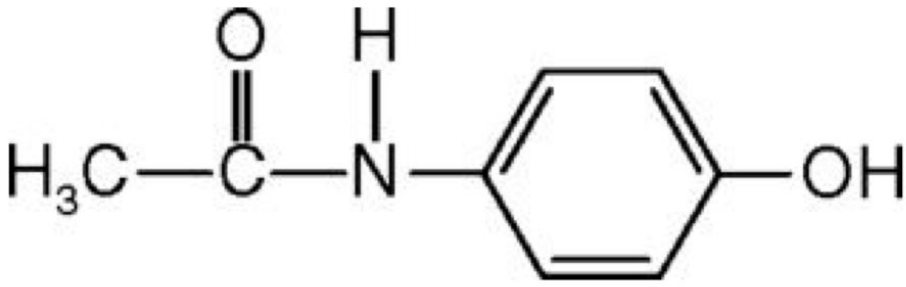
DRUG NAMES

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

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

The Three Types of Drug Names

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



Type of Drug Name	Examples
Chemical Name	*N*-acetyl-*para*-aminophenol
Generic Name (nonproprietary name)	Acetaminophen
Trade Name (proprietary name)	Acephen, Aminophen, Apap, Cetafen, Ed-Apap Children's, Feverall, Genapap, Genebs, Infantaire Drops, Mapap Regular Strength, Masophen, Nortemp Children's, Pain and Fever, Pain Reliever, Q-Pap, Quick Melts Children's Non-Aspirin, Silapap, Tylenol, Valorin

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

TABLE 3-3 The Three Types of Drug Names

Chemical Name.

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

Generic Name.

The generic name of a drug is assigned by the United States Adopted Names Council. Each drug has only one generic name. The generic name is also known as the *nonproprietary* name or *United States Adopted Name*. Generic names are less complex than chemical names but typically more complex than trade names. For reasons presented below, generic names are preferable to trade names for general use.

Trade Name.

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

Trade names must be approved by the FDA. The review process tries to ensure that no two trade names are too similar. In addition, trade names cannot imply unlikely efficacy—which may explain why sibutramine (a new diet pill) is named *Meridia* rather than something more suggestive, like *Fat-B-Gone* or *Pounds Off*.

Which Name To Use, Generic or Trade?

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

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

TABLE 3-4 Generic Names and Trade Names of Some Common Drugs

The Little Problems with Generic Names

In almost all cases, the generic name for a drug is more complicated than its trade name. This fact is illustrated in Table 3-4, which compares the generic and trade names for six common drugs. A simple analysis reveals that the average generic name in the table has 4.3 syllables. In contrast, the average trade name has only 2.3 syllables. That is, the generic names are nearly twice as long as the trade names.

Because generic names are more complex than trade names, generic names can be more difficult to remember and pronounce. As an exercise, try pronouncing the names in Table 3-4. While trade names like *Motrin* and *Prozac* roll off the tongue with ease, their generic counterparts—*ibuprofen* and *fluoxetine*—tend to tie the tongue in knots.

Why is it that generic names are more complicated than trade names? One reason is that the pharmaceutical industry has an important role in establishing generic names. When a pharmaceutical company has developed a new drug, that company submits a suggested generic name to the United States Adopted Names Council, the body responsible for assigning a drug its generic name. As a rule, the Council adopts the name the company suggests. Since, from a marketing perspective, it is to the company's advantage to have a product whose trade name is more easily recognized than its generic name, it seems unlikely that a company will suggest a simple, euphonious generic name. Also contributing to the complexity of generic names are the guidelines established by the Council for naming drugs.

The Big Problems with Trade Names

A Single Drug Can Have Multiple Trade Names.

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

Product Name	Drugs in the Product
Monistat	Miconazole
Monistat 1	Tioconazole
Tavist	Clemastine
Tavist Sinus	Acetaminophen + pseudoephedrine
Sudafed	Pseudoephedrine
Sudafed PE	Phenylephrine
4-Way 12-Hour Nasal Spray	Oxymetazoline
4-Way Fast-Acting Nasal Spray	Phenylephrine
Excedrin Tablets	Acetaminophen + aspirin + caffeine
Excedrin PM	Acetaminophen + diphenhydramine

TABLE 3-5 Some Pharmaceutical Products That Share the Same Trade Name

By clouding communication about drugs, use of trade names can result in "double medication"—with potentially disastrous results. Because patients frequently see more than one physician or nurse practitioner, it is possible for a patient to be given prescriptions for the same drug by two different prescribers. If those prescriptions are written for different brand names, then the two bottles the patient receives will be labeled with different names. Consequently, although both bottles contain the same drug, the patient may be unaware of this fact. If both medications are taken as prescribed, excessive dosing will result. However, if generic names had been used, both labels would bear the same name, thereby informing the patient that both bottles contain the same drug. Given this information, the patient is likely to consult the prescribers to determine if both prescriptions should be honored.

Products with the Same Trade Name May Have Different Active Ingredients.

As indicated in Table 3-5, products that have very similar trade names can actually contain very different drugs. For example, although the two Monistat products have nearly identical trade names, they actually contain two different drugs. Confusion would be avoided by simply labeling these products *miconazole* and *tioconazole,* rather than *Monistat* and *Monistat 1.*

The problem becomes even more complex for products that contain two or more drugs. When such combination products are referred to by trade name, the name is unlikely to indicate either the number of drugs present or their identity. Referring to Table 3-5, there is nothing about the trade name *Excedrin Tablets* to suggest that the product consists of three different drugs: acetaminophen, aspirin, and caffeine. Moreover, there is nothing in the trade names *Excedrin Tablets* and *Excedrin P.M.* to tell us that these two products have different compositions. By discarding the trade names and labeling one product *acetaminophen plus aspirin plus caffeine* and the other *acetaminophen plus diphenhydramine,* we could eliminate any confusion.

The two 4-Way products listed in Table 3-5 further illustrate the potential for confusion. If nothing else, the name *4-Way* suggests that the product contains more than one drug. In fact, the name seems to imply the presence of *four* drugs. However, this implication is not correct. Neither 4-Way preparation is composed of four drugs; rather, they both contain only one drug. Furthermore, note that these similarly named products are, in fact, completely different; they have no ingredients in common. Hence, in the case of these 4-Way products, we can see that the trade name cannot be taken to mean either (1) the presence of four different drugs or (2) that these preparations that bear similar names have the same composition. Had generic names been employed to label these products, there could be no confusion about their makeup.

Perhaps the most disturbing aspect of trade names is illustrated by the reformulation of *Kaopectate,* a well-known antidiarrheal product. In 2003, the manufacturer switched the active ingredient in Kaopectate from attapulgite (which had replaced kaolin and pectate some years earlier) to bismuth subsalicylate. However, although the active ingredient changed, the brand name did not. As a result, new bottles of Kaopectate contain a drug that is completely different from the one found in bottles of Kaopectate produced in 2002—posing a risk for patients who should not take salicylates, but may be

unaware of their presence in the new product. This example illustrates an important point: Manufacturers can reformulate brand-name products whenever they want—without changing the name at all. Hence, there is no guarantee that the brand-name product you buy today contains the same drug as the brand-name product you bought last week, last month, or last year.

In the spring of 1999, the FDA issued a ruling that will help reduce the confusion created by trade names—but only for over-the-counter (OTC) drugs. Under the ruling, generic names for the drugs in OTC products are now clearly and prominently listed on the label, using a standardized format.

Products with the Same Trade Name in the United States and Abroad May Have Different Active Ingredients.

Along with the problems discussed above, trade names present an additional problem for travelers. Why? Because products with the *identical* trade name may have different active ingredients, depending on where the products were made (Table 3-6). As a result, when a prescription for a trade-name product is filled abroad, the patient may receive the wrong drug. For example, Americans in Australia with a prescription for Urex will receive furosemide (a powerful diuretic) rather than the methenamine (a urinary tract antiseptic) that they were expecting. Not only will this lead to inconvenience (frequent urination) and potential danger (dehydration, hypokalemia), but the urinary tract infection will continue unabated. Hence, the patient is exposed to all the risks of medication without getting any of the benefits. Accordingly, to ensure that travelers get the drugs they need, prescriptions should bear generic names of drugs, not trade names.

Trade Name	Country	Active Drug	Therapeutic Use
Norpramin	United States	Desipramine	Depression
	Spain	Omeprazole	Peptic ulcer disease
Flomax	United States	Tamsulosin	Enlarged prostate
	Italy	Morniflumate	Inflammation
Allegra	United States	Fexofenadine	Allergies
	Germany	Frovatriptan	Migraine
Urex	United States	Methenamine	Urinary tract infection
	Australia	Furosemide	Diuresis
Dilacor	United States	Diltiazem	Angina, hypertension, dysrhythmias
	Serbia	Digoxin	Heart failure, dysrhythmias

TABLE 3-6 Products from the United States and Abroad That Have the Same Trade Name but Different Active Ingredients

What If Peas Were Marketed Like Drugs?

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

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

When we want to compare different *brands* of peas, the task is easy. Company A's peas are easily distinguished from those of company B or company C by the presence of a company name and logo on the label. Consequently, thanks to the way peas are marketed, we have no trouble understanding (1) just what we are buying and (2) who made it. As a result, we can easily select the product we want from the manufacturer we like best.

Now let's consider what we could expect if peas were marketed like drugs. Under the new system, pea packages would have no pictures of peas on them. Nor would pea packages proclaim "PEAS" in big letters to help us identify their contents. Instead, pea packages would be emblazoned with trade names like *Vegi-P* or *Producin* or *NuPod-500's*. If peas were marketed using trade names, when we went shopping for peas we'd be obliged to read a lot of fine print to find the product we wanted. And, once we finally did turn up a package with peas in it—for example, the one labeled *NuPod-500's*—we'd probably buy NuPod-500's for life, it being too much trouble to figure out which of the other packages with meaningless names also contain peas. From the point of view of the people who sell NuPod-500's, this technique of marketing by trade names is a terrific arrangement. Consumers will be loyal to their product not because that product is better or cheaper than someone else's, but because product labeling with trade names makes it very difficult to identify the competition so that comparisons can be made. Fortunately, we don't allow this kind of marketing for peas. When we shop for peas, we demand that all pea packages bear the word *peas*—not *Vegi-P* or *NuPod-500's* or any other trade name. Why we permit medicines to be marketed in any less informative a manner is a disturbing question.

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

names, thereby making product identification needlessly and dangerously difficult.

Generic Products Versus Brand-Name Products

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

Are Generic Products and Brand-Name Products Therapeutically Equivalent?

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

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

Would a Difference Between Brand-Name and Generic Products Justify the Use of Trade Names?

Even if generic formulations *were* significantly different from brand-name formulations, this would not justify using trade names to identify preferred products. If clinicians want to prescribe a drug made by a particular company,

they needn't resort to trade names to do so; their preference can be indicated simply by including the manufacturer's name on the prescription. As with peas, if we prefer a particular brand (eg, BIRDS EYE), that's what we ask for. We haven't found it necessary to create a complicated system of alternative names for peas in order to distinguish one brand from another. On the contrary, common sense tells us that such a system of trade names would make it more difficult—not easier—for us to clearly communicate our needs. Perhaps some day we will market medicines with as much common sense as we use for vegetables.

Conclusion Regarding Generic Names and Trade Names

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

OVER-THE-COUNTER DRUGS

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

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

- Americans spend about $20 billion annually on OTC drugs.
- OTC drugs account for 60% of all doses administered.
- Forty percent of Americans take at least one OTC drug every 2 days.
- Four times as many illnesses are treated by a consumer using an OTC drug as by a consumer visiting a prescriber.
- With most illnesses (60% to 95%), initial therapy consists of self-care, including self-medication with an OTC drug.
- The average home medicine cabinet contains 24 OTC preparations.

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

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

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

SOURCES OF DRUG INFORMATION

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

People

Clinicians and Pharmacists.

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

Poison Control Centers.

Poison control centers are located throughout the country. These centers are accessible by telephone, permitting rapid access to information about poisoning with medicines and toxic compounds. Calling the national emergency hotline (1-800-222-1222) will connect you with the certified poison center nearest you.

Pharmaceutical Sales Representatives.

Pharmaceutical sales representatives (drug representatives, detail persons) can be useful sources of drug information. These people know their own products very well, and they can provide detailed, authoritative information about them. Keep in mind, however, that the ultimate job of the drug representative is sales, not education. Because their objective is sales, drug representatives may fail to volunteer negative information about their product. Likewise, they are unlikely to point out superior qualities in a competing drug. (Is a Honda salesperson going to extol the virtues of a Ford?) Such a lack of complete candor does not mean that drug representatives are unethical; they are simply doing their job. However, since full disclosure may be inconsistent with successful sales, the drug representative may not be your best source of information—especially if you are trying to establish an unbiased comparison between the representative's product and a drug from a competing manufacturer.

Published Information

The publications described below are general references. These works cover a broad range of topics but in limited depth. Accordingly, these references are most useful as initial sources of information. If more detail is needed, specialty publications should be consulted. Some important drug references, including the ones described below, are listed in Table 3-7.

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

Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th ed. (Brunton LL, Lazo JS, Parker KL, eds.). New York: McGraw-Hill, 2006

Pharmacotherapy: A Pathophysiologic Approach, 6th ed. (DiPiro JT, et al., eds.). New York: McGraw-Hill, 2005

Applied Therapeutics: The Clinical Use of Drugs, 8th ed. (Koda-Kimble MA, Young LY, Kradjan WA, Guglielmo BJ, Alldredge BK, Corelli RL, eds.). Philadelphia: Lippincott Williams & Wilkins, 2005

Detailed Information on Specific Drugs and Drug Families

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

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

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

United States Pharmacopeia Drug Information (USP DI): Drug Information for the Health Care Professional. Rockville, MD: The United States Pharmacopeial Convention, Inc. [updated bimonthly]

Very Current Information

The Medical Letter. New Rochelle, NY: The Medical Letter, Inc. [published bimonthly]

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

TABLE 3-7 Some Important Drug References

Text-like Books

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

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

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

Newsletters

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

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

Reference Books

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

PDR has a pictorial section for product identification. The PDR is updated annually.

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

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

The Internet

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

KEY POINTS

- The Food, Drug and Cosmetic Act of 1938 was the first legislation to regulate drug safety.
- The Harris-Kefauver Amendments, passed in 1962, were the first legislation to demand that drugs actually be of some benefit.
- The Controlled Substances Act, passed in 1970, set rules for the manufacture and distribution of drugs considered to have potential for abuse.

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

II. BASIC PRINCIPLES OF PHARMACOLOGY

4 Pharmacokinetics

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

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

APPLICATION OF PHARMACOKINETICS IN THERAPEUTICS

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

As a nurse, you will have ample opportunity to apply knowledge of pharmacokinetics in clinical practice. For example, by understanding the reasons behind selection of route, dosage, and dosing schedule, you will be less likely to commit medication errors than will the nurse who, through lack of this knowledge, administers medications by blindly following prescribers' orders. Also,

as noted in Chapter 2, prescribers do make mistakes. Accordingly, you will have occasion to question or even challenge prescribers regarding their selection of dosage, route, or schedule of administration. In order to alter a prescriber's decision, you will need a rational argument to support your position. To present that argument, you will need to understand pharmacokinetics.

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

A NOTE TO CHEMOPHOBES

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

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

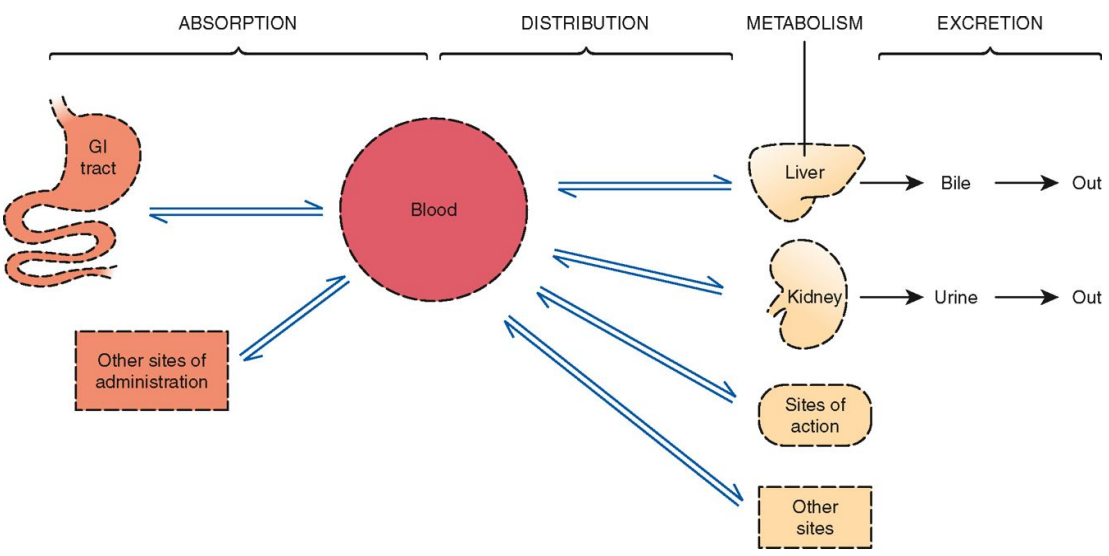


Figure 4-1 The four basic pharmacokinetic processes. Dotted lines represent membranes that must be crossed as drugs move throughout the body.

PASSAGE OF DRUGS ACROSS MEMBRANES

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

Membrane Structure

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

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

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

Three Ways to Cross a Cell Membrane

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

Channels and Pores

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

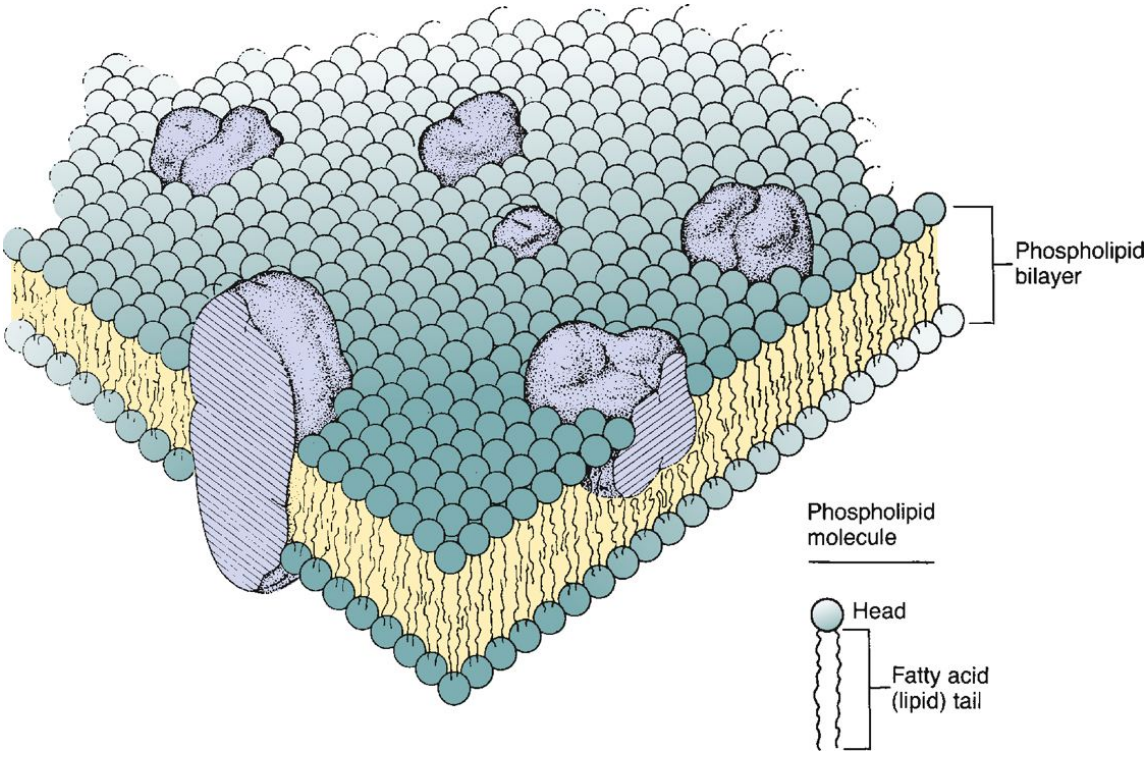


Figure 4-2 Structure of the cell membrane. The cell membrane consists primarily of a double layer of phospholipid molecules. The large globular structures represent protein molecules imbedded in the lipid bilayer.

Transport Systems

Transport systems are carriers that can move drugs from one side of the cell membrane to the other. Some transport systems require the expenditure of energy; others do not. All transport systems are selective: They will not carry just any drug. Whether a transporter will carry a particular drug depends on the drug's structure.

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

transport systems in the kidney that can pump drugs from the blood into the renal tubules.

P-Glycoprotein.

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

Direct Penetration of the Membrane

For most drugs, movement throughout the body is dependent on the ability to penetrate membranes directly. Why? Because (1) most drugs are too large to pass through channels or pores and (2) most drugs lack transport systems to help them cross all of the membranes that separate them from their sites of action, metabolism, and excretion.

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

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

Polar Molecules

Polar molecules are molecules with uneven distribution of electrical charge. That is, positive and negative charges within the molecule tend to congregate separately from one another. Water is the classic example. As depicted in Figure 4-3A, the electrons (negative charges) in the water molecule spend more time in the vicinity of the oxygen atom than in the vicinity of the two hydro-

gen atoms. As a result, the area around the oxygen atom tends to be negatively charged, whereas the area around the hydrogen atoms tends to be positively charged. Kanamycin (Fig. 4-3*B*), an antibiotic, is an example of a polar drug. The hydroxyl groups, which attract electrons, give kanamycin its polar nature.

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

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

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

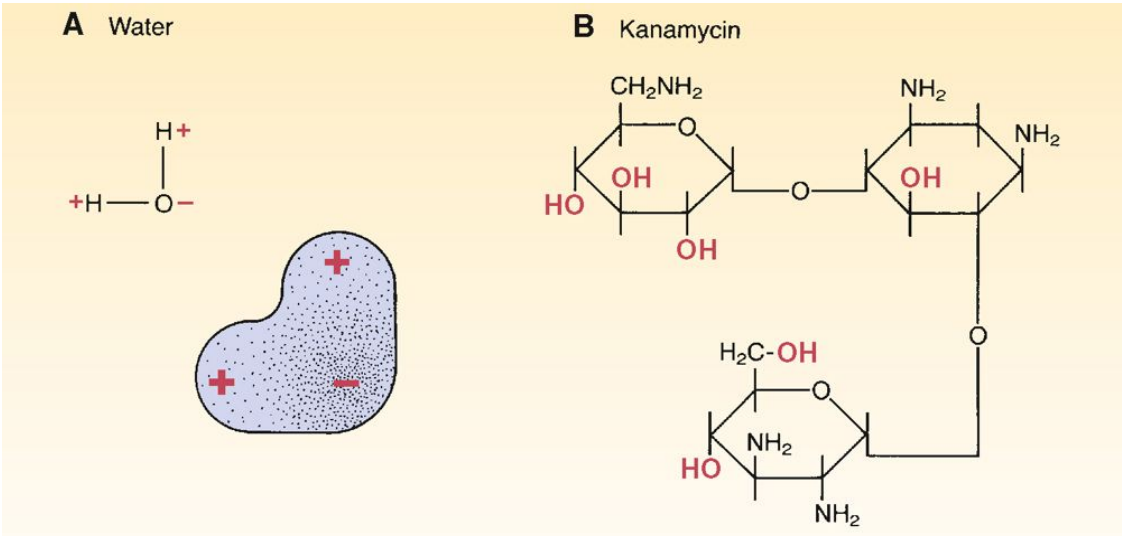


Figure 4-3 Polar molecules. A, Stippling shows the distribution of electrons within the water molecule. As indicated, water's elec-

trons spend more time near the oxygen atom than near the hydrogen atoms, making the area near the oxygen atom somewhat negative and the area near the hydrogen atoms more positive. B, Kanamycin is a polar drug. The -OH groups of kanamycin attract electrons, thereby causing the area around these groups to be more negative than the rest of the molecule.

Ions

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

Quaternary Ammonium Compounds

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

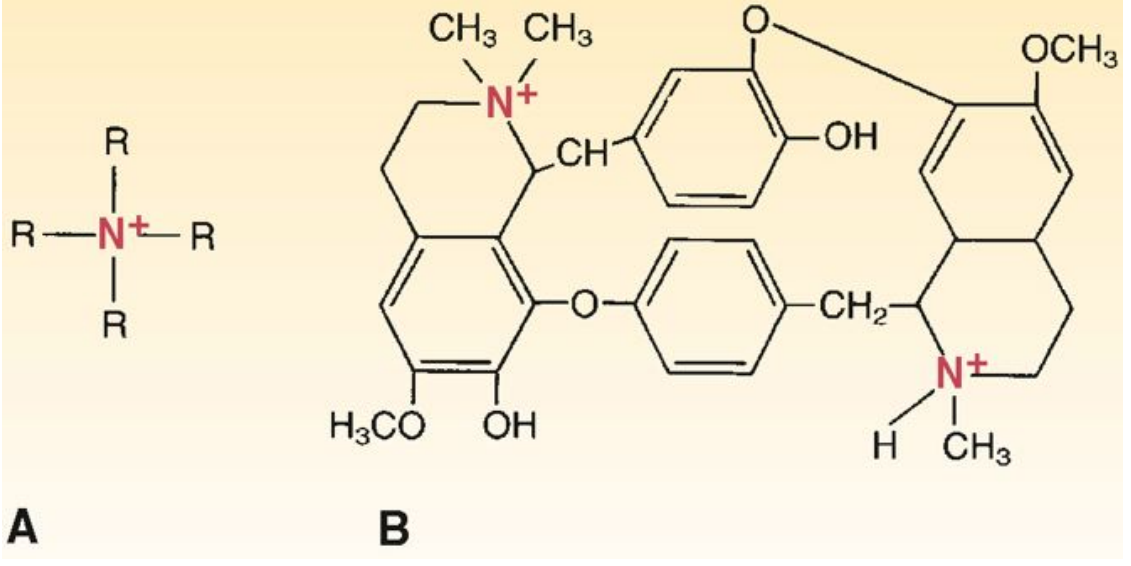


Figure 4-4 Quaternary ammonium compounds. A, The basic structure of quaternary ammonium compounds. Because the nitrogen atom has bonds to four organic radicals, quaternary ammonium compounds always carry a positive charge. Because of this charge, quaternary ammonium compounds are not lipid soluble and cannot cross most membranes. B, Tubocurarine is a representative quaternary ammonium compound. Note that tubocurarine contains two "quaternized" nitrogen atoms.

Tubocurarine (Fig. 4-4*B*) is a representative quaternary ammonium compound. In purified form, tubocurarine can be employed as a muscle relaxant for surgery and other procedures. A crude preparation—curare—is used by South American

Indians as an arrow poison. When employed for hunting, tubocurarine (curare) produces paralysis of the diaphragm and other skeletal muscles, causing death by asphyxiation. Interestingly, even though meat from animals killed with curare is laden with poison, it can be eaten with no ill effect. Why? Because tubocurarine, being a quaternary ammonium compound, cannot cross membranes, and therefore cannot be absorbed from the intestine; as long as it remains in the lumen of the intestine, curare can do no harm. As you might gather, when tubocurarine is used clinically, it cannot be administered by mouth. Instead, it must be injected. Once in the bloodstream, tubocurarine has ready access to its sites of action on the surface of muscles.

pH-Dependent Ionization

Unlike quaternary ammonium compounds, which always carry a charge, certain drugs can exist in either a charged or uncharged form. Many drugs are either weak organic acids or weak organic bases, which can exist in charged and uncharged forms. Whether a weak acid or base carries a charge is determined by the pH of the surrounding medium.

A review of acid-base chemistry will be helpful. An acid is defined as a compound that can give up a hydrogen ion (proton). Put another way, *an acid is a proton donor*. A base is defined as a compound that can take on a hydrogen ion. That is, *a base is a proton acceptor*. When an acid gives up its proton, which is positively charged, the acid itself becomes negatively charged. Conversely,

when a base accepts a proton, the base becomes positively charged. These reactions are depicted in Figure 4-5, showing aspirin as an example of an acid and amphetamine as an example of a base. Because the process of an acid giving up a proton or a base accepting a proton converts the acid or base into a charged particle (ion), the process for either an acid or a base is termed *ionization*.

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

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

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

Ion Trapping (pH Partitioning)

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

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

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

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

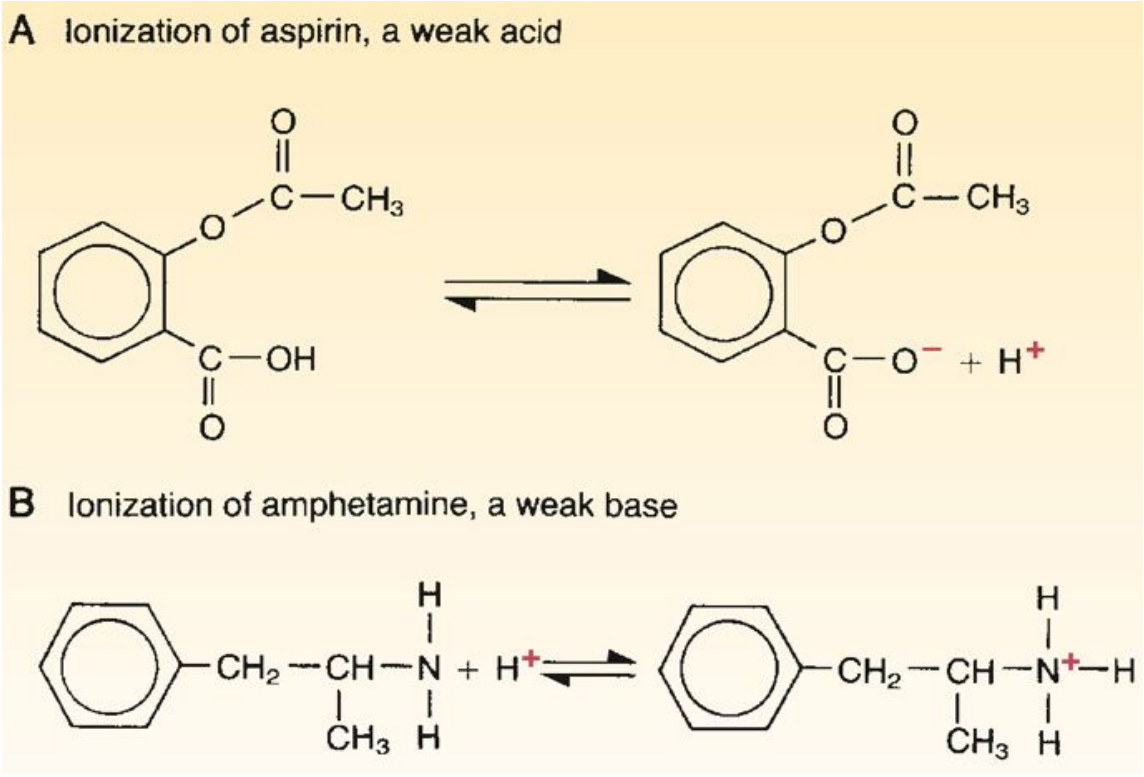


Figure 4-5 Ionization of weak acids and weak bases. The extent of ionization of weak acids (A) and weak bases (B) depends on the pH of their surroundings. The ionized (charged) forms of acids and bases are not lipid soluble and hence do not readily cross membranes. Note that acids ionize by giving up a proton and that bases ionize by taking on a proton.

ABSORPTION

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

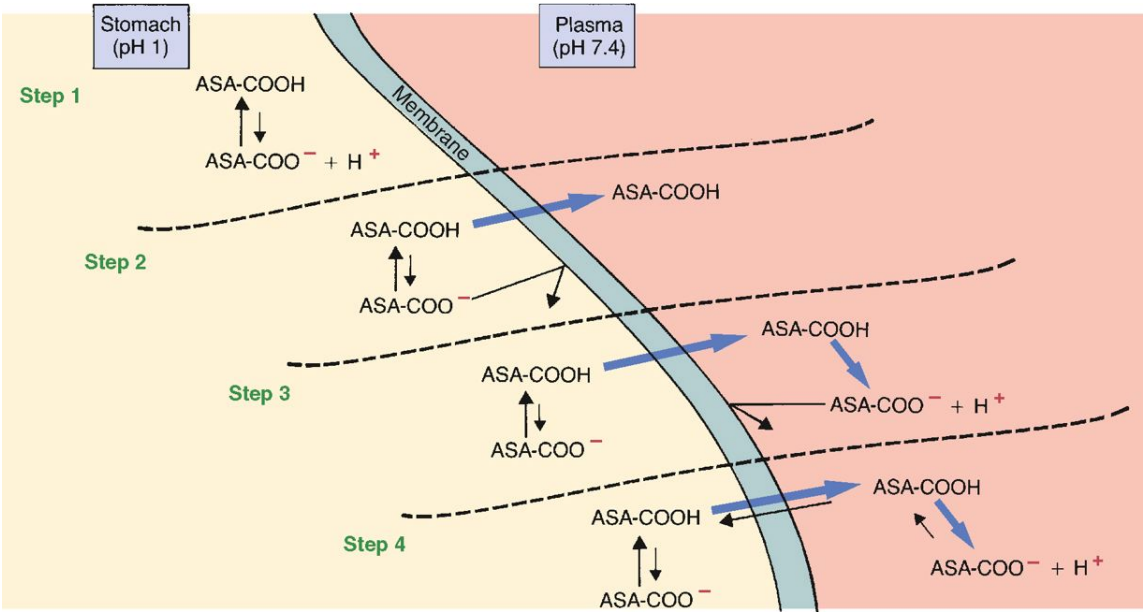


Figure 4-6 Ion trapping of drugs. This figure demonstrates ion trapping using aspirin as an example. Because aspirin is an acidic drug, it will be nonionized in acid media and ionized in alkaline media. As indicated, ion trapping causes molecules of orally administered aspirin to move from the acidic (pH 1) environment of the stomach to the more alkaline (pH 7.4) environment of the plasma, thereby causing aspirin to accumulate in the blood. In the figure, aspirin (acetylsalicylic acid) is depicted as ASA with its COOH (carboxylic acid) group attached. Step 1: Once ingested, ASA dissolves in the stomach contents, after which some ASA molecules give up a proton and become ionized. However, most of the ASA in the stomach remains nonionized. Why? Because the stomach is acidic, and acidic drugs don't ionize in acidic media. Step 2: Because most ASA molecules in the stomach are nonionized (and therefore lipid soluble), most

ASA molecules in the stomach can readily cross the membranes that separate the stomach lumen from the plasma. Because of the concentration gradient that exists between the stomach and the plasma, nonionized ASA molecules will begin moving into the plasma. (Note that, because of their charge, ionized ASA molecules cannot leave the stomach.) Step 3: As the nonionized ASA molecules enter the relatively alkaline environment of the plasma, most give up a proton (H^+) and become negatively charged ions. ASA molecules that become ionized in the plasma cannot diffuse back into the stomach. Step 4: As the nonionized ASA molecules in the plasma become ionized, more nonionized molecules will pass from the stomach to the plasma to replace them. This movement occurs because the laws of diffusion demand equal concentrations of diffusible substances on both sides of a membrane. Because only the nonionized form of ASA is able to diffuse across the membrane, it is this form that the laws of diffusion will attempt to equilibrate. Nonionized ASA will continue to move from the stomach to the plasma until the amount of ionized ASA in plasma has become large enough to prevent conversion of newly arrived nonionized molecules into the ionized form. Equilibrium will then be established between the plasma and the stomach. At equilibrium, there will be equal amounts of nonionized ASA in the stomach and plasma. However, on the plasma side, the amount of ionized ASA will be much larger than on the stomach side. Because there are equal concentrations of nonionized ASA on both sides of the membrane but a much higher concentration of ionized ASA in the plasma, the total concentration of ASA in plasma will be much higher than in the stomach.

Factors Affecting Drug Absorption

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

Rate of Dissolution.

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

Surface Area.

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

Blood Flow.

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

Lipid Solubility.

As a rule, highly lipid-soluble drugs are absorbed more rapidly than drugs whose lipid solubility is low. Why? Because lipid-soluble drugs can readily cross the membranes that separate them from the blood, whereas drugs of low lipid solubility cannot.

pH Partitioning.

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

Characteristics of Commonly Used Routes of Administration

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

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

Intravenous

Barriers to Absorption.

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

Absorption Pattern.

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

Advantages

Rapid Onset.

Intravenous administration results in rapid onset of action. Although rapid onset is not always important, it is clearly beneficial in emergencies.

Control.

Because the entire dose is administered directly into the blood, we have precise control over levels of drug in the blood. This contrasts with the other major routes of administration, and especially with oral administration (see below), in which the amount absorbed is less predictable.

Use of Large Fluid Volumes.

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

Use of Irritant Drugs.

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

Disadvantages

High Cost, Difficulty, and Inconvenience.

Intravenous administration is expensive, difficult, and inconvenient. The cost of IV administration sets and their set-up charges can be substantial. Setting up an IV line takes time and special training. Because of the difficulty involved, most patients are unable to self-administer IV drugs, and therefore must depend on a healthcare professional. Because patients are tethered to

lines and bottles, their mobility is limited. In contrast, oral administration is easy, convenient, and cheap.

Irreversibility.

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

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

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

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

TABLE 4-1 Properties of Major Routes of Drug Administration

Fluid Overload.

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

Infection.

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

Embolism.

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

Lastly, injection of drugs that are not fully dissolved can cause embolism. Particles of undissolved drug are like small grains of sand, which can become embedded in blood vessels and cause blockage. Because of the risk of embolism, you should check IV solutions prior to administration to ensure that drugs are in solution. If the fluid is cloudy or contains particles, the drug is not dissolved and must not be administered.

The Importance of Reading Labels

Not all formulations of the same drug are appropriate for IV administration. Accordingly, it is essential to read the label before giving a drug IV. Two examples illustrate the importance of this admonition. The first is insulin. Only one preparation of insulin, labeled *insulin injection,* can be administered safely IV. Insulin injection is a clear solution formulated for IV use. With one exception, all other insulin preparations are *particulate suspensions*. These prepara-

tions are intended for subQ administration only. Because of their particulate nature, these preparations could prove fatal if given IV. By checking the label, inadvertent IV injection of particulate insulin can be avoided.

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

Intramuscular

Barriers to Absorption.

When a drug is injected IM, the only barrier to absorption is the *capillary wall*. In capillary beds that serve muscles and most other tissues, there are "large" spaces between the cells that compose the capillary wall (Fig. 4-7). Drugs can pass through these spaces with ease, and need not cross cell membranes to enter the bloodstream. Accordingly, like IV administration, IM administration presents no significant barrier to absorption.

Absorption Pattern.

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

Advantages.

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

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

Disadvantages.

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

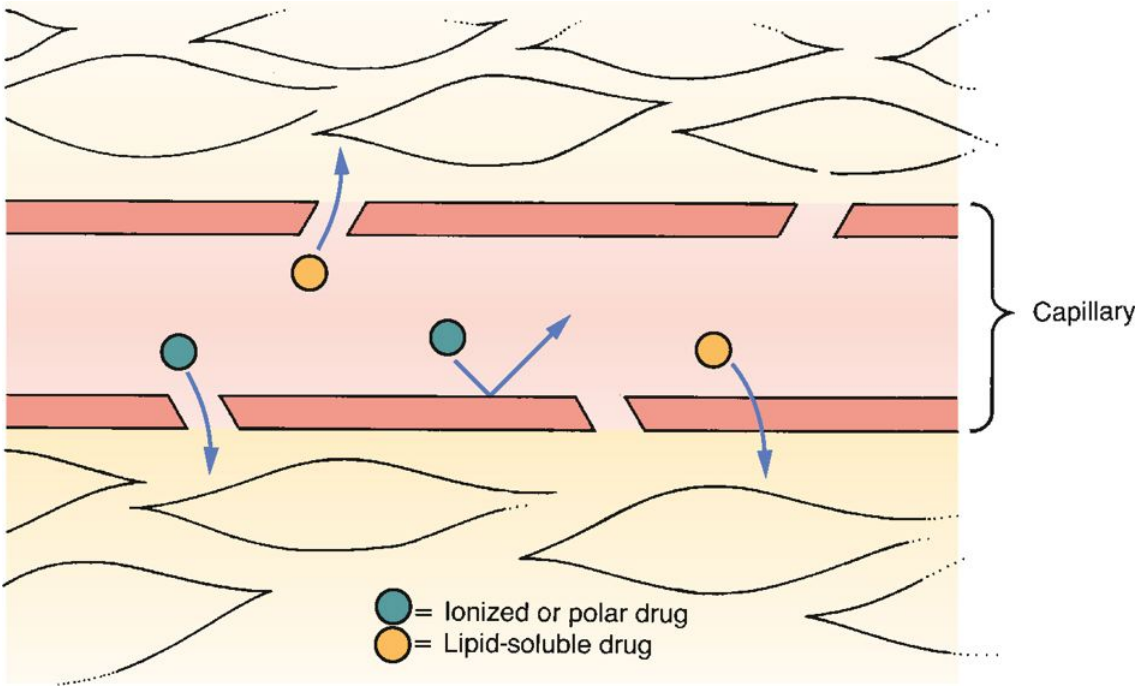


Figure 4-7 Drug movement at typical capillary beds. In most capillary beds, "large" gaps exist between the cells that compose the capillary wall. Drugs and other molecules can pass freely into and out of the bloodstream through these gaps. As illustrated, lipid-soluble compounds can also pass directly through the cells of the capillary wall.

Subcutaneous

The pharmacokinetics of subQ administration are nearly identical to those of IM administration. As with IM administration, there are no significant barriers to absorption:

Once a drug has been injected subQ, it readily enters the blood by passing through the spaces between cells of the capillary wall. As with IM administration, blood flow and drug solubility are the major determinants of how fast absorption takes place. Because of the similarities between subQ and IM administration, these routes have similar advantages (suitability for poorly soluble drugs and depot preparations) and similar drawbacks (discomfort, inconvenience, potential for injury).

Oral

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

Barriers to Absorption.

Following oral administration, drugs may be absorbed from the stomach or intestine. In either case, there are two barriers to cross: (1) the layer of *epithelial cells* that lines the GI tract, and (2) the *capillary wall*. Because the walls of the capillaries that serve the GI tract offer no significant resistance to absorption, the major barrier to absorption is the GI epithelium. To cross this layer of tightly packed cells, drugs must pass *through* cells rather than between them. For some drugs, intestinal absorption may be reduced by *P-glycoprotein,* a transporter that can pump certain drugs *out* of epithelial cells back into the intestinal lumen.

Absorption Pattern.

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

Drug Movement Following Absorption.

Before proceeding, we need to quickly review what happens to drugs following their absorption from the GI tract. As depicted in Figure 4-8, drugs absorbed from all sites along the GI tract (except the oral mucosa and the distal segment of the rectum) must pass through the liver (the major site of drug metabolism) before they can reach the general circulation. For many drugs, this passage is uneventful: they go through the liver, enter the inferior vena cava, and eventually reach the general circulation. Other drugs undergo extensive hepatic metabolism. And still others may undergo *enterohepatic recirculation,* a cycle in which drugs in the liver are taken up into bile, secreted back into the small intestine (via the bile duct), and then reabsorbed back into the portal blood (see Fig. 4-8).*

* Before a drug can be taken up into bile, it must first undergo *glucuronidation,* an enzymatic reaction in which a molecule of glucuronic acid is coupled with the drug. Once the glucuronide form of the drug has been secreted into the intestine, bacterial enzymes cleave off the glucuronic acid, converting the drug back into its original form, which can then be reabsorbed into the hepatic portal circulation.

Advantages.

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

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

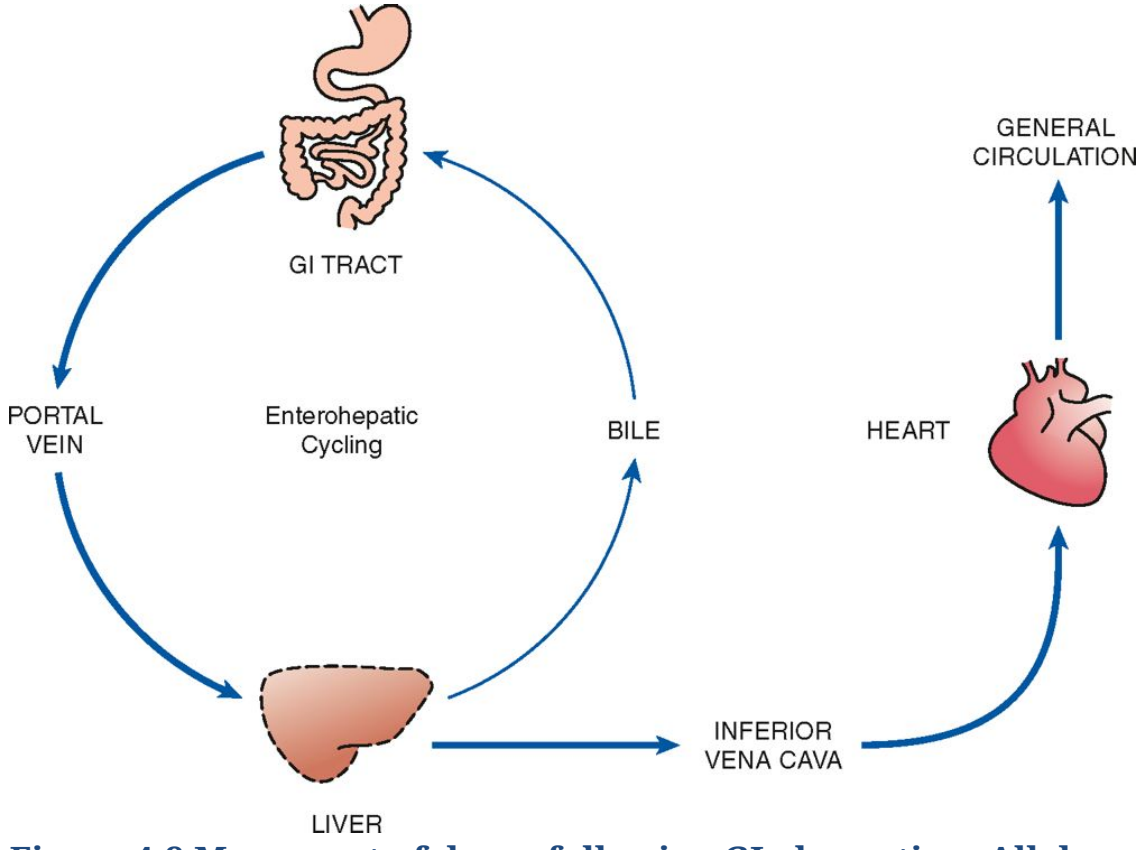


Figure 4-8 Movement of drugs following GI absorption. All drugs absorbed from sites along the GI tract—stomach, small intestine, and large intestine (but not the oral mucosa or distal rectum)—must go through the liver, via the portal vein, on their way toward the heart and the general circulation. For some drugs, passage is uneventful. Others undergo extensive metabolism. Still others undergo excretion into the bile, after which they re-enter the small intestine (via the bile duct), and then either (1) undergo reabsorption into the portal blood, thereby creating a cycle known as enterohepatic recirculation, or (2) exit the body in the stool (not shown).

Disadvantages.

Variability. The major disadvantage of PO therapy is that absorption can be highly variable. That is, a drug administered to patient A may be absorbed

rapidly and completely, whereas the same drug given to patient B may be absorbed slowly and incompletely. This variability makes it difficult to control the concentration of a drug at its sites of action, and therefore makes it difficult to control the onset, intensity, and duration of responses.

Inactivation.

Oral administration can lead to inactivation of certain drugs. Penicillin G, for example, can't be taken orally because it would be destroyed by stomach acid. Similarly, insulin can't be taken orally because it would be destroyed by digestive enzymes. Other drugs (eg, nitroglycerin) undergo extensive inactivation as they pass through the liver, a phenomenon known as the "first-pass effect" (see below under *Special Considerations in Drug Metabolism*).

Patient Requirements

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

Local Irritation

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

Comparing Oral Administration with Parenteral Administration

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

- Emergencies that require rapid onset of drug action.
- Situations in which plasma drug levels must be tightly controlled. (Because of variable absorption, oral administration does not permit tight control of drug levels.)

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

Pharmaceutical Preparations for Oral Administration

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

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

Tablets.

A tablet is a mixture of a drug plus binders and fillers, all of which have been compressed together. Tablets made by different manufacturers can differ in their rates of disintegration and dissolution, causing differences in bioavailability. As a result, two tablets that contain the same amount of the same drug can differ with respect to onset and intensity of effects.

Enteric-Coated Preparations.

Enteric-coated preparations consist of drugs that have been covered with a material designed to dissolve in the intestine but not the stomach. Materials

used for enteric coatings include fatty acids, waxes, and shellac. Because enteric-coated preparations release their contents into the intestine and not the stomach, these preparations are employed for two general purposes: (1) to protect drugs from acid and pepsin in the stomach and (2) to protect the stomach from drugs that can cause gastric discomfort.

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

Sustained-Release Preparations.

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

Additional Routes of Administration

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

heart, joints, nerves, CNS). The unique characteristics of these routes are addressed throughout the book as we discuss specific drugs that employ them.

DISTRIBUTION

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

Blood Flow to Tissues

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

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

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

Exiting the Vascular System

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

Typical Capillary Beds

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

The Blood-Brain Barrier

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

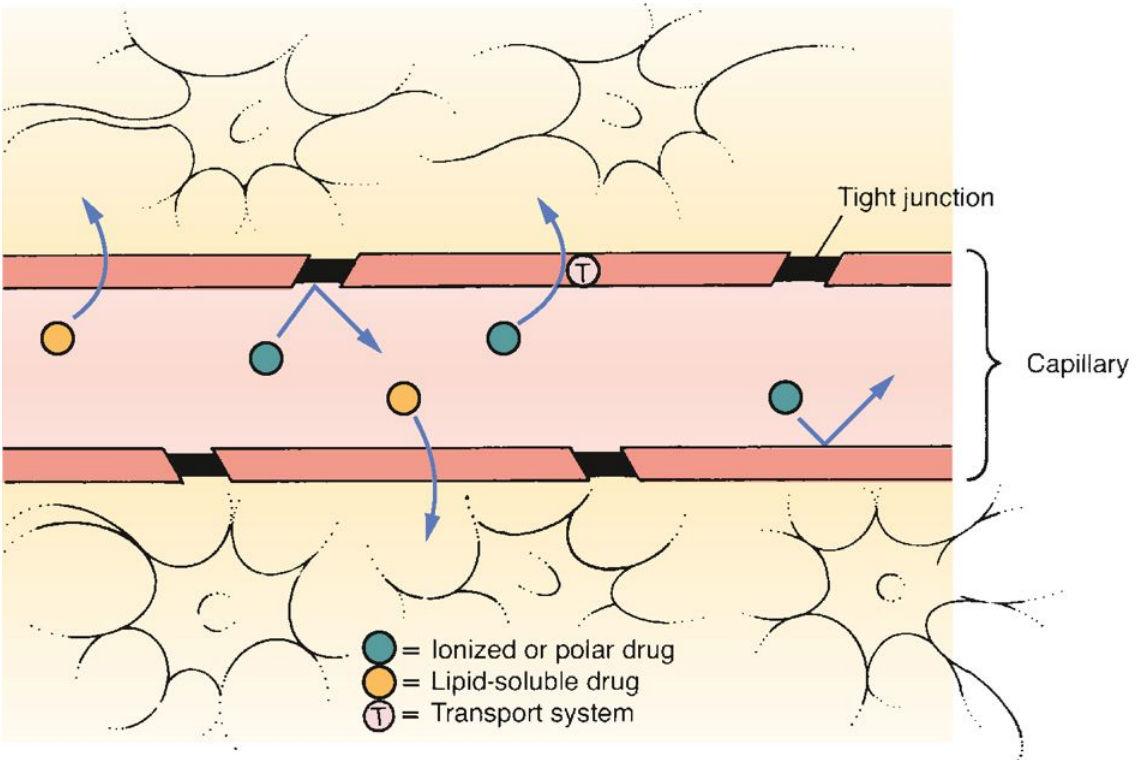


Figure 4-9 Drug movement across the blood-brain barrier. Tight junctions between cells that compose the walls of capillaries in

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

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

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

The blood-brain barrier is not fully developed at birth. As a result, newborns are much more sensitive than older children or adults to medicines that act on the brain. Likewise, neonates are especially vulnerable to CNS poisons.

Placental Drug Transfer

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

Drugs that have the ability to cross the placenta can cause serious harm. Some compounds can cause birth defects, ranging from low birth weight to mental retardation to gross malformations. (Recall the thalidomide experience.) If a pregnant woman is a habitual user of opioids (eg, heroin), her child will

be born drug dependent, and hence will need treatment with a heroin substitute to prevent withdrawal. The use of respiratory depressants (anesthetics and analgesics) during delivery can depress respiration in the neonate. Accordingly, infants exposed to respiratory depressants must be monitored until breathing has normalized.

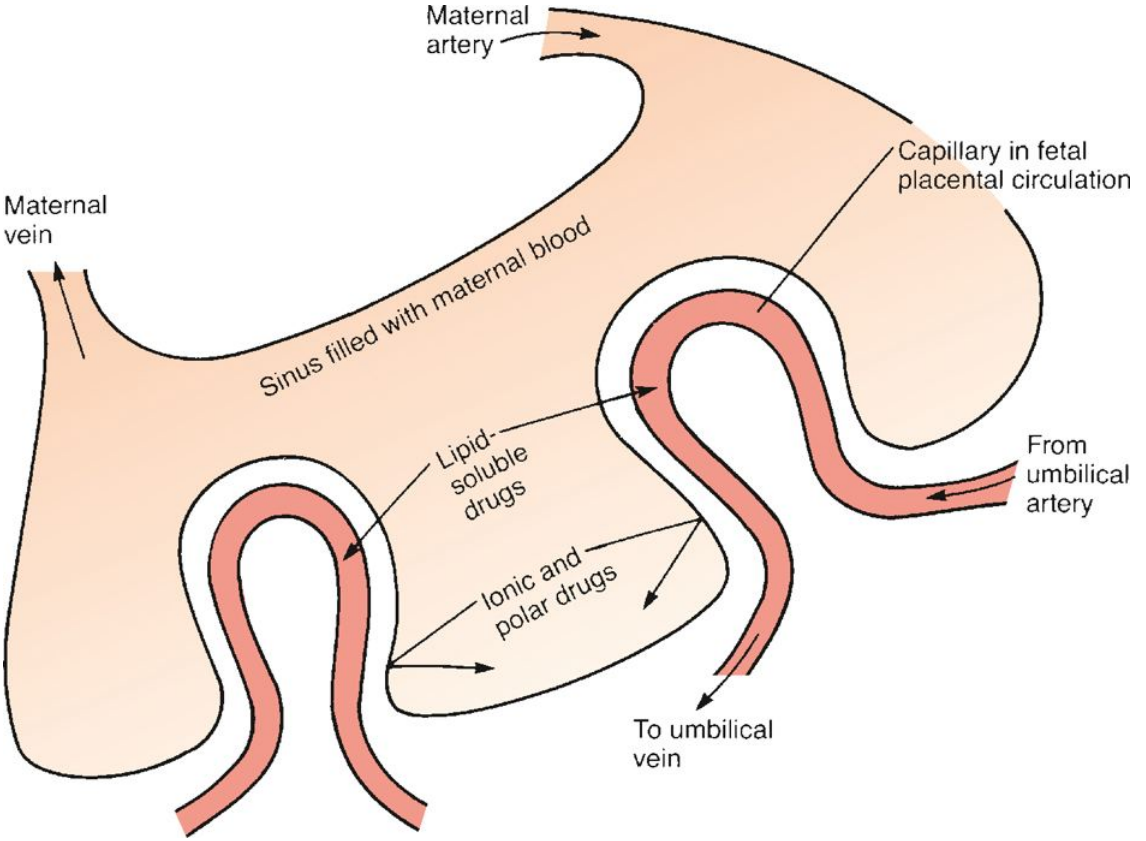


Figure 4-10 Placental drug transfer. To enter the fetal circulation, drugs must cross membranes of the maternal and fetal vascular systems. Lipid-soluble drugs can readily cross these membranes and enter the fetal blood, whereas ions and polar molecules are prevented from reaching the fetal blood.

Protein Binding

Drugs can form reversible bonds with various proteins in the body. Of all the proteins to which drugs can bind, *plasma albumin* is the most important, being

the most abundant protein in plasma. Like other proteins, albumin is a large molecule, having a molecular weight of 69,000. Because of its size, *albumin always remains within the bloodstream:* Albumin is too large to squeeze through pores in the capillary wall, and no transport system exists by which it might leave.

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

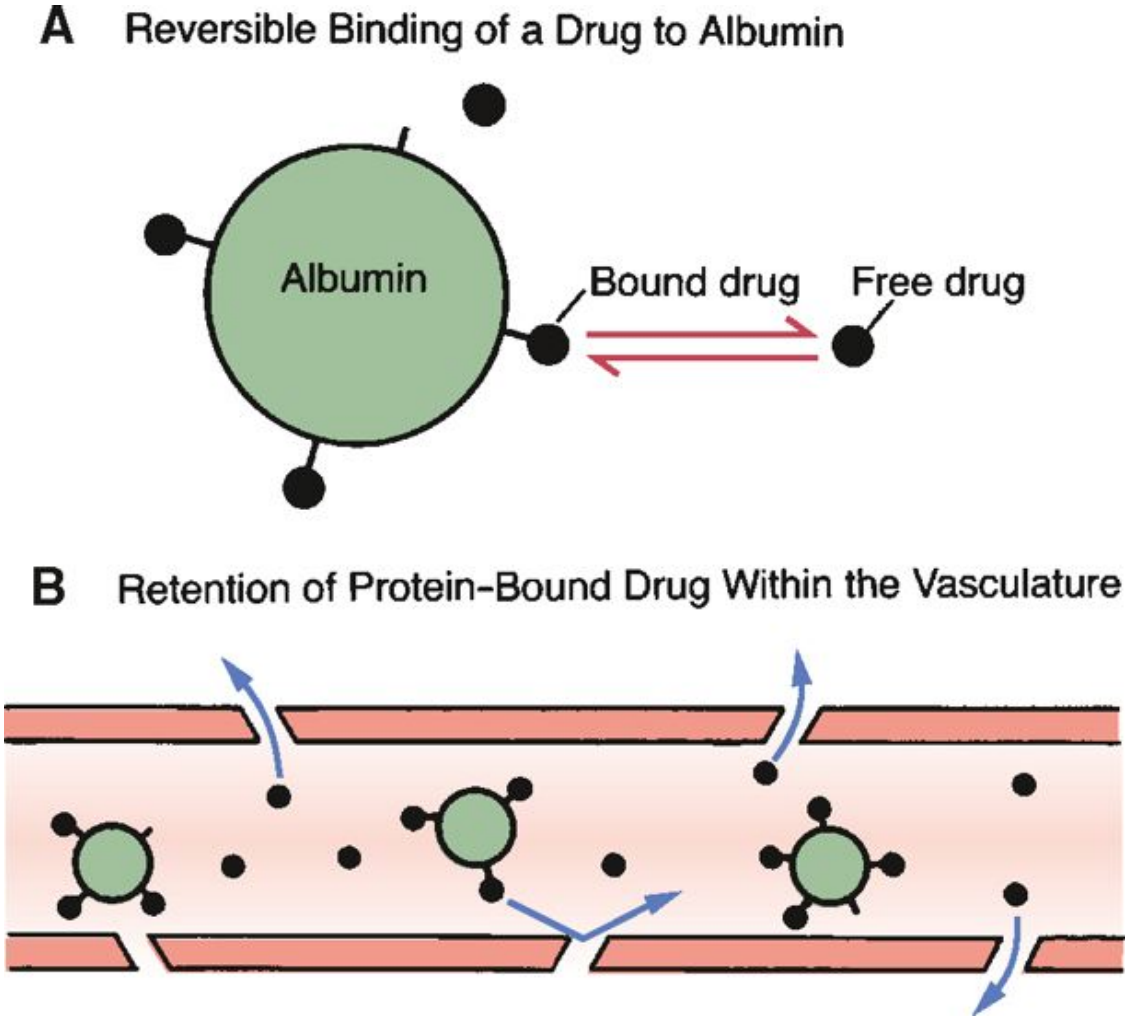


Figure 4-11 Protein binding of drugs. A, Albumin is the most prevalent protein in plasma and the most important of the proteins to which drugs bind. B, Only unbound (free) drug molecules can leave the vascular system. Bound molecules are too large to fit through the pores in the capillary wall.

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

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

In addition to restricting drug distribution, protein binding can be a source of drug interactions. As suggested by Figure 4-11*A*, each molecule of albumin has only a few sites to which drug molecules can bind. Because the number of binding sites is limited, drugs with the ability to bind albumin will compete with one another for binding. As a result, one drug can displace another from albumin, causing the free concentration of the displaced drug to rise. By increasing levels of free drug, competition for binding can increase the intensity of drug responses. Toxicity can result.

Entering Cells

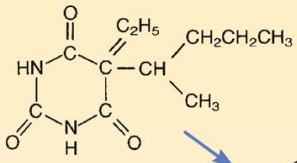
Some drugs must enter cells to reach their sites of action, and practically all drugs must enter cells to undergo metabolism and excretion. The factors that determine the ability of a drug to cross cell membranes are the same factors that determine the passage of drugs across all other membranes, namely,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

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

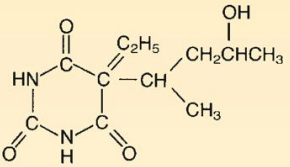
METABOLISM

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

1 Promotion of Renal Drug Excretion
(By Increasing Drug Polarity)



Pentobarbital
(less polar)



"Pentobarbital alcohol"
(more polar)

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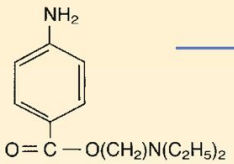
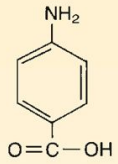
2 Inactivation of Drugs



Procaine (active)



PABA (inactive)

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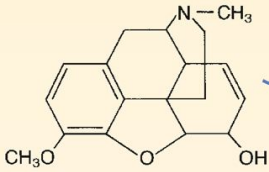
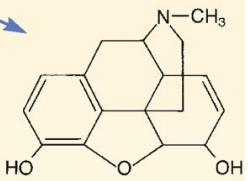
3 Increased Effectiveness of Drugs



Codeine (less effective)



Morphine (more effective)

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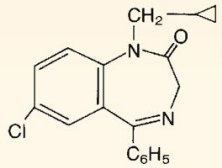
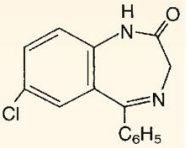
4 Activation of "Prodrugs"



Prazepam (prodrug)



Desmethyldiazepam
(active drug)

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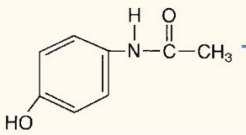
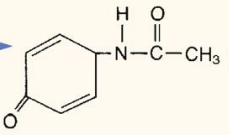
5 Increased Drug Toxicity



Acetaminophen ("safe")



N-acetyl-*p*-benzoquinone

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

Hepatic Drug-Metabolizing Enzymes

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

It is important to appreciate that cytochrome P450 is not a single molecular entity, but rather a group of 12 closely related enzyme families. Three of the cytochrome P450 (CYP) families—designated CYP1, CYP2, and CYP3—metabolize drugs. The other nine families metabolize endogenous compounds (eg, steroids, fatty acids). Each of the three P450 families that metabolize drugs is itself composed of multiple forms, each of which metabolizes only certain drugs. To identify the individual forms of cytochrome P450, we use designations such as CYP1A2, CYP2D6, and CYP3A4, indicating specific members of the CYP1, CYP2, and CYP3 families, respectively. I mention this nomenclature only so that it will be familiar when you come across it in your reading. This information is not intended for memorization.

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

Therapeutic Consequences of Drug Metabolism

Drug metabolism has six possible consequences of therapeutic significance:

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

The reactions shown in Figure 4-12 illustrate these consequences of metabolism.

Accelerated Renal Drug Excretion.

The most important consequence of drug metabolism is promotion of renal drug excretion. As discussed in the next section, the kidney, which is the major organ of drug excretion, is unable to excrete drugs that are highly lipid soluble. By converting lipid-soluble drugs into more polar (less lipid-soluble) compounds, drug metabolism makes it possible for the kidney to excrete many drugs. For certain highly lipid-soluble drugs (eg, thiopental), complete renal excretion would take years were it not for their conversion into more polar compounds by drug-metabolizing enzymes.

Drug Inactivation.

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

Increased Therapeutic Action.

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

Activation of Prodrugs.

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

Increased or Decreased Toxicity.

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

Special Considerations in Drug Metabolism

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

Age.

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

Induction of Drug-Metabolizing Enzymes.

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

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

First-Pass Effect.

The term *first-pass effect* refers to the rapid hepatic inactivation of certain oral drugs. As discussed earlier, when oral drugs are absorbed from the GI tract, they are carried directly to the liver via the hepatic portal vein. If the capa-

city of the liver to metabolize a drug is extremely high, that drug can be completely inactivated on its first pass through the liver. As a result, no therapeutic effects can occur. To circumvent the first-pass effect, a drug that undergoes rapid hepatic metabolism is often administered parenterally. This permits the drug to temporarily bypass the liver, thereby allowing it to reach therapeutic levels in the systemic blood.

Nitroglycerin is the classic example of a drug that undergoes such rapid hepatic metabolism that it is largely without effect following oral administration. However, when administered sublingually (under the tongue), nitroglycerin is very active. Sublingual administration is effective because it permits nitroglycerin to be absorbed directly into the systemic circulation. Once in the circulation, the drug is carried to its sites of action prior to passage through the liver. Hence, therapeutic action can be exerted before the drug is exposed to hepatic enzymes.

Nutritional Status.

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

Competition Between Drugs.

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

EXCRETION

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

Renal Drug Excretion

The kidneys account for the majority of drug excretion. When the kidneys are healthy, they serve to limit the duration of action of many drugs. Conversely,

if renal failure occurs, both the duration and intensity of drug responses may increase.

Steps in Renal Drug Excretion

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

Glomerular Filtration.

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

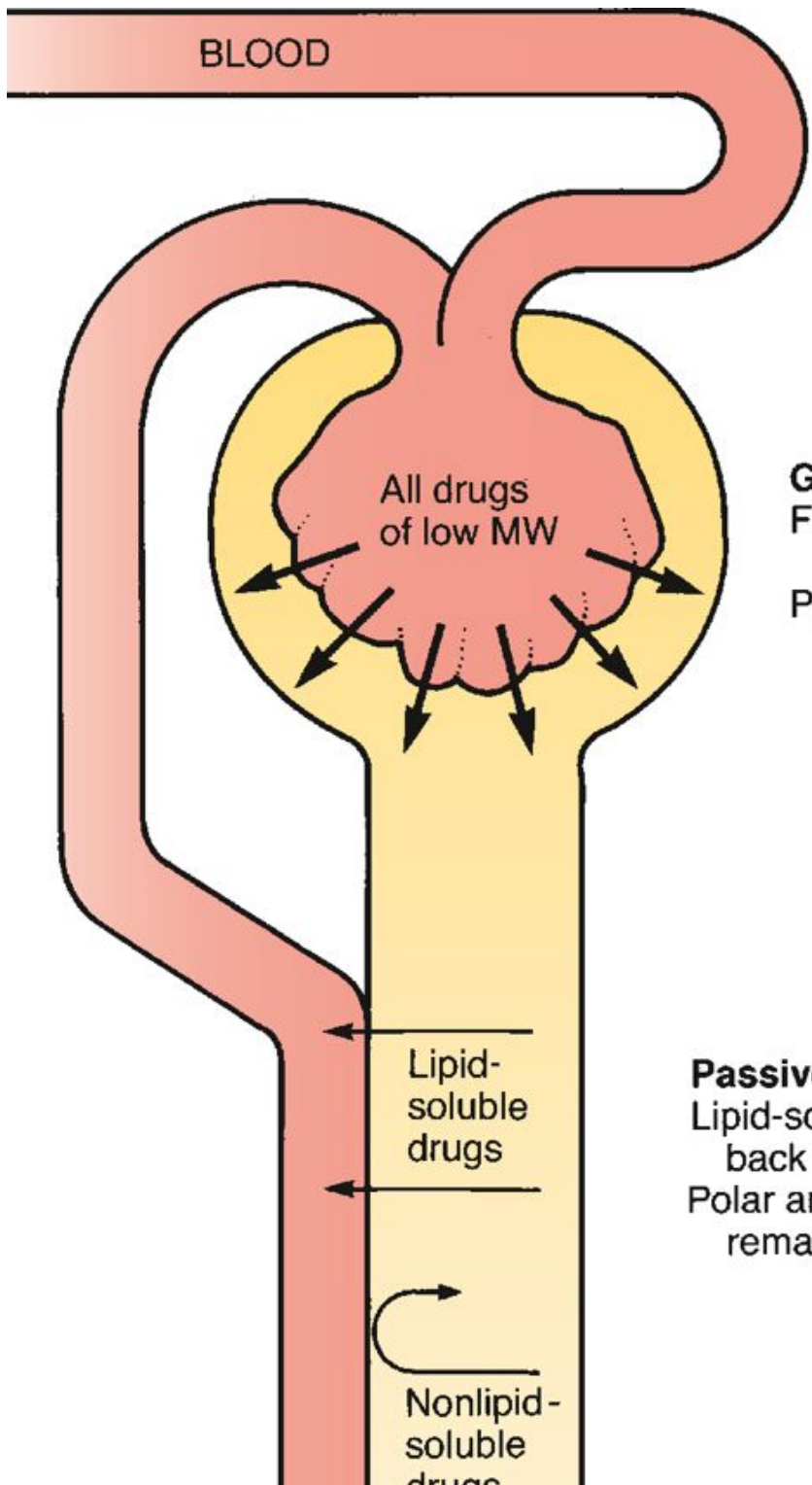
Passive Tubular Reabsorption.

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

Active Tubular Secretion.

There are active transport systems in the kidney tubules that pump drugs from the blood to the tubular urine. The tubules have two primary classes of pumps, one for organic acids and one for organic bases. In addition, tubule

cells contain P-glycoprotein, which can pump a variety of drugs into the urine. These pumps have a relatively high capacity and play a significant role in excreting certain compounds.



Glomerular Filtration
Filtration moves drugs from blood to urine
Protein-bound drugs are not filtered

Passive Reabsorption
Lipid-soluble drugs move back into the blood
Polar and ionized drugs remain in the urine

Figure 4-13 Renal drug excretion. (MW = molecular weight.)

Factors That Modify Renal Drug Excretion

pH-Dependent Ionization.

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

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

Competition for Active Tubular Transport.

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

Competition for transport has been employed clinically to prolong the effects of drugs that normally undergo rapid renal excretion. For example, when administered alone, penicillin is rapidly cleared from the blood by active tubular

transport. Excretion of penicillin can be delayed by concurrent administration of probenecid, an agent that is removed from the blood by the same tubular transport system that pumps penicillin. Hence, if a large dose of probenecid is administered, renal excretion of penicillin will be delayed while the transport system is occupied with moving the probenecid. By delaying penicillin excretion, probenecid prolongs antibacterial effects.

Age.

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

Nonrenal Routes of Drug Excretion

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

Breast Milk

Drugs taken by breast-feeding women can undergo excretion into milk. As a result, breast-feeding can expose the nursing infant to drugs. The factors that influence the appearance of drugs in breast milk are the same factors that determine the passage of drugs across membranes. Accordingly, lipid-soluble drugs will have ready access to breast milk, whereas drugs that are polar, ionized, or protein bound will not enter in significant amounts. Because infants may be harmed by compounds excreted in breast milk, it is recommended that nursing mothers avoid all drugs. If a woman must take medication, she should consult with her prescriber to ensure that the drug will not reach concentrations in her milk that are high enough to harm her baby.

Other Nonrenal Routes of Excretion

The *bile* is an important route of excretion for certain drugs. Recall that bile is secreted into the small intestine and then leaves the body in the feces. In some cases, drugs entering the intestine in bile may undergo reabsorption back into the portal blood. This reabsorption, referred to as *enterohepatic recirculation,* can substantially prolong a drug's sojourn in the body (see Fig. 4-8).

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

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

TIME COURSE OF DRUG RESPONSES

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

Plasma Drug Levels

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

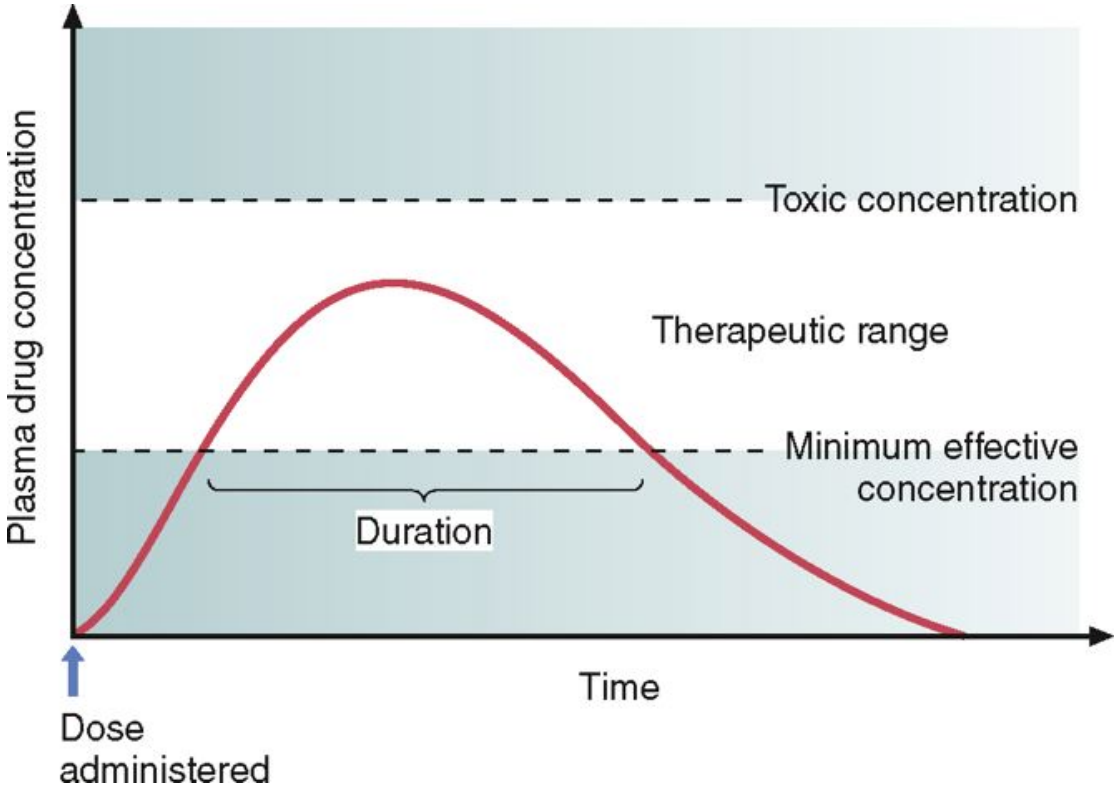


Figure 4-14 Single-dose time course.

Clinical Significance of Plasma Drug Levels

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

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

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

Two Plasma Drug Levels Defined

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

Minimum Effective Concentration.

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

Toxic Concentration.

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

Therapeutic Range

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

The width of the therapeutic range is a major determinant of the ease with which a drug can be used safely. Drugs that have a narrow therapeutic range

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

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

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

Single-Dose Time Course

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

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

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

Drug Half-Life

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

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

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

The concept of half-life is best understood through an example. Morphine provides a good illustration. The half-life of morphine is approximately 3 hours. By definition, this means that body stores of morphine will decrease by 50% every 3 hours—regardless of how much morphine is in the body. If there is 50 mg of morphine in the body, 25 mg (50%) will be lost in 3 hours; if there is only 2 mg of morphine in the body, only 1 mg (50% of 2 mg) will be lost in 3

hours. Note that, in both cases, morphine levels drop by 50% during an interval of one half-life. However, the actual *amount* lost is larger when total body stores of the drug are higher.

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

Drug Levels Produced with Repeated Doses

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

The Process by Which Plateau Drug Levels Are Achieved

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

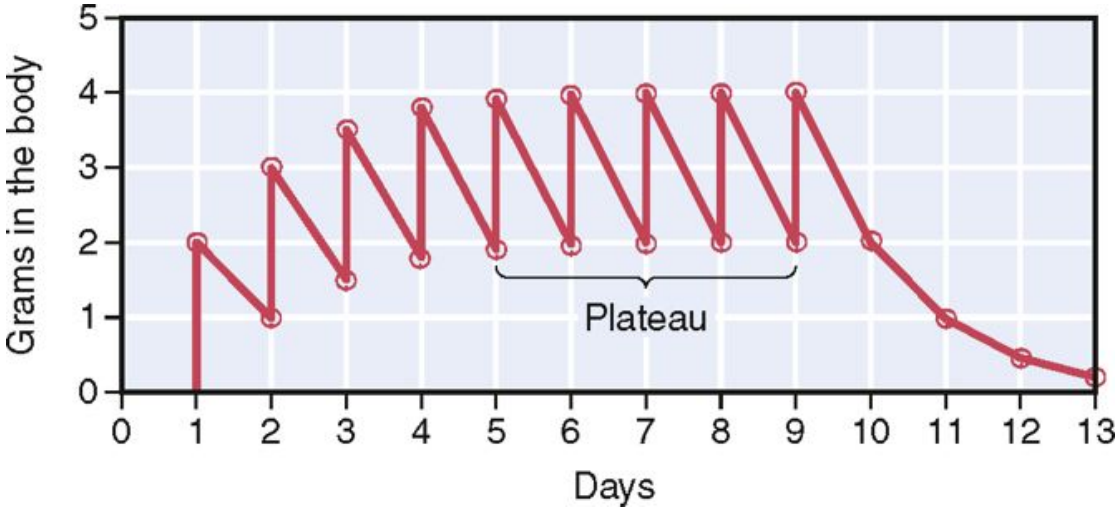


Figure 4-15 Drug accumulation with repeated administration. This figure illustrates the accumulation of a hypothetical drug during repeated administration. The drug has a half-life of 1 day. The dosing schedule is 2 gm given once a day on days 1 through 9. Note that plateau is reached at about the beginning of day 5 (ie, after four half-lives). Note also that, when administration is discontinued, it takes about 4 days (four half-lives) for most (94%) of the drug to leave the body.

The process by which multiple dosing produces a plateau is illustrated in Figure 4-15. The drug in this figure is a hypothetical agent with a half-life of exactly 1 day. The regimen consists of a 2-gm dose administered once daily. For the purpose of illustration, we will assume that absorption takes place instantly. Upon administration of the first 2-gm dose (day 1 in the figure), total body stores go from zero to 2 gm. Within one half-life (1 day), body stores drop by 50%—from 2 gm down to 1 gm. At the beginning of day 2, the second 2-gm dose is given, causing body stores to rise from 1 gm up to 3 gm. Over the next day (one half-life), body stores again drop by 50%, this time from 3 gm down to 1.5 gm. When the third dose is given, body stores go from 1.5 gm up to 3.5 gm. Over the next half-life, stores drop by 50% down to 1.75 gm. When the fourth dose is given, drug levels climb to 3.75 gm and, between doses, levels again drop by 50%, this time to approximately 1.9 gm. When the fifth dose is given (at the beginning of day 5), drug levels go up to about 3.9 gm. This process of accumulation continues until body stores reach 4 gm. When total body

stores of this drug are 4 gm, 2 gm will be lost each day (ie, over one half-life). Since a 2-gm dose is being administered each day, when body stores reach 4 gm, the amount lost between doses will equal the dose administered. At this point, body stores will simply alternate between 4 gm and 2 gm; average body stores will be stable, and plateau will have been reached. Note that the reason that plateau is finally reached is that the actual amount of drug lost between doses gets larger each day. That is, although 50% of total body stores is lost each day, the *amount* in grams grows progressively larger because total body stores are getting larger day by day. Plateau is reached when the amount lost between doses grows to be as large as the amount administered.

Time to Plateau

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

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

Techniques for Reducing Fluctuations in Drug Levels

As we can see in Figure 4-15, when a drug is administered repeatedly, its level will fluctuate between doses. The highest level is referred to as the *peak concentration,* and the lowest level is referred to as the *trough concentration*. How high the peaks and how low the troughs can be will depend upon the drug's

therapeutic range: The peaks must be kept below the toxic concentration, and the troughs must be kept above the MEC. If there is not much difference between the toxic concentration and the MEC, then fluctuations must be kept to a minimum.

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

Loading Doses Versus Maintenance Doses

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

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

Decline from Plateau

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

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

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

KEY POINTS

- Pharmacokinetics consists of four basic processes: absorption, distribution, metabolism, and excretion.
- Pharmacokinetic processes determine the concentration of a drug at its sites of action, and thereby determine the intensity and time course of responses.
- To move around the body, drugs must cross membranes, either by (1) passing through pores, (2) undergoing transport, or (3) penetrating the membrane directly.
- P-glycoprotein—found in the liver, kidney, placenta, intestine, and brain capillaries—can transport a variety of drugs *out* of cells.
- To cross membranes, most drugs must dissolve directly into the lipid bilayer of the membrane. Accordingly, lipid-soluble drugs can cross membranes easily, whereas drugs that are polar or ionized cannot.
- Acidic drugs ionize in basic (alkaline) media, whereas basic drugs ionize in acidic media.
- Absorption is defined as the movement of a drug from its site of administration into the blood.
- Absorption is enhanced by rapid drug dissolution, high lipid solubility of the drug, a large surface area for absorption, and high blood flow at the site of administration.
- Intravenous administration has several advantages: rapid onset, precise control over the amount of drug entering the blood, suitability for use with large volumes of fluid, and suitability for irritant drugs.
- Intravenous administration has several disadvantages: high cost; difficulty; inconvenience; danger because of irreversibility; and the potential for fluid overload, infection, and embolism.
- Intramuscular administration has two advantages: suitability for insoluble drugs and suitability for depot preparations.
- Intramuscular administration has two disadvantages: inconvenience and the potential for discomfort.

- Subcutaneous administration has the same advantages and disadvantages as IM administration.
- Oral administration has the advantages of ease, convenience, economy, and safety.
- The principal disadvantages of oral administration are high variability and possible inactivation by stomach acid, digestive enzymes, and liver enzymes (because oral drugs must pass through the liver before reaching the general circulation).
- Enteric-coated oral formulations are designed to release their contents in the small intestine—not in the stomach.
- Sustained-release oral formulations are designed to release their contents slowly, thereby permitting a longer interval between doses.
- Distribution is defined as the movement of drugs throughout the body.
- In most tissues, drugs can easily leave the vasculature through spaces between the cells that compose the capillary wall.
- The term *blood-brain barrier* refers to the presence of tight junctions between the cells that compose capillary walls in the CNS. Because of this barrier, drugs must pass through the cells of the capillary wall (rather than between them) in order to reach the CNS.
- The membranes of the placenta do not constitute an absolute barrier to the passage of drugs. The same factors that determine drug movements across all other membranes determine the movement of drugs across the placenta.
- Many drugs bind reversibly to plasma albumin. While bound to albumin, drug molecules cannot leave the vascular system.
- Drug metabolism (biotransformation) is defined as the enzymatic alteration of drug structure.
- Most drug metabolism takes place in the liver and is catalyzed by the cytochrome P450 system of enzymes.
- The most important consequence of drug metabolism is promotion of renal drug excretion (by converting lipid-soluble drugs into more polar forms).

- Other consequences of drug metabolism are conversion of drugs to less active (or inactive) forms, conversion of drugs to more active forms, conversion of prodrugs to their active forms, and conversion of drugs to more toxic or less toxic forms.
- Some drugs can induce (stimulate) synthesis of hepatic drug-metabolizing enzymes, and can thereby accelerate their own metabolism and the metabolism of other drugs.
- The term *first-pass effect* refers to the rapid inactivation of some oral drugs as they pass through the liver after being absorbed.
- Most drugs are excreted by the kidneys.
- Renal drug excretion has three steps: glomerular filtration, passive tubular reabsorption, and active tubular secretion.
- Drugs that are highly lipid soluble undergo extensive passive reabsorption back into the blood, and therefore cannot be excreted by the kidney (until they are converted to more polar forms by the liver).
- Drugs can be excreted into breast milk, thereby posing a threat to the nursing infant.
- For most drugs, there is a direct correlation between the level of drug in plasma and the intensity of therapeutic and toxic effects.
- The minimum effective concentration (MEC) is defined as the plasma drug level below which therapeutic effects will not occur.
- The therapeutic range of a drug lies between the MEC and the toxic concentration.
- Drugs with a wide therapeutic range are relatively easy to use safely, whereas drugs with a narrow therapeutic range are difficult to use safely.
- The half-life of a drug is defined as the time required for the amount of drug in the body to decline by 50%.
- Drugs that have a short half-life must be administered more frequently than drugs that have a long half-life.
- When drugs are administered repeatedly, their levels will gradually rise and then reach a steady plateau.

- The time required to reach plateau is equivalent to about four half-lives.
- The time required to reach plateau is independent of dosage size, although the height of the plateau will be higher with larger doses.
- If plasma drug levels fluctuate too much between doses, the fluctuations could be reduced by (1) giving smaller doses at shorter intervals (keeping the total daily dose the same), (2) using a continuous infusion, or (3) using a depot preparation.
- For a drug with a long half-life, it may be necessary to use a loading dose to achieve plateau quickly.
- When drug administration is discontinued, most (94%) of the drug in the body will be eliminated over four half-lives.

5 Pharmacodynamics

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

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

DOSE-RESPONSE RELATIONSHIPS

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

Basic Features of the Dose-Response Relationship

The basic characteristics of dose-response relationships are illustrated in Figure 5-1. Part *A* shows dose-response data plotted on *linear* coordinates. Part *B* shows the same data plotted on *semilogarithmic* coordinates (ie, the scale on which dosage is plotted is logarithmic rather than linear). The most obvious and important characteristic revealed by these curves is that the dose-response relationship is *graded*. That is, as the dosage increases, the response becomes progressively larger. Because drug responses are graded, therapeutic effects can be adjusted to fit the needs of each patient. To tailor treatment to a particular patient, all we need do is raise or lower the dosage until a response of

the desired intensity is achieved. If drug responses were *all-or-nothing* instead of graded, drugs could produce only one intensity of response. If that response were too strong or too weak for a particular patient, there would be nothing we could do to adjust the intensity to better suit the patient. Clearly, the graded nature of the dose-response relationship is essential for successful drug therapy.

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

Maximal Efficacy and Relative Potency

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

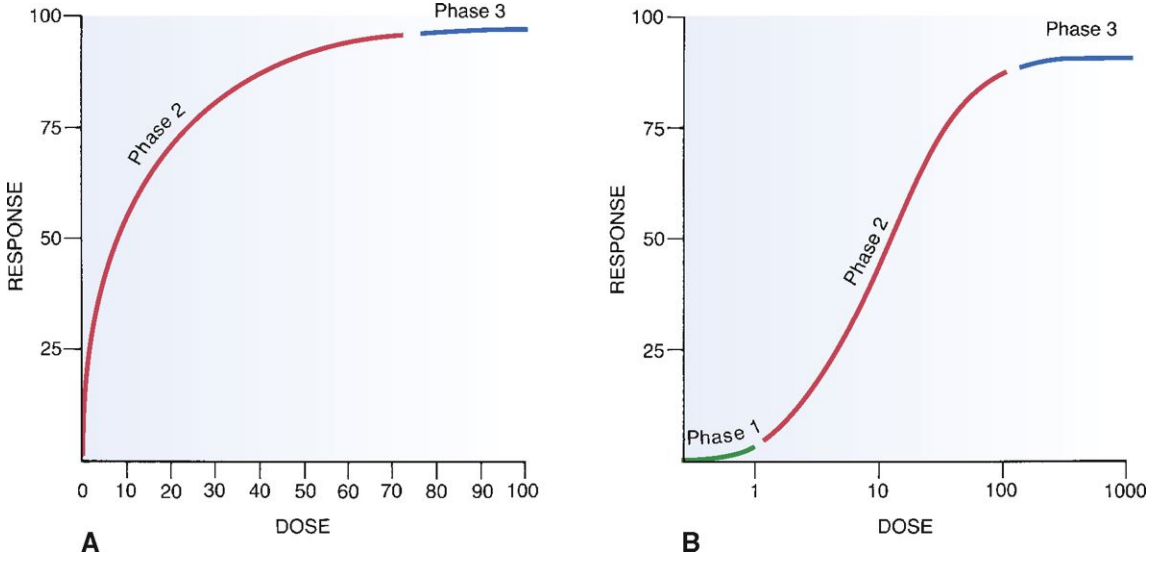


Figure 5-1 Basic components of the dose-response curve. A, A dose-response curve with dose plotted on a linear scale. B, The

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

Maximal Efficacy

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

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

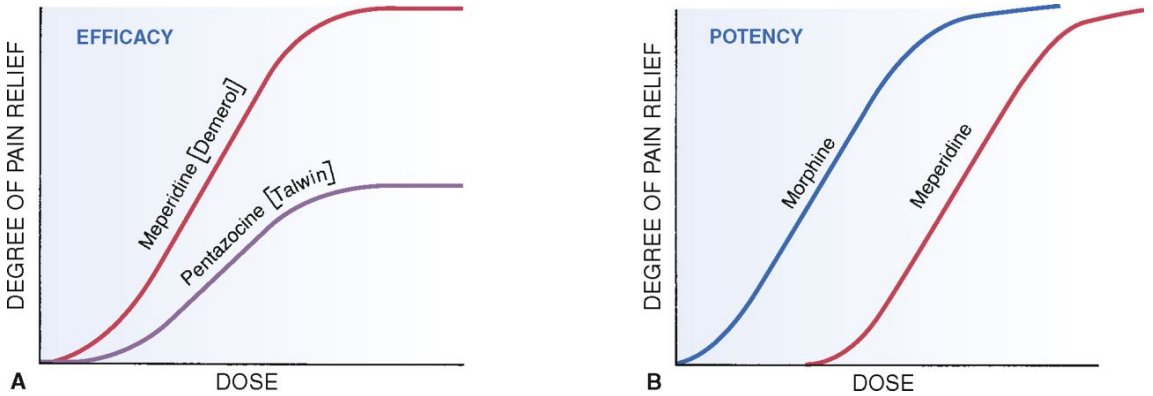


Figure 5-2 Dose-response curves demonstrating efficacy and potency. A, Efficacy, or "maximal efficacy," is an index of the maximal response a drug can produce. The efficacy of a drug is in-

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

Despite what intuition might tell us, a drug with very high maximal efficacy is not always more desirable than a drug with lower efficacy. Recall that we want to match the intensity of the response to the patient's needs. This may be difficult to do with a drug that produces extremely intense responses. For example, certain diuretics (eg, furosemide) have such high maximal efficacy that they can cause dehydration. If we only want to mobilize a modest volume of water, a diuretic with lower maximal efficacy (eg, hydrochlorothiazide) would be preferred. Similarly, if a patient has a headache, we would not select a powerful analgesic (eg, morphine) for relief; rather, we would select an analgesic with lower maximal efficacy, such as aspirin. Put another way, it is neither appropriate nor desirable to hunt squirrels with a cannon.

Relative Potency

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

The concept of potency is illustrated by the curves in Figure 5-2*B*. These curves plot doses for two analgesics—morphine and meperidine—versus the degree of pain relief achieved. As you can see, for any particular degree of pain relief, the required dose of meperidine is larger than the required dose of morphine. Because morphine produces pain relief at lower doses than meperidine, we would say that morphine is more potent than meperidine. That is, a potent drug is one that produces its effects at low doses.

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

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

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

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

DRUG-RECEPTOR INTERACTIONS

Introduction to Drug Receptors

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

We can define a receptor as *any functional macromolecule in a cell to which a drug binds to produce its effects*. Under this broad definition, many cellular components could be considered drug receptors, since drugs bind to many cellular components (eg, enzymes, ribosomes, tubulin) to produce their effects. However, although the formal definition of a receptor encompasses all functional macromolecules, *the term* receptor *is generally reserved for what is arguably the most important group of macromolecules through which drugs act: the body's own receptors for hormones, neurotransmitters, and other regulatory molecules*. The other macromolecules to which drugs bind, such as enzymes and ribosomes, can be thought of simply as target molecules, rather than as true receptors.

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

$$D + R \rightleftharpoons D - R \quad \text{COMPLEX} \rightarrow \text{RESPONSE}$$

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

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

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

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

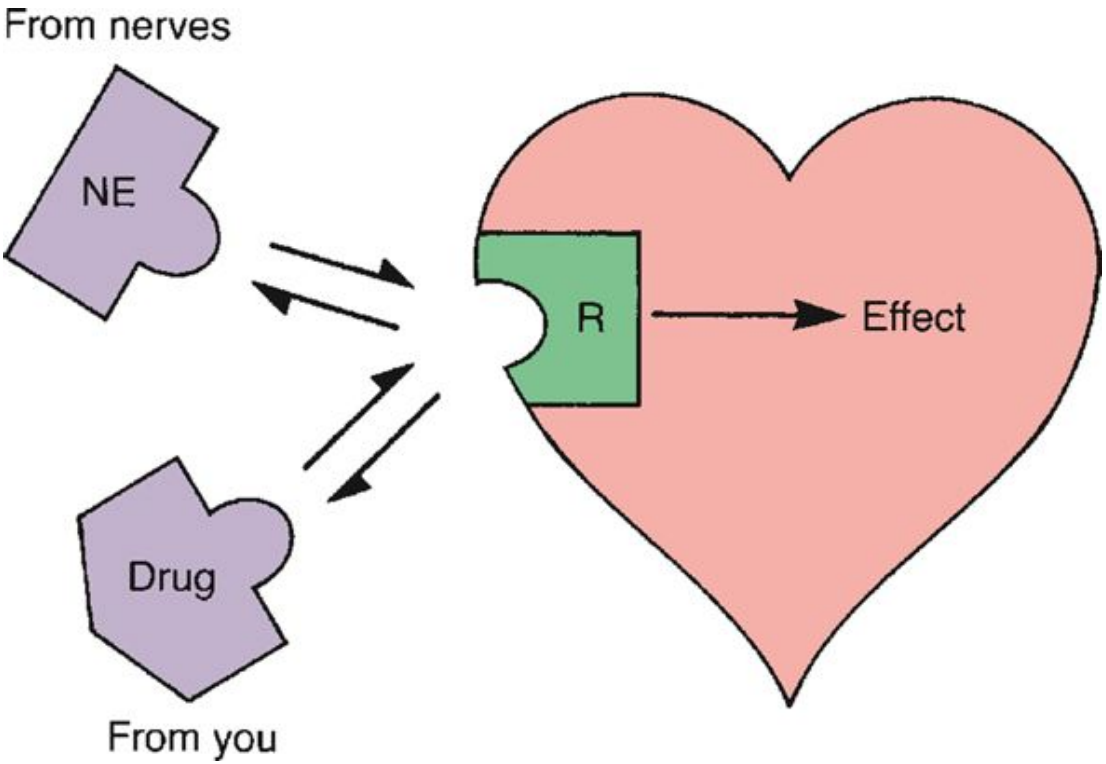


Figure 5-3 Interaction of drugs with receptors for norepinephrine. Under physiologic conditions, cardiac output can be increased by the binding of norepinephrine (NE) to receptors (R) on the heart. Norepinephrine is supplied to these receptors by nerves. These same receptors can be acted on by drugs, which can either mimic the actions of endogenous NE (and thereby increase cardiac output) or block the actions of endogenous NE (and thereby reduce cardiac output).

The same cardiac receptors whose function is regulated by endogenous NE can also serve as receptors for drugs. That is, just as endogenous molecules can bind to these receptors, so can compounds that enter the body as drugs. The

binding of drugs to these receptors can have one of two effects: (1) drugs can *mimic* the action of endogenous NE (and thereby increase cardiac output), or (2) drugs can *block* the action of endogenous NE (and thereby prevent stimulation of the heart by autonomic neurons).

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

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

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

The Four Primary Receptor Families

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

Cell Membrane–Embedded Enzymes.

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

Ligand-Gated Ion Channels.

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

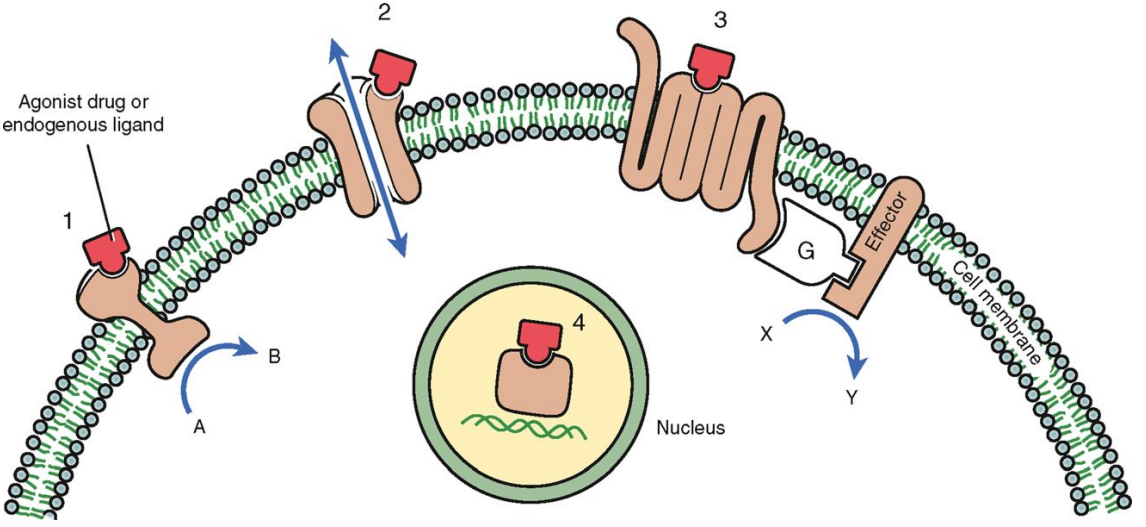


Figure 5-4 The four primary receptor families. 1, Cell membrane–embedded enzyme. 2, Ligand-gated ion channel. 3, G pro-

tein–coupled receptor system (G = G protein). 4, Transcription factor. (See text for details.)

G Protein–Coupled Receptor Systems.

G protein–coupled receptor systems have three components: the receptor itself, G protein (so named because it binds GTP), and an effector (typically an ion channel or an enzyme). These systems work as follows: binding of an endogenous ligand or agonist drug activates the receptor, which in turn activates G protein, which in turn activates the effector. Responses to activation of this type of system develop rapidly. Numerous endogenous ligands, including NE, serotonin, histamine, and many peptide hormones, act through G protein–coupled receptor systems.

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

Transcription Factors.

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

Receptors and Selectivity of Drug Action

In Chapter 1 we noted that selectivity is a highly desirable characteristic of a drug, in that the more selective a drug is, the fewer side effects it will produce.

Selective drug action is possible, in large part, because drugs act through specific receptors.

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

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

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

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

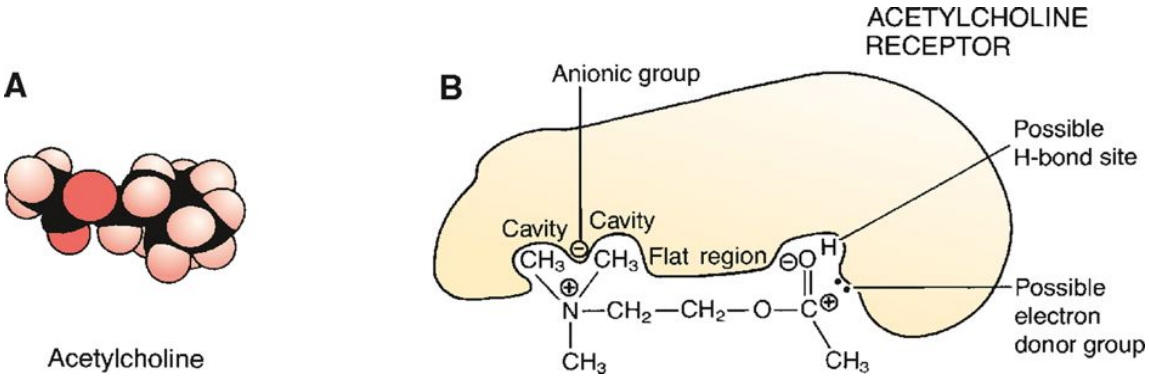


Figure 5-5 Interaction of acetylcholine with its receptor. A, Three-dimensional model of the acetylcholine molecule. B, Binding of acetylcholine to its receptor. Note how the shape of acetylcholine closely matches the shape of the receptor. Note also how the positive charges on acetylcholine align with the negative sites on the receptor.

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

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

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

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

Theories of Drug-Receptor Interaction

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

Simple Occupancy Theory

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

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

Modified Occupancy Theory

The modified occupancy theory of drug-receptor interaction explains certain observations that cannot be accounted for with the simple occupancy theory. The simple occupancy theory assumes that all drugs acting at a particular receptor are identical with respect to (1) the ability to bind to the receptor and

(2) the ability to influence receptor function once binding has taken place. The modified occupancy theory is based on different assumptions.

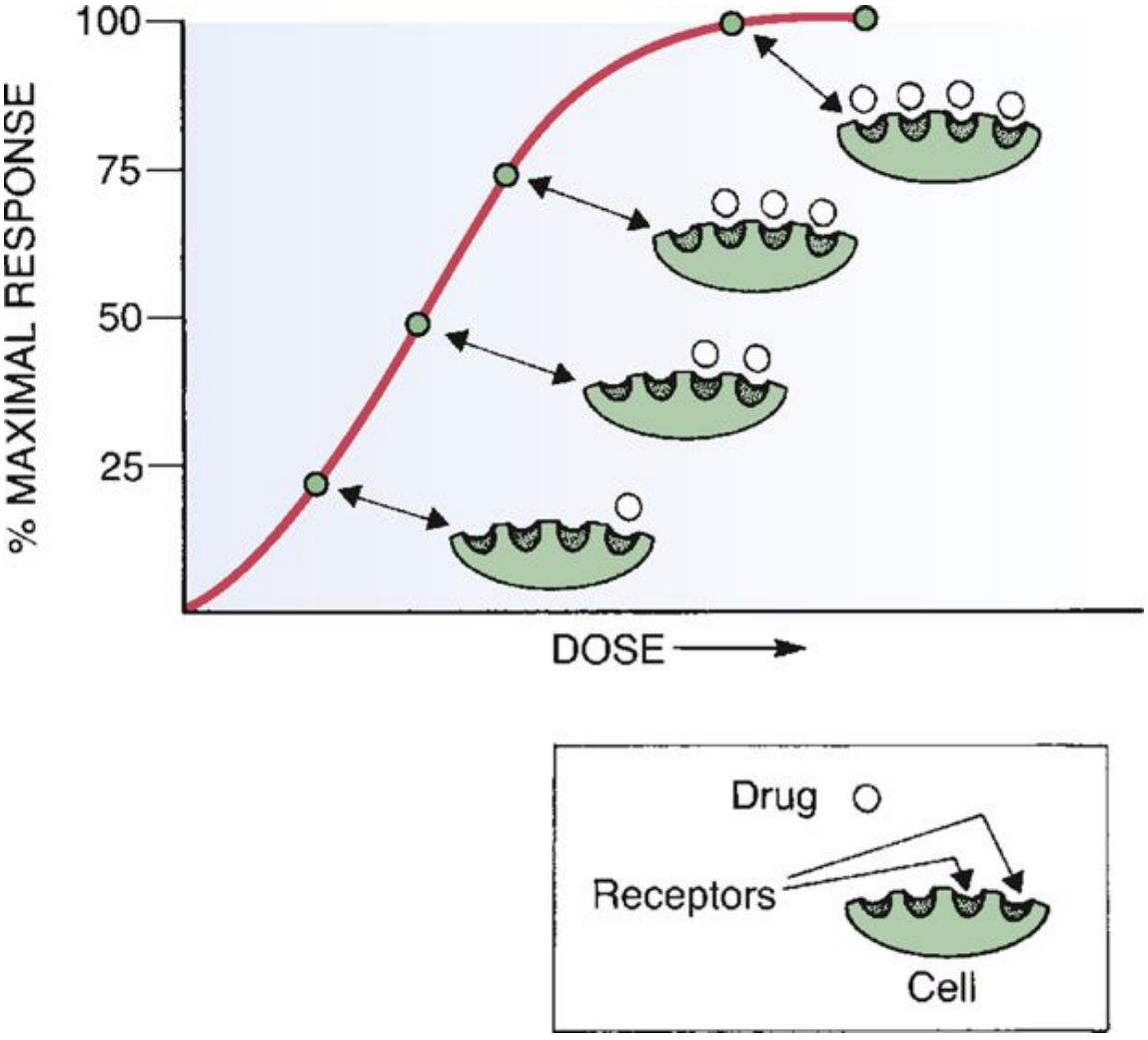


Figure 5-6 Model of simple occupancy theory. The simple occupancy theory states that the intensity of response to a drug is proportional to the number of receptors occupied; maximal response is reached with 100% receptor occupancy. Because the hypothetical cell in this figure has only four receptors, maximal response is achieved when all four receptors are occupied. (Please note: Real cells have thousands of receptors.)

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

Affinity.

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

The affinity of a drug for its receptors is reflected in its *potency*. Because they are strongly attracted to their receptors, drugs with high affinity can bind to their receptors when present in low concentrations. Because they bind to receptors at low concentrations, drugs with high affinity are effective in low doses. That is, *drugs with high affinity are very potent*. Conversely, drugs with low affinity must be present in high concentrations to bind to their receptors. Accordingly, these drugs are less potent.

Intrinsic Activity.

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

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

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

Agonists, Antagonists, and Partial Agonists

As noted, when drugs bind to receptors they can do one of two things: they can either *mimic* the action of endogenous regulatory molecules or they can *block* the action of endogenous regulatory molecules. Drugs that mimic the body's own regulatory molecules are called *agonists*. Drugs that block the actions of endogenous regulators are called *antagonists*. Like agonists, *partial agonists* also mimic the actions of endogenous regulatory molecules, but they produce responses of intermediate intensity.

Agonists

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

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

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

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

Antagonists

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

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

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

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

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

Noncompetitive Versus Competitive Antagonists.

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

Noncompetitive (Insurmountable) Antagonists.

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

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

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

Competitive (Surmountable) Antagonists.

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

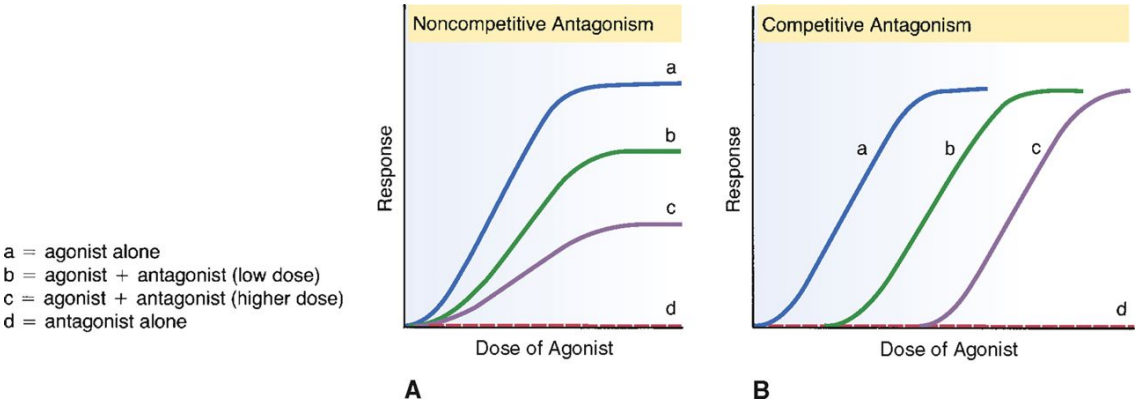


Figure 5-7 Dose-response curves in the presence of competitive and noncompetitive antagonists. A, Effect of a noncompetitive antagonist on the dose-response curve of an agonist. Note that noncompetitive antagonists decrease the maximal response achievable with an agonist. B, Effect of a competitive antagonist on the dose-response curve of an agonist. Note that the maximal response achievable with the agonist is not reduced. Competitive antagonists simply increase the amount of agonist required to produce any given intensity of response.

Because competitive antagonists bind reversibly to receptors, the inhibition they cause is *surmountable*. In the presence of sufficiently high amounts of agonist, agonist molecules will occupy all receptors and inhibition will be completely overcome. The dose-response curves shown in Figure 5-7*B* illustrate the process of overcoming the effects of a competitive antagonist with large doses of an agonist.

Partial Agonists

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

Partial agonists are interesting in that they can act as *antagonists* as well as *agonists*. For example, when pentazocine is administered by itself, it occupies

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

Regulation of Receptor Sensitivity

Receptors are dynamic components of the cell. In response to continuous activation or continuous inhibition, the number of receptors on the cell surface can change, as can their sensitivity to agonist molecules (drugs and endogenous ligands). For example, when the receptors of a cell are continually exposed to an *agonist,* the cell usually becomes less responsive. When this occurs, the cell is said to be *desensitized* or *refractory,* or to have undergone *down-regulation*. Several mechanisms may be responsible, including destruction of receptors by the cell and modification of receptors such that they respond less fully. Continuous exposure to antagonists has the opposite effect, causing the cell to become *hypersensitive* (also referred to as *supersensitive*). One mechanism that can cause hypersensitivity is synthesis of more receptors.

DRUG RESPONSES THAT DO NOT INVOLVE RECEPTORS

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

Common examples of "receptorless drugs" include antacids, antiseptics, saline laxatives, and chelating agents. Antacids reduce gastric acidity by direct chemical interaction with stomach acid. The antiseptic action of ethyl alcohol results from precipitating bacterial proteins. Magnesium sulfate, a powerful laxative, acts by retaining water in the intestinal lumen through an osmotic effect. Dimercaprol, a chelating agent, prevents toxicity from heavy metals (eg, arsenic, mercury) by forming complexes with these compounds. All of

these pharmacologic effects are the result of simple physical or chemical interactions, and not interactions with cellular receptors.

INTERPATIENT VARIABILITY IN DRUG RESPONSES

The dose required to produce a therapeutic response can vary substantially among patients. Why? Because people differ from one another. In this section we consider interpatient variation as a general issue. The specific kinds of differences that underlie variability in drug responses are discussed in Chapter 8.

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

Measurement of Interpatient Variability

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

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

The data from our hypothetical experiment are plotted in Figure 5-8. The plot is called a *frequency distribution curve*. We can see from the curve that a wide range of doses is required to produce the desired response in all subjects. For some subjects, a dose of only 100 mg was sufficient to produce the target response. For other subjects, the therapeutic endpoint was not achieved until the dose totaled 240 mg.

The ED*50*

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

The ED*50* can be considered a "standard" dose and, as such, is frequently the dose selected for initial treatment. After evaluating a patient's response to this "standard" dose, we can then adjust subsequent doses up or down to meet the patient's needs.

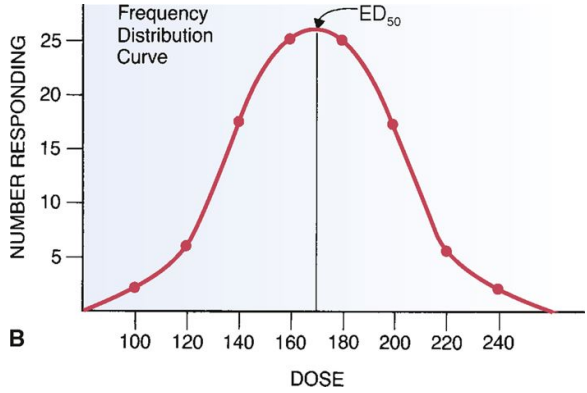
Clinical Implications of Interpatient Variability

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

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

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

A



B

Figure 5-8 Interpatient variation in drug responses. A, Data from tests of a hypothetical acid suppressant in 100 patients. The goal of the study is to determine the dosage required by each patient to elevate gastric pH to 5. Note the wide variability in doses needed to produce the target response for the 100 subjects. B, Frequency distribution curve for the data in A. The dose at the middle of the curve is termed the ED50—the dose that will produce a predefined intensity of response in 50% of the population.

- *When given an average effective dose (ED**50**), some patients will be undertreated, whereas others will have received more drug than they need.* Accordingly, when therapy is initiated with a dose equivalent to the ED**50**, it is especially important to evaluate the response. Patients who fail to respond may need an increase in dosage. Conversely, patients who show signs of toxicity will need a dosage reduction.

- *Because drug responses are not completely predictable, you must look at the patient* (and not the Physicians' Desk Reference) *to determine if too much or too little medication has been administered.* In other words, doses should be adjusted on the basis of the patient's response and not just on the basis of what some reference says is supposed to work. For example, although many postoperative patients receive adequate pain relief with an “average” dose of morphine, this dose is not appropriate for everyone: An average dose may be effective for some patients, ineffective for others, and toxic for still others. Clearly, dosage must be adjusted on the basis of the patient's response, and must not be given in blind compliance with the dosage recommended in a book.

- *Because of variability in responses, nurses, patients, and other concerned individuals must evaluate actual responses and be prepared to inform the prescriber about these responses so that proper adjustments in dosage can be made.*

THE THERAPEUTIC INDEX

The therapeutic index is a measure of a drug's safety. The therapeutic index, determined using laboratory animals, is defined as *the ratio of a drug's LD**50** to its ED**50***. (The LD**50**, or average lethal dose, is the dose that is lethal to 50% of the animals treated.) A large (or high) therapeutic index indicates that a drug is relatively safe. Conversely, a small (or low) therapeutic index indicates that a drug is relatively unsafe.

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

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

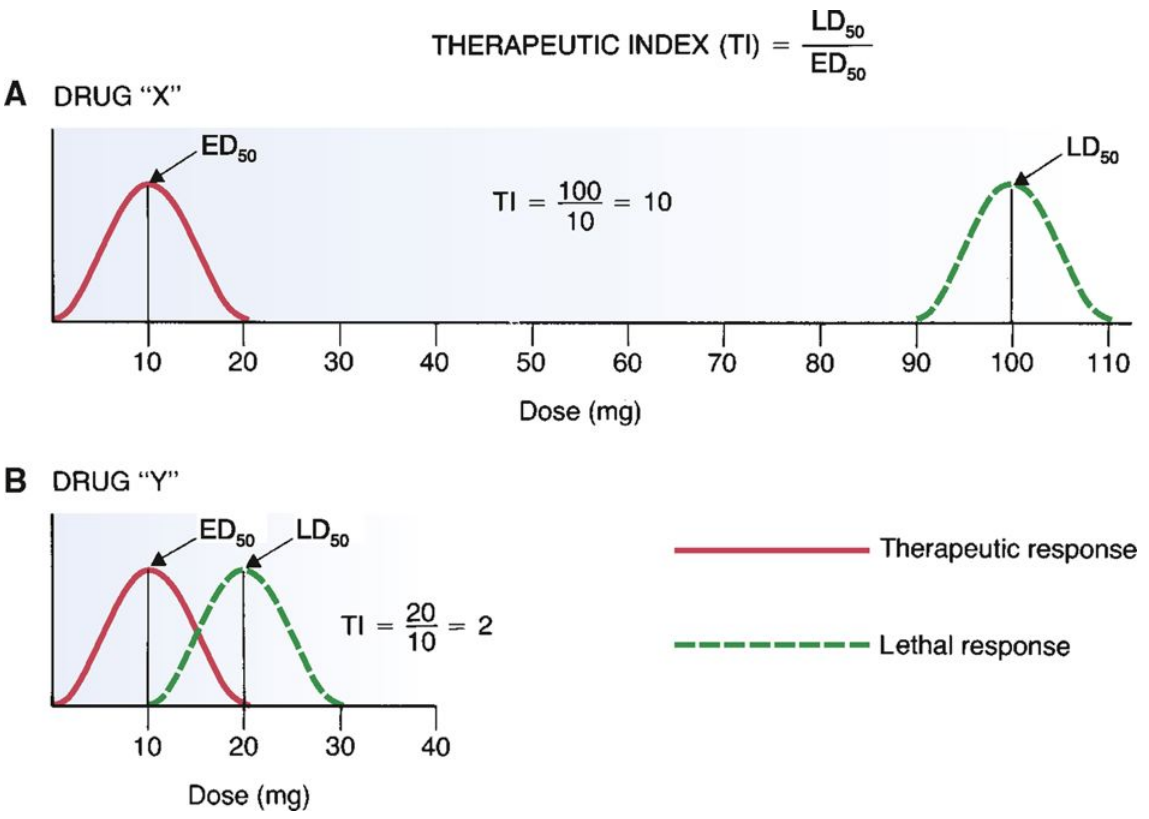


Figure 5-9 The therapeutic index. A, Frequency distribution curves indicating the ED50 and LD50 for drug "X." Because its LD50 is much greater than its ED50, drug X is relatively safe. B, Frequency distribution curves indicating the ED50 and LD50 for drug "Y." Because its LD50 is very close to its ED50, drug Y is not very safe. Also note the overlap between the effective-dose curve and the lethal-dose curve.

KEY POINTS

- Pharmacodynamics is the study of the biochemical and physiologic effects of drugs and the molecular mechanisms by which those effects are produced.
- For most drugs, the dose-response relationship is graded. That is, the response gets more intense with increasing dosage.

- Maximal efficacy is defined as the biggest effect a drug can produce.
- Although efficacy is important, there are many situations in which a drug with relatively low efficacy is preferable to a drug with very high efficacy.
- A potent drug is simply a drug that produces its effects at low doses. As a rule, potency is not important.
- Potency and efficacy are independent qualities. Drug A can be more effective than drug B even though drug B may be more potent. Also, drugs A and B can be equally effective, although one may be more potent than the other.
- A receptor can be defined as any functional macromolecule in a cell to which a drug binds to produce its effects.
- Binding of drugs to their receptors is almost always reversible.
- The receptors through which drugs act are normal points of control for physiologic processes.
- Under physiologic conditions, receptor function is regulated by molecules supplied by the body.
- All that drugs can do at receptors is mimic or block the action of the body's own regulatory molecules.
- Because drug action is limited to mimicking or blocking the body's own regulatory molecules, drugs cannot give cells new functions. Rather, drugs can only alter the rate of pre-existing processes.
- Receptors make selective drug action possible.
- There are four primary families of receptors: cell membrane–embedded enzymes, ligand-gated ion channels, G protein–coupled receptor systems, and transcription factors.
- If a drug interacts with only one type of receptor, and if that receptor type regulates just a few processes, then the effects of the drug will be relatively selective.
- If a drug interacts with only one type of receptor, but that receptor type regulates multiple processes, then the effects of the drug will be nonselective.
- If a drug interacts with multiple receptors, its effects will be nonselective.

- Selectivity does not guarantee safety.
- The term *affinity* refers to the strength of the attraction between a drug and its receptor.
- Drugs with high affinity have high relative potency.
- The term *intrinsic activity* refers to the ability of a drug to activate receptors.
- Drugs with high intrinsic activity have high maximal efficacy.
- Agonists are molecules that activate receptors.
- In terms of the modified occupancy theory, agonists have both affinity and high intrinsic activity. Affinity allows them to bind to receptors, while intrinsic activity allows them to activate the receptor after binding.
- Antagonists are drugs that prevent receptor activation by endogenous regulatory molecules and by other drugs.
- In terms of the modified occupancy theory, antagonists have affinity for receptors but no intrinsic activity. Affinity allows the antagonist to bind to receptors, but lack of intrinsic activity prevents the bound antagonist from causing receptor activation.
- Antagonists have no observable effects in the absence of agonists.
- Partial agonists have only moderate intrinsic activity. Hence their maximal efficacy is lower than that of full agonists.
- Partial agonists can act as agonists (if there is no full agonist present) and as antagonists (if a full agonist is present).
- Continuous exposure of cells to agonists can result in receptor desensitization (aka refractoriness or downregulation), whereas continuous exposure to antagonists can result in hypersensitivity (aka supersensitivity).
- Some drugs act through simple physical or chemical interactions with other small molecules rather than through receptors.
- The ED***50*** is defined as the dose required to produce a defined therapeutic response in 50% of the population.
- The initial dose of a drug is necessarily an approximation. Subsequent doses must be “fine-tuned” based on the patient's response.

- An average effective dose (ED***50***) is perfect for some people, insufficient for others, and excessive for still others.
- Because drug responses are not completely predictable, you must look at the patient (and not some drug reference book) to determine if dosage is appropriate.
- The therapeutic index—defined as the LD***50***:ED***50*** ratio—is a measure of a drug's safety. Drugs with a high therapeutic index are safe. Drugs with a low therapeutic index are not safe.

6 Drug Interactions

In this chapter we consider the interactions of drugs with other drugs, with foods, and with dietary supplements. Our principal focus is on the mechanisms and clinical consequences of drug-drug interactions and drug-food interactions. Drug-supplement interactions are discussed briefly here and at greater length in Chapter 107.

DRUG-DRUG INTERACTIONS

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

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

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

Consequences of Drug-Drug Interactions

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

Intensification of Effects

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

Increased Therapeutic Effects.

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

Increased Adverse Effects.

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

Reduction of Effects

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

Reduced Therapeutic Effects.

The interaction between propranolol and albuterol represents a detrimental inhibitory interaction. Albuterol is taken by people with asthma to dilate the

bronchi. Propranolol, a drug for cardiovascular disorders, can act in the lung to block the effects of albuterol. Hence, if propranolol and albuterol are taken together, propranolol can reduce albuterol's therapeutic effects. Inhibitory actions such as this, which can result in therapeutic failure, are clearly detrimental.

Reduced Adverse Effects.

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

Creation of a Unique Response

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

Basic Mechanisms of Drug-Drug Interactions

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

Direct Chemical or Physical Interactions

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

Direct interactions occur most commonly when drugs are combined in IV solutions. Frequently, but not always, the interaction produces a precipitate. If a precipitate appears when drugs are mixed together, that solution should be discarded. Keep in mind, however, that direct drug interactions may not always leave visible evidence. Hence you cannot rely on simple inspection to re-

veal all direct interactions. Because drugs can interact in solution, *never combine two or more drugs in the same container unless it has been established that a direct interaction will not occur.*

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

Pharmacokinetic Interactions

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

Altered Absorption.

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

- By elevating gastric pH, antacids can decrease the ionization of basic drugs in the stomach, thereby increasing the ability of basic drugs to cross membranes and be absorbed. Antacids have the opposite effect on acidic drugs.
- Laxatives can reduce absorption of other drugs by accelerating their passage through the intestine.
- Drugs that depress peristalsis (eg, morphine, atropine) prolong drug transit time in the intestine, thereby increasing the time for absorption.
- Drugs that induce vomiting can decrease absorption of oral drugs.
- Cholestyramine and certain other adsorbent drugs, which are administered orally but do not undergo absorption, can adsorb other drugs onto themselves, thereby preventing absorption of the other drugs into the blood.
- Drugs that reduce regional blood flow can reduce absorption of other drugs from that region. For example, when epinephrine is injected together with a local anesthetic (as is often done), the epinephrine causes local vasocon-

striction, thereby reducing regional blood flow and delaying absorption of the anesthetic.

Altered Distribution.

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

Competition for Protein Binding.

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

Alteration of Extracellular pH.

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

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

Altered Metabolism.

Altered metabolism is one of the most important—and most complex—mechanisms by which drugs interact. Some drugs *increase* the metabolism of other drugs, and some drugs *decrease* the metabolism of other drugs.

Drugs that increase the metabolism of other drugs do so by inducing synthesis of hepatic drug-metabolizing enzymes. Drugs that decrease the metabolism of other drugs do so by inhibiting those enzymes.

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

Induction of CYP Isozymes.

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

CYP	Substrates	Inhibitors	Inducers
CYP1A2	Caffeine, clomipramine, clozapine, sertraline, theophylline	Cimetidine	Omeprazole
		Fluoroquinolones	Tobacco
		Fluvoxamine	
		Ticlopidine	
CYP2C9	Diclofenac, ibuprofen, irbesartan, losartan, piroxicam, tamoxifen, tolbutamide, warfarin	Azole antifungals	Rifampin
		Fluvastatin	
		Imatinib	
		Zafirlukast	
CYP2C19	Diazepam, lansoprazole, nelfinavir, omeprazole, pantoprazole, voriconazole	Cimetidine	Rifampin
		Fluvoxamine	
		Isoniazid	
CYP2D6	*CNS Drugs:* amitriptyline, atomoxetine, desipramine, haloperidol, imipramine, paroxetine, risperidone, thioridazine	Amiodarone	
		Cimetidine	
		Fluoxetine	
	Antidysrhythmic Drugs: mexiletine, propafenone	Haloperidol	
		Imatinib	
	Beta Blockers: metoprolol, propranolol, timolol	Paroxetine	
		Quinidine	
	Opioids: codeine, dextromethorphan, hydrocodone	Ritonavir	
CYP3A4	*Calcium Channel Blockers:* diltiazem, felodipine, nifedipine, nimodipine, nisoldipine, nitrendipine, verapamil	Amiodarone	Barbiturates
		Azole antifungals	Carbamazepine
	Immunosuppressants: cyclosporine, tacrolimus	Clarithromycin	Isoniazid
		Efavirenz	Phenytoin
	Steroids: 17-beta-estradiol, budesonide, cortisol, progesterone, testosterone	Erythromycin	Rifampin
		Grapefruit juice	St. John's wort
	Macrolide Antibiotics: clarithromycin, erythromycin, troleandomycin	Indinavir	
		Mibefradil	
	Anticancer Drugs: cyclophosphamide, gefitinib, ifosfamide, tamoxifen, vinblastine, vincristine	Imatinib	
		Nefazodone	
	Benzodiazepines: alprazolam, midazolam, triazolam	Nevirapine	
		Ritonavir	
	Opioids: alfentanil, fentanyl, sufentanil	Troleandomycin	
	HMG-CoA Reductase Inhibitors: atorvastatin, lovastatin, simvastatin		
	HIV Protease Inhibitors: amprenavir, indinavir, nelfinavir, ritonavir, saquinavir		
	Others: eletriptan, quinidine, sildenafil, ziprasidone		

Adapted from The Medical Letter 45(1158):47, 2003.

CNS = central nervous system, HIV = human immunodeficiency virus, HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.

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

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

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

Inhibition of CYP Isozymes.

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

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

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

Altered Renal Excretion.

Drugs can alter all three phases of renal excretion: filtration, reabsorption, and active secretion. By doing so, one drug can alter the renal excretion of another. Glomerular filtration can be decreased by drugs that reduce cardiac output: A reduction in cardiac output decreases renal blood flow, which de-

creases drug filtration at the glomerulus, which in turn decreases the rate of drug excretion. By altering urinary pH, one drug can alter the ionization of another, and thereby increase or decrease the extent to which that drug undergoes passive tubular reabsorption. Lastly, competition between two drugs for active tubular secretion can decrease the renal excretion of both agents.

Interactions That Involve P-Glycoprotein.

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

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

Drugs that inhibit PGP will have opposite effects.

Pharmacodynamic Interactions

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

Interactions at the Same Receptor.

Interactions that occur at the same receptor are almost always *inhibitory*. Inhibition occurs when an antagonist drug blocks access of an agonist drug to its receptor. These agonist-antagonist interactions are described in Chapter 5. There are many agonist-antagonist interactions of clinical importance. Some reduce therapeutic effects and are therefore undesirable. Others reduce toxicity and are of obvious benefit. The interaction between naloxone and morphine noted above is an example of a beneficial inhibitory interaction: By blocking access of morphine to its receptors, naloxone can reverse all symptoms of morphine overdose.

Interactions Resulting from Actions at Separate Sites.

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

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

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

Combined Toxicity

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

Clinical Significance of Drug-Drug Interactions

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

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

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

Although a large number of important interactions have been documented, many more are yet to be identified. Therefore, if a patient develops unusual symptoms, it is wise to suspect that a drug interaction may be the cause—especially since yet another drug might be given to control the new symptoms.

Minimizing Adverse Drug-Drug Interactions

We can minimize adverse interactions in several ways. The most obvious is to minimize the number of drugs a patient receives. Indiscriminate use of multiple-drug therapy does not constitute good treatment—and increases the risk of undesired interactions. A second and equally important way to avoid

detrimental interactions is to take a thorough drug history. A history that identifies all drugs the patient is taking allows the prescriber to adjust the regimen accordingly. Please note, however, that patients taking illicit drugs or over-the-counter preparations may fail to report such drug use. You should be aware of this possibility and make a special effort to ensure that the patient's drug use profile is complete. Additional measures for reducing adverse interactions include adjusting the dosage when an inducer of metabolism is added to or deleted from the regimen, adjusting the timing of administration to minimize interference with absorption, monitoring for early signs of toxicity when combinations of toxic agents cannot be avoided, and being especially vigilant when the patient is taking a drug with a narrow therapeutic range.

DRUG-FOOD INTERACTIONS

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

Impact of Food on Drug Absorption

Decreased Absorption.

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

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

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

Increased Absorption.

With some drugs, food increases the extent of absorption. When this occurs, peak effects are heightened. For example, a high-calorie meal more than doubles the absorption of saquinavir [Invirase], a drug for HIV infection. If saquinavir is taken without food, absorption may be insufficient for antiviral activity.

Impact of Food on Drug Metabolism: The Grapefruit Juice Effect

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

Grapefruit juice raises drug levels mainly by inhibiting metabolism. Specifically, grapefruit juice inhibits CYP3A4, an isozyme of cytochrome P450 found in the liver and the intestinal wall. Inhibition of the *intestinal* isozyme is much greater than inhibition of the liver isozyme. By inhibiting CYP3A4, grapefruit juice decreases the intestinal metabolism of many drugs (see Table 6-2), and thereby increases the amount available for absorption. As a result, blood levels of these drugs rise, causing peak effects to be more intense. Since inhibition of CYP3A4 in the liver is minimal, grapefruit juice does not usually affect metabolism of drugs after they have been absorbed. Importantly, grapefruit juice has little or no effect on drugs administered IV. Why? Because, with IV administration, intestinal metabolism is not involved. Inhibition of CYP3A4 is dose dependent: The more grapefruit juice the patient drinks, the greater the inhibition.

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

Inhibition of CYP3A4 persists after grapefruit juice is consumed. Therefore, a drug needn't be administered concurrently with grapefruit juice for an interaction to occur. Put another way, metabolism can still be inhibited even if a patient drinks grapefruit juice in the morning but waits until later in the day to take his or her medicine. In fact, when grapefruit juice is consumed on a regular basis, inhibition can persist up to 3 days after the last glass.

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

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

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

Impact of Food on Drug Toxicity

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

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

Drug	Indications	Potential Consequences of Increased Drug Levels
Dihydropyridine CCBs: amlodipine, felodipine, nicardipine, nifedipine, nimodipine, nisoldipine	Hypertension; angina pectoris	Toxicity: flushing, headache, tachycardia, hypotension
Nondihydropyridine CCBs: diltiazem, verapamil	Hypertension; angina pectoris	Toxicity: bradycardia, AV heart block, hypotension, constipation
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin (minimal effect on atorvastatin, fluvastatin, pravastatin, or rosuvastatin)	Lower cholesterol	Toxicity: headache, GI disturbances, liver and muscle toxicity
Amiodarone	Cardiac dysrhythmias	Toxicity
Caffeine	Prevents sleepiness	Toxicity: restlessness, insomnia, convulsions, tachycardia
Carbamazepine	Seizures; bipolar disorder	Toxicity: ataxia, drowsiness, nausea, vomiting, tremor
Buspirone	Anxiety	Drowsiness, dysphoria
Triazolam	Anxiety; insomnia	Increased sedation
Midazolam	Induction of anesthesia; conscious sedation	Increased sedation
Saquinavir	HIV infection	Increased therapeutic effect
Cyclosporine	Prevents rejection of organ transplants	Increased therapeutic effects; if levels rise too high, renal and hepatic toxicity will occur

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

Impact of Food on Drug Action

Although most drug-food interactions concern drug absorption or drug metabolism, food may also (rarely) have a direct impact on drug action. For example, foods rich in vitamin K (eg, broccoli, Brussels sprouts, cabbage) can reduce the effects of warfarin, an anticoagulant. How? As discussed in Chapter 51, warfarin acts by inhibiting vitamin K–dependent clotting factors. Accordingly, when vitamin K is more abundant, warfarin is less able to inhibit the clotting factors, and therapeutic effects decline.

Timing of Drug Administration with Respect to Meals

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

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

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

Medication orders frequently fail to indicate when a drug should be administered with respect to meals. As a result, inappropriate administration may

occur. If you are uncertain about when to give a drug, ask the prescriber if it should be taken on an empty stomach or with food, and if there are any foods or beverages to avoid.

DRUG-SUPPLEMENT INTERACTIONS

Dietary supplements (herbal medicines and other nontraditional remedies) are used widely in the United States, creating the potential for frequent and significant interactions with conventional drugs. Of greatest concern are interactions that reduce beneficial responses to conventional drugs and interactions that increase toxicity. How do these interactions occur? Through the same pharmacokinetic and pharmacodynamic mechanisms by which conventional drugs interact with each other. Unfortunately, reliable information about dietary supplements is largely lacking—including information on interactions with conventional agents. Interactions that *have* been well documented are discussed as appropriate throughout this text. Dietary supplements and their interactions are discussed at length in Chapter 107.

KEY POINTS

- Some drug-drug interactions are intended and beneficial; others are unintended and detrimental.
- Drug-drug interactions may result in intensified effects, diminished effects, or an entirely new effect.
- Potentiative interactions are beneficial when they increase therapeutic effects and detrimental when they increase adverse effects.
- Inhibitory interactions are beneficial when they decrease adverse effects and detrimental when they decrease beneficial effects.
- Because drugs can interact in solution, never combine two or more drugs in the same container unless you are certain that a direct interaction will not occur.
- Drug interactions can result in increased or decreased absorption.

- Competition for protein binding rarely results in a sustained or significant increase in plasma levels of free drug.
- Drugs that induce hepatic drug-metabolizing enzymes can accelerate the metabolism of other drugs.
- When an inducing agent is added to the regimen, it may be necessary to increase the dosages of other drugs. Conversely, when an inducing agent is discontinued, dosages of other drugs may need to be reduced.
- A drug that inhibits the metabolism of other drugs will increase their levels. Sometimes the result is beneficial, but usually it's detrimental.
- Drugs that act as antagonists at a particular receptor will diminish the effects of drugs that act as agonists at that receptor. The result may be beneficial (if the antagonist prevents toxic effects of the agonist) or detrimental (if the antagonist prevents therapeutic effects of the agonist).
- Drugs that are toxic to the same organ should not be combined (if at all possible).
- We can help reduce the risk of adverse interactions by minimizing the number of drugs the patient is given and by taking a thorough drug history.
- Food may reduce the rate or extent of drug absorption. Reducing the extent of absorption reduces peak therapeutic responses; reducing the rate of absorption merely delays the onset of effects.
- For some drugs, food may increase the extent of absorption.
- Grapefruit juice can inhibit the intestinal metabolism of certain drugs, thereby increasing their absorption, which in turn increases their blood levels.
- Foods may increase drug toxicity. The combination of an MAO inhibitor with tyramine-rich food is the classic example.
- When the medication order says to administer a drug on an empty stomach, this means administer it either 1 hour before a meal or 2 hours after.
- Conventional drugs can interact with dietary supplements. The biggest concerns are increased toxicity and reduced therapeutic effects of the conventional agent.

7 Adverse Drug Reactions and Medication Errors

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

ADVERSE DRUG REACTIONS

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

Scope of the Problem

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

Although ADRs can occur in all patients, some patients are more vulnerable than others. Adverse events are most common in the elderly and the very young. (Patients over 60 account for nearly 50% of all ADR cases.) Severe illness also increases the risk of an ADR. Likewise, adverse events are more common in patients receiving multiple drugs than in patients taking just one.

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

Definitions

Side Effect

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

Toxicity

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

Allergic Reaction

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

The intensity of an allergic reaction is determined primarily by the degree of sensitization of the immune system—not by drug dosage. Put another way, *the intensity of allergic reactions is largely independent of dosage*. As a result, a dose that elicits a very strong reaction in one allergic patient may elicit a very mild reaction in another. Furthermore, since a patient's sensitivity to a drug can

change over time, a dose that elicits a mild reaction early in treatment may produce an intense reaction later on.

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

Idiosyncratic Effect

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

Iatrogenic Disease

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

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

Physical Dependence

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

Although physical dependence is usually associated with "narcotics" (heroin, morphine, and other opioids), these are not the only dependence-inducing drugs. In addition to the opioids, a variety of other centrally acting drugs (eg, ethanol, barbiturates, amphetamines) can promote dependence. Furthermore, some drugs that work outside the central nervous system can cause physical dependence of a sort. Because a variety of drugs can cause physical dependence of one type or another, and because withdrawal reactions have the potential for harm, *patients should be warned against abrupt discontinuation of any medication without first consulting a knowledgeable health professional*.

Carcinogenic Effect

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

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

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

Teratogenic Effect

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

Organ-Specific Toxicity

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

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

Hepatotoxic Drugs

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

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

TABLE 7-1 Some Hepatotoxic Drugs

Statins and Other Lipid-Lowering Drugs

Atorvastatin [Lipitor]

Fenofibrate [Tricor]

Fluvastatin [Lescol]

Gemfibrozil [Lopid]
Lovastatin [Mevacor]
Niacin [Niaspan, others]
Pravastatin [Pravachol]
Simvastatin [Zocor]

Oral Hypoglycemics

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

Antiseizure Drugs

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

Antifungal Drugs

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

Drugs for Tuberculosis

Isoniazid
Pyrazinamide
Rifampin [Rifadin]

Immunosuppressants

Azathioprine [Imuran]
Methotrexate [Rheumatrex]

Antiretroviral Drugs

Nevirapine [Viramune]
Ritonavir [Norvir]

Other Drugs

Acetaminophen [Tylenol, others], but only when combined with alcohol, or taken in excessive dosage

Amiodarone [Cordarone]

Diclofenac [Voltaren]

Duloxetine [Cymbalta]

Halothane [Fluothane]

Leflunomide [Arava]

Methyldopa [Aldomet]

Nefazodone [Serzone]

Nitrofurantoin [Macrodantin]

Tacrine [Cognex]

Tamoxifen [Nolvadex]

Zileuton [Zyflo]

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

Combining a hepatotoxic drug with certain other drugs may increase the risk of liver damage. A good example is the combination of acetaminophen [Tylenol] with alcohol. When taken in *therapeutic* doses* in the absence of alcohol, acetaminophen cannot harm the liver. However, if the drug is taken with just two or three drinks, severe liver injury can result.

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

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

* Excessive (toxic) doses of acetaminophen, by itself, can harm the liver.

QT Interval Drugs

The term *QT interval drugs*—or simply *QT drugs*—refers to the ability of some medications to prolong the QT interval on the electrocardiogram, thereby creating a risk of serious dysrhythmias. As discussed in Chapter 48 (Antidysrhythmic Drugs), the QT interval is a measure of the time required for the ventricles to repolarize after each contraction. When the QT interval is prolonged, patients can develop a dysrhythmia known as *torsades de pointes,* which can progress to potentially fatal ventricular fibrillation.

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

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

Identifying Adverse Drug Reactions

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

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

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

Combining a hepatotoxic drug with certain other drugs may increase the risk of liver damage. A good example is the combination of acetaminophen [Tylenol] with alcohol. When taken in *therapeutic* doses* in the absence of alcohol, acetaminophen cannot harm the liver. However, if the drug is taken with just two or three drinks, severe liver injury can result.

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- Did symptoms abate when the drug was discontinued?
- Did symptoms reappear when the drug was reinstituted?
- Is the illness itself sufficient to explain the event?
- Are other drugs in the regimen sufficient to explain the event?

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

Adverse Reactions to New Drugs

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

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

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

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

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

Page ____ of ____

Form Approved: OMB No. 0910-0291, Expires:10/31/08
See OMB statement on reverse.

FDA USE ONLY

Triage unit
sequence #

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. **Patient Identifier**
In confidence

2. **Age at Time of Event, or Date of Birth:**

3. **Sex**
☐ Female
☐ Male

4. **Weight**
_____ lb
or _____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☐ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*

☐ Death: _____ *(mm/dd/yyyy)*
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☐ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. **Date of Event** *(mm/dd/yyyy)*

4. **Date of this Report** *(mm/dd/yyyy)*
09/14/2007

5. **Describe Event, Problem or Product Use Error**

6. **Relevant Tests/Laboratory Data, Including Dates**

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

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*
#1
#2

2.	Dose or Amount	Frequency	Route
#1			
#2			

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1
#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. **Lot #**
#1
#2

7. **Expiration Date**
#1
#2

9. **NDC # or Unique ID**

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**

2. **Common Device Name**

3. **Manufacturer Name, City and State**

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient
Serial #	Other #	☐ Other:

6. **If Implanted, Give Date** *(mm/dd/yyyy)*

7. **If Explanted, Give Date** *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?**
☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**

Phone #

E-mail

2. **Health Professional?**
☐ Yes ☐ No

3. **Occupation**

4. **Also Reported to:**
☐ Manufacturer
☐ User Facility
☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, please an "X" in this box:** ☐

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

Ways to Minimize Adverse Drug Reactions

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

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

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

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

Lastly, we must be aware that patients with chronic disorders are especially vulnerable to ADRs. In this group are patients with hypertension, epilepsy, heart disease, and psychoses. When drugs must be used long term, the patient

should be informed about the adverse effects that may develop over time and should be monitored for their appearance.

MEDICATION ERRORS

Medication errors are a major cause of morbidity and mortality, as documented in two landmark reports: *To Err is Human,* released in 1999, and *Preventing Medication Errors,* released in 2006. Both were produced by special committees of the Institute of Medicine (IOM), a branch of the National Academies. According to the IOM reports, every year medication errors injure at least 1.5 million Americans, and kill an estimated 7000. The financial costs are staggering: Among hospitalized patients alone, treatment of drug-related injuries costs about $3.5 billion a year. Some authorities argue that the IOM estimates exaggerate the problem; others argue that the estimates are too low. However, all agree that medication errors are a real problem—even if the IOM estimates *are* in dispute. In response to the IOM reports, healthcare organizations throughout the country have intensified efforts to reduce medical errors and thereby improve patient safety.

What's a Medication Error and Who Makes Them?

The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) defines a medication error as "any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use." Note that, by this definition, medication errors can be made by many people—beginning with workers in the pharmaceutical industry, followed by people in the healthcare delivery system, and ending with patients and their family members.

In the hospital setting, a medication order must be processed by several people before it reaches the patient. All of these people can make a mistake. Fortunately, most are also in a position to catch mistakes made by others. The process typically begins with a physician or nurse practitioner writing a

prescription; then someone transcribes the order; in the pharmacy, someone enters the order into a computer; then a pharmacy technician prepares the order, after which a pharmacist checks it; and finally a nurse checks the order again and then administers the drug. Each of these people is in a position to make an error. Except for the prescriber, each is also in a position to catch errors made by others as the order moves down the line. Because the nurse is the last person in the sequence, the nurse is the patient's last line of defense against mistakes—and also the last person with the opportunity to make one. Note also that the nurse is the only person whose actions are not routinely checked by anyone else. Because the nurse is the last person who can catch mistakes made by others, and because no one is there to catch mistakes the nurse might make, the nurse bears a heavy responsibility for ensuring patient safety. Can you think of a better reason to learn all you can about drugs?

Types of Medication Errors

Medication errors fall into 13 major categories (Table 7-3). Some types of errors cause harm directly, and some cause harm indirectly. For example, giving an excessive dose can cause direct harm (adverse effects or even death) from having too much drug in the body. Conversely, giving too little medication can lead to harm, not through direct effects of the drug, but through failure to adequately treat the patient's illness. According to the 1999 IOM report, among *fatal* medication errors, the most common types are giving an overdose (36.4%), giving the wrong drug (16.2%), and using the wrong route (9.5%).

Wrong patient
Wrong drug
Wrong route
Wrong time
Wrong dose
Overdose
Underdose
Extra dose
Omitted dose
Wrong dosage form
Wrong diluent
Wrong strength/concentration
Wrong infusion rate
Wrong technique (includes inappropriate crushing of tablets)
Deteriorated drug error (dispensing a drug after its expiration date)
Wrong duration of treatment (continuing too long or stopping too soon)

TABLE 7-3 Types of Medication Errors

Causes of Medication Errors

Medication errors can result from many causes (Table 7-4). Among fatal medication errors, the 1999 IOM report identified three categories—human factors, communication mistakes, and name confusion—that account for 90% of all errors. Of the human factors that can cause errors, performance deficits (eg, administering a drug IV instead of IM) are the most common (29.8%), followed by knowledge deficits (14.2%) and miscalculation of dosage (13%).

Cause	Examples
Human Factors	
Performance deficit	Administration by IV infusion when IM injection was intended
Knowledge deficit	Failure to know and follow reasonable practice standards
Miscalculation of dosage	
Drug preparation error	Using the wrong diluent; using the wrong amount of diluent; adding the wrong drug; adding the wrong amount of drug
Computer error	Incorrect selection from a list by computer operator; incorrect programming into the database; inadequate screening for allergies, interactions, etc.
Stocking error	Error in stocking or restocking; error in cart filling
Transcription error	Original to paper/carbon paper; original to computer; original to fax
Stress	High-volume workload, etc.
Fatigue or lack of sleep	
Communication	
Written miscommunication	Illegible handwriting; misreading or failure to read; confusion regarding decimal point placement in dosage
Oral miscommunication	
Name Confusion	
Trade name confusion	Name sounds or looks like another drug name
Generic name confusion	Name sounds or looks like another drug name
Packaging, Formulations, and Delivery Devices	
Inappropriate packaging	Topical product packaged in sterile IV multidose vial
Tablet or capsule confusion	Confusion because the tablet or capsule is similar in color, shape, or size to tablets or capsules that contain a different drug or a different strength of the same drug

TABLE 7-4 Causes of Medication Errors

Miscommunication involving oral and written orders underlies 15.8% of fatal errors. Poor handwriting is an infamous cause of mistakes. In one example, an order for 2 mg of warfarin (an anticoagulant) was misread as 5 mg, and resulted in death from hemorrhage. In another case, a woman with arthritis died because her prescription to take 10 mg of methotrexate (an immunosuppressant) once a week was misread as 10 mg once a day. Because of illegible handwriting by prescribers, pharmacists make an estimated 150 million phone calls a year for clarification. When patients are admitted to the hospital, errors can result from poor communication regarding medications they were taking at home. For example, a child who was taking cisapride at home died because his prescription for one-fourth of a 10-mg tablet 4 times a day was incorrectly transcribed to read one 10-mg tablet 4 times a day. Other causes of communication errors include careless use of zeros and decimal points, and confusion between metric and apothecary units.

Confusion over drug names underlies 15% of all reports to the Medication Errors Reporting Program (see below). Why is there confusion? Because many drugs have names that sound like or look like the names of other drugs. Table 7-5 lists some good examples, such as *Anaspaz/Antispas, Nasarel/Nizoral,* and *Renagel/Remegel*. Note that most of the examples in Table 7-5 are trade names, not generic names. The potential for lethal confusion among trade names is a powerful reason for abandoning them in favor of universal use of generic names. (In case you skipped the discussion on trade names in Chapter 3, your author feels very strongly that trade names should be outlawed.) To reduce name-related medication errors, all hospitals are now required to have a "read-back" system, in which verbal orders given to pharmacists or medical staff are transcribed and then read back to the prescriber.

Amicar	*Amikin*
Amicar	*Omacar*
Anaspaz	*Antispas*
Carbastat	*Carbatrol*
Celebrex	*Cerebyx*
Clinoril	*Clozaril*
Clomiphene	Clomipramine
Cycloserine	Cyclosporine
Depo-Estradiol	*Depo-Testadiol*
Dioval	*Diovan*
Estratab	*Estratest*
Etidronate	Etretinate
Flomax	*Volmax*
Inderal	*Adderall*
Lamictal	*Lamisil*
Levoxine	*Levoxyl*
Lithobid	*Lithostat*
Lodine	Iodine
Lomotil	*Lamictal*
Naprelan	*Naprosyn*
Nasarel	*Nizoral*
Neoral	*Neosar*
Nephron	*Nephrox*
Nicoderm	*Nitroderm*
Plendil	*Pletal*
Preven	*Preveon*
Renagel	*Remegel*
Sarafem	*Serophene*
Serentil	*Seroquel*
Synagis	*Synergis*
Tamiflu	*Theraflu*

TABLE 7-5 Examples of Drugs with Names That Sound Alike or Look Alike*

Ways to Reduce Medication Errors

Healthcare organizations throughout the country are working to design and implement measures to reduce medication errors. A central theme in these efforts is to change institutional culture—from one that focuses on "naming, shaming, and blaming" those who make mistakes to one focused on designing institution-wide processes and systems that can prevent errors from happening. Measures stressed in the 2006 IOM report include (1) helping and encouraging patients and their families to be active, informed members of the healthcare team, and (2) giving healthcare providers the tools and information needed to prescribe, dispense, and administer drugs as safely as possible.

TABLE 7-6 Sixteen Ways to Cut Medication Errors*

Institutional Culture

- Establish an organizational commitment to a culture of safety.
- Provide medication safety education for all new and existing professional employees.
- Maintain ongoing recognition of safety innovation.
- Create a nonpunitive environment that encourages identification of errors and the development of new patient safety systems.

Infrastructure

- Designate a medication safety coordinator/officer and identify physician champions.
- Promote greater use of clinical pharmacists in high-risk areas.
- Establish area-specific guidelines for unit-stocked medications.
- Establish a mechanism to ensure availability of critical medication information to all members of the patient's care team.

Clinical Practice

- Eliminate dangerous abbreviations and dose designations.

- Implement safety checklists for high-alert medications.
- Implement safety checklists for infusion pumps.
- Develop limitations and safeguards regarding verbal orders.
- Perform failure-mode analysis during procurement process.
- Implement triggers and markers to indicate potential adverse medication events.

Technology

- Eliminate the use of infusion pumps that lack free-flow protection.
- Prepare for implementation of computerized prescriber order entry systems.

    - These strategies are recommended in the Regional Medication Safety Program for Hospitals (RMSPH), developed by a consortium of hospitals in southeastern Pennsylvania.

In southeastern Pennsylvania, a consortium of hospitals has developed a unique system for reducing medication errors. This system, known as the Regional Medication Safety Program for Hospitals (RMSPH), can be considered a model for other hospitals to follow. The RMSPH has a total of 16 action goals divided into four major categories: institutional culture, infrastructure, clinical practice, and technology (Table 7-6). Note that creating an institutional culture dedicated to safety tops the list, and that the institutional environment should be nonpunitive so as to encourage both the identification of errors and the development of new safety systems. This is a radical departure from the past, when organizations focused largely on identifying and punishing caregivers who made mistakes. As you read through Table 7-6, the potential benefits of all 16 objectives should be apparent. To aid practitioners in achieving these 16 goals, the RMSPH contains a "tool kit" with detailed supporting information on how to meet each objective. For example, the kit includes safety checklists to follow when using high-alert drugs, such as anticoagulants, thrombolytics, and neuromuscular blocking agents. (About 20 such drugs cause 80% of medication error-related deaths.)

Some measures to reduce errors have had remarkable success. For example,

- Replacing handwritten medication orders with a computerized order entry system has reduced medication errors by 50%. (The 2006 IOM report recommends that all prescriptions be written electronically by the year 2010.)
- In ICUs, medication errors have been reduced by 66% by having a senior clinical pharmacist accompany physicians on rounds.
- Hospitals in the Department of Veterans Affairs (VA) system have reduced medication errors by up to 70% with a bar-code system. In this system, all nurses and patients wear bar-coded ID strips, and all medications have bar codes too. Before giving a medication, the nurse scans all three codes into a computer, which then either (1) verifies that the patient-drug match is correct and adverse interactions are unlikely or (2) flashes a warning if there is a potential problem. (In 2006, the FDA issued a rule requiring that all hospitals employ a bar-code system like the one used in VA hospitals.)

As noted above, many medication errors result from errors in communication. To help reduce such errors, the Institute for Safe Medication Practices (ISMP) has compiled a list of error-prone abbreviations, symbols, and dose designations (Table 7-7), and has recommended against their use. This list includes eight entries (at the top of Table 7-7) that have been *banned* by The Joint Commission (TJC), formerly known as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). These banned abbreviations can no longer be used by hospitals and other organizations that require TJC accreditation.

Abbreviations, Symbols, or Dose Designations	Intended Meaning	Potential Misinterpretation	Preferred Alternative
Abbreviations and Notations for Which the Alternative MUST be Used (TJC Mandated)			
U or u	Unit	Misread as 0 or 4 (eg, 4U seen as 40; 4u seen as 44); mistaken to mean "cc" so dose given in volume instead of units (eg, 4u mistaken to mean 4cc)	Write "unit"
IU	International unit	Misread as IV (intravenous) or "10"	Write "international unit"
q.d./Q.D.	Every day	Misread as q.i.d. (four times a day)	Write "daily"
q.o.d./Q.O.D.	Every other day	Misread as q.d. (daily) or q.i.d. (four times a day)	Write "every other day"
MS or MSO_4	Morphine sulfate	Mistaken as magnesium sulfate	Write "morphine sulfate"
$MgSO_4$	Magnesium sulfate	Mistaken as morphine sulfate	Write "magnesium sulfate"
Trailing zero after final decimal point (eg, 1.0 mg)	1 mg	Mistaken as 10 mg if the decimal point is missed	Never write a zero by itself after a decimal point
Leading decimal point not preceded by a zero (eg, .5 mg)	0.5 mg	Mistaken as 5 mg if the decimal point is missed	Write "0" before a leading decimal point
Some Abbreviations and Notations for Which the Alternative is RECOMMENDED (but not yet TJC Mandated)			
μg	Microgram	Mistaken as "mg"	Write "mcg"
cc	Cubic centimeters	Mistaken as "u" (units)	Write "mL"
IN	Intranasal	Mistaken as "IM" or "IV"	Write "intranasal" or "NAS"
H.S., hs	Half-strength; at bedtime	Mistaken as opposite of what was intended	Write "half-strength" or "at bedtime"
qhs	At bedtime	Mistaken as qhr (every hour)	Write "at bedtime"
q1d	Daily	Mistaken as q.i.d. (four times daily)	Write "daily"
q6PM, etc.	Nightly at 6 PM	Mistaken as every 6 hours	Write "nightly at 6 PM"
T.I.W.	Three times a week	Mistaken as three times a day or twice weekly	Write "three times weekly"
SC, SQ, sub q	Subcutaneous	SC mistaken as "SL" (sublingual); SQ mistaken as "5 every"; the "q" in "sub q" mistaken as "every" (eg, a heparin dose ordered "sub q 2 hours before surgery" mistaken as "every 2 hours before surgery")	Write "subQ," "sub-Q," "every" "subcut," or "subcutaneously"
D/C	Discharge or discontinue	Premature discontinuation of medications if D/C (intended to mean "discharge") has been interpreted as "discontinued" when followed by a list of discharge medications	Write "discharge" or "discontinue"
AD, AS, AU	Right ear, left ear, each ear	Mistaken as OD, OS, OU (right eye, left eye, each eye)	Write "right ear," "left ear," or "each ear"
OD, OS, OU	Right eye, left eye, each eye	Mistaken as AD, AS, AU (right ear, left ear, each ear)	Write "right eye," "left eye," or "each eye"
Per os	By mouth, orally	The "os" can be mistaken as "left eye" (OS = oculus sinister)	Write "PO," "by mouth," or "orally"
> or <	Greater than or less than	Mistaken for the opposite	Write "greater than" or "less than"
AZT	Zidovudine [Retrovir]	Mistaken as azathioprine or aztreonam	Write complete drug name
CPZ	Prochlorperazine [Compazine]	Mistaken as chlorpromazine	Write complete drug name
ARA A	Vidarabine	Mistaken as cytarabine (ARA C)	Write complete drug name
HCT	Hydrocortisone	Mistaken as hydrochlorothiazide	Write complete drug name
HCTZ	Hydrochlorothiazide	Mistaken as hydrocortisone	Write complete drug name

Adapted from a list compiled by the Institute for Safe Medication Practices, as modified in 2005. The complete list is available online at www.ismp.org/PDF/ErrorProne.pdf

TJC = The Joint Commission, formerly known as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).

TABLE 7-7 Abbreviations, Symbols, and Dose Designations That Can Promote Medication Errors

There is a wealth of information available on reducing medication errors. If you would like more, a good place to start is the 2006 IOM report: *Reducing Medication Errors*. You can purchase the full report or download free summaries from the National Academies Press at *www.nap.edu/catalog.php?record_id=11623*. Comprehensive information can also be found at *www.nccmerp.org*, the web site of the National Coordinating Council for Medication Error Reporting and Prevention. The NCC MERP was established to facilitate the reporting, understanding, and prevention of medication errors. Member organizations include the American Nurses Association, American Medical Association, American Hospital Association, FDA, and U.S. Pharmacopeia (USP). The NCC MERP web site has extensive recommendations for reducing medication errors related to drug administration, medication dispensing, and verbal medication orders and prescriptions. In addition, the site presents recommendations for promoting and standardizing bar coding on medication packaging. Even more information is available from the ISMP (at *www.ismp.org/MSAarticles/AHA-ISMP.html*) and the FDA (at *www.fda.gov/cder/drug/mederrors*).

How to Report a Medication Error

You can report a medication error via the *Medication Errors Reporting (MER) Program,* a nationwide program set up by the U.S. Pharmacopeia in cooperation with the ISMP. All reporting is confidential and can be done by phone or fax, or through the Internet. Details on submitting a report are available online at *www.usp.org/hqi/patientSafety/mer/*. The MER Program encourages participation by all healthcare providers, including pharmacists, nurses, physicians, and students. The objective is not to establish blame, but to improve patient safety by increasing our knowledge of medication errors. All information gathered by the MER Program is forwarded to the FDA, the ISMP, and the product manufacturer. The form for submitting a report is shown in Figure 7-2.

KEY POINTS

- An adverse drug reaction can be defined as any noxious, unintended, and undesired effect that occurs at normal drug doses.
- Patients at increased risk of adverse drug events include the very young, the elderly, the very ill, and those taking multiple drugs.
- An iatrogenic disease is a drug- or physician-induced disease.
- An idiosyncratic effect is an adverse drug reaction based on a genetic predisposition.
- A carcinogenic effect is a drug-induced cancer.
- A teratogenic effect is a drug-induced birth defect.
- The intensity of an allergic drug reaction is based on the degree of immune system sensitization—not on drug dosage.
- Drugs are the most common cause of acute liver failure, and hepatotoxicity is the most common reason for removing drugs from the market.
- Drugs that prolong the QT interval pose a risk of torsades de pointes, a dysrhythmia that can progress to fatal ventricular fibrillation.
- At the time a new drug is released, it may well be able to cause adverse effects that are as yet unreported.
- Measures to minimize adverse drug events include avoiding drugs that are likely to harm a particular patient, monitoring the patient for signs and symptoms of likely adverse effects, educating the patient about possible adverse effects, and monitoring organs that are vulnerable to a particular drug.
- Medication errors are a major cause of morbidity and mortality.
- Medication errors can be made by many people, including pharmaceutical workers, pharmacists, prescribers, transcriptionists, nurses, and patients and their families.
- In a hospital, a medication order is processed by several people. Each is in a position to introduce errors, and, except for the prescriber, each is in a position to catch errors made by others.

- The nurse is the patient's last line of defense against medication errors made by others—and the last person with the opportunity to introduce an error.
- Because the nurse is the last person who can catch mistakes made by others, and because no one is there to catch mistakes the nurse might make, the nurse bears a unique responsibility for ensuring patient safety.
- The three most common *types* of fatal medication errors are giving an overdose, giving the wrong drug, and using the wrong route.
- The three most common *causes* of fatal medication errors are human factors (eg, performance or knowledge deficits), miscommunication (eg, because of illegible prescriber handwriting), and confusion caused by similarities in drug names.
- At the heart of efforts to reduce medication errors is a change in institutional culture—from a punitive system focused on "naming, blaming, and shaming" to a nonpunitive system in which medication errors can be discussed openly, thereby facilitating the identification of errors and the development of new safety procedures.
- Effective measures for reducing medication errors include (1) using a safety checklist for high-alert drugs; (2) replacing handwritten medication orders with a computerized order entry system; (3) having a clinical pharmacist accompany ICU physicians on rounds; (4) avoiding error-prone abbreviations; (5) helping and encouraging patients and their families to be active, informed participants in the healthcare team; and (6) using a computerized bar-code system that (a) identifies the administering nurse and (b) ensures that the drug is going to the right patient and that adverse interactions are unlikely.

USP MEDICATION ERRORS REPORTING PROGRAM

Presented in cooperation with the Institute for Safe Medication Practices

USP is an FDA MEDWATCH partner

Reporters should not provide any individually identifiable health information, including names of practitioners, names of patients, names of healthcare facilities, or dates of birth (age is acceptable).

Date and time of event:

Please describe the error. Include description/sequence of events, type of staff involved, and work environment (e.g., code situation, change of shift, short staffing, no 24-hr. pharmacy, floor stock). If more space is needed, please attach a separate page.

Did the error reach the patient? ❑ **Yes** ❑ No

Was the incorrect medication, dose, or dosage form administered to or taken by the patient? ❑ Yes ❑ No

Circle the appropriate Error Outcome Category (select one—see back for details): A B C D E F G H I

Describe the direct result of the error on the patient (e.g., death, type of harm, additional patient monitoring).

Indicate the possible error cause(s) and contributing factor(s) (e.g., abbreviation, similar names, distractions, etc.).

Indicate the location of the error (e.g., hospital, outpatient or community pharmacy, clinic, nursing home, patient's home, etc.).

What type of staff or healthcare practitioner made the initial error?

Indicate if other practitioner(s) were also involved in the error (type of staff perpetuating error).

What type of staff or healthcare practitioner discovered the error or recognized the potential for error?

How was the error (or potential for error) discovered/intercepted?

If available, provide patient age, gender, diagnosis. Do not provide any patient identifiers.

Please complete the following for the product(s) involved. (If more space is needed for additional products, please attach a separate page.)

	Product #1	Product #2
Brand/Product Name (If Applicable)		
Generic Name		
Manufacturer		
Labeler		
Dosage Form		
Strength/Concentration		
Type and Size of Container		

Reports are most useful when relevant materials such as product label, copy of prescription/order, etc., can be reviewed.

Can these materials be provided? ❑ **Yes** ❑ **No** **Please specify:**

Suggest any recommendations to prevent recurrence of this error, or describe policies or procedures you instituted or plan to institute to prevent future similar errors.

Name and Title/Profession ( ) Telephone Number ( ) Fax Number

Facility/Address and Zip E-mail

Address/Zip (where correspondence should be sent)

Your name, contact information, and a copy of this report are routinely shared with the Institute for Safe Medication Practices (ISMP). Copies of reports will be sent to third parties such as the manufacturer/labeler, and to the Food and Drug Administration (FDA). You havethe option of including your name on these copies.

In addition to releasing my name and contact information to ISMP, USP may release my identity to these third parties as follows (check boxes that apply):

❑ **The manufacturer and/or labeler as listed above** ❑ **FDA** ❑ **Other persons requesting a copy of this report** ❑ **Anonymous to all third parties**

Signature **Date**

Return to:
USP CAPS
12601 Twinbrook Parkway
Rockville, MD 20852-1790

Submit via the Web at
www.usp.org/mer
Call Toll Free: 800-23-ERROR
(800-233-7767) or
FAX: 301-816-8520

Date Received by USP	File Access Number

WEPDF

Figure 7-2 Form for reporting medication errors to the USP Medication Errors Reporting Program.

8 Individual Variation in Drug Responses

Individual variation in drug responses has been a recurrent theme throughout the early chapters of this text. We noted that, because of individual variation, we must tailor drug therapy to each patient. In this chapter, we discuss the major factors that can cause one patient to respond to drugs differently than another. With this information, you will be better prepared to reduce individual variation in drug responses, thereby maximizing the benefits of treatment and reducing the potential for harm. Much of this chapter is a review of information presented in previous chapters.

BODY WEIGHT AND COMPOSITION

If we do not adjust dosage, body size can be a significant determinant of drug effects. Recall that the intensity of the response to a drug is determined in large part by the concentration of the drug at its sites of action—the higher the concentration, the more intense the response. Common sense tells us that, if we give the same dose to a small person and a large person, the drug will achieve a higher concentration in the small person, and therefore will produce more intense effects. To compensate for this potential source of individual variation, dosages must be adapted to the size of the patient.

When adjusting dosage to account for body weight, the clinician may base the adjustment on body surface area rather than on weight per se. Why? Because surface area determinations account not only for the patient's weight but also for how fat or lean he or she may be. Since percentage body fat can change drug distribution, and since altered distribution can change the concentration of a drug at its sites of action, dosage adjustments based on body surface area provide a more precise means of controlling drug responses than do adjustments based on weight alone.

AGE

Drug sensitivity varies with age. Infants are especially sensitive to drugs, as are the elderly. In the very young, heightened drug sensitivity is the result of organ immaturity. In the elderly, heightened sensitivity results largely from organ degeneration. Other factors that affect sensitivity in the elderly are increased

severity of illness, the presence of multiple pathologies, and treatment with multiple drugs. The clinical challenge created by heightened drug sensitivity in the very young and in the elderly is discussed at length in Chapters 10 and 11, respectively.

PATHOPHYSIOLOGY

Abnormal physiology can alter drug responses. In this section we examine the impact of four pathologic conditions: (1) kidney disease, (2) liver disease, (3) acid-base imbalance, and (4) altered electrolyte status.

Kidney Disease

Kidney disease can reduce drug excretion, causing drugs to accumulate in the body. If dosage is not lowered, drugs may accumulate to toxic levels. Accordingly, if a patient is taking a drug that is eliminated by the kidneys, and if renal function declines, dosage must be decreased.

The impact of kidney disease is illustrated in Figure 8-1, which shows the decline in plasma levels of kanamycin (an antibiotic) following injection into two patients, one with healthy kidneys and one with renal failure. (Elimination of kanamycin is exclusively renal.) As indicated, kanamycin levels fall off rapidly in the patient with good kidney function. In this patient, the drug's half-life is brief—only 1.5 hours. In contrast, drug levels decline very slowly in the patient with renal failure. Because of kidney disease, the half-life of kanamycin has increased by nearly 17-fold—from 1.5 hours to 25 hours. Under these conditions, if dosage is not reduced, kanamycin will quickly accumulate to dangerous levels.

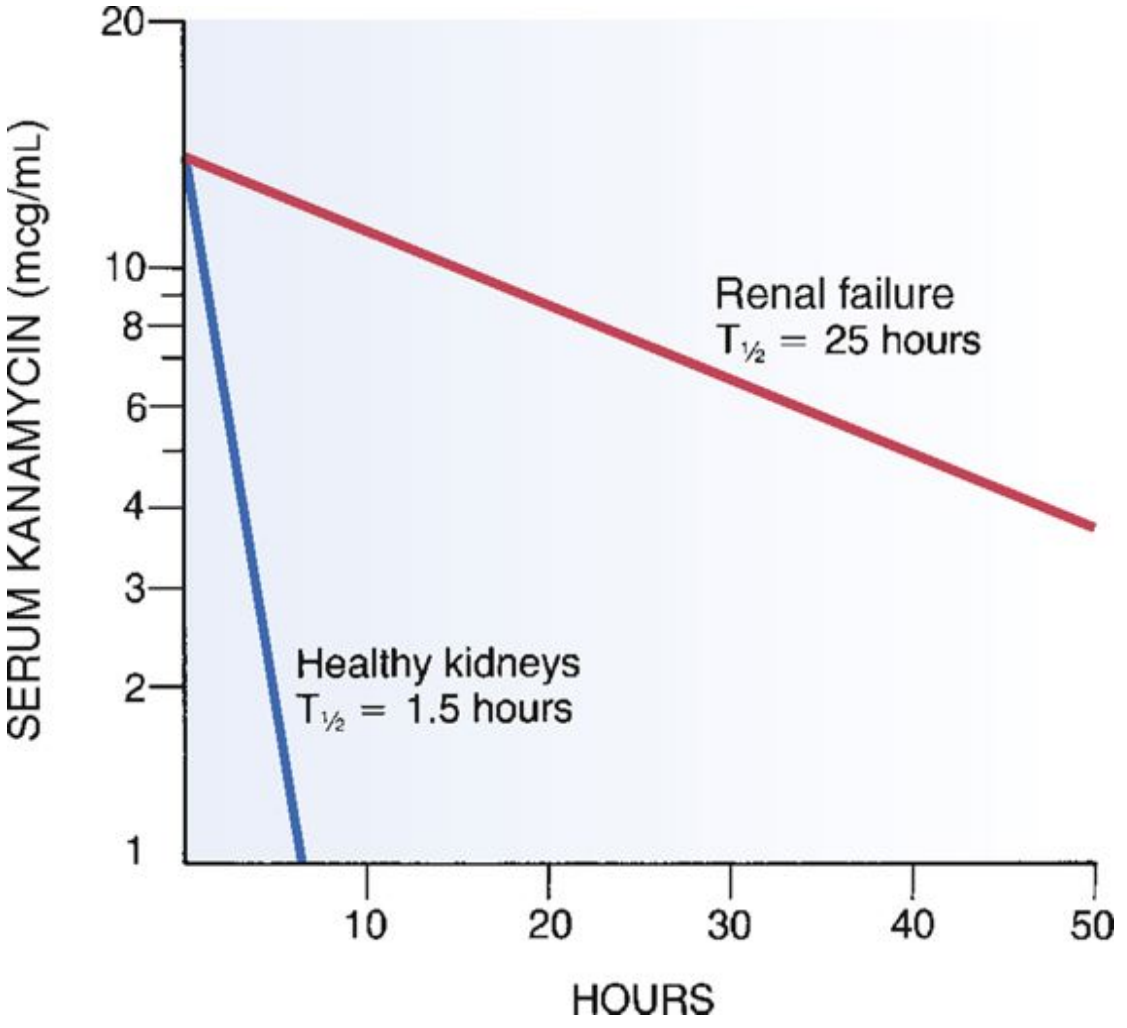


Figure 8-1 Effect of renal failure on kanamycin half-life. Kanamycin was administered at time "0" to two patients, one with healthy kidneys and one with renal failure. Note that drug levels declined very rapidly in the patient with healthy kidneys and extremely slowly in the patient with renal failure, indicating that renal failure greatly reduced the capacity to remove this drug from the body. (T½ = half-life.)

Liver Disease

Like kidney disease, liver disease can cause drugs to accumulate. Recall that the liver is the major site of drug metabolism. Hence, if liver function declines,

rates of metabolism will decline too, and drug levels will climb. Accordingly, to prevent accumulation to toxic levels, dosage must be reduced if liver disease develops. Of course, this guideline applies only to those drugs that are eliminated primarily by the liver, not to drugs that are eliminated by the kidneys and other nonhepatic routes.

Acid-Base Imbalance

By altering pH partitioning (see Chapter 4), changes in acid-base status can alter the absorption, distribution, metabolism, and excretion of drugs.

Figure 8-2 illustrates the impact of altered acid-base status on drug distribution. Specifically, it shows the results of altered acid-base status on the distribution of phenobarbital (a weak acid) in a dog. The upper curve shows plasma levels of phenobarbital. The lower curve shows plasma pH. Acid-base status was altered by having the dog inhale a mixture of gas rich in carbon dioxide (CO_2), thereby causing respiratory acidosis. In the figure, acidosis is indicated by the drop in plasma pH. Note that the decline in pH is associated with a parallel drop in levels of phenobarbital. Upon discontinuation of CO_2, plasma pH returned to normal and phenobarbital levels moved upward.

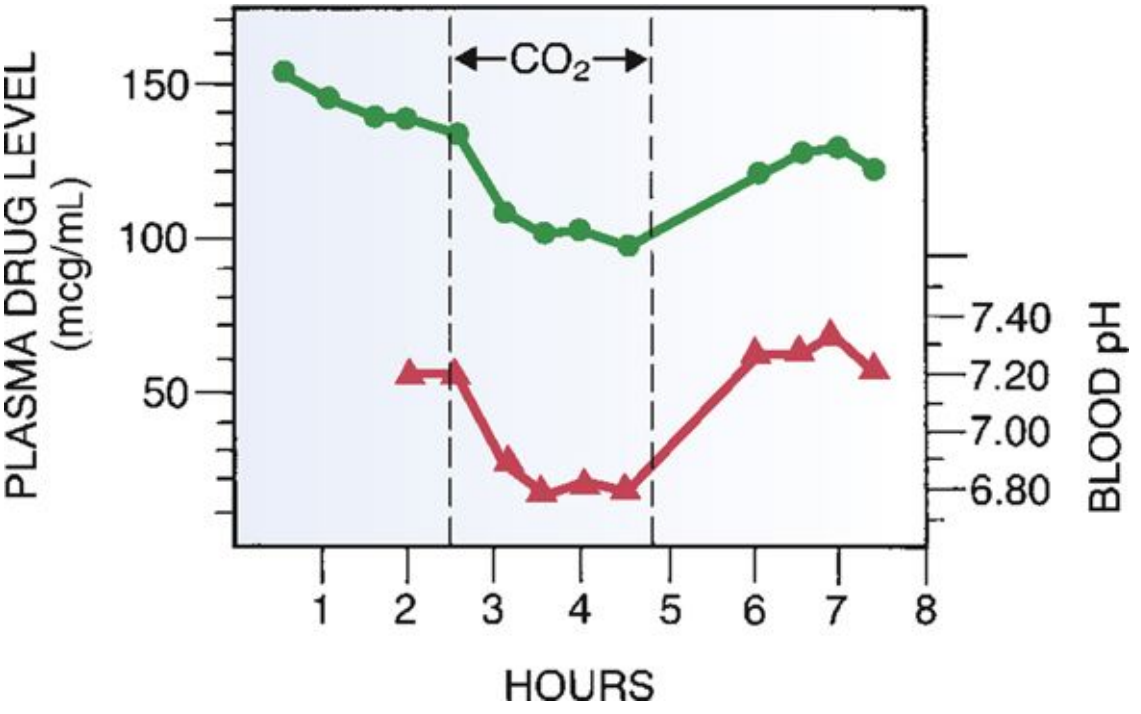


Figure 8-2 Altered drug distribution in response to altered plasma pH. Lower curve, Plasma (extracellular) pH. Note the decline in pH in response to inhalation of CO2. Upper curve, Plasma levels of phenobarbital. Note the decline in plasma drug levels during the period of extracellular acidosis. This decline results from the redistribution of phenobarbital into cells. (See text for details.)

(Redrawn from Waddell WJ, Butler TC: The distribution and excretion of phenobarbital. J Clin Invest 36:1217, 1957.)

Why did acidosis alter plasma levels of phenobarbital? Recall that, because of pH partitioning, if there is a difference in pH on two sides of a membrane, a drug will accumulate on the side where the pH most favors its ionization. Hence, because acidic drugs ionize in alkaline media, acidic drugs will accumulate on the alkaline side of the membrane. Conversely, basic drugs will accumulate on the acidic side. Since phenobarbital is a weak acid, it tends to accumulate in alkaline environments. Accordingly, when the dog inhaled CO2, causing extracellular pH to decline, phenobarbital left the plasma and entered cells, where the environment was less acidic (more alkaline) than in plasma.

When CO_2 administration ceased and plasma pH returned to normal, the pH partitioning effect caused phenobarbital to leave cells and re-enter the blood, causing blood levels to rise.

Altered Electrolyte Status

Electrolytes (eg, potassium, sodium, calcium, magnesium) have important roles in cell physiology. Consequently, when electrolyte levels become disturbed, multiple cellular processes can be disrupted. Excitable tissues (nerves and muscles) are especially sensitive to alterations in electrolyte status. Given that disturbances in electrolyte balance can have widespread effects on cell physiology, we might expect that electrolyte imbalances would cause profound and widespread effects on responses to drugs. However, this does not seem to be the case; examples in which electrolyte changes have a significant impact on drug responses are rare.

Perhaps the most important example of an altered drug effect occurring in response to electrolyte imbalance involves digoxin, a drug for heart disease. The most serious toxicity of digoxin is production of potentially fatal dysrhythmias. The tendency of digoxin to disturb cardiac rhythm is related to levels of potassium: When potassium levels are depressed, the ability of digoxin to induce dysrhythmias is greatly increased. Accordingly, all patients receiving digoxin must undergo regular measurement of serum potassium to ensure that levels remain within a safe range. Digoxin toxicity and its relationship to potassium levels are discussed at length in Chapter 47.

TOLERANCE

Tolerance can be defined as *decreased responsiveness to a drug as a result of repeated drug administration*. Patients who are tolerant to a drug require higher doses to produce effects equivalent to those that could be achieved with lower doses before tolerance developed. There are three categories of drug tolerance: (1) pharmacodynamic tolerance, (2) metabolic tolerance, and (3) tachyphylaxis.

Pharmacodynamic Tolerance

The term *pharmacodynamic tolerance* refers to the familiar type of tolerance associated with long-term administration of drugs such as morphine and heroin.

The person who is pharmacodynamically tolerant requires increased drug levels to produce effects that could formerly be elicited at lower drug levels. Put another way, in the presence of pharmacodynamic tolerance, the minimum effective concentration (MEC) of a drug is abnormally high. Pharmacodynamic tolerance is the result of adaptive processes that occur in response to chronic receptor occupation.

Metabolic Tolerance

Metabolic tolerance is defined as tolerance resulting from accelerated drug metabolism. This form of tolerance is brought about by the ability of certain drugs (eg, barbiturates) to induce synthesis of hepatic drug-metabolizing enzymes, thereby causing rates of drug metabolism to increase. Because of increased metabolism, dosage must be increased to maintain therapeutic drug levels. Unlike pharmacodynamic tolerance, which causes the MEC to increase, metabolic tolerance does not affect the MEC.

The experiment summarized in Table 8-1 demonstrates the development of metabolic tolerance in response to repeated administration of pentobarbital, a central nervous system depressant. The study employed two groups of rabbits, a control group and an experimental group. Rabbits in the experimental group were pretreated with pentobarbital for 3 days (60 mg/kg/day subQ) and then given an IV challenging dose (30 mg/kg) of the same drug. Drug effect (sleeping time) and plasma drug levels were then measured. The control rabbits received the challenging dose of pentobarbital but did not receive any pretreatment. As indicated in Table 8-1, the challenging dose of pentobarbital had less effect on the pretreated rabbits than on the control animals. Specifically, whereas the control rabbits slept an average of 67 minutes, the pretreated rabbits slept only 30 minutes—less than half the sleeping time seen in controls.

Results	Type of Pretreatment	
	None	Pentobarbital
Sleeping time (minutes)	67 ± 4	30 ± 7
Pentobarbital half-life in plasma (minutes)	79 ± 3	26 ± 2
Plasma level of pentobarbital upon awakening (mcg/mL)	9.9 ± 1.4	7.9 ± 0.6

Data from Remmer H: Drugs as activators of drug enzymes. *In* Brodie BB, Erdos EG (eds): Metabolic Factors Controlling Duration of Drug Action (Proceedings of First International Pharmacological Meeting, Vol 6). New York: Macmillan, 1962:235. (See text for details.)

TABLE 8-1 Development of Metabolic Tolerance as a Result of Repeated Pentobarbital Administration

Why was pentobarbital less effective in the pretreated animals? The data on half-life suggest an answer. As shown in the table, the half-life of pentobarbital was much shorter in the experimental group than in the control group. Since pentobarbital is eliminated primarily by hepatic metabolism, the reduced half-life indicates accelerated metabolism. This increase in metabolism, which was brought on by pentobarbital pretreatment, explains why the experimental rabbits were more tolerant than the controls.

You might ask, "How do we know that the experimental rabbits had not developed *pharmacodynamic* tolerance?" The answer lies in the plasma drug levels when the rabbits awoke. In the pretreated rabbits, the waking drug levels were slightly below the waking drug levels in the control group. Had the experimental animals developed pharmacodynamic tolerance, they would have required an *increase* in drug concentration to maintain sleep. Hence, if pharmacodynamic tolerance were present, drug levels would have been abnormally high at the time of awakening, rather than reduced.

Tachyphylaxis

Tachyphylaxis is a form of tolerance that can be defined as a reduction in drug responsiveness brought on by repeated dosing *over a short time*. Hence, unlike pharmacodynamic and metabolic tolerance, which take days to develop, tachyphylaxis occurs quickly. Tachyphylaxis is not a common mechanism of drug tolerance.

Transdermal nitroglycerin provides a good example of tachyphylaxis. When nitroglycerin is administered using a transdermal patch, effects are lost in less than 24 hours (if the patch is left in place around the clock). As discussed in Chapter 50, the loss of effect results from depletion of a cofactor required for nitroglycerin to act. When nitroglycerin is administered on an intermittent schedule, rather than continuously, the cofactor can be replenished and no loss of effect occurs.

PLACEBO EFFECT

A *placebo* is a preparation that is devoid of intrinsic pharmacologic activity. Hence, any response that a patient may have to a placebo is based solely on his or her psychologic reaction to the idea of taking a medication and not to any direct physiologic or biochemical action of the placebo itself. The primary use of the placebo is as a control preparation during clinical trials.

In pharmacology, the *placebo effect* is defined as that component of a drug response that is caused by psychologic factors and not by the biochemical or physiologic properties of the drug. Although it is impossible to assess with precision the contribution that psychologic factors make to the overall response to any particular drug, it is widely believed that, with practically all medications, some fraction of the total response results from a placebo effect. Although placebo effects are determined by psychologic factors and not physiologic ones, the presence of a placebo response does not imply that a patient's original pathology was “all in the head.”

Not all placebo responses are beneficial; placebo responses can also be negative. If a patient believes that a medication is going to be effective, then placebo responses are likely to help promote recovery. Conversely, if a patient is convinced that a particular medication is ineffective or perhaps even harmful, then placebo effects are likely to detract from his or her progress.

Because the placebo effect depends on the patient's attitude toward medicine, fostering a positive attitude may help promote beneficial effects. In this regard, it is desirable that all members of the healthcare team present the patient with an optimistic (but realistic) assessment of the effects that therapy is likely to produce. It is also important that members of the team be consistent with one another; the beneficial placebo responses may well be decreased if, for example, nurses on the day shift repeatedly reassure a patient about the likely benefits of his or her regimen, while nurses on the night shift express pessimism about those same drugs.

Until recently, the power of the placebo effect was unquestioned by most clinicians and researchers. However, new evidence suggests that responses to placebos may be much smaller than previously believed (Box 8-1).

VARIABILITY IN ABSORPTION

Both the rate and extent of drug absorption can vary among patients. As a result, both the timing and intensity of responses can be changed. Differences in manufacturing are a major cause of variability in drug absorption. Other causes include the presence or absence of food, diarrhea or constipation, and differences in gastric emptying time. Several causes of variable absorption are discussed in previous chapters, primarily Chapter 4 (Pharmacokinetics) and Chapter 6 (Drug Interactions), and hence their discussion here is brief.

BOX 8-1 HAS THE PLACEBO LOST ITS EFFECT?

In 1955, H. K. Beecher wrote his famous paper—"The Powerful Placebo"[1]—which was heralded as solid proof for the long-held (but largely unsubstantiated) belief that placebos can effectively relieve symptoms in many patients. This widely cited paper had gone unchallenged until 2001, when two Danish scientists—Hróbjartsson and Gøtzsche—wrote their own paper on the subject, titled "Is the Placebo Powerless?"[2] From their research, the Danes concluded that, at least in the context of clinical trials, placebo treatment has little or no measurable effect. Who's right? Let's consider both papers and see if we can decide.

Beecher analyzed the data from 15 placebo-controlled clinical trials. In all of these trials, patients in the placebo groups were evaluated at baseline,

treated with placebo for a prescribed time, and then re-evaluated. Beecher then looked to see if improvement took place between baseline and the end of the treatment period. Based on his analysis, he concluded "It is evident that placebos have a high degree of effectiveness, decided improvement ... being produced in 35.2% of cases." Pretty impressive. Unfortunately, there's a flaw: How do we know the placebos produced the benefits? Perhaps 35.2% of the patients would have improved with no treatment, owing simply to the natural course of their disease or to other factors. After all, many people *do* get better on their own—without doctors, drugs, placebos, or anything else. Furthermore, although Beecher claims to have selected the 15 papers at random, this seems improbable in that 7 of them were his own.

To address questions left open by Beecher, Hróbjartsson and Gøtzsche took a different approach. First, they analyzed data from 114 published trials—not just 15. More than 8500 patients were involved. More importantly, in all of these trials, placebo treatment was compared with *no treatment*. That is, in each trial, some subjects received placebo treatment and some received no treatment. (Of course, in most [112] of the trials, there was a third group of subjects who received an active treatment.) The trials involved 40 clinical conditions, including anemia, asthma, hypertension, hyperglycemia, epilepsy, Parkinson's disease, schizophrenia, depression, smoking, and pain. In 38 of the trials, the measured outcomes were *objective* (eg, reduction in blood pressure, increase in red blood cell count), and in 76 the outcomes were *subjective* (eg, improvement in mood, reduction of pain). Of the 114 trials, 45 evaluated pharmacologic interventions, 26 evaluated physical interventions, and 43 evaluated psychologic interventions. The type of placebo employed was matched to the active treatment: for the pharmacologic studies, typical placebo treatment consisted of giving a lactose pill; for the physical studies (eg, evaluating the effect of transcutaneous electrical nerve stimulation on pain), typical placebo treatment consisted of performing the procedure but with the equipment turned off; and for the psychologic studies (eg, evaluating the effect of psychotherapy on depression), typical placebo treatment consisted of nondirectional, neutral discussion between the patient and the treatment provider.

What did the analysis reveal? In trials with *objective* outcomes, placebo treatment had *virtually no measurable effect:* outcomes in patients receiving placebo treatment were identical to those in patients receiving no treatment at all.

However, in some trials with *subjective* outcomes, placebo treatment *did* have a convincing effect—but it was small, and limited primarily to studies of *pain*. In their conclusion, the authors stated, "We found little evidence that placebos in general have powerful clinical effects," although they go on to say they did find "significant effects of placebo ... for the treatment of pain." In addition, they concede that their analysis does "leave open the question of whether placebo effects in clinical practice might differ from placebo effects among research subjects."

Is this the end of the story? Is the placebo effect really just a myth? Well, we really can't say. Yes, the Danish study, which was far superior to Beecher's, failed to reveal a powerful effect of placebo treatment. However, this does not prove there is no placebo effect. Rather, it may simply indicate that we can't readily measure a placebo effect in clinical trials. There are some good arguments supporting this possibility:

- If the placebo response is based primarily on the clinician-patient relationship, then, even if there is a placebo response, it would be invisible in clinical trials—because subjects who receive placebo treatment and those who receive no treatment all share the same relationship with the clinician.
- Placebo responses (assuming they exist) are based on the patient's strong belief that he or she is getting an effective treatment. However, in clinical trials, there is always *doubt*—because all participants are aware that they may be getting a placebo, rather than the real deal. In the presence of significant doubt, the placebo effect may be greatly diminished. If this is true, then placebo effects would not be expected in clinical trials.
- If placebo effects exist only in real practice—and not in clinical trials—then proving their existence may well be impossible. Why? Because we'd have to do a clinical trial to prove they exist—and we already know we can't see them in clinical trials.

What's the bottom line? First, owing to a major weakness in design, Beecher's study does not constitute proof that placebos have beneficial effects. Second, by using a more appropriate design, Hróbjartsson and Gøtzsche have shown clearly that, in the context of clinical trials, placebo interventions are largely devoid of measurable effects—with the exception of producing modest reductions in pain. Third, although Hróbjartsson and Gøtzsche failed to see a

placebo effect, their study does not rule out the possibility that, in the real world, placebo treatments can indeed be beneficial. However, this is yet to be proved—and possibly never will be.

1 Beecher HK: The powerful placebo. JAMA 159:1602–1606, 1955.

2 Hróbjartsson A, Gøtzsche PC: Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med 344:1594–1602, 2001.

Bioavailability

The term *bioavailability* refers to the ability of a drug to reach the systemic circulation from its site of administration. Different preparations of the same drug can vary in bioavailability. As discussed in Chapter 4, such factors as tablet disintegration time, enteric coatings, and sustained-release formulations can alter bioavailability, and can thereby make drug responses variable.

Differences in bioavailability occur primarily with oral preparations and not with parenteral preparations. Fortunately, even with oral agents, when differences in bioavailability do exist between preparations, those differences are usually so small as to lack clinical significance.

Differences in bioavailability are of greatest concern for drugs with a narrow therapeutic range. Why? Because with these agents, a relatively small change in drug level can produce a significant change in response: A small decline in drug level may cause therapeutic failure, whereas a small increase in drug level may cause toxicity. Under these conditions, differences in bioavailability could have a significant impact.

Other Causes of Variable Absorption

Several factors in addition to bioavailability can alter drug absorption, and thereby lead to variations in drug responses. Alterations in gastric pH can affect absorption through the pH partitioning effect. For drugs that undergo absorption in the intestine, absorption will be delayed when gastric emptying time is prolonged. Diarrhea can reduce absorption by accelerating transport of drugs through the intestine. Conversely, constipation can enhance absorption by prolonging the time available for absorption. The presence of food in the stomach tends to *slow* the absorption of most drugs, without reducing the total amount absorbed. However, in some cases, food can decrease the *extent* of

absorption as well. For example, absorption of tetracycline is reduced substantially by milk or any other dairy product that contains calcium. Lastly, there are multiple mechanisms by which drug interactions can decrease or increase absorption (see Chapter 6).

GENETICS

A patient's unique genetic makeup can lead to drug responses that are qualitatively and quantitatively different from those of the population at large. Adverse effects and therapeutic effects may be changed. The major underlying causes of altered responses are alterations in genes that code for drug-metabolizing enzymes and drug targets.

Pharmacogenomics—the study of how genes affect individual drug responses—is an active area of research. In the future, pharmacogenetic analysis should enable us to pick a drug and dosage that best fits the patient's genotype, thereby reducing the risk of adverse reactions, increasing the likelihood of a strong therapeutic response, and decreasing the cost, inconvenience, and risk associated with prescribing a drug to which the patient is unlikely to respond. Although pharmacogenomics is a young science, it is already having an effect: The Food and Drug Administration (FDA) recently recommended that patients using two drugs—warfarin [Coumadin] and carbamazepine [Tegretol]—undergo genetic testing prior to treatment.

Altered Drug Metabolism

The most common mechanism by which genetic differences modify drug responses is alteration of drug-metabolizing enzymes. Such gene-based changes can either accelerate or retard the metabolism of many drugs, as illustrated in the following examples:

- Warfarin—an anticoagulant with a low therapeutic index (TI)—is metabolized very slowly in some patients. Why? Because their genes code for altered forms of cytochrome P450-2C9 (CYP2C9), the enzyme that converts warfarin to an inactive form. If dosage is not kept low in these patients, warfarin may accumulate to levels that cause bleeding. To reduce the risk of bleeding, the FDA now recommends that patients be tested for variants of the gene that codes for CYP2C9.

- About 1 in 3500 Europeans metabolize succinylcholine (a muscle relaxant) very slowly, owing to production of an altered form of butyrylcholinesterase, the enzyme that, in most people, metabolizes the drug very rapidly. If given succinylcholine, people with the abnormal enzyme can experience paralysis that is dangerously prolonged.
- Among white Americans, about 52% metabolize isoniazid (a drug for tuberculosis) slowly and 48% metabolize it rapidly. Why? Because, owing to genetic differences, these people produce two different forms of *N*-acetyltransferase-2, the enzyme that metabolizes isoniazid. If dosage is not adjusted for these differences, the rapid metabolizers may experience treatment failure and the slow metabolizers may experience toxicity.
- In the United States, about 1% of the population produces a form of dihydropyrimidine dehydrogenase that does a poor job of metabolizing fluorouracil, a drug used against cancer. Several people with this inherited difference, while receiving standard doses of fluorouracil, have died from central nervous system injury owing to accumulation of the drug to toxic levels.
- Approximately 1 in 14 Caucasians has a form of cytochrome P450 that is unable to convert codeine into morphine, the active form of codeine. As a result, codeine cannot relieve their pain.

For drugs that have a high TI, altered rates of metabolism may not affect the clinical outcome. However, if the TI is low, then relatively small increases in drug levels can lead to toxicity, and relatively small decreases can lead to therapeutic failure. Clearly, in these cases, altered rates of metabolism can be of great clinical significance.

Altered Drug Targets

Genetic variations can alter the structure of drug receptors and other target molecules, and can thereby influence drug responses. For example, the beneficial effects of warfarin are greatly reduced in patients with a variant form of vitamin K epoxide reductase (VKORC1), the enzyme that warfarin inhibits to produce its effects. Hence, as for CYP2C9 noted above, the FDA recommends testing warfarin users for variants in the gene coding for VKORC1. Other drug targets that can be altered by gene variants include beta*2*-adrenergic receptors (important in the therapy of heart disease and asthma), dopamine

receptors (important in the treatment of schizophrenia), estrogen receptors (important in the treatment of osteoporosis), and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (important in the management of high cholesterol).

Other Ways Genetics Can Influence Drug Responses

Some genetically determined drug responses are based on factors other than changes in drug metabolism or drug targets. For example, some people of Asian ancestry are at high risk of life-threatening skin reactions to carbamazepine [Tegretol] owing to production of unusual human leukocyte antigens (HLAs), known as HLA-B*1502. To reduce risk, the FDA recommends that patients of Asian descent be screened for the HLA-B*1502 gene before carbamazepine is used.

Three other examples follow:

- Trastuzumab [Herceptin], a drug for breast cancer, only works against tumors that overexpress the HER2 protein.
- Tamoxifen [Nolvadex] may prevent development of breast cancer in women at high risk—but only in women with mutations in the *BRCA2* gene, not the *BRCA1* gene.
- Inherited differences in coagulation factors increase the risk of deep vein thrombosis in women using oral contraceptives.

GENDER

Men and women can respond differently to the same drug. A drug may be more effective in men than in women, or vice versa. Likewise, adverse effects may be more intense in men than in women, or vice versa. Unfortunately, for most drugs, we don't know much about gender-related differences. Why? Because, until recently, essentially all drug research was done in men. Nonetheless, enough research *has* been done to indicate that significant gender-related differences really do exist. Here are four examples:

- When used to treat heart failure, digoxin may *increase* mortality in women while having no effect on mortality in men (see Chapter 47, Box 47-1).

- Alcohol is metabolized more slowly by women than by men. As a result, a woman who drinks the same amount as a man (on a weight-adjusted basis) will become more intoxicated.
- Certain opioid analgesics (eg, pentazocine, nalbuphine) are much more effective in women than in men. As a result, pain relief can be achieved at lower doses in women.
- Quinidine causes greater QT interval prolongation in women than in men. As a result, women given the drug are more likely to develop torsades de pointes, a potentially fatal cardiac dysrhythmia.

In 1997, the FDA put pressure on drug companies to include women in trials of new drugs, especially drugs directed at serious or life-threatening illnesses. The information generated by these trials will permit drug therapy in women to be more rational than is possible today. In the meantime, clinicians must keep in mind that the information currently available may fail to accurately predict responses in female patients. Accordingly, clinicians should remain alert for treatment failures and unexpected adverse effects.

It is important to appreciate that gender- and race-related differences in drug responses are, ultimately, genetically based. Hence, the preceding can be considered an extension of our discussion on pharmacogenomics.

RACE

Race-related drug responses have two primary determinants: *genetic variations* and *psychosocial factors*. Hence, to a large extent, discussion here is an extension of our discussion on pharmacogenomics. However, keep in mind that, in addition to genetics, psychosocial factors are important determinants of how individuals in a particular ethnic group respond to drugs.

In general, "race" is not very helpful as a basis for predicting individual variation in drug responses. Why? To start with, race is nearly impossible to define. Do we define it by skin color and other superficial characteristics? Or do we define it by group genetics? If we define race by skin color, how dark must skin be, for example, to define a patient as "black?" On the other hand, if we define race by group genetics, how many black ancestors must an African American have to be considered genetically "black?" And what about most people, whose ancestry is ethnically heterogeneous? Latinos, for

example, represent a mix of multiple ethnic backgrounds from three continents. I think you get the picture. So, if a prescriber can't even decide what "race" a patient belongs to, it would seem very difficult indeed to use race as a basis for making therapeutic decisions.

Of course, what we really care about is not race per se, but rather the specific genetic and psychosocial factors—shared by many members of an ethnic group—that influence drug responses. Armed with this knowledge, we can identify group members who share those genetic and/or psychosocial factors and tailor drug therapy accordingly. Perhaps more importantly, application of this knowledge is not limited to members of the ethnic group from which the knowledge arose: We can use it in the management of *all* patients, regardless of ethnic background. How can this be? Owing to ethnic heterogeneity, these factors are not limited to members of any one race. Hence, once we know about a factor (eg, a specific genetic variation), we can screen all patients for it, and, if it's present, adjust drug therapy as indicated.

This discussion of race-based therapy would be incomplete without mentioning BiDil, a fixed-dose combination of two vasodilators: isosorbide dinitrate (ISDN) and hydralazine, both of which have been available separately for years. In 2005, BiDil became the first drug product approved by the FDA for treating members of just one race, specifically, African Americans. Approval was based on results of the African-American Heart Failure Trial (A-HeFT), which showed that, in self-described black patients, adding ISDN plus hydralazine to standard therapy of heart failure reduced 1-year mortality by 43%—a very impressive and welcome result. Does BiDil benefit African Americans more than white Americans? We don't know: No white patients were enrolled in A-HeFT, so the comparison can't be made. The bottom line? Even though BiDil is approved for treating a specific racial group, there's no proof that it wouldn't work just as well (or even better) in some other group. Why then, you might ask, was A-HeFT conducted? Partly because of older data suggesting a possible increased benefit in black patients. However, the principal reason seems to be a combination of regulatory and market incentives, which made it worthwhile for NitroMed, the manufacturer of BiDil, to limit research to blacks. Here's the story. NitroMed holds two patents on BiDil, one for the fixed-dose combination itself, and one for using the combination in black patients. By getting FDA approval for black patients only, NitroMed ac-

quired patent protection through the year 2020—13 years longer than it would have gotten in the absence of the race-specific indication. Of course, now that BiDil is approved, physicians are free to prescribe it for anyone. So the ploy of getting race-specific approval did not actually limit the number of patients NitroMed could profit from. Is this a great country, or what?

FAILURE TO TAKE MEDICINE AS PRESCRIBED

Medications are not always administered as prescribed: dosage size and timing may be altered, doses may be omitted, and extra doses may be taken. Failure to administer medication as prescribed is a common explanation for variability in the response to a prescribed dose. As a rule, such failure results either from poor patient adherence (compliance) or from medication errors made by hospital staff.

Adherence can be hard to achieve. Factors that can influence adherence include manual dexterity, visual acuity, intellectual capacity, psychologic state, attitude toward drugs, and the ability to pay for medication. As noted in Chapter 3, patient education that is both clear and convincing may help improve adherence, and may thereby help reduce variability.

Medication errors are an obvious source of individual variation. Medication errors can originate with physicians, nurses, technicians, and pharmacists. However, since the nurse is usually the last member of the healthcare team to check medications prior to administration, it is ultimately the nurse's responsibility to ensure that medication errors are avoided. Medication errors are discussed at length in Chapter 7.

DRUG INTERACTIONS

A drug interaction is a process in which one drug alters the effects of another. Drug interactions can be an important source of variability. The mechanisms by which one drug can alter the effects of another and the clinical consequences of drug interactions are discussed at length in Chapter 6.

DIET

Diet can affect responses to drugs, primarily by affecting the patient's general health status. A diet that promotes good health can enable drugs to elicit

therapeutic responses and increase the patient's capacity to tolerate adverse effects. Poor nutrition can have the opposite effect.

Starvation can reduce protein binding of drugs (by decreasing the level of plasma albumin). Because of reduced binding, levels of free drug rise, thereby making drug responses more intense. For certain drugs (eg, warfarin), the resultant increase in effects could be disastrous.

Although nutrition can affect drug responses by the general mechanisms noted, there are but few examples of a specific nutrient affecting the response to a specific drug. Perhaps the best example involves the monoamine oxidase (MAO) inhibitors, drugs used to treat depression. The most serious adverse effect of these drugs is malignant hypertension, which can be triggered by foods that contain tyramine, a breakdown product of the amino acid tyrosine. Accordingly, patients taking MAO inhibitors must rigidly avoid all tyramine-rich foods (eg, beef liver, ripe cheeses, yeast products, Chianti wine). The interaction of tyramine-containing foods with MAO inhibitors is discussed at length in Chapter 32.

KEY POINTS

- In order to maximize beneficial drug responses and minimize harm, we must adjust therapy to account for sources of individual variation.
- As a rule, small patients need smaller doses than large patients.
- Dosage adjustments made to account for size are often based on body surface area, rather than simply on body weight.
- Infants and the elderly are more sensitive to drugs than are older children and younger adults.
- Kidney disease can decrease drug excretion, thereby causing drug levels to rise. To prevent toxicity, drugs that are eliminated by the kidneys should be given in reduced dosage.
- Liver disease can decrease drug metabolism, thereby causing levels to rise. To prevent toxicity, drugs that are eliminated by the liver should be given in reduced dosage.

- When a patient becomes tolerant to a drug, the dosage must be increased to maintain beneficial effects.
- Pharmacodynamic tolerance results from adaptive changes that occur in response to prolonged drug exposure. Pharmacodynamic tolerance increases the MEC of a drug.
- Pharmacokinetic tolerance results from accelerated drug metabolism. Pharmacokinetic tolerance does not increase the MEC.
- A placebo effect is defined as the component of a drug response that can be attributed to psychologic factors, rather than to direct physiologic or biochemical actions of the drug. Solid proof that most placebo effects are real is lacking.
- Bioavailability refers to the ability of a drug to reach the systemic circulation from its site of administration.
- Differences in bioavailability matter most for drugs that have a narrow therapeutic range.
- Alterations in the genes that code for drug-metabolizing enzymes can result in increased or decreased metabolism of many drugs.
- Genetic variations can alter the structure of drug receptors and other target molecules, and can thereby influence drug responses.
- Therapeutic and adverse effects of drugs may differ between males and females. Unfortunately, for most drugs, data are insufficient to predict what the differences might be.
- Race is a poor predictor of drug responses. What really matters is not race, but rather the specific genetic variations and psychosocial factors, shared by some group members, that can influence drug responses.
- Poor patient adherence is a major source of individual variation.

III. DRUG THERAPY ACROSS THE LIFESPAN

9 Drug Therapy During Pregnancy and Breast-Feeding

Our topic for this chapter is drug therapy in women who are pregnant or breast-feeding. The clinical challenge is to provide effective treatment for the mother while avoiding harm to the fetus or nursing infant. Unfortunately, meeting this challenge is confounded by a shortage of reliable data on toxicity from drug use during pregnancy or breast-feeding.

DRUG THERAPY DURING PREGNANCY: BASIC CONSIDERATIONS

Drug use during pregnancy is common: About two-thirds of pregnant women take at least one medication, and the majority take more. Some drugs are used to treat pregnancy-related conditions, such as nausea, constipation, and preeclampsia. Some are used to treat chronic disorders, such as hypertension, diabetes, and epilepsy. And some are used for infectious diseases or cancer. In addition to taking these therapeutic agents, pregnant women may take drugs of abuse, such as alcohol, cocaine, and heroin.

Drug therapy in pregnancy presents a vexing dilemma. In pregnant patients, as in all other patients, the benefits of treatment must balance the risks. Of course, when drugs are used during pregnancy, risks apply to the fetus as well as the mother. Unfortunately, the risks for most drugs used in pregnancy have not been determined—hence the dilemma: The prescriber is obliged to balance risks versus benefits, without knowing what the risks really are. The reasons that underlie our lack of knowledge are discussed below under *Identification of Teratogens*.

Despite the imposing challenge of balancing risks versus benefits, drug therapy during pregnancy cannot and should not be avoided. The health of the fetus depends on the health of the mother. Hence, conditions that threaten the mother's health must be addressed—for the sake of the baby as well as the mother. Chronic asthma is a good example. Uncontrolled maternal asthma is far more dangerous to the fetus than the drugs used to treat it. Among asthmatic women

who fail to take medication, the incidence of stillbirth is doubled. If all women with asthma took medication, an estimated 2000 babies would be saved each year.

Physiologic Changes During Pregnancy and Their Impact on Drug Disposition and Dosing

Pregnancy brings on physiologic changes that can alter drug disposition. Changes in the kidney, liver, and GI tract are of particular interest. Because of these changes, a compensatory change in dosage may be needed.

By the third trimester, renal blood flow is doubled, causing a large increase in glomerular filtration rate. As a result, there is accelerated clearance of drugs that are eliminated by glomerular filtration. Elimination of lithium, for example, is increased by 100%. To compensate for accelerated excretion, dosage must be increased.

For some drugs, hepatic metabolism increases during pregnancy. Three anticonvulsants—phenytoin, carbamazepine, and valproic acid—provide examples.

Tone and motility of the bowel decrease in pregnancy, causing intestinal transit time to increase. Because of prolonged transit, there is more time for drugs to be absorbed. In theory, this could increase levels of drugs whose absorption is normally poor. Similarly, there is more time for reabsorption of drugs that undergo enterohepatic recirculation, and hence effects of these drugs could be prolonged. In both cases, a reduction in dosage might be needed.

Placental Drug Transfer

Essentially all drugs can cross the placenta, although some cross more readily than others. The factors that determine drug passage across the membranes of the placenta are the same factors that determine drug passage across all other membranes. Accordingly, drugs that are lipid soluble cross the placenta easily, whereas drugs that are ionized, highly polar, or protein bound cross with difficulty. Nonetheless, for practical purposes, the clinician should assume that *any drug taken during pregnancy will reach the fetus*.

Adverse Reactions During Pregnancy

Drugs taken during pregnancy can adversely affect both the mother and fetus. The effect of greatest concern is teratogenesis (production of birth defects). This issue is discussed separately below. Not only are pregnant women subject to the same adverse effects as everyone else, they may also suffer effects unique to pregnancy. For example, when heparin (an anticoagulant) is taken by pregnant women, it can cause osteoporosis, which in turn can cause compression fractures of the spine. Use of prostaglandins (eg, misoprostol), which stimulate uterine contraction, can cause abortion. Conversely, use of aspirin near term can suppress contractions in labor. In addition, aspirin increases the risk of serious bleeding.

Regular use of dependence-producing drugs (eg, heroin, barbiturates, alcohol) during pregnancy can result in the birth of a drug-dependent infant. If the infant is not supplied with a drug that can support its dependence, a withdrawal syndrome will ensue. Symptoms include shrill crying, vomiting, and extreme irritability. The neonate should be weaned from dependence by giving progressively smaller doses of the drug on which he or she is dependent.

Certain pain relievers used during delivery can depress respiration in the neonate. The infant should be closely monitored until respiration is normal.

DRUG THERAPY DURING PREGNANCY: TERATOGENESIS

The term *teratogenesis* is derived from *teras,* the Greek word for monster. Translated literally, teratogenesis means *to produce a monster*. Consistent with this derivation, we usually think of birth defects in terms of gross malformations, such as cleft palate, clubfoot, and hydrocephalus. However, birth defects are not limited to distortions of gross anatomy; they also include neurobehavioral and metabolic anomalies.

Incidence and Causes of Congenital Anomalies

The incidence of *major* structural abnormalities (eg, abnormalities that are life threatening or require surgical correction) is between 1% and 3%. Half of these are obvious and are reported at birth. The other half involve internal organs (eg, heart, liver, GI tract) and are not discovered until later in life or at autopsy. The incidence of minor structural abnormalities is unknown, as is the

incidence of functional abnormalities (eg, growth retardation, mental retardation).

Congenital anomalies have multiple causes, including genetic heritage, environmental chemicals, and drugs. Genetic factors account for about 25% of all birth defects. Of the genetically based anomalies, Down's syndrome is the most common. Less than 1% of all birth defects are caused by drugs. For the majority of congenital anomalies, the cause is unknown.

Teratogenesis and Stage of Development

Fetal sensitivity to teratogens changes during development, and hence the effect of a teratogen is highly dependent upon when the drug is given. As shown in Figure 9-1, development occurs in three major stages: the *preimplantation/presomite period* (conception through week 2), the *embryonic period* (weeks 3 through 8), and the *fetal period* (week 9 through term). During the preimplantation/presomite period, teratogens act in an "all-or-nothing" fashion. That is, if the dose is sufficiently high, the result is death of the conceptus. Conversely, if the dose is sublethal, the conceptus is likely to recover fully.

Gross malformations are produced by exposure to teratogens during the *embryonic period* (roughly the first trimester). This is the time when the basic shape of internal organs and other structures is being established. Hence, it is not surprising that interference at this stage results in conspicuous anatomic distortions. Because the fetus is especially vulnerable during the embryonic period, expectant mothers must take special care to avoid exposure to teratogens during this time.

Teratogen exposure during the *fetal period* (ie, the second and third trimesters) usually disrupts *function* rather than gross anatomy. Of the developmental processes that occur in the fetal period, growth and development of the brain are especially important. Disruption of brain development can result in learning deficits and behavioral abnormalities.

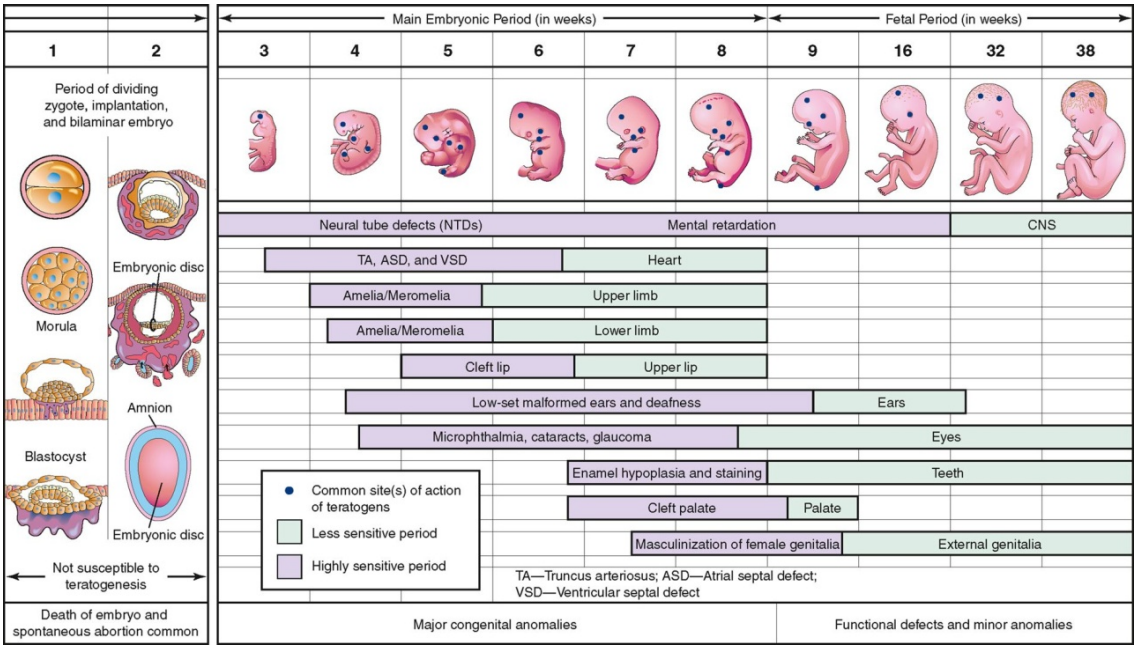


Figure 9-1 Effects of teratogens at various stages of development of the fetus.

Identification of Teratogens

For the following reasons, human teratogens are extremely difficult to identify:

- The incidence of congenital anomalies is generally low.
- Animal tests may not be applicable.
- Prolonged exposure may be required.
- Teratogenic effects may be delayed.
- Behavioral effects are difficult to document.
- Controlled experiments can't be done in humans.

As a result, only a few drugs are considered *proven* teratogens. Drugs whose teratogenicity has been documented (or at least is highly suspected) are listed in Table 9-1. It is important to note, however, that *lack of proof of teratogenicity does not mean that a drug is safe;* it only means that the available data are insufficient to make a definitive judgment. Conversely, *proof of teratogenicity does not*

mean that every exposure will result in a birth defect. In fact, with most teratogens, the risk of malformation following exposure is only about 10%.

Drug	Teratogenic Effect
Anticancer/Immunosuppressant Drugs	
Cyclophosphamide	CNS malformation, secondary cancer
Methotrexate	CNS and limb malformations
Antiseizure Drugs	
Carbamazepine	Neural tube defects
Phenytoin	Growth retardation, CNS defects
Valproic acid	Neural tube defects
Sex Hormones	
Androgens (eg, danazol)	Masculinization of the female fetus
Diethylstilbestrol	Vaginal carcinoma in female offspring
Other Drugs	
Alcohol	Fetal alcohol syndrome, stillbirth, spontaneous abortion, low birth weight, mental retardation
Angiotensin-converting enzyme inhibitors	Renal failure, renal tubular dysgenesis, skull hypoplasia (from exposure during the second and third trimesters)
Antithyroid drugs (propylthiouracil, methimazole)	Goiter and hypothyroidism
Isotretinoin and other vitamin A derivatives (etretinate, megadoses of vitamin A)	Multiple defects (CNS, craniofacial, cardiovascular, others)
Lithium	Ebstein's anomaly (cardiac defects)
Nonsteroidal anti-inflammatory drugs	Premature closure of the ductus arteriosus
Oral hypoglycemic drugs (eg, tolbutamide)	Neonatal hypoglycemia
Tetracycline	Tooth and bone anomalies

TABLE 9-1 Drugs That Should Be Avoided During Pregnancy Because of Proven or Strongly Suspected Teratogenicity*

To prove that a drug is a teratogen, three criteria must be met:

- The drug must cause a characteristic set of malformations.
- It must act only during a specific window of vulnerability (eg, weeks 4 through 7 of gestation).
- The incidence of malformations should increase with increasing dosage and duration of exposure.

Obviously, we can't do experiments in humans to see if a drug meets these criteria. The best we can do is systematically collect and analyze data on drugs taken during pregnancy in the hope that useful information on teratogenicity will be revealed. Studies in animals may be of limited value, in part because teratogenicity may depend on species. That is, drugs that are teratogens in laboratory animals may nonetheless be safe in humans. Conversely, and more importantly, drugs that fail to cause anomalies in animals may later prove teratogenic in humans. The most notorious example is thalidomide. In studies with pregnant animals, thalidomide was harmless. However, when thalidomide was taken by pregnant women, about 30% had babies with severe malformations. The take-home message is this: *Lack of teratogenicity in animals is not proof of safety in humans*. Accordingly, we cannot assume that a new drug is safe for use in human pregnancy just because it has met Food and Drug Administration (FDA) requirements, which are based on tests done in pregnant animals.

Some teratogens act quickly, whereas others require prolonged exposure. Thalidomide represents a fast-acting teratogen: a single dose can cause malformation. In contrast, alcohol (ethanol) must be taken repeatedly in high doses if gross malformation is to result. (Lower doses of alcohol may produce subtle anomalies.) Because a single exposure to a rapid-acting teratogen can produce obvious malformation, rapid-acting teratogens are easier to identify than slow-acting teratogens.

Teratogens that produce delayed effects are among the hardest to identify. The best example is diethylstilbestrol, an estrogenic substance that causes vaginal cancer in female offspring 18 or so years after birth.

Teratogens that affect behavior may be nearly impossible to identify. Behavioral changes are often delayed, and therefore may not become apparent until the child goes to school. By this time, it may be difficult to establish a correlation between drug use during pregnancy and the behavioral deficit. Furthermore, if the deficit is subtle, it may not even be recognized.

FDA Pregnancy Risk Categories

In 1983, the FDA established a system for classifying drugs according to their probable risks to the fetus. According to this system, *drugs can be put into one of five risk categories: A, B, C, D, and X* (Table 9-2). Drugs in Risk Category A are the least dangerous; controlled studies have been done in pregnant women and have failed to demonstrate a risk of fetal harm. In contrast, drugs in Category X are the most dangerous; these drugs are known to cause human fetal harm, and their risk to the fetus outweighs any possible therapeutic benefit. Drugs in Categories B, C, and D are progressively more dangerous than drugs in Category A and less dangerous than drugs in Category X. The law does not require classification of drugs that were in use before 1983; hence many drugs are not classified.

Category	Category Description
A	*Remote Risk of Fetal Harm:* Controlled studies in women have been done and have failed to demonstrate a risk of fetal harm during the first trimester, and there is no evidence of risk in later trimesters.
B	*Slightly More Risk Than A:* Animal studies show no fetal risk, but controlled studies have not been done in women. *or* Animal studies do show a risk of fetal harm, but controlled studies in women have failed to demonstrate a risk during the first trimester, and there is no evidence of risk in later trimesters.
C	*Greater Risk Than B:* Animal studies show a risk of fetal harm, but no controlled studies have been done in women. *or* No studies have been done in women or animals.
D	*Proven Risk of Fetal Harm:* Studies in women show proof of fetal damage, but the potential benefits of use during pregnancy may be acceptable despite the risks (eg, treatment of life-threatening disease for which safer drugs are ineffective). A statement on risk will appear in the "WARNINGS" section of drug labeling.
X	*Proven Risk of Fetal Harm:* Studies in women or animals show definite risk of fetal abnormality. *or* Adverse reaction reports indicate evidence of fetal risk. The risks clearly outweigh any possible benefit. A statement on risk will appear in the "CONTRAINDICATIONS" section of drug labeling.

TABLE 9-2 FDA Pregnancy Risk Categories

Although the current rating system is helpful, it is far from ideal, and hence the FDA has proposed major revisions. Specifically, the FDA plans to phase out the use of letter categories, and replace them with detailed information about the effects of drugs during pregnancy. The format employed will have three sections:

- *Fetal Risk Summary*—This section will describe what we know about drug effects on the fetus, and will offer a conclusion, such as, "Human data indicate this drug increases the risk of cardiac abnormalities."
- *Clinical Considerations*—This section will describe the likely effects if a drug is taken before a woman knows she is pregnant. The section will also discuss the risks to the mother and fetus of the disease being treated, along with dosing information, and ways to deal with complications.
- *Data*—This section will give detailed evidence from human and animal studies regarding the information presented in the Fetal Risk Summary.

Minimizing the Risk of Drug-Induced Teratogenesis

Common sense tells us that the best way to minimize teratogenesis is to minimize use of drugs. If possible, pregnant women should avoid drugs entirely. At the least, all *unnecessary* drug use should be eliminated. Alcohol and cocaine, for example, which are known to harm the developing fetus, have no valid indications, and their use cannot be justified. Nurses and other health professionals should warn pregnant women against use of all nonessential drugs.

As noted, some disease states (eg, epilepsy, asthma, diabetes) pose a greater risk to fetal health than do the drugs used for treatment. However, even with these disorders, in which drug therapy reduces the risk of disease-induced fetal harm, we must still take steps to minimize harm from drugs. Accordingly, drugs that pose a high risk of teratogenesis should be discontinued and safer alternatives substituted.

Rarely, a pregnant woman has a disease that requires use of drugs that have a high probability of causing teratogenesis. Some anticancer drugs, for example, are highly toxic to the developing fetus, yet cannot be ethically withheld from the pregnant patient. If a woman elects to use such drugs, termination of pregnancy should be considered.

Reducing the risk of teratogenesis also applies to female patients who are *not* pregnant. Why? Because about 50% of pregnancies are unintended. Accordingly, if a women of reproductive age is taking a teratogenic medication, she should be educated about the teratogenic risk as well as the necessity of using at least one reliable form of birth control.

Responding to Teratogen Exposure

When a pregnant woman has been exposed to a known teratogen, the first step is to determine exactly when the drug was taken, and exactly when the pregnancy began. If drug exposure was not during the period of organogenesis (ie, weeks 3 through 8), the patient should be reassured that the risk of drug-induced malformation is minimal. In addition, she should be reminded that 3% of all babies have some kind of conspicuous malformation, independent of teratogen exposure. This is important because otherwise the drug is sure to be blamed if the baby is abnormal.

What should be done if the exposure *did* occur during organogenesis? First, a reference (eg, Briggs GG, Freeman RK, Yaffe SJ: *Drugs in Pregnancy and Lactation, 8th Edition*. Philadelphia: JB Lippincott, 2008) should be consulted to determine the type of malformation expected. Next, at least two ultrasound scans should be done to assess the extent of injury. If the malformation is severe, termination of pregnancy should be considered. If the malformation is minor (eg, cleft palate), it may be correctable by surgery, either shortly after birth or later in childhood.

DRUG THERAPY DURING BREAST-FEEDING

Drugs taken by lactating women can be excreted in breast milk. If drug concentrations in milk are high enough, a pharmacologic effect can occur in the infant, raising the possibility of harm. Unfortunately, very little systematic research has been done on this issue. As a result, although a few drugs are known to be hazardous (Table 9-3), the possible danger posed by many others remains undetermined.

Although nearly all drugs can enter breast milk, the extent of entry varies greatly. The factors that determine entry into breast milk are the same factors that determine passage of drugs across membranes. Accordingly, drugs that

are lipid soluble enter breast milk readily, whereas drugs that are ionized, highly polar, or protein bound tend to be excluded.

TABLE 9-3 Drugs That Are Contraindicated During Breast-Feeding

Controlled Substances

Amphetamine

Cocaine

Heroin

Marijuana

Phencyclidine

Anticancer Agents/Immunosuppressants

Cyclophosphamide

Cyclosporine

Doxorubicin

Methotrexate

Others

Bromocriptine

Ergotamine

Lithium

Most drugs can be detected in milk, but concentrations are generally too low to be harmful. Hence, breast-feeding is usually safe, even though drugs are being taken. Nonetheless, prudence is always in order: If the nursing mother can avoid drugs, she certainly should. Moreover, when drugs *must* be used, steps should be taken to minimize risk. These include:

- Dosing immediately *after* breast-feeding (to minimize drug concentrations in milk at the next feeding)
- Avoiding drugs that have a long half-life
- Avoiding sustained-release formulations
- Choosing drugs that tend to be excluded from milk

- Choosing drugs that are least likely to affect the infant (Table 9-4)
- Avoiding drugs that are known to be hazardous (see Table 9-3)
- Using the lowest effective dosage for the shortest possible time

Drug Category	Drugs and Drug Groups of Choice	Comments
Analgesic drugs	Acetaminophen, flurbiprofen, ibuprofen, ketorolac, mefenamic acid, morphine, sumatriptan	Sumatriptan may be given for migraine. Morphine may be given for severe pain.
Anticoagulant drugs	Acenocoumarol, heparin (unfractionated and low molecular weight), warfarin	Among breast-fed infants whose mothers were taking warfarin, the drug was undetectable in plasma and bleeding time was not affected.
Antidepressant drugs	Sertraline, tricyclic antidepressants	Other antidepressants, such as fluoxetine [Prozac], may be given with caution.
Antiepileptic drugs	Carbamazepine, phenytoin, valproic acid	The estimated level of exposure to these drugs in breastfed infants is less than 10% of the therapeutic dose standardized by weight.
Antihistamines ($histamine_1$ blockers)	Loratadine	Other antihistamines may be given, but data on the concentrations of these drugs in breast milk are lacking.
Antimicrobial drugs	Aminoglycosides, cephalosporins, macrolides, penicillins	Avoid chloramphenicol and tetracycline.
Beta-adrenergic antagonists	Labetalol, propranolol	Angiotensin-converting enzyme inhibitors and calcium channel–blocking agents are also considered safe.
Endocrine drugs	Insulin, levothyroxine, propylthiouracil	The estimated level of exposure to propylthiouracil in breastfed infants is less than 1% of the therapeutic dose standardized by weight; thyroid function of the infants is not affected.

TABLE 9-4 Drugs of Choice for Breast-Feeding Women*

KEY POINTS

- Because hepatic metabolism and glomerular filtration increase during pregnancy, dosages of some drugs may need to be increased.
- Lipid-soluble drugs cross the placenta readily, whereas drugs that are ionized, polar, or protein bound cross with difficulty. Nonetheless, all drugs cross to some extent.
- When prescribing drugs during pregnancy, the clinician must try to balance the benefits of treatment versus the risks—often without knowing what the risks really are.
- About 3% of all babies are born with gross structural malformations.
- Less than 1% of birth defects are caused by drugs.
- Teratogen-induced gross malformations result from exposure early in pregnancy (weeks 3 through 8 of gestation), the time of organogenesis.
- Functional impairments (eg, mental retardation) result from exposure to teratogens later in pregnancy.
- For most drugs, we lack reliable data on the risks of use during pregnancy.
- Lack of teratogenicity in animals is not proof of safety in humans.
- Some drugs (eg, thalidomide) cause birth defects with just one dose, whereas others (eg, alcohol) require prolonged exposure.
- FDA Pregnancy Risk Categories indicate the relative risks of drug use. Drugs in Category X pose the highest risk of fetal harm and are contraindicated during pregnancy.
- Any woman of reproductive age who is taking a known teratogen must be counseled about the teratogenic risk and the necessity of using at least one reliable form of birth control.

- Drugs that are lipid soluble readily enter breast milk, whereas drugs that are ionized, polar, or protein bound tend to be excluded. Nonetheless, all drugs enter to some extent.
- Although most drugs can be detected in breast milk, concentrations are usually too low to harm the nursing infant.
- If possible, drugs should be avoided during breastfeeding.
- If drugs cannot be avoided during breast-feeding, common sense dictates choosing drugs known to be safe (Table 9-4) and avoiding drugs known to be dangerous (Table 9-3).

10 Drug Therapy in Pediatric Patients

Patients who are very young or very old respond differently to drugs than the rest of the population. Most differences are *quantitative*. Specifically, patients in both age groups are more sensitive to drugs than other patients, and they show greater individual variation. Drug sensitivity in the very young results largely from *organ system immaturity*. Drug sensitivity in the elderly results largely from *organ system degeneration*. Because of heightened drug sensitivity, patients in both age groups are at increased risk of ADVERSE DRUG REACTIONS. In this chapter we discuss the physiologic factors that underlie heightened drug sensitivity in pediatric patients, as well as ways to promote safe and effective drug use. Drug therapy in geriatric patients is the topic of Chapter 11.

Pediatrics covers all patients up to the age of 16. Because of ongoing growth and development, pediatric patients in different age groups present different therapeutic challenges. Traditionally, the pediatric population is subdivided into six groups:

- Premature infants (less than 36 weeks' gestational age)
- Full-term infants (36 to 40 weeks' gestational age)
- Neonates (first 4 postnatal weeks)
- Infants (weeks 5 to 52 postnatal)
- Children (1 to 12 years)
- Adolescents (12 to 16 years)

Not surprisingly, as young patients grow older, they become more like adults physiologically, and hence more like adults with regard to drug therapy. Conversely, the very young—those less than 1 year old, and especially those less than 1 month old—are very different from adults. If drug therapy in these patients is to be safe and effective, we must account for these differences.

Pediatric drug therapy is made even more difficult by insufficient drug information: Fully two-thirds of drugs used in pediatrics have never been tested in children. As a result, we lack reliable information on dosing, pharmacokinetics, and effects, both therapeutic and adverse. Is this lack of knowledge causing

adverse events and even death? Possibly, but no one knows. Is it preventing optimal treatment? Probably, but again, we just don't know. To help expand our knowledge, Congress enacted two important laws: the *Best Pharmaceuticals for Children Act,* passed in 2002, and the *Pediatric Research Equity Act of 2003*. Both are designed to promote drug research in children. What we have learned so far underscores both the state of our ignorance and the need for much more work. For example, of the drugs studied to date:

- About 20% were ineffective in children, even though they *were* effective in adults.
- About 30% caused unanticipated side effects, some of them potentially lethal.
- About 20% required dosages different from those that had been extrapolated from dosages used in adults.

As more studies are done, the huge gaps in our knowledge will shrink. In the meantime, we must still treat children with drugs—even though we lack the information needed to prescribe rationally. Hence, similar to drug therapy during pregnancy, prescribers must try to balance benefits versus risks, without knowing with precision what the benefits and risks really are.

PHARMACOKINETICS: NEONATES AND INFANTS

As discussed in Chapter 4, pharmacokinetic factors determine the concentration of a drug at its sites of action, and hence determine the intensity and duration of responses. If drug levels are elevated, responses will be more intense. If drug elimination is delayed, responses will be prolonged. Because the organ systems that regulate drug levels are not fully developed in the very young, these patients are at risk of both possibilities: drug effects that are unusually intense *and* prolonged. By accounting for pharmacokinetic differences in the very young, we can increase the chances that drug therapy will be both effective and safe.

Figure 10-1 illustrates how drug levels differ between infants and adults following administration of equivalent doses (ie, doses adjusted for body weight). When a drug is administered *intravenously* (Fig. 10-1A), levels decline more slowly in the infant than in the adult. As a result, drug levels in the infant remain above the minimum effective concentration (MEC) longer than in the adult, thereby causing effects to be prolonged. When a drug is administered

subcutaneously (Fig. 10-1*B*), not only do levels in the infant remain above the MEC *longer* than in the adult, but these levels also rise *higher,* causing effects to be more intense as well as prolonged. From these illustrations, it is clear that adjustment of dosage for infants on the basis of body size alone is not sufficient to achieve safe results.

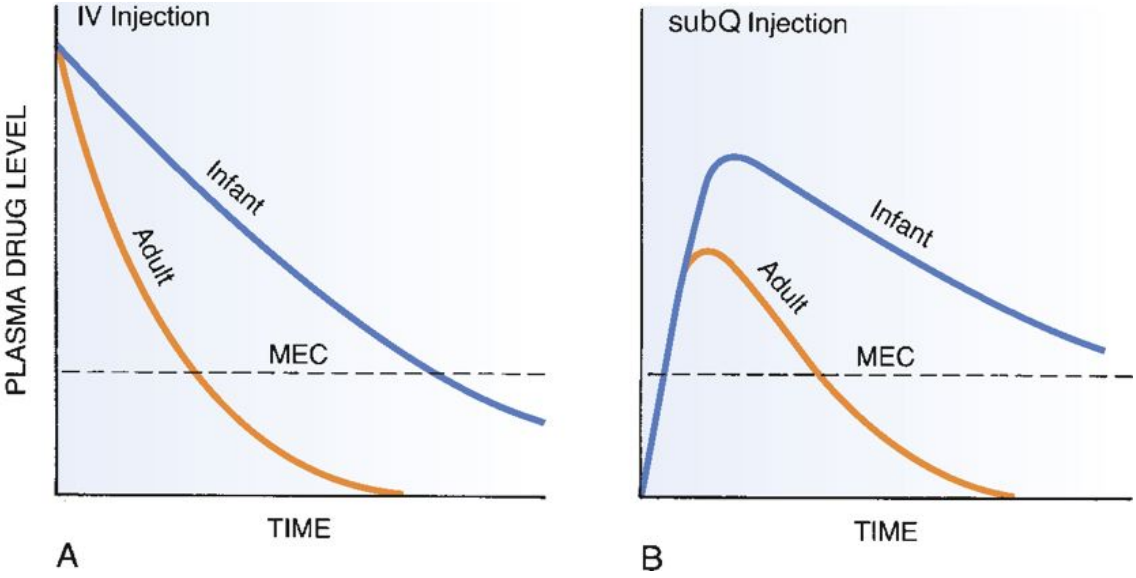


Figure 10-1 Comparison of plasma drug levels in adults and infants. A, Plasma drug levels following IV injection. Dosage was adjusted for body weight. Note that plasma levels remain above the minimum effective concentration (MEC) much longer in the infant. B, Plasma drug levels following subQ injection. Dosage was adjusted for body weight. Note that both the maximum drug level and the duration of action are greater in the infant.

If small body size is not the major reason for heightened drug sensitivity in infants, what is? The increased sensitivity of infants is due largely to the immature state of five pharmacokinetic processes: (1) drug absorption, (2) protein binding of drugs, (3) exclusion of drugs from the central nervous system (CNS) by the blood-brain barrier, (4) hepatic drug metabolism, and (5) renal drug excretion.

Absorption

Oral Administration.

Gastrointestinal physiology in the infant is very different from that in the adult. As a result, drug absorption may be enhanced or impeded, depending on the physicochemical properties of the drug involved.

Gastric emptying time is both prolonged and irregular in early infancy, and then gradually reaches adult values by 6 to 8 months. For drugs that are absorbed primarily from the stomach, delayed gastric emptying enhances absorption. On the other hand, for drugs that are absorbed primarily from the intestine, absorption is delayed. Because gastric emptying time is irregular, the precise impact on absorption is not predictable.

Gastric acidity is very low 24 hours after birth and does not reach adult values for 2 years. Because of low acidity, absorption of acid-labile drugs is increased.

Intramuscular Administration.

Drug absorption following IM injection in the *neonate* is *slow* and *erratic*. Delayed absorption is due in part to low blood flow through muscle during the first days of postnatal life. By early *infancy,* absorption of IM drugs becomes more *rapid* than in neonates and adults.

Percutaneous Absorption.

Because the skin of the very young is thin, percutaneous drug absorption is significantly greater than in older children and adults. This increases the risk of toxicity from topical drugs.

Distribution

Protein Binding.

Binding of drugs to albumin and other plasma proteins is limited in the infant. Why? Because (1) the amount of albumin is relatively low and (2) endogenous compounds (eg, fatty acids, bilirubin) compete with drugs for available binding sites. Consequently, drugs that ordinarily undergo extensive protein binding in adults undergo much less binding in infants. As a result, the concentration of *free* levels of such drugs is relatively high in the infant, thereby intensifying effects. To ensure that effects are not too intense, dosages in infants

should be reduced. Protein-binding capacity reaches adult values within 10 to 12 months.

Blood-Brain Barrier.

The blood-brain barrier is not fully developed at birth. As a result, drugs and other chemicals have relatively easy access to the CNS, making the infant especially sensitive to drugs that affect CNS function. Accordingly, all medicines employed for their CNS effects (eg, morphine, phenobarbital) should be given in reduced dosage. Dosage should also be reduced for drugs used for actions *outside* the CNS if those drugs are capable of producing CNS toxicity as a side effect.

Hepatic Metabolism

The drug-metabolizing capacity of newborns is low. As a result, neonates are especially sensitive to drugs that are eliminated primarily by hepatic metabolism. When these drugs are used, dosages must be reduced. The capacity of the liver to metabolize many drugs increases rapidly about 1 month after birth, and approaches adult levels a few months later. Complete maturation of the liver develops by 1 year.

The data in Table 10-1 illustrate the limited drug-metabolizing capacity of newborns. These data are from experiments on the metabolism and effects of hexobarbital (a CNS depressant) in newborn and adult animals. *Metabolism* was measured in microsomal enzyme preparations made from the livers of *guinea pigs*. The *effect* of hexobarbital—CNS depression—was assessed in *mice*. Duration of sleeping time following hexobarbital injection was used as the index of CNS depression.

Age	Percentage of Hexobarbital Metabolized (in 1 hr)	Duration of Drug-Induced Sleep	
		10-mg/kg Dose	50-mg/kg Dose
Newborn	"0"	6 hr	Eternal*
Adult	28–39	Less than 5 min	12–22 min

Data from Jondorf WR, Maickel RP, Brodie BB: Inability of newborn mice and guinea pigs to metabolize drugs. Biochem Pharmacol 1:352, 1958.

TABLE 10-1 Comparison of the Metabolism and Effect of Hexobarbital in Adult Versus Newborn Animals

As indicated in Table 10-1, the drug-metabolizing capacity of the adult liver is much greater than the drug-metabolizing capacity of the newborn liver. Whereas the adult liver preparation metabolized an average of 33% of the hexobarbital presented to it, there was virtually no measurable metabolism by the newborn preparation.

The physiologic impact of limited drug-metabolizing capacity is indicated by observing sleeping time in newborns versus sleeping time in adults following injection of hexobarbital. As shown in Table 10-1, a low dose (10 mg/kg) of hexobarbital caused adult mice to sleep less than 5 minutes. In contrast, the same dose caused newborns to sleep 6 hours. The differential effects on adults and newborns are much more dramatic at a higher dose (50 mg/kg): Whereas the adults merely slept longer, the newborns *died*.

Renal Excretion

Renal drug excretion is significantly reduced at birth. Renal blood flow, glomerular filtration, and active tubular secretion are all low during infancy. Because the drug-excreting capacity of infants is limited, drugs that are eliminated primarily by renal excretion must be given in reduced dosage. Adult levels of renal function are achieved by 1 year.

	Average Infant	Average Adult
Body Weight (kg)	3.5	70
Inulin Clearance		
Rate (mL/min)	3 (approximate)	130
Half-time (min)	630	120
***Para*-aminohippuric Acid (PAH) Clearance**		
Rate (mL/min)	12 (approximate)	650
Half-time (min)	160	43

Adapted from Goldstein A, Aronow L, Kalman SM: Principles of Drug Action: The Basis of Pharmacology, 2nd ed. New York: Churchill Livingstone, 1974:215.

TABLE 10-2 Renal Function in Adults Versus Infants

The data in Table 10-2 illustrate the limited ability of the infant kidney to excrete foreign compounds. These data show rates of renal excretion for two compounds: inulin and *para*-aminohippuric acid (PAH). Inulin is excreted entirely by glomerular filtration. PAH is excreted by a combination of glomerular filtration and active tubular secretion. Note that the half-life for inulin is 630 minutes in infants but only 120 minutes in adults. Since inulin is eliminated by glomerular filtration alone, these data tell us that the glomerular filtration rate in the infant is much slower than in the adult. From the data for clearance of PAH, taken together with the data for clearance of inulin, we can conclude that tubular secretion in infants is also much slower than in adults.

PHARMACOKINETICS: CHILDREN 1 YEAR AND OLDER

By the age of 1 year, most pharmacokinetic parameters in children are similar to those in adults. Hence, drug sensitivity in children over the age of 1 is more like that of adults than that of the very young. Although pharmacokinetically similar to adults, children do differ in one important way: They metabolize drugs *faster* than adults. Drug-metabolizing capacity is markedly elevated until the age of 2 years, and then gradually declines. A further sharp decline takes place at puberty, when adult values are reached. Because of enhanced

drug metabolism in children, an increase in dosage or a reduction in dosing interval may be needed for drugs that are eliminated by hepatic metabolism.

ADVERSE DRUG REACTIONS

Like adults, pediatric patients are subject to adverse reactions when drug levels rise too high. In addition, pediatric patients are vulnerable to unique adverse effects related to organ system immaturity and to ongoing growth and development. Among these age-related effects are growth suppression (caused by glucocorticoids), discoloration of developing teeth (caused by tetracyclines), and kernicterus (caused by sulfonamides). Table 10-3 presents a list of drugs that can cause unique adverse effects in pediatric patients of various ages. These drugs should be avoided in patients whose age puts them at risk.

Drug	Adverse Effect
Androgens	Premature puberty in males; reduced adult height from premature epiphyseal closure
Aspirin and other salicylates	Severe intoxication from acute overdose (acidosis, hyperthermia respiratory depression); Reye's syndrome in children with chickenpox or influenza
Chloramphenicol	Gray syndrome (neonates and infants)
Fluoroquinolones	Tendon rupture
Glucocorticoids	Growth suppression with prolonged use
Hexachlorophene	CNS toxicity (infants)
Nalidixic acid	Cartilage erosion
Phenothiazines	Sudden infant death syndrome
Sulfonamides	Kernicterus (neonates)
Tetracyclines	Staining of developing teeth

CNS = central nervous system.

TABLE 10-3 Adverse Drug Reactions Unique to Pediatric Patients

DOSAGE DETERMINATION

Because of the pharmacokinetic factors discussed above, dosage selection for pediatric patients is difficult. Selecting a dosage is especially difficult in the very young, since pharmacokinetic factors are undergoing rapid change.

Pediatric doses have been established for a few drugs but not for most. For drugs that do not have an established pediatric dose, dosage can be extrapolated from adult doses. The method of conversion employed most commonly is based on body surface area: Please note that initial pediatric doses—whether based on established pediatric doses or extrapolated from adult doses—are at best an *approximation*. Subsequent doses must be adjusted on the basis of clinical outcome and plasma drug concentrations. These adjustments are especially important in neonates and younger infants. Clearly, if dosage adjustments are to be optimal, it is essential that we monitor the patient for therapeutic and adverse responses.

PROMOTING ADHERENCE

Achieving accurate and timely dosing requires informed participation of the child's parents or guardian and, to the extent possible, active involvement of the child. Effective education is critical. The following issues should be addressed:

- Dosage size and timing
- Route and technique of administration
- Duration of treatment
- Drug storage
- The nature and time course of desired responses
- The nature and time course of adverse responses

Written instructions should be provided. For techniques of administration that are difficult, a demonstration should be made, after which the parents should repeat the procedure to ensure they understand. With young children, spills and spitting out are common causes of inaccurate dosing; parents should be taught to estimate the amount of drug lost and to re-administer that amount, being careful not to overcompensate. When more than one person is

helping medicate a child, all participants should be warned against multiple dosing. Multiple dosing can be avoided by maintaining a drug administration chart. With some disorders—especially infections—symptoms may resolve before the prescribed course of treatment has been completed. Parents should be instructed to complete the full course nonetheless. Additional ways to promote adherence include (1) selecting the most convenient dosage form and dosing schedule, (2) suggesting mixing oral drugs with food or juice (when allowed) to improve palatability, (3) providing a calibrated medicine spoon or syringe for measuring liquid formulations, and (4) taking extra time with young or disadvantaged parents to help ensure conscientious and skilled participation.

KEY POINTS

- The majority of drugs used in pediatrics have never been tested in children. As a result, we lack reliable information on which to base drug selection or dosage.
- Because of organ system immaturity, very young patients are highly sensitive to drugs.
- In neonates and young infants, drug responses may be unusually intense and prolonged.
- Absorption of IM drugs in *neonates* is slower than in adults. In contrast, absorption of IM drugs in *infants* is more rapid than in adults.
- Protein-binding capacity is limited early in life. Hence, free concentrations of some drugs may be especially high.
- The blood-brain barrier is not fully developed at birth. Hence, neonates are especially sensitive to drugs that affect the CNS.
- The drug-metabolizing capacity of neonates is low. Hence, neonates are especially sensitive to drugs that are eliminated primarily by hepatic metabolism.
- Renal excretion of drugs is low in neonates. Hence, drugs that are eliminated primarily by the kidney must be given in reduced dosage.

- In children 1 year and older, most pharmacokinetic parameters are similar to those in adults. Hence, drug sensitivity is more like that of adults than the very young.
- Children (1 to 12 years) differ pharmacokinetically from adults in that children metabolize drugs faster.
- Initial pediatric doses are at best an approximation. Hence, subsequent doses must be adjusted on the basis of clinical outcome and plasma drug levels.

11 Drug Therapy in Geriatric Patients

Drug use among the elderly is disproportionately high. Whereas the elderly (those 65 years and older) constitute only 12% of the U.S. population, they consume 31% of the nation's prescribed drugs. Reasons for this intensive use of drugs include increased severity of illness, multiple pathologies, and excessive prescribing.

Drug therapy in the elderly represents a special therapeutic challenge. As a rule, older patients are more sensitive to drugs than younger adults, and they show wider individual variation. In addition, the elderly experience more adverse drug reactions and drug-drug interactions. The principal factors underlying these complications are (1) altered pharmacokinetics (secondary to organ system degeneration), (2) multiple and severe illnesses, (3) multiple-drug therapy, and (4) poor adherence. To help ensure that drug therapy is as safe and effective as possible, *individualization of treatment is essential: Each patient must be monitored for desired and adverse responses, and the regimen must be adjusted accordingly*. Because the elderly typically suffer from chronic illnesses, the usual objective is to reduce symptoms and improve quality of life, since cure is generally impossible.

PHARMACOKINETIC CHANGES IN THE ELDERLY

The aging process can affect all phases of pharmacokinetics. From early adulthood on, there is a gradual, progressive decline in organ function. This decline can alter the absorption, distribution, metabolism, and excretion of drugs. As a rule, these pharmacokinetic changes increase drug sensitivity (largely from reduced hepatic and renal drug elimination). It should be noted, however, that the extent of change varies greatly among patients: Pharmacokinetic changes may be minimal in patients who have remained physically fit, whereas they may be dramatic in patients who have aged less fortunately. Accordingly, you should keep in mind that age-related changes in pharmacokinetics are not only a potential source of increased sensitivity to drugs, they are also a potential source of increased variability. The physiologic changes that underlie alterations in pharmacokinetics are summarized in Table 11-1.

Absorption

Altered GI absorption is not a major factor in drug sensitivity in the elderly. As a rule, the *percentage* of an oral dose that becomes absorbed does not change with age. However, the *rate* of absorption may be slowed (because of delayed gastric emptying and reduced splanchnic blood flow). As a result, drug responses may be somewhat delayed. Gastric acidity is reduced in the elderly and may alter the absorption of certain drugs. Some drug formulations, for example, require high acidity to dissolve, and hence their absorption may be decreased.

Distribution

Four major factors can alter drug distribution in the elderly: (1) increased percent body fat, (2) decreased percent lean body mass, (3) decreased total body water, and (4) reduced concentration of serum albumin. The increase in body fat seen in the elderly provides a storage depot for *lipid-soluble* drugs (eg, thiopental). As a result, plasma levels of these drugs are reduced, causing a reduction in responses. Because of the decline in lean body mass and total body water, *water-soluble* drugs (eg, ethanol) become distributed in a smaller volume than in younger adults. As a result, the concentration of these drugs is increased, causing effects to be more intense. Although albumin levels are only slightly reduced in healthy adults, these levels can be significantly reduced in adults who are malnourished. Because of reduced albumin levels, protein binding of drugs decreases, causing levels of free drug to rise. As a result, drug effects may be more intense.

Metabolism

Rates of hepatic drug metabolism tend to decline with age. Principal factors underlying the decline are reduced hepatic blood flow, reduced liver mass, and decreased activity of some hepatic enzymes. Because liver function is diminished, the half-lives of certain drugs may be increased, thereby prolonging responses. Responses to oral drugs that ordinarily undergo extensive first-pass metabolism may be enhanced. It must be noted, however, that the degree of decline in drug metabolism varies greatly among individuals. As a result, we cannot predict whether drug responses will be significantly reduced in any particular patient.

Excretion

Renal drug function, and hence drug excretion, undergoes progressive decline beginning in early adulthood. *Drug accumulation secondary to reduced renal excretion is the most important cause of adverse drug reactions in the elderly*. The decline in renal function is the result of reductions in renal blood flow, glomerular filtration rate, active tubular secretion, and number of nephrons. Coexistence of renal pathology can further compromise kidney function. The degree of decline in renal function varies greatly among individuals. Accordingly, when patients are taking drugs that are eliminated primarily by the kidneys, renal function should be assessed. In the elderly, the proper index of renal function is *creatinine clearance,* not *serum creatinine levels*. Creatinine levels do not reflect kidney function in the elderly because the source of serum creatinine—lean muscle mass—declines in parallel with the decline in kidney function. As a result, creatinine levels may be normal even though renal function is greatly reduced.

TABLE 11-1 Physiologic Changes That Can Affect Pharmacokinetics in the Elderly

Absorption of Drugs

Increased gastric pH

Decreased absorptive surface area

Decreased splanchnic blood flow

Decreased GI motility

Delayed gastric emptying

Distribution of Drugs

Increased body fat

Decreased lean body mass

Decreased total body water

Decreased serum albumin

Decreased cardiac output

Metabolism of Drugs

Decreased hepatic blood flow

Decreased hepatic mass

Decreased activity of hepatic enzymes

Excretion of Drugs

Decreased renal blood flow

Decreased glomerular filtration rate

Decreased tubular secretion

Decreased number of nephrons

PHARMACODYNAMIC CHANGES IN THE ELDERLY

Alterations in receptor properties may underlie altered sensitivity to some drugs. However, information on such pharmacodynamic changes is limited. In support of the possibility of altered pharmacodynamics is the observation that beta-adrenergic blocking agents (drugs used primarily for cardiac disorders) are *less* effective in the elderly than in younger adults, even when present in the same concentrations. Possible explanations for this observation include (1) a reduction in the number of beta receptors and (2) a reduction in the affinity of beta receptors for beta-receptor blocking agents. Other drugs (warfarin, certain central nervous system depressants) produce effects that are more intense in the elderly, suggesting a possible increase in receptor number, receptor affinity, or both. Unfortunately, our knowledge of pharmacodynamic changes in the elderly is restricted to a few families of drugs.

ADVERSE DRUG REACTIONS AND DRUG INTERACTIONS

Adverse drug reactions (ADRs) are 7 times more common in the elderly than in younger adults, accounting for about 16% of hospital admissions among older individuals and 50% of all medication-related deaths. The vast majority of these reactions are dose related, not idiosyncratic. Symptoms in the elderly are often nonspecific (eg, dizziness, cognitive impairment), making identification of ADRs difficult.

Perhaps surprisingly, the increase in ADRs seen in the elderly is not the direct result of aging per se. Rather, multiple factors predispose older patients to ADRs. The most important are:

- Drug accumulation secondary to reduced renal function
- Polypharmacy (treatment with multiple drugs)
- Greater severity of illness
- The presence of multiple pathologies
- Greater use of drugs that have a low therapeutic index (eg, digoxin, a drug for heart failure)
- Increased individual variation secondary to altered pharmacokinetics
- Inadequate supervision of long-term therapy
- Poor patient adherence

The majority of ADRs in the elderly are avoidable. Measures that can reduce their incidence include:

- Taking a thorough drug history, including over-the-counter medications
- Accounting for the pharmacokinetic and pharmacodynamic changes that occur with aging
- Initiating therapy with low doses
- Monitoring clinical responses and plasma drug levels to provide a rational basis for dosage adjustment
- Employing the simplest regimen possible
- Monitoring for drug-drug interactions and iatrogenic illness
- Periodically reviewing the need for continued drug therapy, and discontinuing medications as appropriate
- Encouraging the patient to dispose of old medications
- Taking steps to promote adherence (see below)
- Avoiding drugs on the Beers list (see below)

The *Beers list* identifies drugs with a high likelihood of causing adverse effects in the elderly. Accordingly, drugs on this list should generally be avoided. A partial listing of these drugs appears in Table 11-2. The full list, updated in 2003, is available online at *http://archinte.ama-assn.org/cgi/reprint/163/22/2716*.

Drugs	Reason for Concern	Alternative Treatments
Analgesics		
Ketorolac [Toradol]	GI bleeding	Mild pain: acetaminophen, ibuprofen
Meperidine [Demerol]	Not effective at usual doses, confusion	Moderate to severe pain: morphine, oxycodone
Propoxyphene [Darvon]	No better than acetaminophen, but has the ADRs of opioids	
Antidepressants		
Amitriptyline [Elavil]	Anticholinergic effects (constipation, urinary retention, blurred vision)	SSRIs (other than daily fluoxetine) or other antidepressants
Doxepin [Sinequan]		
Fluoxetine [Prozac], taken daily	Long half-life; agitation, insomnia, anorexia	SSRI with a shorter half-life (eg, sertraline [Zoloft])
Antihistamines, First Generation		
Chlorpheniramine [Chlor-Trimeton, others]	Anticholinergic effects (constipation, urinary retention, blurred vision)	Second-generation antihistamines, such as cetirizine [Zyrtec], fexofenadine [Allegra], or loratadine [Claritin]
Diphenhydramine [Benadryl, others]		
Hydroxyzine [Vistaril]		
Promethazine [Phenergan, others]		
Antihypertensives		
Alpha-adrenergic blocking agents	Hypotension, dry mouth, incontinence	Thiazide diuretic, ACE inhibitor, beta-adrenergic blocker, calcium channel blocker
Doxazosin [Cardura]		
Prazosin [Minipress]		
Terazosin [Hytrin]		
Clonidine [Catapres]	Orthostatic hypotension, adverse CNS effects	
Guanethidine		
Methyldopa [Aldomet]	Orthostatic hypotension, depression	
Reserpine	Bradycardia, depression	
	Depression, impotence, sedation, orthostatic hypotension	
Sedative-Hypnotics		
Barbiturates	Physical dependence; compared with other hypnotics, higher risk of falls, confusion, cognitive impairment	Temazepam [Restoril], zolpidem [Ambien], zaleplon [Sonata], ramelteon [Rozerem], eszopiclone [Lunesta]
Benzodiazepines, long acting	Prolonged sedation	A short-acting benzodiazepine (eg, lorazepam [Ativan]) given in low dosage)
Chlordiazepoxide [Librium]		
Diazepam [Valium, others]		
Flurazepam [Dalmane]		
Drugs for Urge Incontinence		
Oxybutynin [Ditropan]	Urinary retention, confusion, hallucinations, sedation	Behavioral therapy (eg, bladder retraining, urge suppression)
Tolterodine [Detrol]		
Muscle Relaxants		
Carisoprodol [Soma]	Anticholinergic effects, sedation, cognitive impairment; may not be effective at tolerable dosage	For spasticity, use an antispasmodic (eg, baclofen [Lioresal]) or nerve block
Cyclobenzaprine [Flexeril, others]		
Metaxalone [Skelaxin]		
Methocarbamol [Robaxin]		

Adapted from Fick DM, Cooper JW, Wade WE, et al: Updating the Beers criteria for potentially inappropriate medication use in older adults. Arch Intern Med 163:2716–2724, 2003. (*Note:* The paper by Fick et al. lists many drugs in addition to those in this table.)

ACE = angiotensin-converting enzyme, ADR = adverse drug reaction, CNS = central nervous system, GI = gastrointestinal, SSRI = selective serotonin reuptake inhibitor.

TABLE 11-2 Some Drugs to Generally Avoid in the Elderly

PROMOTING ADHERENCE

As many as 40% or more of elderly patients fail to take their medicines as prescribed. Some patients never fill their prescriptions, some fail to refill their prescriptions, and some don't follow the prescribed dosing schedule. Nonadherence can result in therapeutic failure (from underdosing or erratic dosing) or toxicity (from overdosing). Of the two possibilities, underdosing with resulting therapeutic failure is by far (90%) the more common.

Multiple factors underlie nonadherence to the prescribed regimen (Table 11-3). Among these are forgetfulness; failure to comprehend instructions (because of intellectual, visual, or auditory impairment); inability to pay for medications; and use of complex regimens (several drugs taken several times a day). All of these factors can contribute to *unintentional* nonadherence. However, in the majority of cases (about 75%), nonadherence among the elderly is *intentional*. The principal reason given for intentional nonadherence is the patient's conviction that the drug was simply not needed in the dosage prescribed. Unpleasant side effects and expense also contribute to intentional nonadherence.

Several measures can promote adherence, including:

- Simplifying the regimen so that the number of drugs and doses per day is as small as possible
- Explaining the treatment plan using clear, concise verbal and written instructions
- Choosing an appropriate dosage form (eg, a liquid formulation if the patient has difficulty swallowing)

TABLE 11-3 Factors That Contribute to Poor Adherence in the Elderly

Multiple chronic disorders
Multiple prescription medications
Multiple doses/day for each medication
Multiple prescribers
Changes in the regimen (addition of drugs, changes in dosage size or timing)
Cognitive or physical impairment (reduction in memory, hearing, visual acuity, color discrimination, or manual dexterity)
Living alone
Recent discharge from hospital
Low literacy
Inability to pay for drugs
Personal conviction that a drug is unnecessary or the dosage too high

Presence of side effects

- Labeling drug containers clearly, and avoiding containers that are difficult to open by patients with impaired dexterity (eg, those with arthritis)
- Suggesting the use of a calendar, diary, or pill counter to record drug administration
- Asking the patient if he or she has access to a pharmacy and can afford the medication
- Enlisting the aid of a friend, relative, or visiting healthcare professional
- Monitoring for therapeutic responses, adverse reactions, and plasma drug levels

It must be noted, however, that the benefits of these measures will be restricted primarily to patients whose nonadherence is *unintentional*. Unfortunately, these measures are generally inapplicable to the patient whose nonadherence is *intentional*. For these patients, intensive education may help.

KEY POINTS

- Older patients are generally more sensitive to drugs than are younger adults, and they show wider individual variation.
- Individualization of therapy for the elderly is essential: Each patient must be monitored for desired and adverse responses, and the regimen must be adjusted accordingly.
- Aging-related organ decline can change drug absorption, distribution, metabolism, and (especially) excretion.
- The *rate* of drug absorption may be slowed in the elderly, although the *extent* of absorption is usually unchanged.
- Plasma concentrations of lipid-soluble drugs may be low in the elderly, and concentrations of water-soluble drugs may be high.
- Reduced liver function may prolong drug effects.

- Reduced renal function, with resultant drug accumulation, is the most important cause of adverse drug reactions in the elderly.
- Because the degree of renal impairment among the elderly varies, creatinine clearance (a test of renal function) should be determined for all patients taking drugs that are eliminated primarily by the kidneys.
- Adverse drug reactions are much more common in the elderly than in younger adults.
- Factors underlying the increase in adverse reactions include polypharmacy, severe illness, multiple pathologies, and treatment with dangerous drugs.
- Nonadherence is common among the elderly.
- Reasons for *unintentional* nonadherence include forgetfulness, side effects, low income, complex regimens, and failure to comprehend instructions.
- Most cases (75%) of nonadherence among the elderly are *intentional*. Reasons include expense, side effects, and the patient's conviction that the drug is unnecessary or the dosage too high.

IV. PERIPHERAL NERVOUS SYSTEM DRUGS

Introduction

12 Basic Principles of Neuropharmacology

Neuropharmacology can be defined as *the study of drugs that alter processes controlled by the nervous system*. Neuropharmacologic drugs produce effects equivalent to those produced by excitation or suppression of neuronal activity. Neuropharmacologic agents can be divided into two broad categories: (1) peripheral nervous system drugs and (2) central nervous system (CNS) drugs.

The neuropharmacologic drugs constitute a large and important family of therapeutic agents. These drugs are used to treat conditions ranging from depression to epilepsy to hypertension to asthma. The clinical significance of these agents is reflected in the fact that over 25% of this text is dedicated to them.

Why do we have so many neuropharmacologic drugs? The answer lies in a concept discussed in Chapter 5: Most therapeutic agents act by helping the body help itself. That is, most drugs produce their therapeutic effects by coaxing the body to perform normal processes in a fashion that benefits the patient. Since the nervous system participates in the regulation of practically all bodily processes, practically all bodily processes can be influenced by drugs that alter neuronal regulation. By mimicking or blocking neuronal regulation, neuropharmacologic drugs can modify such diverse processes as skeletal muscle contraction, cardiac output, vascular tone, respiration, GI function, uterine motility, glandular secretion, and functions unique to the CNS, such as ideation, mood, and perception of pain. Given the broad spectrum of processes that neuropharmacologic drugs can alter, and given the potential benefits to be gained by manipulating those processes, it should be no surprise that neuropharmacologic drugs have widespread clinical applications.

We begin our study of neuropharmacology by discussing peripheral nervous system drugs (Chapter 14 through 19), after which we discuss CNS drugs

(Chapters 20 through 39). The principal rationale for this order of presentation is that our understanding of peripheral nervous system pharmacology is much clearer than our understanding of CNS pharmacology. Why? Because the peripheral nervous system is much less complex than the CNS, and also more accessible to experimentation. By placing our initial focus on the peripheral nervous system, we can establish a firm knowledge base in neuropharmacology before proceeding to the less definitive and vastly more complex realm of CNS pharmacology.

HOW NEURONS REGULATE PHYSIOLOGIC PROCESSES

As a rule, if we want to understand the effects of a drug on a particular physiologic process, we must first understand the process itself. Accordingly, if we wish to understand the impact of drugs on neuronal regulation of bodily function, we must first understand how neurons regulate bodily function when drugs are absent.

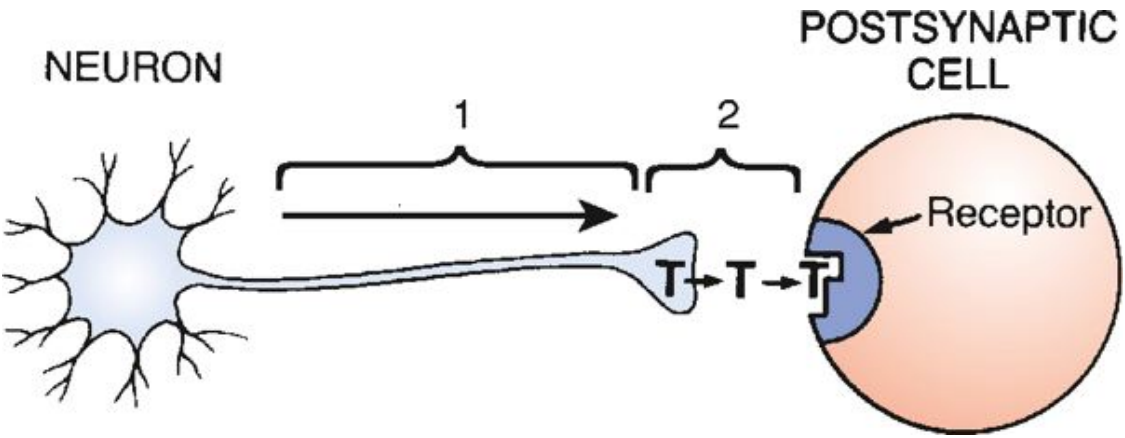


Figure 12-1 How neurons regulate other cells. There are two basic steps in the process by which neurons elicit responses from other cells: (1) axonal conduction and (2) synaptic transmission. (T = neurotransmitter.)

Figure 12-1 illustrates the basic process by which neurons elicit responses from other cells. The figure depicts two cells: a neuron and a postsynaptic cell. The postsynaptic cell might be another neuron, a muscle cell, or a cell within a secretory gland. As indicated, there are two basic steps—*axonal conduction* and *synaptic transmission*—in the process by which the neuron influences the

behavior of the postsynaptic cell. Axonal conduction is simply the process of conducting an action potential down the axon of the neuron. Synaptic transmission is the process by which information is carried across the gap between the neuron and the postsynaptic cell. As shown in the figure, synaptic transmission requires the release of neurotransmitter molecules from the axon terminal followed by binding of these molecules to receptors on the postsynaptic cell. As a result of transmitter-receptor binding, a series of events is initiated in the postsynaptic cell, leading to a change in its behavior. The precise nature of the change depends on the identity of the neurotransmitter and the type of cell involved. If the postsynaptic cell is another neuron, it may increase or decrease its firing rate; if the cell is part of a muscle, it may contract or relax; and if the cell is glandular, it may increase or decrease secretion.

BASIC MECHANISMS BY WHICH NEUROPHARMACOLOGIC AGENTS ACT

Sites of Action: Axons Versus Synapses

In order to influence a process under neuronal control, a drug can alter one of two basic neuronal activities: axonal conduction or synaptic transmission. *Most neuropharmacologic agents act by altering synaptic transmission*. Only a few alter axonal conduction. Why do drugs usually target synaptic transmission? Because drugs that alter synaptic transmission can produce effects that are much more *selective* than those produced by drugs that alter axonal conduction.

Axonal Conduction

Drugs that act by altering axonal conduction are not very selective. Recall that the process of conducting an impulse along an axon is essentially the same in all neurons. As a consequence, a drug that alters axonal conduction will affect conduction in all nerves to which it has access. Such a drug cannot produce selective effects.

Local anesthetics are the only drugs proved to work by altering (decreasing) axonal conduction. Because these agents produce nonselective inhibition of axonal conduction, they suppress transmission in any nerve they reach.

Hence, although local anesthetics are certainly valuable, their indications are limited.

Synaptic Transmission

In contrast to drugs that alter axonal conduction, drugs that alter synaptic transmission can produce effects that are highly selective. Why? Because synapses, unlike axons, differ from one another. Synapses at different sites employ different transmitters. In addition, for most transmitters, the body employs more than one type of receptor. Hence, by using a drug that selectively influences a specific type of neurotransmitter or receptor, we can alter one neuronally regulated process while leaving most others unchanged. Because of their relative selectivity, drugs that alter synaptic transmission have many uses.

Receptors

The ability of a neuron to influence the behavior of another cell depends, ultimately, upon the ability of that neuron to alter receptor activity on the target cell. As discussed, neurons alter receptor activity by releasing transmitter molecules, which diffuse across the synaptic gap and bind to receptors on the postsynaptic cell. If the target cell lacked receptors for the transmitter that a neuron released, that neuron would be unable to affect the target cell.

The effects of neuropharmacologic drugs, like those of neurons, depend on altering receptor activity. That is, no matter what its precise mechanism of action, a neuropharmacologic drug ultimately works by influencing receptor activity on target cells. This commonsense concept is central to understanding the actions of neuropharmacologic drugs. In fact, this concept is so critical to our understanding of neuropharmacologic agents that I will repeat it: *The impact of a drug on a neuronally regulated process is dependent on the ability of that drug to directly or indirectly influence receptor activity on target cells*.

Steps in Synaptic Transmission

To understand how drugs alter receptor activity, we must first understand the steps by which synaptic transmission takes place, since it is by modifying these steps that neuropharmacologic drugs influence receptor function. The steps in synaptic transmission are summarized in Figure 12-2.

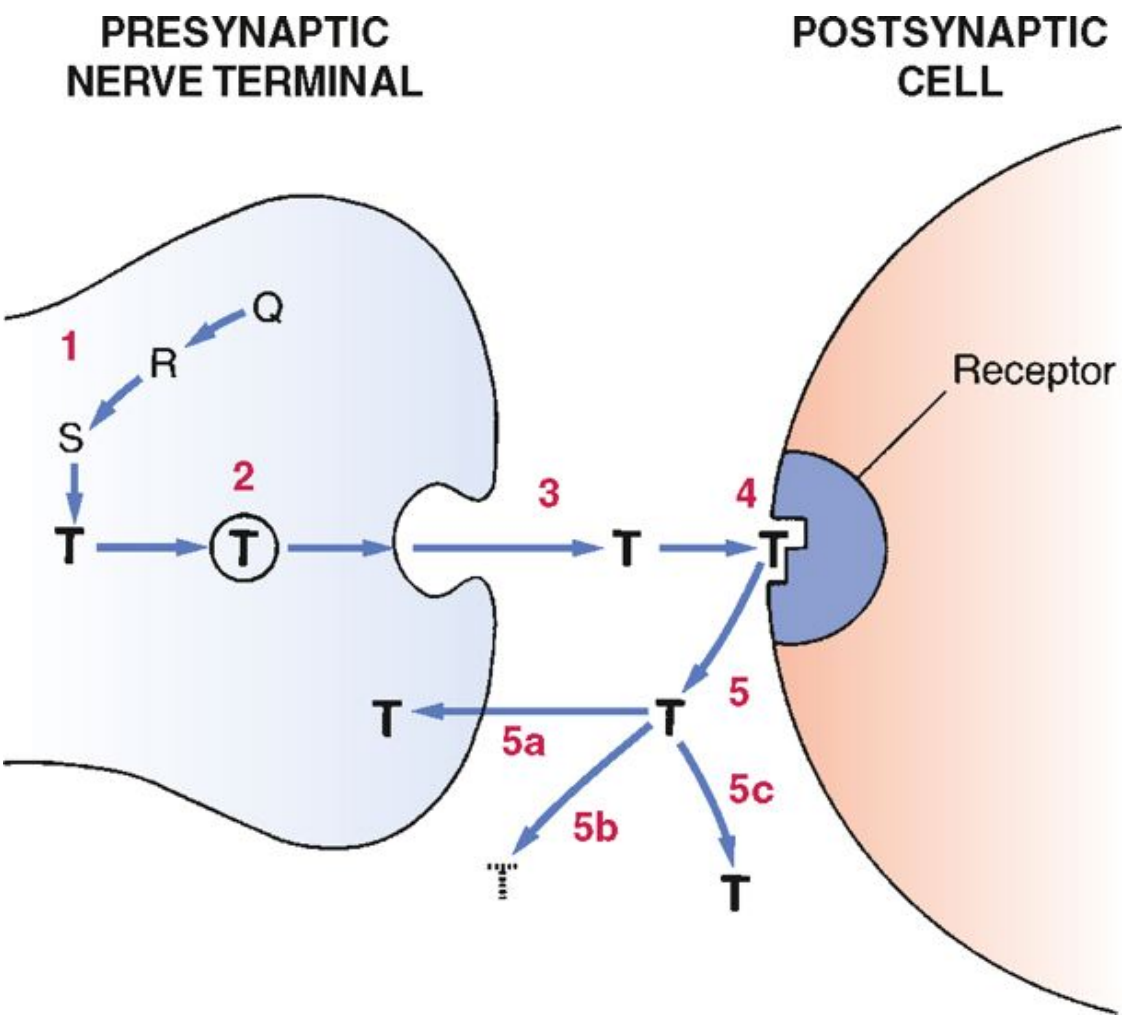


Figure 12-2 Steps in synaptic transmission. Step 1, Synthesis of transmitter (T) from precursor molecules (Q, R, and S). Step 2, Storage of transmitter in vesicles. Step 3, Release of transmitter: In response to an action potential, vesicles fuse with the terminal membrane and discharge their contents into the synaptic gap. Step 4, Action at receptor: Transmitter binds (reversibly) to its receptor on the postsynaptic cell, causing a response in that cell. Step 5, Termination of transmission: Transmitter dissociates from its receptor and is then removed from the synaptic gap by (a) reuptake into the nerve terminal, (b) enzymatic degradation, or (c) diffusion away from the gap.

Step 1: Transmitter Synthesis.

For synaptic transmission to take place, molecules of transmitter must be present in the nerve terminal. Hence, we can look upon transmitter synthesis as the first step in transmission. In the figure, the letters Q, R, and S represent the precursor molecules from which the transmitter (T) is made.

Step 2: Transmitter Storage.

Once transmitter is synthesized, it must be stored until the time of its release. Transmitter storage takes place within vesicles—tiny packets present in the axon terminal. Each nerve terminal contains a large number of transmitter-filled vesicles.

Step 3: Transmitter Release.

Release of transmitter is triggered by the arrival of an action potential at the axon terminal. The action potential initiates a process in which vesicles undergo fusion with the terminal membrane, causing release of their contents into the synaptic gap. Each action potential causes only a small fraction of all vesicles present in the axon terminal to discharge their contents.

Step 4: Receptor Binding.

Following release, transmitter molecules diffuse across the synaptic gap and then undergo *reversible* binding to receptors on the postsynaptic cell. This binding initiates a cascade of events that result in altered behavior of the postsynaptic cell.

Step 5: Termination of Transmission.

Transmission is terminated by dissociation of transmitter from its receptors, followed by removal of free transmitter from the synaptic gap. Transmitter can be removed from the synaptic gap by three processes: (1) reuptake, (2) enzymatic degradation, and (3) diffusion. In those synapses where transmission is terminated by reuptake, axon terminals contain “pumps” that transport transmitter molecules back into the neuron from which they were released (Step 5a in Fig. 12-2). Following reuptake, molecules of transmitter may be degraded, or they may be packaged in vesicles for reuse. In synapses where transmitter is cleared by enzymatic degradation (Step 5b), the synapse con-

tains large quantities of transmitter-inactivating enzymes. Although simple diffusion away from the synaptic gap (Step 5c) is a potential means of terminating transmitter action, this process is very slow and generally of little significance.

Effects of Drugs on the Steps of Synaptic Transmission

As emphatically noted, all neuropharmacologic agents (except local anesthetics) produce their effects by directly or indirectly altering receptor activity. We also noted that the way in which drugs alter receptor activity is by interfering with synaptic transmission. Because synaptic transmission has multiple steps, the process offers a number of potential targets for drugs. In this section, we examine the specific ways in which drugs can alter the steps of synaptic transmission. By way of encouragement, although this information may appear complex, it isn't. In fact, it's largely self-evident.

Before discussing specific mechanisms by which drugs can alter receptor activity, we need to understand what drugs are capable of doing to receptors in general terms. From the broadest perspective, when a drug influences receptor function, that drug can do just one of two things: it can enhance receptor activation or it can reduce receptor activation. What do we mean by receptor activation? For our purposes, we can define *activation* as *an effect on receptor function equivalent to that produced by the natural neurotransmitter at a particular synapse*. Hence, a drug whose effects mimic the effects of a natural transmitter would be said to *increase* receptor activation. Conversely, a drug whose effects were equivalent to reducing the amount of natural transmitter available for receptor binding would be said to *decrease* receptor activation.

Please note that activation of a receptor does not necessarily mean that a physiologic process will go faster; receptor activation can also make a process go slower. For example, a drug that mimics acetylcholine at receptors on the heart will cause the heart to beat more slowly. Since the effect of this drug on receptor function mimicked the effect of the natural neurotransmitter, we would say that the drug activated acetylcholine receptors, even though activation caused heart rate to decline.

Having defined receptor activation, we are ready to discuss the mechanisms by which drugs, acting on specific steps of synaptic transmission, can increase

or decrease receptor activity. These mechanisms are summarized in Table 12-1. As we consider these mechanisms one by one, their commonsense nature should become apparent.

Step of Synaptic Transmission	Drug Action	Impact on Receptor Activation*
1. Synthesis of transmitter	Increased synthesis of T	Increase
	Decreased synthesis of T	Decrease
	Synthesis of "super" T	Increase
2. Storage of transmitter	Reduced storage of T	Decrease
3. Release of transmitter	Promotion of T release	Increase
	Inhibition of T release	Decrease
4. Binding to receptor	Direct receptor activation	Increase
	Enhanced response to T	Increase
	Blockade of T binding	Decrease
5. Termination of transmission	Blockade of T reuptake	Increase
	Inhibition of T breakdown	Increase

T = transmitter.

TABLE 12-1 Effects of Drugs on Synaptic Transmission and the Resulting Impact on Receptor Activation

* Receptor activation is defined as producing an effect equivalent to that produced by the natural transmitter that acts on a particular receptor.

Transmitter Synthesis.

There are three different effects that drugs are known to have on transmitter synthesis. They can (1) increase transmitter synthesis, (2) decrease transmitter synthesis, or (3) cause the synthesis of transmitter molecules that are more effective than the natural transmitter itself.

The impact of increased or decreased transmitter synthesis on receptor activity should be obvious. A drug that increases transmitter synthesis will cause receptor activation to increase. The process is this: As a result of increased transmitter synthesis, storage vesicles will contain transmitter in abnormally high amounts. Hence, when an action potential reaches the axon terminal, more transmitter will be released, and therefore more transmitter will be available to receptors on the postsynaptic cell, causing activation of those receptors to increase. Conversely, a drug that decreases transmitter synthesis will cause the transmitter content of vesicles to decline, resulting in reduced transmitter release and decreased receptor activation.

Some drugs can cause neurons to synthesize transmitter molecules whose structure is different from that of normal transmitter molecules. For example, by acting as substrates for enzymes in the axon terminal, drugs can be converted into "super" transmitters (molecules whose ability to activate receptors is greater than that of the naturally occurring transmitter at a particular site). Release of these supertransmitters will cause receptor activation to increase. In theory, it should be possible to cause the synthesis of *faulty* transmitter molecules (ie, molecules with a reduced ability to activate a particular receptor). However, we have no medicines that are known to act this way.

Transmitter Storage.

Drugs that interfere with transmitter storage will cause receptor activation to decrease. Why? Because disruption of storage depletes vesicles of their transmitter content, thereby decreasing the amount of transmitter available for release.

Transmitter Release.

Drugs can either *promote* or *inhibit* transmitter release. Drugs that promote release will increase receptor activation. Conversely, drugs that inhibit release will reduce receptor activation. The amphetamines (CNS stimulants) represent drugs that act by promoting transmitter release. Botulinum toxin, in contrast, acts by inhibiting transmitter release.*

* Botulinum toxin blocks release of acetylcholine from the neurons that control skeletal muscles, including the muscles of respiration. The potential for disaster is obvious.

Receptor Binding.

Many drugs act directly at receptors. These agents can either (1) bind to receptors and cause activation, (2) bind to receptors and thereby block receptor activation by other agents, or (3) bind to receptor components and thereby enhance receptor activation by the natural transmitter at the site.

In the terminology introduced in Chapter 5, drugs that directly activate receptors are called *agonists,* whereas drugs that prevent receptor activation are called *antagonists*. We have no special name for drugs that bind to receptors and thereby enhance the effects of the natural transmitter. The direct-acting receptor agonists and antagonists constitute the largest and most important groups of neuropharmacologic drugs.

Examples of drugs that act directly at receptors are numerous. Drugs that bind to receptors and cause *activation* include morphine (used for its effects on the CNS), epinephrine (used mainly for its effects on the cardiovascular system), and insulin (used for its effects in diabetes). Drugs that bind to receptors and *prevent* their activation include naloxone (used to treat overdose with morphine-like drugs), antihistamines (used to treat allergic disorders), and propranolol (used to treat hypertension, angina pectoris, and cardiac dysrhythmias). The principal examples of drugs that bind to receptors and thereby enhance the actions of a natural transmitter are the benzodiazepines. Drugs in this family, which includes diazepam [Valium] and related agents, are used to treat anxiety, seizure disorders, and muscle spasm.

Termination of Transmitter Action.

Drugs can interfere with the termination of transmitter action by two mechanisms: (1) blockade of transmitter reuptake and (2) inhibition of transmitter degradation. Drugs that act by either mechanism will cause the concentration of transmitter in the synaptic gap to rise, thereby causing receptor activation to increase.

MULTIPLE RECEPTOR TYPES AND SELECTIVITY OF DRUG ACTION

As we discussed in Chapter 1, selectivity is one of the most desirable qualities a drug can have. Why? Because a selective drug is able to alter a disease process while leaving other physiologic processes largely unaffected.

Many neuropharmacologic agents display a high degree of selectivity. This selectivity is possible because the nervous system works through multiple types of receptors to regulate processes under its control. If neurons had only one or two types of receptors through which to act, selective effects by neuropharmacologic drugs could not be achieved.

The relationship between multiple receptor types and selective drug action is illustrated by Mort and Merv, whose unique physiologies are depicted in Figure 12-3. Let's begin with Mort. Mort can perform four functions: he can pump blood, digest food, shake hands, and empty his bladder. As indicated in the figure, all four functions are under neuronal control, and, in all cases, that control is exerted by activation of the same type of receptor (designated A).

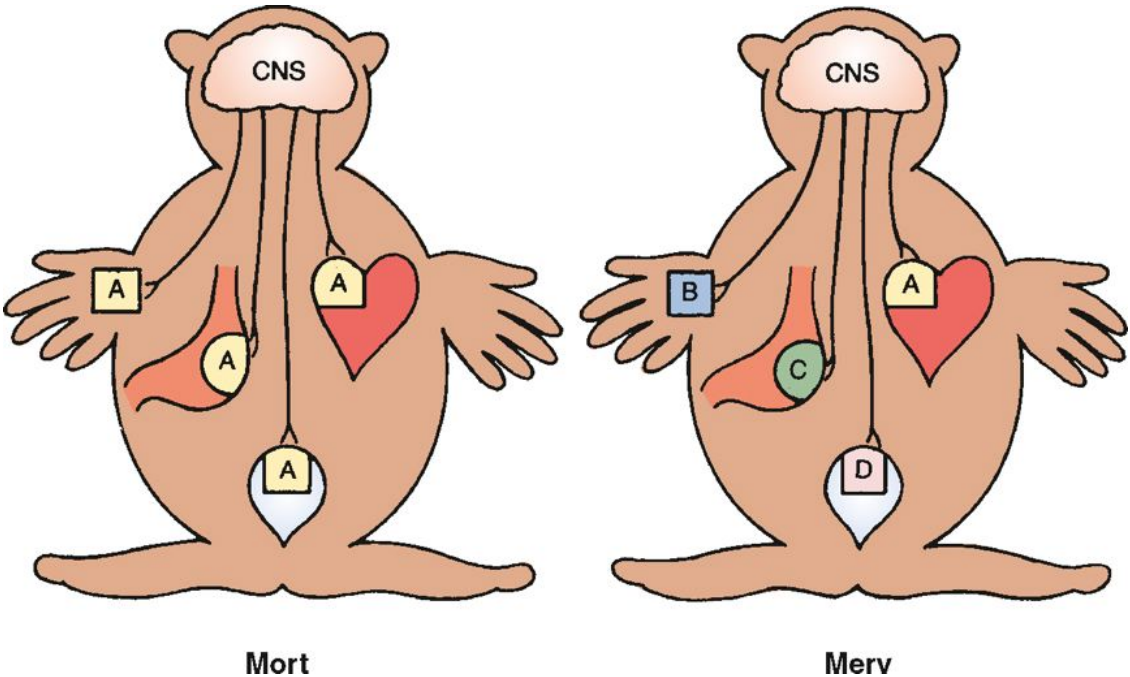


Figure 12-3 Multiple drug receptors and selective drug action. Mort, All of Mort's organs are regulated through activation of type A receptors. Drugs that affect type A receptors on one organ

will affect type A receptors on all other organs. Hence, selective drug action is impossible. Merv, Merv has four types of receptors (A, B, C, and D) to regulate his four organs. A drug that acts at one type of receptor will not affect the others. Hence, selective drug action is possible.

As long as Mort remains healthy, having only one type of receptor to regulate his various functions is no problem. Selective *physiologic* regulation can be achieved simply by sending impulses down the appropriate nerves. When there is a need to increase cardiac output, impulses are sent down the nerve to his heart; when digestion is needed, impulses are sent down the nerve to his stomach; and so forth.

Although having only one receptor type is no disadvantage when all is well, if Mort gets sick, having only one receptor type creates a therapeutic problem. Let's assume he develops heart disease and we need to give a drug that will help increase cardiac output. To stimulate cardiac function, we need to administer a drug that will activate receptors on his heart. Unfortunately, since the receptors on his heart are the same as the receptors on his other organs, a drug that stimulates cardiac function will stimulate his other organs too. Consequently, any attempt to improve cardiac output with drugs will necessarily be accompanied by side effects. These will range from silly (compulsive handshaking) to embarrassing (enuresis) to hazardous (gastric ulcers). Such side effects are not likely to elicit either gratitude or adherence. Please note that all of these undesirable effects are the direct result of Mort having a nervous system that works through just one type of receptor to regulate all organs. That is, the presence of only one receptor type has made selective drug action impossible.

Now let's consider Merv. Although Merv appears to be Mort's twin, Merv differs in one important way: Whereas all functions in Mort are regulated through just one type of receptor, Merv employs different receptors to control each of his four functions. Because of this simple but important difference, the selective drug action that was impossible with Mort can be achieved easily with Merv. We can, for example, selectively enhance cardiac function in Merv without risking the side effects to which Mort was predisposed. This can be done simply by administering an agonist agent that binds selectively to re-

ceptors on the heart (type A receptors). If this medication is sufficiently selective for type A receptors, it will not interact with receptor types B, C, or D. Hence, function in structures regulated by those receptors will be unaffected. Note that our ability to produce selective drug action in Merv is made possible because his nervous system works through different types of receptors to regulate function in his various organs. The message from this example is clear: *The more types of receptors we have to work with, the greater our chances of producing selective drug effects.*

AN APPROACH TO LEARNING ABOUT PERIPHERAL NERVOUS SYSTEM DRUGS

As discussed, to understand the ways in which drugs can alter a process under neuronal control, we must first understand how the nervous system itself regulates that process. Accordingly, when preparing to study peripheral nervous system pharmacology, you must first establish a working knowledge of the peripheral nervous system itself. In particular, you need to know two basic types of information about peripheral nervous system function. First, you need to know the types of receptors through which the peripheral nervous system works when influencing the function of a specific organ. Second, you need to know what the normal response to activation of those receptors is. All of the information you need about peripheral nervous system function is reviewed in Chapter 13.

Once you understand the peripheral nervous system itself, you can go on to learn about peripheral nervous system drugs. Although learning about these drugs will require significant effort, the learning process itself is straightforward. To understand any particular peripheral nervous system drug, you need three types of information: (1) the type (or types) of receptor through which the drug acts; (2) the normal response to activation of those receptors; and (3) what the drug in question does to receptor function (ie, does it increase or decrease receptor activation?). Armed with these three types of information, you can predict the major effects of any peripheral nervous system drug.

An example will illustrate this process. Let's consider a drug named *isoproterenol*. The first information we need is the identity of the receptors at which isoproterenol acts. Isoproterenol acts at two types of receptors, named beta***1*** and beta***2***. Next, we need to know the normal responses to activation of these

receptors. The most prominent responses to activation of beta*1* receptors are *increased heart rate* and *increased force of cardiac contraction*. The primary responses to activation of beta*2* receptors are *bronchial dilation* and *elevation of glucose levels in blood*. Lastly, we need to know whether isoproterenol increases or decreases the activation of beta*1* and beta*2* receptors. At both types of receptor, isoproterenol causes *activation*. Armed with these three primary pieces of information about isoproterenol, we can now predict the principal effects of this drug. By *activating* beta*1* and beta*2* receptors, isoproterenol can elicit three major responses: (1) increased cardiac output (by increasing heart rate and force of contraction); (2) dilation of the bronchi; and (3) elevation of blood glucose. Depending on the patient to whom this drug is given, these responses may be beneficial or detrimental.

From this example, you can see how easy it is to predict the effects of a peripheral nervous system drug. Accordingly, I strongly encourage you to take the approach suggested when studying these agents. That is, for each peripheral nervous system drug, you should learn (1) the identity of the receptors at which that drug acts, (2) the normal responses to activation of those receptors, and (3) whether the drug increases or decreases receptor activation.

KEY POINTS

- Except for local anesthetics, which suppress axonal conduction, all neuropharmacologic drugs act by altering synaptic transmission.
- Synaptic transmission consists of five basic steps: transmitter synthesis, transmitter storage, transmitter release, binding of transmitter to its receptors, and termination of transmitter action by dissociation of transmitter from the receptor followed by transmitter reuptake or degradation.
- Ultimately, the impact of a drug on a neuronally regulated process depends on the drug's ability to directly or indirectly alter receptor activity on target cells.
- Drugs can do one of two things to receptor function: they can increase receptor activation or they can decrease receptor activation.
- Drugs that increase transmitter synthesis increase receptor activation.

- Drugs that decrease transmitter synthesis decrease receptor activation.
- Drugs that promote synthesis of "super" transmitters increase receptor activation.
- Drugs that impede transmitter storage decrease receptor activation.
- Drugs that promote transmitter release increase receptor activation.
- Drugs that suppress transmitter release decrease receptor activation.
- Agonist drugs increase receptor activation.
- Antagonist drugs decrease receptor activation.
- Drugs that bind to receptors and enhance the actions of the natural transmitter at the receptor increase receptor activation.
- Drugs that block transmitter reuptake increase receptor activation.
- Drugs that inhibit transmitter degradation increase receptor activation.
- The presence of multiple receptor types increases our ability to produce selective drug effects.
- For each peripheral nervous system drug that you study, you should learn the identity of the receptors at which the drug acts, the normal responses to activation of those receptors, and whether the drug increases or decreases receptor activation.

13 Physiology of the Peripheral Nervous System

To understand peripheral nervous system drugs, we must first understand the peripheral nervous system itself. The purpose of this chapter is to help you develop that understanding.

It's not uncommon for students to be at least slightly apprehensive about studying the peripheral nervous system—especially the autonomic component. In fact, it's not uncommon for students who have studied this subject before to be thoroughly convinced that they will never, ever really understand it. This reaction is unfortunate in that, although there is a lot to know about the peripheral nervous system, the information is not terribly difficult. In this chapter, I take a nontraditional approach to teaching the material. Hopefully, this approach will facilitate your learning.

Since our ultimate goal concerns pharmacology—and not physiology—I do not address everything there is to know about the peripheral nervous system. Rather, I limit the discussion to those aspects of peripheral nervous system physiology that have a direct bearing on your ability to understand drugs.

DIVISIONS OF THE NERVOUS SYSTEM

The nervous system has two main divisions, the *central nervous system* and the *peripheral nervous system*. The central nervous system is subdivided into the brain and spinal cord.

The peripheral nervous system has two major subdivisions: (1) the *somatic motor system* and (2) the *autonomic nervous system*. The autonomic nervous system is further subdivided into the *parasympathetic nervous system* and the *sympathetic nervous system*. The somatic motor system controls voluntary movement of muscles. The two subdivisions of the autonomic nervous system regulate many "involuntary" processes.

The autonomic nervous system is the principal focus of this chapter. The somatic motor system is also considered, but discussion is brief.

OVERVIEW OF AUTONOMIC NERVOUS SYSTEM FUNCTIONS

The autonomic nervous system has three principal functions: (1) regulation of the *heart;* (2) regulation of *secretory glands* (salivary, gastric, sweat, and bronchial glands); and (3) regulation of *smooth muscles* (muscles of the bronchi, blood vessels, urogenital system, and GI tract). These regulatory activities are shared between the sympathetic and parasympathetic divisions of the autonomic nervous system.

Functions of the Parasympathetic Nervous System

The parasympathetic nervous system performs seven regulatory functions that have particular relevance to drugs. Specifically, stimulation of appropriate parasympathetic nerves causes

- Slowing of heart rate
- Increased gastric secretion
- Emptying of the bladder
- Emptying of the bowel
- Focusing the eye for near vision
- Constricting the pupil
- Contracting bronchial smooth muscle

Just how the parasympathetic nervous system elicits these responses is discussed later under *Functions of Cholinergic Receptor Subtypes*.

From the above we can see that the parasympathetic nervous system is concerned primarily with what might be called the "housekeeping" chores of the body (digestion of food and excretion of wastes). In addition, the system helps control vision and conserve energy (by reducing cardiac work).

Therapeutic agents that alter parasympathetic nervous system function are used primarily for their effects on the GI tract, bladder, and eye. Occasionally, these drugs are also used for effects on the heart and lungs.

A variety of poisons act by mimicking or blocking effects of parasympathetic stimulation. Among these are insecticides, nerve gases, and toxic compounds found in certain mushrooms and plants.

Functions of the Sympathetic Nervous System

The sympathetic nervous system has three main functions:

- Regulating the cardiovascular system
- Regulating body temperature
- Implementing the "fight-or-flight" reaction

The sympathetic nervous system exerts multiple influences on the heart and blood vessels. Stimulation of sympathetic nerves to the heart increases cardiac output. Stimulation of sympathetic nerves to arterioles and veins causes vasoconstriction. Release of epinephrine from the adrenal medulla results in vasoconstriction in most vascular beds and vasodilation in certain others. By influencing the heart and blood vessels, the sympathetic nervous system can achieve three homeostatic objectives:

- Maintenance of blood flow to the brain
- Redistribution of blood flow during exercise
- Compensation for loss of blood, primarily by causing vasoconstriction

The sympathetic nervous system helps regulate body temperature in three ways: (1) By regulating blood flow to the skin, sympathetic nerves can increase or decrease heat loss. By *dilating* surface vessels, sympathetic nerves increase blood flow to the skin and thereby accelerate heat loss. Conversely, *constricting* cutaneous vessels conserves heat. (2) Sympathetic nerves to sweat glands promote secretion of sweat, thereby helping the body cool. (3) By inducing piloerection (erection of hair), sympathetic nerves can promote heat conservation.

When we are faced with adversity, the sympathetic nervous system orchestrates the fight-or-flight response, which consists of

- Increasing heart rate and blood pressure
- Shunting blood away from the skin and viscera and into skeletal muscles
- Dilating the bronchi to improve oxygenation
- Dilating the pupils (perhaps to enhance visual acuity)
- Mobilizing stored energy, thereby providing glucose for the brain and fatty acids for muscles

The sensation of being "cold with fear" is brought on by shunting of blood away from the skin. The phrase "wide-eyed with fear" may be based on pupillary dilation.

Many therapeutic agents produce their effects by altering functions under sympathetic control. These drugs are used primarily for effects on the heart, blood vessels, and lungs. Agents that alter cardiovascular function are used to treat hypertension, heart failure, angina pectoris, and other disorders. Drugs affecting the lungs are used primarily for asthma.

BASIC MECHANISMS BY WHICH THE AUTONOMIC NERVOUS SYSTEM REGULATES PHYSIOLOGIC PROCESSES

To understand how drugs influence processes under autonomic control, we must first understand how the autonomic nervous system itself regulates those activities. The basic mechanisms by which the autonomic nervous system regulates physiologic processes are discussed below.

Patterns of Innervation and Control

Most structures under autonomic control are innervated by sympathetic nerves *and* parasympathetic nerves. The relative influence of sympathetic and parasympathetic nerves depends on the organ under consideration.

In many organs that receive dual innervation, the influence of sympathetic nerves *opposes* that of parasympathetic nerves. For example, in the heart, *sympathetic* nerves *increase* heart rate, whereas *parasympathetic* nerves *slow* heart rate (Fig. 13-1).

In some organs that receive nerves from both divisions of the autonomic nervous system, the effects of sympathetic and parasympathetic nerves are *complementary,* rather than opposite. For example, in the male reproductive system, erection is regulated by parasympathetic nerves while ejaculation is controlled by sympathetic nerves. If attempts at reproduction are to succeed, cooperative interaction of both systems is needed.

A few structures under autonomic control receive innervation from only one division. The principal example is blood vessels, which are innervated exclusively by sympathetic nerves.

In summary, there are three basic patterns of autonomic innervation and regulation:

- Innervation by *both* divisions of the autonomic nervous system in which the effects of the two divisions are *opposed*
- Innervation by *both* divisions of the autonomic nervous system in which the effects of the two divisions are *complementary*
- Innervation and regulation by *only one* division of the autonomic nervous system

Feedback Regulation

Feedback regulation is a process that allows a system to adjust itself by responding to incoming information. Practically all physiologic processes are regulated at least in part by feedback control.

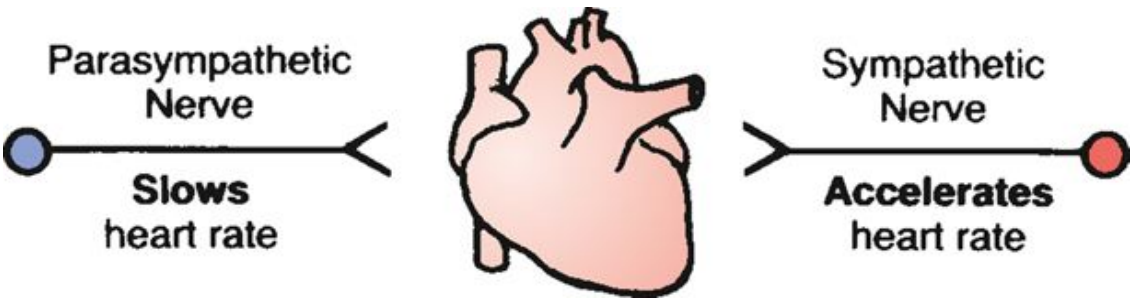


Figure 13-1 Opposing effects of parasympathetic and sympathetic nerves.

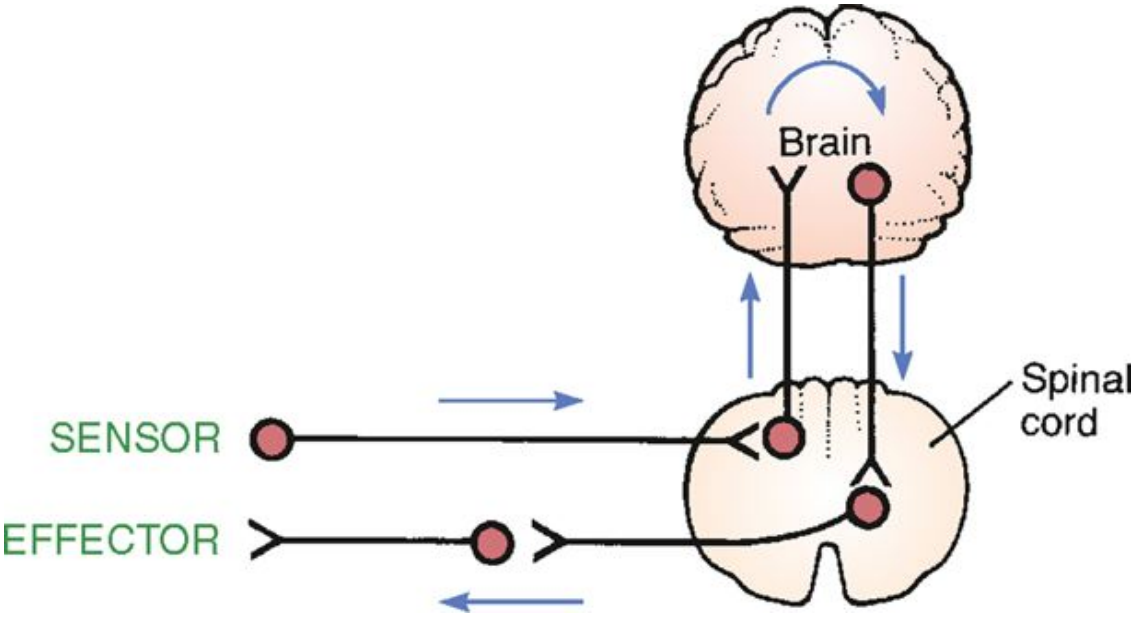


Figure 13-2 Feedback loop of the autonomic nervous system.

Figure 13-2 depicts a feedback loop typical of those used by the autonomic nervous system. The main elements of this loop are (1) a *sensor,* (2) an *effector,* and (3) neurons connecting the sensor to the effector. The purpose of the sensor is to monitor the status of a physiologic process. Information picked up by the sensor is sent to the central nervous system (spinal cord and brain), where it is integrated with other relevant information. Signals (instructions for change) are then sent from the central nervous system along nerves of the autonomic system to the effector. In response to these instructions, the effector makes appropriate adjustments in the process. The entire procedure is termed a *reflex.*

Baroreceptor Reflex.

From a pharmacologic perspective, the most important feedback loop of the autonomic nervous system is one that helps regulate blood pressure. This system is referred to as the *baroreceptor reflex.* (Baroreceptors are receptors that sense blood pressure.) This reflex is important to us because it frequently opposes our attempts to modify blood pressure with drugs.

Feedback (reflex) control of blood pressure is achieved as follows: (1) Baroreceptors located in the carotid sinus and aortic arch monitor changes in blood

pressure and send this information to the brain. (2) In response to alterations in blood pressure, the brain sends impulses along nerves of the autonomic nervous system, instructing the heart and blood vessels to behave in such a way as to restore blood pressure to normalcy. Accordingly, when blood pressure *falls,* the baroreceptor reflex causes vasoconstriction and elevation of cardiac output so as to bring blood pressure back up. Conversely, when blood pressure *rises* too high, the baroreceptor reflex causes vasodilation and a reduction in cardiac output, thereby causing blood pressure to drop. The baroreceptor reflex is discussed in greater detail in Chapter 42 (Review of Hemodynamics).

Autonomic Tone

The term *autonomic tone* refers to the steady, day-to-day influence exerted by the autonomic nervous system on a particular organ or organ system. Autonomic tone provides a basal level of control over which reflex regulation is superimposed.

When an organ is innervated by both divisions of the autonomic nervous system, one division—either sympathetic or parasympathetic—provides most of the basal control, thereby obviating conflicting instruction. Recall that, when an organ receives nerves from both divisions of the autonomic nervous system, those nerves frequently exert opposing influences. If both divisions were to send impulses simultaneously, the resultant conflicting instructions would be counterproductive (like running heating and air conditioning simultaneously.) By having only one division of the autonomic nervous system provide the basal control to an organ, conflicting signals are avoided.

The branch of the autonomic nervous system that controls organ function most of the time is said to provide the *predominant tone* to that organ. *In most organs, the parasympathetic nervous system provides the predominant tone*. The vascular system, which is regulated almost exclusively by the *sympathetic* nervous system, is the principal exception.

ANATOMIC CONSIDERATIONS

Although we know a great deal about the anatomy of the peripheral nervous system, very little of this information helps us understand peripheral nervous

system drugs. The few details that *do* pertain to pharmacology are summarized in Figure 13-3.

Parasympathetic Nervous System

Pharmacologically relevant aspects of parasympathetic anatomy are shown in Figure 13-3. Note that there are *two* neurons in the pathway leading from the spinal cord to organs innervated by parasympathetic nerves. The junction (synapse) between these two neurons occurs within a structure called a *ganglion*. (A ganglion is simply a lump created by a group of nerve cell bodies.) Not surprisingly, the neurons that go from the spinal cord to the parasympathetic ganglia are called *preganglionic neurons,* whereas the neurons that go from the ganglia to effector organs are called *postganglionic neurons*. The anatomy of the parasympathetic nervous system offers two general sites at which drugs can act: (1) the synapses between preganglionic neurons and postganglionic neurons and (2) the junctions between postganglionic neurons and their effector organs.

Sympathetic Nervous System

Pharmacologically relevant aspects of sympathetic nervous system anatomy are illustrated in Figure 13-3. As you can see, these features are nearly identical to those of the parasympathetic nervous system. Like the parasympathetic nervous system, the sympathetic nervous system employs two neurons in the pathways leading from the spinal cord to organs under its control. As with the parasympathetic nervous system, the junctions between those neurons are located in *ganglia*. Neurons leading from the spinal cord to the sympathetic ganglia are termed *preganglionic neurons,* and neurons leading from ganglia to effector organs are termed *postganglionic neurons*.

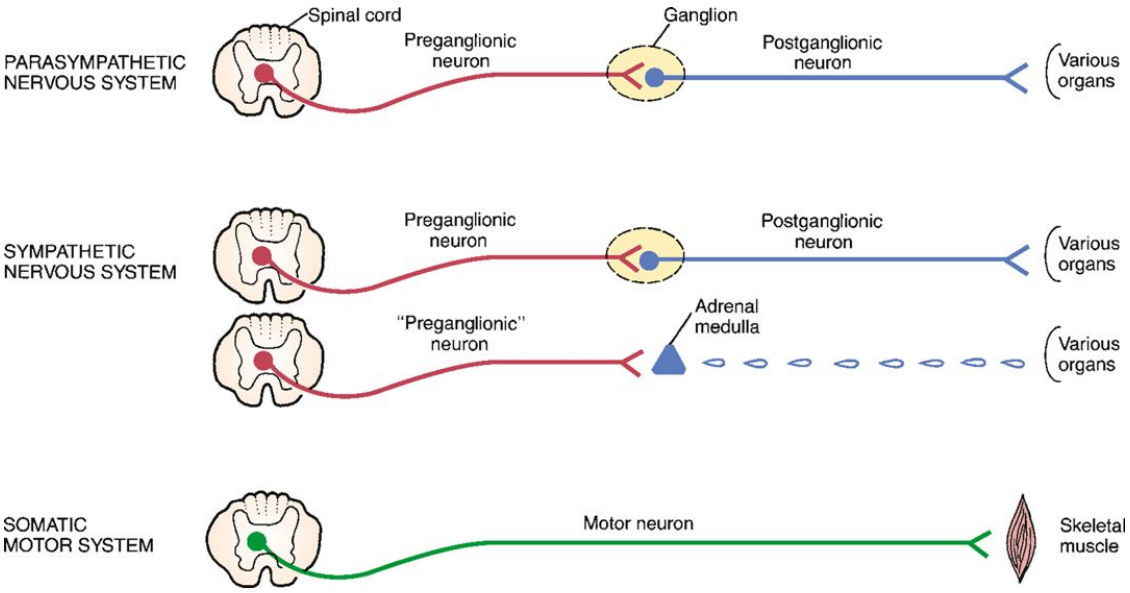


Figure 13-3 The basic anatomy of the parasympathetic and sympathetic nervous systems and the somatic motor system.

The *medulla of the adrenal gland* is a feature of the sympathetic nervous system that requires comment. Although not a neuron per se, the adrenal medulla can be looked on as the functional equivalent of a postganglionic neuron of the sympathetic nervous system. (The adrenal medulla influences the body by releasing epinephrine into the bloodstream, which then produces effects much like those that occur in response to stimulation of postganglionic sympathetic nerves.) Because the adrenal medulla is similar in function to a postganglionic neuron, it is appropriate to refer to the nerve leading from the spinal cord to the adrenal as preganglionic, even though there is no ganglion, as such, in this pathway.

As with the parasympathetic nervous system, drugs that affect the sympathetic nervous system have two general sites of action: (1) the synapses between preganglionic and postganglionic neurons (including the adrenal medulla), and (2) the junctions between postganglionic neurons and their effector organs.

Somatic Motor System

Pharmacologically relevant anatomy of the somatic motor system is depicted in Figure 13-3. Note that there is *only one* neuron in the pathway from the spinal cord to the muscles innervated by somatic motor nerves. Because this pathway contains only one neuron, peripherally acting drugs that affect somatic motor system function have only one site of action: the *neuromuscular junction* (ie, the junction between the somatic motor nerve and the muscle).

INTRODUCTION TO TRANSMITTERS OF THE PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system employs three neurotransmitters: *acetylcholine, norepinephrine,* and *epinephrine*. Any given junction in the peripheral nervous system uses only one of these transmitter substances. A fourth compound—*dopamine*—may also serve as a peripheral nervous system transmitter, but this role has not been demonstrated conclusively.

To understand peripheral nervous system pharmacology, it is necessary to know the identity of the transmitter employed at each of the junctions of the peripheral nervous system. This information is summarized in Figure 13-4. As indicated, *acetylcholine* is the transmitter employed at most junctions of the peripheral nervous system. Acetylcholine is the transmitter released by (1) all preganglionic neurons of the parasympathetic nervous system, (2) all preganglionic neurons of the sympathetic nervous system, (3) all postganglionic neurons of the parasympathetic nervous system, (4) all motor neurons to skeletal muscles, and (5) most postganglionic neurons of the sympathetic nervous system that go to sweat glands.

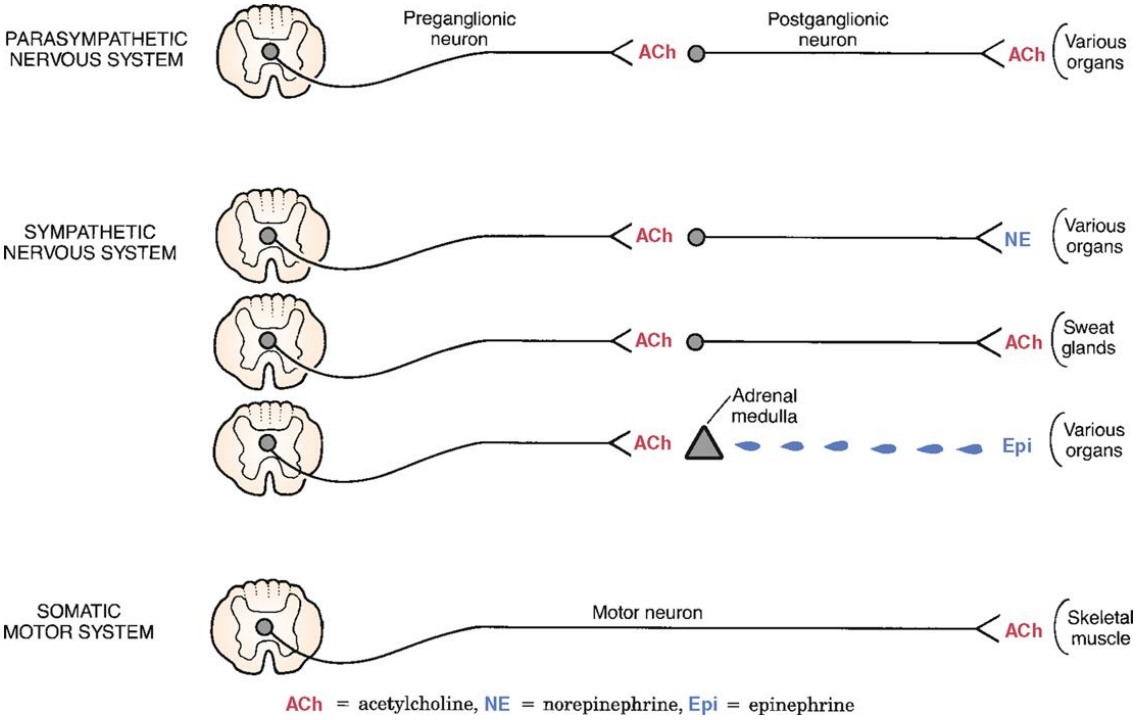


Figure 13-4 Transmitters employed at specific junctions of the peripheral nervous system. Summary:1.All preganglionic neurons of the parasympathetic and sympathetic nervous systems release acetylcholine as their transmitter.2.All postganglionic neurons of the parasympathetic nervous system release acetylcholine as their transmitter.3.Most postganglionic neurons of the sympathetic nervous system release norepinephrine as their transmitter.4.Postganglionic neurons of the sympathetic nervous system that innervate sweat glands release acetylcholine as their transmitter.5.Epinephrine is the principal transmitter released by the adrenal medulla.6.All motor neurons to skeletal muscles release acetylcholine as their transmitter.

Norepinephrine is the transmitter released by practically all postganglionic neurons of the sympathetic nervous system. The only exceptions are the postganglionic sympathetic neurons that go to sweat glands, which employ acetylcholine as their transmitter.

Epinephrine is the major transmitter released by the adrenal medulla. (The adrenal medulla also releases some norepinephrine.)

Much of what follows in this chapter is based on the information summarized in Figure 13-4. Accordingly, I strongly urge you to learn (memorize) this information now.

INTRODUCTION TO RECEPTORS OF THE PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system works through several different types of receptors. Understanding these receptors is central to understanding peripheral nervous system pharmacology. All effort that you invest in learning about these receptors now will be richly rewarded as we discuss peripheral nervous system drugs in the chapters to come.

Primary Receptor Types: Cholinergic Receptors and Adrenergic Receptors

There are two basic categories of receptors associated with the peripheral nervous system: *cholinergic receptors* and *adrenergic receptors*. Cholinergic receptors are defined as receptors that mediate responses to acetylcholine. These receptors mediate responses at all junctions where acetylcholine is the transmitter. Adrenergic receptors are defined as receptors that mediate responses to epinephrine (adrenaline) and norepinephrine. These receptors mediate responses at all junctions where norepinephrine or epinephrine is the transmitter.

Subtypes of Cholinergic and Adrenergic Receptors

Not all cholinergic receptors are the same; likewise, not all adrenergic receptors are the same. For each of these two major receptor classes there are receptor subtypes. There are three major subtypes of cholinergic receptors, referred to as nicotinic***N***, nicotinic***M***, and muscarinic.* There are four major subtypes of adrenergic receptors, referred to as alpha***1***, alpha***2***, beta***1***, and beta***2***.

In addition to the four major subtypes of adrenergic receptors, there is another adrenergic receptor type, referred to as the *dopamine* receptor. Although dopamine receptors are classified as adrenergic, these receptors do not re-

spond to epinephrine or norepinephrine. Rather, they respond only to dopamine, a neurotransmitter found primarily in the central nervous system.

* Evidence gathered over the last decade indicates that muscarinic receptors, like nicotinic receptors, come in subtypes. Five have been identified. Of these, only three—designated M*1*, M*2*, and M*3*—have clearly identified functions. At this time, practically all drugs that affect muscarinic receptors are nonselective. Accordingly, since our understanding of these receptors is limited, and since drugs that can selectively alter their function are few, we will not discuss muscarinic receptor subtypes further in this chapter. However, we will discuss them in Chapter 14, in the context of drugs for overactive bladder, one of which is highly selective for M*3* receptors.

EXPLORING THE CONCEPT OF RECEPTOR SUBTYPES

The concept of receptor subtypes is important and potentially confusing. In this section we discuss what a receptor subtype is and why receptor subtypes matter.

What Do We Mean by the Term *Receptor Subtype?*

Receptors that respond to the same transmitter but nonetheless are different from one another would be called receptor subtypes. For example, peripheral receptors that respond to acetylcholine can be found (1) in ganglia of the autonomic nervous system, (2) at neuromuscular junctions, and (3) on organs regulated by the parasympathetic nervous system. However, even though all of these receptors can be activated by acetylcholine, there is clear evidence that the receptors at these three sites are, in fact, different from one another. Hence, although all of these receptors belong to the same major receptor category (cholinergic), they are sufficiently different as to constitute distinct receptor subtypes.

How Do We Know That Receptor Subtypes Exist?

Historically, our knowledge of receptor subtypes came from observing responses to drugs. In fact, were it not for drugs, receptor subtypes might never have been discovered.

The data in Table 13-1 illustrate the types of drug responses that led to the realization that receptor subtypes exist. These data summarize the results of

an experiment designed to study the effects of a natural transmitter (acetylcholine) and a series of drugs (nicotine, muscarine, *d*-tubocurarine, and atropine) on two tissues: skeletal muscle and ciliary muscle. (The ciliary muscle is the muscle responsible for focusing the eye for near vision.) As these data indicate, although skeletal muscle and ciliary muscle both contract in response to acetylcholine, these tissues differ in their responses to drugs. In the discussion below, we examine the selective responses of these tissues to drugs and see how those responses reveal the existence of receptor subtypes.

	Response	
Drug	**Skeletal Muscle**	**Ciliary Muscle**
Acetylcholine	Contraction	Contraction
Nicotine	Contraction	No response
Muscarine	No response	Contraction
Acetylcholine		
After *d*-tubocurarine	No response	Contraction
After atropine	Contraction	No response

TABLE 13-1 Responses of Skeletal Muscle and Ciliary Muscle to a Series of Drugs

At synapses on skeletal muscle and ciliary muscle, acetylcholine is the transmitter employed by neurons to elicit contraction. Because both types of muscle respond to acetylcholine, it is safe to conclude that both muscles have receptors for this substance. Because acetylcholine is the natural transmitter for these receptors, we would classify these receptors as *cholinergic*.

What do the effects of nicotine on skeletal muscle and ciliary muscle suggest? The effects of nicotine on these muscles suggest four possible conclusions: (1) Because skeletal muscle contracts when nicotine is applied, we can conclude that skeletal muscle has receptors at which nicotine can act. (2) Because ciliary muscle does *not* respond to nicotine, we can tentatively conclude that ciliary

muscle does not have receptors for nicotine. (3) Because nicotine mimics the effects of acetylcholine on skeletal muscle, we can conclude that nicotine may act at the same receptors on skeletal muscle as does acetylcholine. (4) Because both types of muscle have receptors for acetylcholine, and because nicotine appears to act only at the acetylcholine receptors on skeletal muscle, we can tentatively conclude that the acetylcholine receptors on skeletal muscle are different from the acetylcholine receptors on ciliary muscle.

What do the responses to muscarine suggest? The conclusions that can be drawn regarding responses to muscarine are exactly parallel to those drawn for nicotine. These conclusions are: (1) ciliary muscle has receptors that respond to muscarine, (2) skeletal muscle may not have receptors for muscarine, (3) muscarine may be acting at the same receptors on ciliary muscle as does acetylcholine, and (4) the receptors for acetylcholine on ciliary muscle may be different from the receptors for acetylcholine on skeletal muscle.

The responses of skeletal muscle and ciliary muscle to nicotine and muscarine suggest, but do not prove, that the cholinergic receptors on these two tissues are different. However, the responses of these two tissues to d-*tubocurarine* and *atropine,* both of which are receptor *blocking agents,* eliminate any doubts as to the presence of cholinergic receptor subtypes. When both types of muscle are pretreated with *d*-tubocurarine and then exposed to acetylcholine, the response to acetylcholine is blocked—but only in skeletal muscle. Tubocurarine pretreatment does not reduce the ability of acetylcholine to stimulate ciliary muscle. Conversely, pretreatment with atropine selectively blocks the response to acetylcholine in ciliary muscle—but atropine does nothing to prevent acetylcholine from stimulating receptors on skeletal muscle. Because tubocurarine can selectively block cholinergic receptors in skeletal muscle, whereas atropine can selectively block cholinergic receptors in ciliary muscle, we can conclude with certainty that the receptors for acetylcholine in these two types of muscle must be different.

The data just discussed illustrate the essential role of drugs in revealing the presence of receptor subtypes. If acetylcholine were the only probe that we had, all that we would have been able to observe is that both skeletal muscle and ciliary muscle can respond to this agent. This simple observation would provide no basis for suspecting that the receptors for acetylcholine in these

two tissues were different. It is only through the use of selectively acting drugs that the presence of receptor subtypes was initially revealed.

Today, the technology for identifying receptors and their subtypes is extremely sophisticated—not that studies like the one just discussed are no longer of value. In addition to performing traditional drug-based studies, scientists are now cloning receptors using DNA hybridization technology. As you can imagine, this allows us to understand receptors in ways that were unthinkable in the past.*

* In addition to revealing exciting new information about receptors previously identified, this spiffy technology is so powerful that new receptors and receptor subtypes are being discovered at a dizzying rate. Which means, of course, that students in the future will have many more receptors to contend with than you do. So, when it seems like you're working awfully hard to master the information on receptors in this chapter and the ones that follow, look on the bright side—you could be studying pharmacology 10 years from now.

How Can Drugs Be More Selective Than Natural Transmitters at Receptor Subtypes?

Drugs achieve their selectivity for receptor subtypes by having structures that are different from those of natural transmitters. The relationship between structure and receptor selectivity is illustrated in Figure 13-5. In this figure, cartoon drawings are used to represent drugs (nicotine and muscarine), receptor subtypes (nicotinic and muscarinic), and acetylcholine (the natural transmitter at nicotinic and muscarinic receptors). From the structures shown, we can easily imagine how acetylcholine is able to interact with both kinds of receptor subtypes, whereas nicotine and muscarine can interact only with the receptor subtypes whose structure is complementary to their own. By synthesizing chemicals that are structurally related to natural transmitters, pharmaceutical chemists have been able to produce drugs that are more selective for specific receptor subtypes than are the natural transmitters that act at those sites.

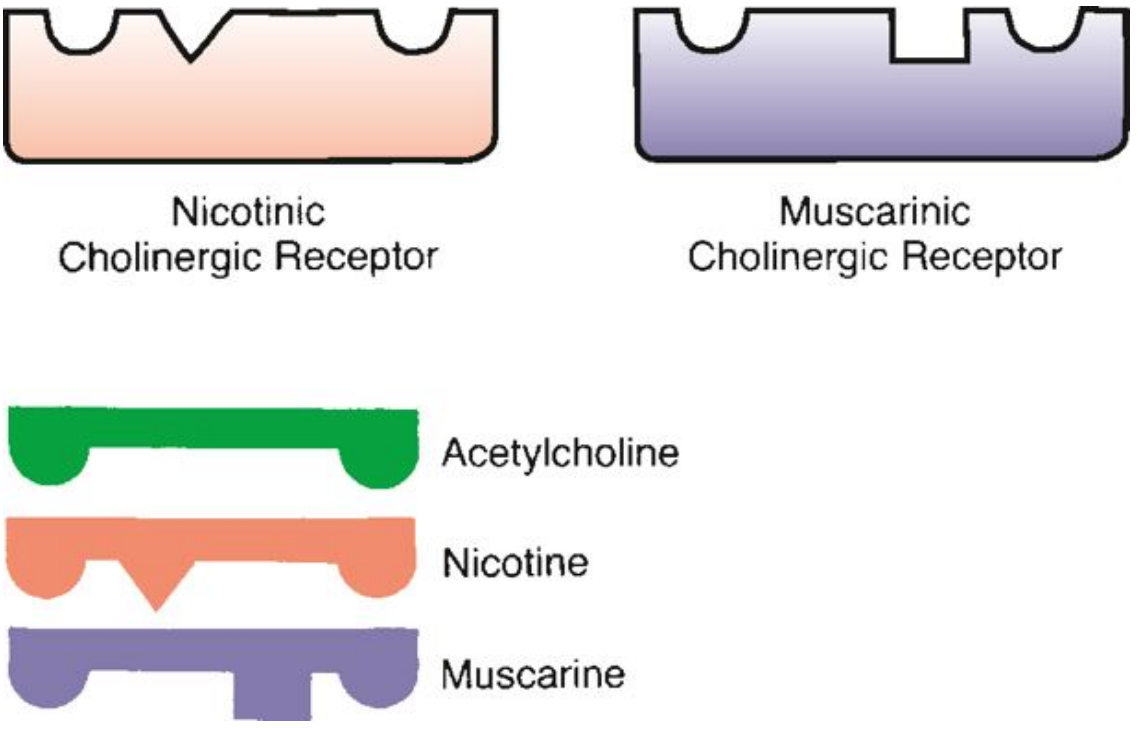


Figure 13-5 Drug structure and receptor selectivity. These cartoon figures illustrate the relationship between structure and receptor selectivity. The structure of acetylcholine allows this transmitter to interact with both receptor subtypes. In contrast, because of their unique structures, nicotine and muscarine are selective for the cholinergic receptor subtypes whose structure complements their own.

Why Do Receptor Subtypes Exist?

It is not unreasonable for us to wonder why Mother Nature bothered to create more than one type of receptor for any given transmitter. Unfortunately, a definitive answer to that question will have to come from Mother Nature herself. That is, the physiologic benefits of having multiple receptor subtypes for the same transmitter are not immediately obvious. In fact, as noted earlier, were it not for drugs, we probably wouldn't know that receptor subtypes existed at all.

Do Receptor Subtypes Matter to Us? You Bet!

Although receptor subtypes are of uncertain physiologic relevance, from the viewpoint of therapeutics, receptor subtypes are invaluable. The presence of receptor subtypes makes possible a dramatic increase in drug selectivity. For example, thanks to the existence of subtypes of cholinergic receptors (and the development of drugs selective for those receptor subtypes), it is possible to influence the activity of certain cholinergic receptors (eg, receptors of the neuromuscular junction) without altering the activity of all other cholinergic receptors (eg, the cholinergic receptors found in all autonomic ganglia and all target organs of the parasympathetic nervous system). Were it not for the existence of receptor subtypes, a drug that acted on cholinergic receptors at one site would alter the activity of cholinergic receptors at all other sites. Clearly, the existence of receptor subtypes for a particular transmitter makes possible drug actions that are much more selective than could be achieved if all of the receptors for that transmitter were the same.

LOCATIONS OF RECEPTOR SUBTYPES

Since many of the drugs discussed in the following chapters are selective for specific receptor subtypes, knowledge of the sites at which specific receptor subtypes are located will help us predict which organs a drug will affect. Accordingly, in laying our foundation for studying peripheral nervous system drugs, it is important to learn the sites at which the subtypes of adrenergic and cholinergic receptors are located. This information is summarized in Figure 13-6. You will find it very helpful to master the contents of this figure before proceeding much further. (In the interest of minimizing confusion, subtypes of adrenergic receptors in Figure 13-6 are listed simply as alpha and beta rather than as alpha***1***, alpha***2***, beta***1***, and beta***2***. The locations of all four subtypes of adrenergic receptors are discussed in the section that follows.)

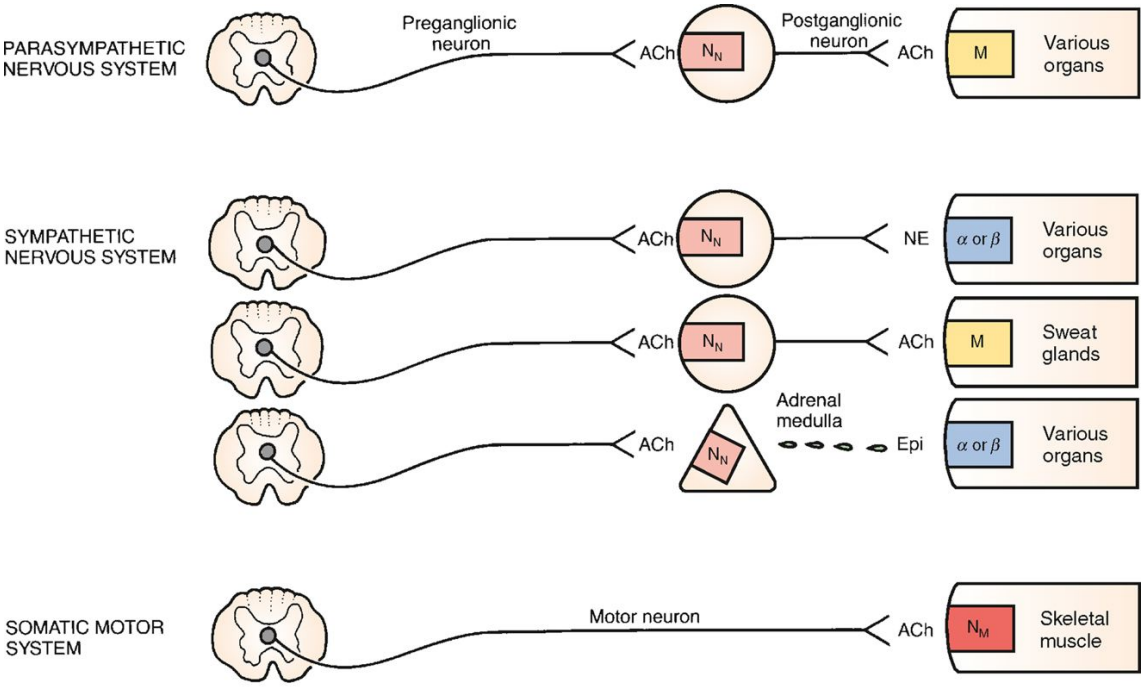


Figure 13-6 Locations of cholinergic and adrenergic receptor subtypes. Summary:1.NicotinicN receptors are located on the cell bodies of all postganglionic neurons of the parasympathetic and sympathetic nervous systems. NicotinicN receptors are also located on cells of the adrenal medulla.2.NicotinicM receptors are located on skeletal muscle.3.Muscarinic receptors are located on all organs regulated by the parasympathetic nervous system (ie, organs innervated by postganglionic parasympathetic nerves). Muscarinic receptors are also located on sweat glands.4.Adrenergic receptors—alpha, beta, or both—are located on all organs (except sweat glands) regulated by the sympathetic nervous system (ie, organs innervated by postganglionic sympathetic nerves). Adrenergic receptors are also located on organs regulated by epinephrine released from the adrenal medulla.

FUNCTIONS OF CHOLINERGIC AND ADRENERGIC RECEPTOR SUBTYPES

Knowledge of receptor function is an absolute requirement for understanding peripheral nervous system drugs. By knowing the receptors at which a drug acts, and by knowing what those receptors do, we can predict the major effects of any peripheral nervous system drug.

Tables 13-2 and 13-3 summarize the pharmacologically relevant functions of peripheral nervous system receptors. Table 13-2 summarizes responses elicited by activation of cholinergic receptor subtypes. Table 13-3 summarizes responses to activation of adrenergic receptor subtypes. Before attempting to study specific peripheral nervous system drugs, you should master (memorize) the contents of the appropriate table. Table 13-2 should be mastered before studying cholinergic drugs (Chapters 14, 15, and 16). Table 13-3 should be mastered before studying adrenergic drugs (Chapters 17, 18, and 19). If you study these tables in preparation for learning about peripheral nervous system drugs, you will find the process of learning the pharmacology relatively simple (and perhaps even enjoyable). Conversely, if you attempt to study the pharmacology without first mastering the appropriate table, you are likely to meet with frustration.

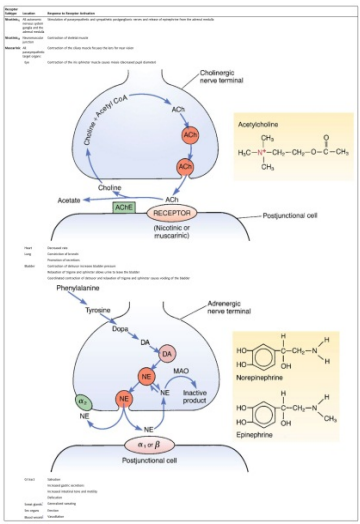


TABLE 13-2 Functions of Peripheral Cholinergic Receptor Subtypes

* Although sweating is due primarily to stimulation of muscarinic receptors by acetylcholine, the nerves that supply acetylcholine to sweat glands belong to the sympathetic nervous system rather than the parasympathetic nervous system.

† Cholinergic receptors on blood vessels are not associated with the nervous system.

Functions of Cholinergic Receptor Subtypes

Table 13-2 summarizes the pharmacologically relevant responses to activation of the three major subtypes of cholinergic receptors: nicotinic***N***, nicotinic***M***, and muscarinic. Please commit the information in this table to memory.

We can group responses to cholinergic receptor activation into three major categories based on the subtype of receptor involved:

- Activation of *nicotinic**N*** (neuronal) receptors promotes *ganglionic transmission* at all ganglia of the sympathetic and parasympathetic nervous systems. In addition, activation of nicotinic***N*** receptors promotes *release of epinephrine from the adrenal medulla*.
- Activation of *nicotinic**M*** (muscle) receptors causes *contraction of skeletal muscle*.
- Activation of *muscarinic* receptors, which are located on target organs of the parasympathetic nervous system, elicits an appropriate response from the organ involved. Specifically, muscarinic activation causes (1) increased glandular secretions (from pulmonary, gastric, intestinal, and sweat glands); (2) contraction of smooth muscle in the bronchi and GI tract; (3) slowing of heart rate; (4) contraction of the sphincter muscle of the iris, resulting in miosis (reduction in pupillary diameter); (5) contraction of the ciliary muscle of the eye, causing the lens to focus for near vision; (6) dilation of blood vessels; and (7) voiding of the urinary bladder (by causing contraction of the detrusor muscle [which forms the bladder wall] and relaxation of the trigone and sphincter muscles [which block the bladder neck when contracted]).

Muscarinic cholinergic receptors on blood vessels require additional comment. These receptors are not associated with the nervous system in any way. That is, no nerves terminate at vascular muscarinic receptors. It is not at all clear as to how, or even if, these receptors are activated physiologically. However, regardless of their physiologic relevance, the cholinergic receptors on blood vessels do have *pharmacologic* significance. Why? Because drugs that

are able to activate these receptors cause vasodilation, which in turn causes blood pressure to fall.

Functions of Adrenergic Receptor Subtypes

Adrenergic receptor subtypes and their functions are summarized in Table 13-3. You should commit this information to memory.

Alpha*1* Receptors

Alpha*1* receptors are located in the eyes, blood vessels, male sex organs, prostatic capsule, and bladder (trigone and sphincter).

Ocular alpha*1* receptors are present on the *radial muscle* of the iris. Activation of these receptors leads to mydriasis (dilation of the pupil). As depicted in Table 13-3, the fibers of the radial muscle are arranged like the spokes of a wheel. Because of this configuration, contraction of the radial muscle causes the pupil to enlarge. (If you have difficulty remembering that *mydriasis* means pupillary enlargement, whereas *miosis* means pupillary constriction, just remember that mydriasis [enlargement] is a bigger word than miosis.)

Activation of alpha*1* receptors in *blood vessels* produces *vasoconstriction*. Alpha*1* receptors are present on veins and on arterioles in many capillary beds.

Activation of alpha*1* receptors in the *sexual apparatus of males* causes *ejaculation*.

Activation of alpha*1* receptors in smooth muscle of the *bladder* (trigone and sphincter) and *prostatic capsule* causes *contraction*.

Alpha*2* Receptors

Alpha*2* receptors of the peripheral nervous system are located on *nerve terminals* (see Table 13-3) and not on the organs innervated by the autonomic nervous system. Because alpha*2* receptors are located on nerve terminals, these receptors are referred to as *presynaptic* or *prejunctional*. The function of these receptors is to regulate transmitter release. As depicted in Table 13-3, norepinephrine can bind to alpha*2* receptors located on the same neuron from which the norepinephrine was released. The consequence of this norepinephrine-receptor interaction is suppression of further norepinephrine release. Hence, presynaptic alpha*2* receptors can help reduce transmitter

release when too much transmitter has accumulated in the synaptic gap. Drug effects resulting from activation of *peripheral* alpha*2* receptors are of minimal clinical significance.

Alpha*2* receptors are also present in the central nervous system. In contrast to peripheral alpha*2* receptors, central alpha*2* receptors are therapeutically relevant. We will consider these receptors in later chapters.

Beta*1* Receptors

Beta*1* receptors are located in the heart and the kidney. *Cardiac* beta*1* receptors have great therapeutic significance. Activation of these receptors increases *heart rate, force of contraction*, and *velocity of impulse conduction through the atrioventricular (AV) node*.

Activation of beta*1* receptors in the *kidney* causes release of *renin* into the blood. Since renin promotes synthesis of angiotensin, a powerful vasoconstrictor, activation of renal beta*1* receptors is a means by which the nervous system helps elevate blood pressure. (The role of renin in the regulation of blood pressure is discussed in depth in Chapter 43.)

Beta*2* Receptors

Beta*2* receptors mediate several important processes. Activation of beta*2* receptors in the lung leads to *bronchial dilation*. Activation of beta*2* receptors in the uterus causes *relaxation of uterine smooth muscle*. Activation of beta*2* receptors in arterioles of the heart, lungs, and skeletal muscles causes *vasodilation* (an effect opposite to that of alpha*1* activation). Activation of beta*2* receptors in the liver and skeletal muscle promotes *glycogenolysis* (breakdown of glycogen into glucose), thereby increasing blood levels of glucose. In addition, activation of beta*2* receptors in skeletal muscle enhances contraction.

Dopamine Receptors

In the periphery, the only dopamine receptors of clinical significance are located in the vasculature of the kidney. Activation of these receptors *dilates renal blood vessels,* thereby enhancing renal perfusion.

In the central nervous system, receptors for dopamine are of great therapeutic significance. The functions of these receptors are discussed in Chapter 21

(Drugs for Parkinson's Disease) and Chapter 31 (Antipsychotic Agents and Their Use in Schizophrenia).

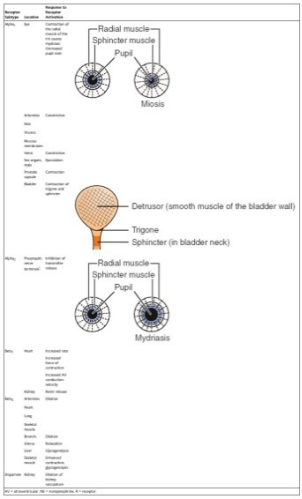


TABLE 13-3 Functions of Peripheral Adrenergic Receptor Subtypes

* Alpha*2* receptors in the central nervous system are postsynaptic.

RECEPTOR SPECIFICITY OF THE ADRENERGIC TRANSMITTERS

The receptor specificity of adrenergic transmitters is more complex than the receptor specificity of acetylcholine. Whereas acetylcholine can activate all three subtypes of cholinergic receptors, not every adrenergic transmitter (epinephrine, norepinephrine, dopamine) can interact with each of the five subtypes of adrenergic receptors.

Receptor specificity of adrenergic transmitters is as follows: (1) *epinephrine* can activate all alpha and beta receptors, but not dopamine receptors; (2) *norepinephrine* can activate alpha*1*, alpha*2*, and beta*1* receptors, but not beta*2* or dopamine receptors; and (3) *dopamine* can activate alpha*1*, beta*1*, and dopamine receptors. (Note that dopamine itself is the only transmitter capable of activating dopamine receptors.) Receptor specificity of the adrenergic transmitters is summarized in Table 13-4.

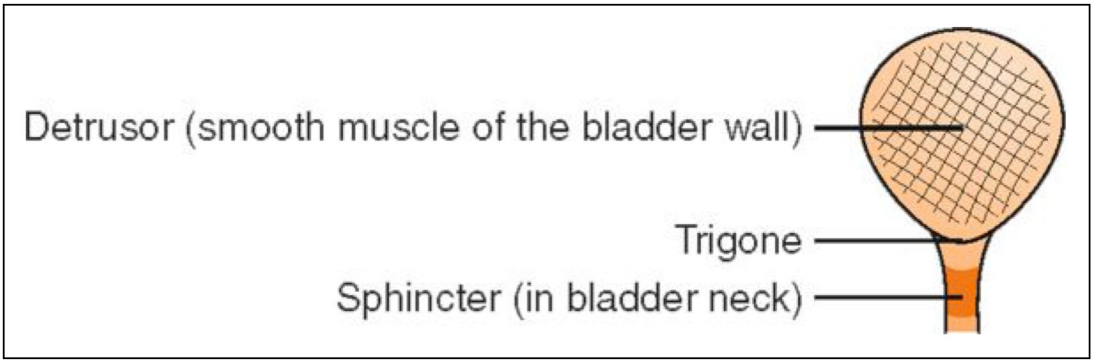


TABLE 13-4 Receptor Specificity of Adrenergic Transmitters*

* Arrows indicate the range of receptors that the transmitters can activate.

Knowing that epinephrine is the only transmitter that acts at beta*2* receptors can serve as an aid to remembering the functions of this receptor subtype. Recall that epinephrine is released from the adrenal medulla—not from neurons—and that the function of epinephrine is to prepare the body for fight or flight. Accordingly, since epinephrine is the only transmitter that activates beta*2* receptors, and since epinephrine is released only in preparation for fight or flight, times of fight or flight will be the only occasions on which beta*2* receptors will undergo significant physiologic activation. As it turns out, the physiologic changes elicited by beta*2* activation are precisely those needed for success in the fight-or-flight response. Specifically, activation of beta*2* receptors will (1) dilate blood vessels in the heart, lungs, and skeletal muscles, thereby increasing blood flow to these organs; (2) dilate the bronchi, thereby increasing oxygenation; (3) increase glycogenolysis, thereby increasing available energy; and (4) relax uterine smooth muscle, thereby preventing delivery (a process that would be inconvenient for a pregnant woman preparing to fight or flee). Accordingly, if you think of the physiologic requirements for success during fight or flight, you will have a good picture of the responses that beta*2* activation can cause.

TRANSMITTER LIFE CYCLES

In this section we consider the life cycles of acetylcholine, norepinephrine, and epinephrine. Because a number of drugs produce their effects by interfering with specific phases of the transmitters' life cycles, knowledge of these cycles helps us understand drug actions.

Life Cycle of Acetylcholine

The life cycle of acetylcholine (ACh) is depicted in Figure 13-7. The cycle begins with synthesis of ACh from two precursors: choline and acetylcoenzyme A. Following synthesis, ACh is stored in vesicles and later released in response to an action potential. Following release, ACh binds to receptors (nicotinic***N***, nicotinic***M***, or muscarinic) located on the postjunctional cell. Upon dissociating from its receptors, ACh is destroyed almost instantaneously by *acetylcholinesterase* (AChE), an enzyme present in abundance on the surface of the postjunctional cell. AChE degrades ACh into two inactive products: acetate and choline. Uptake of choline into the cholinergic nerve terminal completes the life cycle of ACh. Note that an inactive substance (choline), and not the active transmitter (acetylcholine), is taken back up for reuse.

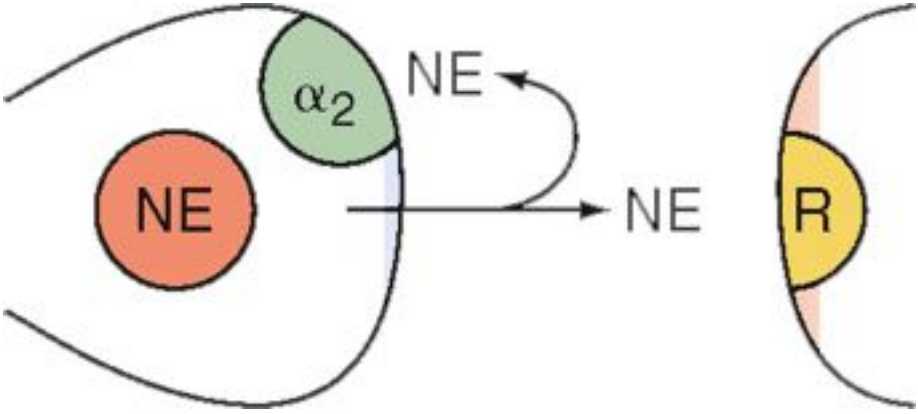


Figure 13-7 Life cycle of acetylcholine. Note that transmission is terminated by enzymatic degradation of ACh and not by uptake of intact ACh back into the nerve terminal. (Acetyl CoA = acetylcoenzyme A, ACh = acetylcholine, AChE = acetylcholinesterase.)

Therapeutic and toxic agents can interfere with the ACh life cycle at several points. Botulinum toxin inhibits ACh release. A number of medicines and poisons act at cholinergic receptors to mimic or block the actions of ACh. Several therapeutic and toxic agents act by inhibiting AChE, thereby causing ACh to accumulate in the junctional gap.

Life Cycle of Norepinephrine

The life cycle of norepinephrine is depicted in Figure 13-8. As indicated, the cycle begins with synthesis of norepinephrine from a series of precursors. The final step of synthesis takes place within vesicles, where norepinephrine is then stored prior to release. Following release, norepinephrine binds to adrenergic receptors. As shown in the figure, norepinephrine can interact with *postsynaptic* alpha*1* and beta receptors and with *presynaptic* alpha*2* receptors. Transmission is terminated by *reuptake* of norepinephrine back into the nerve terminal. (Note that the termination process for norepinephrine differs from that for acetylcholine, whose effects are terminated by enzymatic degradation rather than reuptake.) Following reuptake, norepinephrine can undergo one of two fates: (1) uptake into vesicles for reuse or (2) inactivation by monoamine oxidase (MAO), an enzyme found in the nerve terminal.

Practically every step in the life cycle of norepinephrine can be altered by therapeutic agents. We have drugs that alter the synthesis, storage, and release of norepinephrine; we have drugs that act at adrenergic receptors to mimic or block the effects of norepinephrine; we have drugs, such as cocaine and tricyclic antidepressants, that inhibit the reuptake of norepinephrine (and thereby intensify transmission); and we have drugs that inhibit the breakdown of norepinephrine by MAO, causing an increase in the amount of transmitter available for release.

	Adrenergic Receptor Subtype				
Transmitter	$Alpha_1$	$Alpha_2$	$Beta_1$	$Beta_2$	Dopamine
Epinephrine	←	—	—	→	
Norepinephrine	←	—	→		
Dopamine	↔		↔		↔

Figure 13-8 Life cycle of norepinephrine. Note that transmission is terminated by reuptake of NE into the nerve terminal and not by enzymatic degradation. Note also the structural similarity between epinephrine and norepinephrine. (DA = dopamine, MAO = monoamine oxidase, NE = norepinephrine.)

Life Cycle of Epinephrine

The life cycle of epinephrine is much like that of norepinephrine—although there are significant differences. The cycle begins with synthesis of epinephrine within chromaffin cells of the adrenal medulla. These cells produce epinephrine by first making norepinephrine, which is then converted enzymatically to epinephrine. (Because sympathetic neurons lack the enzyme needed to convert norepinephrine to epinephrine, epinephrine is not produced in sympathetic nerves.) Following synthesis, epinephrine is stored in vesicles to await release. Once released, epinephrine travels via the bloodstream to target organs throughout the body. Termination of epinephrine's actions is accomplished primarily by hepatic metabolism, and not by uptake into nerves.

I know it's a lot of work, but there's really no way around it: You've got to incorporate this information into your personal database (ie, ya gotta memorize it).

KEY POINTS

- The peripheral nervous system has two major divisions: the autonomic nervous system and the somatic motor system.
- The autonomic nervous system has two major divisions: the sympathetic nervous system and the parasympathetic nervous system.
- The parasympathetic nervous system has several functions relevant to pharmacology: it slows heart rate, increases gastric secretion, empties the bladder and bowel, focuses the eye for near vision, constricts the pupil, and contracts bronchial smooth muscle.
- Principal functions of the sympathetic nervous system are regulation of the cardiovascular system, regulation of body temperature, and implementation of the fight-or-flight response.
- In some organs (eg, the heart), sympathetic and parasympathetic nerves have opposing effects. In other organs (eg, male sex organs), the sympathetic and parasympathetic systems have complementary effects. And in still other

organs (notably blood vessels), function is regulated by only one branch of the autonomic nervous system.

- The baroreceptor reflex helps regulate blood pressure.
- In most organs regulated by the autonomic nervous system, the parasympathetic nervous system provides the dominant tone.
- In blood vessels, the sympathetic nervous system provides the dominant tone.
- Pathways from the spinal cord to organs under sympathetic and parasympathetic control consist of two neurons: a preganglionic neuron and a postganglionic neuron.
- The adrenal medulla is the functional equivalent of a postganglionic sympathetic neuron.
- Somatic motor pathways from the spinal cord to skeletal muscles have only one neuron.
- The peripheral nervous system employs three transmitters: acetylcholine, norepinephrine, and epinephrine.
- Acetylcholine is the transmitter released by all preganglionic neurons of the sympathetic nervous system, all preganglionic neurons of the parasympathetic nervous system, all postganglionic neurons of the parasympathetic nervous system, postganglionic neurons of the sympathetic nervous system that go to sweat glands, and all motor neurons.
- Norepinephrine is the transmitter released by all postganglionic neurons of the sympathetic nervous system, except those that go to sweat glands.
- Epinephrine is the major transmitter released by the adrenal medulla.
- There are three major subtypes of cholinergic receptors: nicotinic***N***, nicotinic***M***, and muscarinic.
- There are four major subtypes of adrenergic receptors: alpha***1***, alpha***2***, beta***1***, and beta***2***.
- Although receptor subtypes are of uncertain physiologic significance, they are of great pharmacologic significance.

- Activation of nicotinic***N*** receptors promotes transmission at all autonomic ganglia, and promotes release of epinephrine from the adrenal medulla.
- Activation of nicotinic***M*** receptors causes contraction of skeletal muscle.
- Activation of muscarinic receptors increases glandular secretion (from pulmonary, gastric, intestinal, and sweat glands); contracts smooth muscle in the bronchi and GI tract; slows heart rate; contracts the iris sphincter; contracts the ciliary muscle (thereby focusing the lens for near vision); dilates blood vessels; and promotes bladder voiding (by contracting the bladder detrusor muscle and relaxing the trigone and sphincter).
- Activation of alpha***1*** receptors contracts the radial muscle of the eye (causing mydriasis), constricts veins and arterioles, promotes ejaculation, and contracts smooth muscle in the prostatic capsule and bladder (trigone and sphincter).
- Activation of *peripheral* alpha***2*** receptors is of minimal pharmacologic significance.
- Activation of beta***1*** receptors increases heart rate, force of myocardial contraction, and conduction velocity through the AV node, and promotes release of renin by the kidney.
- Activation of beta***2*** receptors dilates the bronchi, relaxes uterine smooth muscle, increases glycogenolysis, enhances contraction of skeletal muscle, and dilates arterioles (in the heart, lungs, and skeletal muscle).
- Activation of dopamine receptors dilates blood vessels in the kidney.
- Neurotransmission at cholinergic junctions is terminated by degradation of acetylcholine by acetylcholinesterase.
- Neurotransmission at adrenergic junctions is terminated by reuptake of intact norepinephrine into nerve terminals.
- Following reuptake, norepinephrine may be stored in vesicles for reuse or destroyed by monoamine oxidase.

Introduction to Cholinergic Drugs

The cholinergic drugs are agents that influence the activity of cholinergic receptors. Most of these drugs act directly at cholinergic receptors, where they either mimic or block the actions of acetylcholine. Some of these drugs—the cholinesterase inhibitors—influence cholinergic receptors indirectly by preventing the breakdown of acetylcholine.

The cholinergic drugs have both therapeutic and toxicologic significance. Therapeutic applications are limited but valuable. The toxicology of cholinergic drugs is extensive, encompassing such agents as nicotine, insecticides, and compounds designed for chemical warfare.

There are six categories of cholinergic drugs. These categories, along with representative agents, are summarized in Table 1. The *muscarinic agonists*, represented by bethanechol, selectively mimic the effects of acetylcholine at muscarinic receptors. The *muscarinic antagonists*, represented by atropine, selectively block the effects of acetylcholine (and other agonists) at muscarinic receptors. *Ganglionic stimulating agents*, represented by nicotine itself, selectively mimic the effects of acetylcholine at nicotinic***N*** receptors of autonomic ganglia. *Ganglionic blocking agents*, represented by mecamylamine, selectively block ganglionic nicotinic***N*** receptors. *Neuromuscular blocking agents*, represented by *d*-tubocurarine and succinylcholine, selectively block the effects of acetylcholine at nicotinic***M*** receptors at the neuromuscular junction. The *cholinesterase inhibitors*, represented by neostigmine and physostigmine, prevent the breakdown of acetylcholine by acetylcholinesterase, and thereby increase the activation of all cholinergic receptors.

Category	Representative Drugs
Muscarinic agonists	Bethanechol
Muscarinic antagonists	Atropine
Ganglionic stimulating agents	Nicotine
Ganglionic blocking agents	Mecamylamine
Neuromuscular blocking agents	*d*-Tubocurarine, succinylcholine
Cholinesterase inhibitors	Neostigmine, physostigmine

TABLE 1 Categories of Cholinergic Drugs

Table 2 is your master key to understanding the cholinergic drugs. This table lists the three subtypes of cholinergic receptors (muscarinic, nicotinic***N***, and nicotinic***M***) and indicates for each receptor type: (1) location, (2) responses to activation, (3) drugs that produce activation (agonists), and (4) drugs that prevent activation (antagonists). This information, along with the detailed information on cholinergic receptor function summarized in Table 13-2, is just about all you need to predict the actions of cholinergic drugs.

	Receptor Subtype		
	Muscarinic	**Nicotinic$_N$**	**Nicotinic$_M$**
Receptor Location	Sweat glands Blood vessels All organs regulated by the parasympathetic nervous system	All ganglia of the autonomic nervous system	Neuromuscular junctions (NMJs)
Effects of Receptor Activation	Many, including: ↓ Heart rate ↑ Gland secretion Smooth muscle contraction	Promotes ganglionic transmission	Skeletal muscle contraction
Receptor Agonists	Bethanechol	Nicotine	(Nicotine*)
	Cholinesterase inhibitors: physostigmine, neostigmine (these drugs indirectly activate all cholinergic receptors)		
Receptor Antagonists	Atropine	Mecamylamine	*d*-Tubocurarine, succinylcholine

TABLE 2 Summary of Cholinergic Drugs and Their Receptors

An example will demonstrate the combined value of Tables 2 and Table 13-2. Let's consider *bethanechol*. As indicated in Table 2, bethanechol is a selective *agonist* at *muscarinic* cholinergic receptors. Referring to Table 13-2, we see that activation of muscarinic receptors can produce the following: ocular effects (miosis and ciliary muscle contraction), slowing of heart rate, bronchial constriction, urination, glandular secretion, stimulation of the GI tract, penile erection, and vasodilation. Since bethanechol *activates* muscarinic receptors, the drug is capable of eliciting all of these responses. Hence, by knowing which receptors bethanechol activates (from Table 2), and by knowing what those re-

ceptors do (from Table 13-2), you can predict the kinds of responses you might expect bethanechol to produce.

In the chapters that follow, we will employ the approach just described. That is, for each cholinergic drug discussed, you will want to know (1) the receptors that the drug affects, (2) the normal responses to activation of those receptors, and (3) whether the drug in question increases or decreases receptor activation. All of this information is contained in Tables 2 and Table 13-2. Accordingly, if you master the information in these tables now, you will be prepared to follow discussions in succeeding chapters with relative ease—and perhaps even pleasure. In contrast, if you postpone mastery of these tables, you are likely to find it both difficult and dissatisfying to proceed.

Cholinergic Drugs

14 Muscarinic Agonists and Antagonists

The muscarinic agonists and antagonists produce their effects through direct interaction with muscarinic receptors. The muscarinic agonists cause receptor activation; the antagonists produce receptor blockade.

MUSCARINIC AGONISTS

The muscarinic agonists bind to muscarinic receptors and thereby cause receptor activation. Since nearly all muscarinic receptors are associated with the parasympathetic nervous system, responses to muscarinic agonists closely resemble those produced by stimulation of parasympathetic nerves. Accordingly, muscarinic agonists are also known as *parasympathomimetic agents*.

Bethanechol

Bethanechol [Urecholine] embodies the characteristics that typify all muscarinic agonists, and hence will serve as our prototype for the group.

Mechanism of Action

Bethanechol is a direct-acting muscarinic agonist. The drug binds reversibly to muscarinic cholinergic receptors and causes activation. At therapeutic doses, bethanechol acts selectively at muscarinic receptors, having little or no effect on nicotinic receptors, either in ganglia or in skeletal muscle.

Pharmacologic Effects

Bethanechol can elicit all of the responses typical of muscarinic receptor activation. Accordingly, we can readily predict the effects of bethanechol by knowing the information on muscarinic responses summarized in Table 13-2.

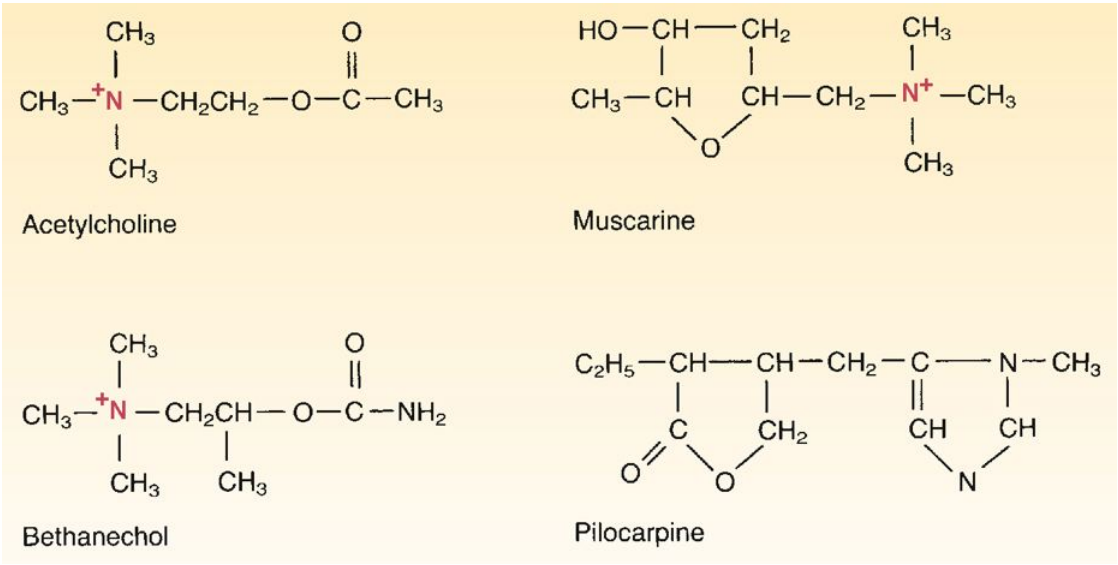


Figure 14-1 Structures of muscarinic agonists. Note that, with the exception of pilocarpine, all of these agents are quaternary ammonium compounds, and hence always carry a positive charge. Because of this charge, these compounds cross membranes poorly.

The principal structures affected by muscarinic activation are the *heart, exocrine glands, smooth muscles*, and *eye*. Muscarinic agonists act on the heart to cause bradycardia (decreased heart rate) and on exocrine glands to increase sweating, salivation, bronchial secretions, and secretion of gastric acid. In smooth muscles of the lung and GI tract, muscarinic agonists promote contraction. The result is constriction of the bronchi and increased tone and motility of GI smooth muscle. In the bladder, muscarinic activation causes *contraction* of the detrusor muscle and *relaxation* of the trigone and sphincter; the result is bladder emptying. In vascular smooth muscle, these drugs cause relaxation; the resultant vasodilation can produce hypotension. Activation of muscarinic receptors in the eye has two effects: (1) miosis (pupillary constriction); and (2) contraction of the ciliary muscle, resulting in accommodation for near vision. (The ciliary muscle, which is attached to the lens, focuses the eye for near vision by altering lens curvature.)

Pharmacokinetics

Bethanechol is available for oral administration only. (A subQ formulation, available in the past, has been withdrawn.) With oral use, effects begin in 30 to 60 minutes and persist about 1 hour. Because bethanechol is a quaternary ammonium compound (Fig. 14-1), the drug crosses membranes poorly. As a result, only a small fraction of each dose is absorbed.

Dosage of Atropine	Response Produced
Low Doses	Salivary glands—decreased secretion
	Sweat glands—decreased secretion
	Bronchial glands—decreased secretion
	Heart—increased rate
	Eye—mydriasis, blurred vision
	Urinary tract—interference with voiding
	Intestine—decreased tone and motility
	Lung—dilation of bronchi
High Doses	Stomach—decreased acid secretion
Note that doses of atropine that are high enough to decrease gastric acid secretion or dilate the bronchi will also affect all other structures under muscarinic control. As a result, atropine and most other muscarinic antagonists are not very desirable for treating peptic ulcer disease or asthma.	

TABLE 14-1 Relationship Between Dosage and Responses to Atropine

Therapeutic Uses

Although bethanechol can produce a broad spectrum of pharmacologic effects, its clinical applications are limited. The principal indication is urinary retention.

Urinary Retention.

Bethanechol relieves urinary retention by activating muscarinic receptors of the urinary tract. Muscarinic activation relaxes the trigone and sphincter muscles and increases voiding pressure (by contracting the detrusor muscle, which composes the bladder wall). Bethanechol is used to treat urinary retention in postoperative and postpartum patients. The drug should not be used to treat urinary retention caused by physical obstruction of the urinary tract. Why? Because increased pressure in the tract in the presence of blockage could cause injury. When patients are treated with bethanechol, a bedpan or urinal should be readily available.

Gastrointestinal Uses.

Bethanechol has been used on an investigational basis to treat *gastroesophageal reflux*. Benefits may result from increased esophageal motility and increased pressure in the lower esophageal sphincter.

Bethanechol can help treat disorders associated with GI paralysis. Benefits derive from increased tone and motility of GI smooth muscle. Specific applications are *adynamic ileus, gastric atony*, and *postoperative abdominal distention*. Bethanechol should not be given if physical obstruction of the GI tract is present. Why? Because, in the presence of blockage, increased propulsive contractions might result in damage to the intestinal wall.

Adverse Effects

In theory, bethanechol can produce the full range of muscarinic responses as side effects. However, with oral dosing, side effects are relatively rare. (When the drug was available for subQ administration, side effects were much more common.)

Cardiovascular System.

Bethanechol can cause *hypotension* (secondary to vasodilation) and *bradycardia*. Accordingly, the drug is contraindicated for patients with low blood pressure or low cardiac output.

Alimentary System.

At usual therapeutic doses, bethanechol can cause *excessive salivation, increased secretion of gastric acid, abdominal cramps*, and *diarrhea*. Higher doses can cause involuntary defecation. Bethanechol is contraindicated in patients with gastric ulcers, because stimulation of acid secretion could intensify gastric erosion, causing bleeding and possibly perforation. The drug is also contraindicated for patients with *intestinal obstruction* and for those recovering from recent *surgery of the bowel*. In both cases, the ability of bethanechol to increase the tone and motility of intestinal smooth muscle could result in rupture of the bowel wall.

Urinary Tract.

Because of its ability to contract the bladder detrusor, and thereby *increase pressure within the urinary tract*, bethanechol can be hazardous to patients with urinary tract obstruction or weakness of the bladder wall. In both groups, elevation of pressure within the urinary tract could rupture the bladder. Accordingly, bethanechol is contraindicated for patients with either disorder.

Exacerbation of Asthma.

By activating muscarinic receptors in the lungs, bethanechol can cause bronchoconstriction. Accordingly, the drug is contraindicated for patients with latent or active asthma.

Dysrhythmias in Hyperthyroid Patients.

Bethanechol can cause dysrhythmias in hyperthyroid patients. Accordingly, the drug is contraindicated for these people. The mechanism of dysrhythmia induction is explained below.

If given to hyperthyroid patients, bethanechol may increase heart rate to the point of initiating a dysrhythmia. (Note that increased heart rate is opposite to the effect that muscarinic agonists have in most patients.) When hyperthyroid patients are given bethanechol, their initial cardiovascular responses are like

those of anyone else: bradycardia and hypotension. In reaction to hypotension, the baroreceptor reflex attempts to return blood pressure to normal. Part of this reflex involves the release of norepinephrine from sympathetic nerves that regulate heart rate. In patients who are *not* hyperthyroid, norepinephrine release serves to increase cardiac output, and thereby helps restore blood pressure. However, in hyperthyroid patients, norepinephrine can induce cardiac dysrhythmias. The reason for this unusual response is that, in hyperthyroid patients, the heart is exquisitely sensitive to the effects of norepinephrine; hence, relatively small amounts can cause stimulation sufficient to elicit a dysrhythmia.

Preparations, Dosage, and Administration

Bethanechol [Urecholine] is available in tablets (5, 10, 25, and 50 mg) for oral therapy. (Bethanechol solution for subQ therapy has been withdrawn.) For adults, the oral dosage ranges from 10 to 50 mg given 3 to 4 times a day. Administration with meals can cause nausea and vomiting, and hence dosing should be done 1 hour before meals or 2 hours after.

Other Muscarinic Agonists

Cevimeline

Actions and Uses.

Cevimeline [Evoxac] is a derivative of acetylcholine with actions much like those of bethanechol. The drug is indicated for relief of xerostomia (dry mouth) in patients with Sjögren's syndrome, an autoimmune disorder characterized by xerostomia, keratoconjunctivitis sicca (inflammation of the cornea and conjunctiva), and connective tissue disease (typically rheumatoid arthritis). Dry mouth results from extensive damage to salivary glands. Left untreated, dry mouth can lead to multiple complications, including periodontal disease, dental caries, altered taste, oral ulcers and candidiasis, and difficulty eating and speaking. Cevimeline relieves dry mouth by activating muscarinic receptors on residual healthy tissue in salivary glands, thereby promoting salivation. The drug also increases tear production, which can help relieve keratoconjunctivitis. Because it stimulates salivation, cevimeline may also benefit

patients with xerostomia induced by radiation therapy for head and neck cancer, although the drug is not approved for this use.

Adverse Effects.

Adverse effects result from activating muscarinic receptors, and hence are similar to those of bethanechol. The most common effects are excessive *sweating* (18.9%), *nausea* (13.8%), *rhinitis* (11.2%), and *diarrhea* (10.3%). To compensate for fluid loss caused by sweating and diarrhea, patients should increase fluid intake. Like bethanechol, cevimeline promotes *miosis* (constriction of the pupil) and may also *blur vision*. Both actions can make driving dangerous, especially at night.

Activation of cardiac muscarinic receptors can reduce heart rate and slow cardiac conduction. Accordingly, cevimeline should be used with caution in patients with a history of heart disease.

Because muscarinic activation increases airway resistance, cevimeline is contraindicated for patients with uncontrolled asthma and should be used with caution in patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease.

Because miosis can exacerbate symptoms of both narrow-angle glaucoma and iritis (inflammation of the iris), cevimeline is contraindicated for people with these disorders.

Drug Interactions.

Cevimeline can intensify cardiac depression caused by beta blockers (because both drugs decrease heart rate and cardiac conduction).

Beneficial effects of cevimeline can be antagonized by drugs that block muscarinic receptors. Among these are atropine, tricyclic antidepressants (eg, imipramine), antihistamines (eg, diphenhydramine), and phenothiazine antipsychotics (eg, chlorpromazine).

Preparations, Dosage, and Administration.

Cevimeline [Evoxac] is available in 30-mg capsules. The dosage is 30 mg 3 times a day. The drug may be administered with food to reduce gastric upset.

Pilocarpine

Pilocarpine is a muscarinic agonist used mainly for topical therapy of glaucoma, an ophthalmic disorder characterized by elevated intraocular pressure with subsequent injury to the optic nerve. The basic pharmacology of pilocarpine and its use in glaucoma are discussed in Chapter 103 (Drugs for the Eye).

In addition to its use in glaucoma, pilocarpine is approved for oral therapy of dry mouth resulting from Sjögren's syndrome or from salivary gland damage caused by radiation therapy of head and neck cancer. For these applications, pilocarpine is available in 5-mg tablets under the trade name *Salagen*. The recommended dosage is 5 mg 3 or 4 times a day. At this dosage, the principal adverse effect is sweating, which occurs in 29% of patients. However, if dosage is excessive, pilocarpine can produce the full spectrum of muscarinic effects.

Acetylcholine

Clinical use of acetylcholine [Miochol-E] is limited primarily to producing rapid miosis (pupil constriction) following lens delivery in cataract surgery. Two factors explain the limited utility of this drug. First, acetylcholine lacks selectivity (in addition to activating muscarinic cholinergic receptors, acetylcholine can also activate all nicotinic cholinergic receptors). Second, because of rapid destruction by cholinesterase, acetylcholine has a half-life that is extremely short—too short for most clinical applications.

Muscarine

Although muscarine is not used clinically, this agent has historic and toxicologic significance. Muscarine is of historic interest because of its role in the discovery of cholinergic receptor subtypes. The drug has toxicologic significance because of its presence in certain poisonous mushrooms.

Toxicology of Muscarinic Agonists

Sources of Muscarinic Poisoning.

Muscarinic poisoning can result from ingestion of certain mushrooms and from overdose with two kinds of medications: (1) direct-acting muscarinic agonists (eg, bethanechol, pilocarpine), and (2) cholinesterase inhibitors.

Of the mushrooms that cause poisoning, only a few do so through muscarinic activation. Mushrooms of the *Inocybe* and *Clitocybe* species have lots of muscarine, hence their ingestion can produce typical signs of muscarinic toxicity. Interestingly, *Amanita muscaria*, the mushroom from which muscarine was originally extracted, actually contains very little muscarine; poisoning by this mushroom is due to toxins other than muscarinic agonists.

Symptoms.

Manifestations of muscarinic poisoning result from excessive activation of muscarinic receptors. Prominent symptoms are profuse salivation, lacrimation (tearing), visual disturbances, bronchospasm, diarrhea, bradycardia, and hypotension. Severe poisoning can produce cardiovascular collapse.

Treatment.

Management is direct and specific: administer *atropine* (a selective muscarinic blocking agent) and provide supportive therapy. By blocking access of muscarinic agonists to their receptors, atropine can reverse most signs of toxicity.

MUSCARINIC ANTAGONISTS (ANTICHOLINERGIC DRUGS)

Muscarinic antagonists competitively block the actions of acetylcholine at muscarinic receptors. Because the majority of muscarinic receptors are located on structures innervated by parasympathetic nerves, the muscarinic antagonists are also known as *parasympatholytic drugs*. Additional names for these agents are *antimuscarinic drugs, muscarinic blockers*, and *anticholinergic drugs*.

The term *anticholinergic* can be a source of confusion and requires comment. This term is unfortunate in that it implies blockade at *all* cholinergic receptors. However, as normally used, the term *anticholinergic* only denotes blockade of *muscarinic* receptors. Therefore, when a drug is characterized as being anticholinergic, you can take this to mean that it produces selective *muscarinic* blockade—and not blockade of all cholinergic receptors. In this chapter, I use the terms *muscarinic antagonist* and *anticholinergic agent* interchangeably.

Atropine

Atropine [Sal-Tropine, AtroPen, others] is the best known muscarinic antagonist and will serve as our prototype for the group. The actions of all other muscarinic blockers are much like those of this drug.

Atropine is found naturally in a variety of plants, including *Atropa belladonna* (deadly nightshade) and *Datura stramonium* (aka Jimson weed, stinkweed, and devil's apple). Because of its presence in *Atropa belladonna*, atropine is referred to as a *belladonna alkaloid*.

Mechanism of Action

Atropine produces its effects through competitive blockade at muscarinic receptors. Like all other receptor antagonists, atropine has no direct effects of its own. Rather, all responses to atropine result from *preventing receptor activation* by endogenous acetylcholine (or by drugs that act as muscarinic agonists).

At therapeutic doses, atropine produces selective blockade of muscarinic cholinergic receptors. However, if the dosage is sufficiently high, the drug will produce some blockade of nicotinic receptors too.

Pharmacologic Effects

Since atropine acts by causing muscarinic receptor blockade, its effects are opposite to those caused by muscarinic activation. Accordingly, we can readily predict the effects of atropine by knowing the normal responses to muscarinic receptor activation (see Table 13-2) and by knowing that atropine will reverse those responses. Like the muscarinic agonists, the muscarinic antagonists exert their influence primarily on the *heart, exocrine glands, smooth muscles*, and *eye*.

Heart.

Atropine *increases heart rate*. Because activation of cardiac muscarinic receptors decreases heart rate, blockade of these receptors will cause heart rate to increase.

Exocrine Glands.

Atropine *decreases secretion* from salivary glands, bronchial glands, sweat glands, and the acid-secreting cells of the stomach. Note that these effects are opposite to those of muscarinic agonists, which increase secretion from exocrine glands.

Smooth Muscle.

By preventing activation of muscarinic receptors on smooth muscle, atropine causes *relaxation of the bronchi, decreased tone of the urinary bladder detrusor*, and *decreased tone and motility of the GI tract*. In the absence of an exogenous muscarinic agonist (eg, bethanechol), muscarinic blockade has no effect on vascular smooth muscle tone. Why? Because there is no parasympathetic innervation to muscarinic receptors in blood vessels.

Eye.

Blockade of muscarinic receptors on the iris sphincter causes *mydriasis* (dilation of the pupil). Blockade of muscarinic receptors on the ciliary muscle produces *cycloplegia* (relaxation of the ciliary muscle), thereby focusing the lens for far vision.

Central Nervous System (CNS).

At therapeutic doses, atropine can cause mild CNS *excitation*. Toxic doses can cause *hallucinations* and *delirium*, which can resemble psychosis. Extremely high doses can result in coma, respiratory arrest, and death.

Dose Dependency of Muscarinic Blockade.

It is important to note that not all muscarinic receptors are equally sensitive to blockade by atropine and most other anticholinergic drugs: At some sites, muscarinic receptors can be blocked with relatively low doses, whereas at other sites much higher doses are needed. Table 14-1 indicates the sequence in which specific muscarinic receptors are blocked as the dose of atropine is increased.

Differences in receptor sensitivity to muscarinic blockers are of clinical significance. As indicated in Table 14-1, the doses needed to block muscarinic receptors in the stomach and bronchial smooth muscle are higher than the doses needed to block muscarinic receptors at all other locations. Accordingly,

if we want to use atropine to treat peptic ulcer disease (by suppressing gastric acid secretion) or asthma (by dilating the bronchi), we cannot do so without also affecting the heart, exocrine glands, many smooth muscles, and the eye. Because of these obligatory side effects, atropine and most other muscarinic antagonists are not preferred drugs for treating peptic ulcers or asthma.

Pharmacokinetics

Atropine may be administered orally, topically (to the eye), and by injection (IM, IV, and subQ). The drug is rapidly absorbed following oral administration and distributes to all tissues, including the CNS. Elimination is by a combination of hepatic metabolism and urinary excretion. Atropine has a half-life of approximately 3 hours.

Therapeutic Uses

Preanesthetic Medication.

The cardiac effects of atropine can be helpful during surgery. Procedures that stimulate baroreceptors of the carotid body can initiate reflex slowing of the heart, resulting in profound bradycardia. Since this reflex is mediated by muscarinic receptors on the heart, pretreatment with atropine can prevent dangerous reductions in heart rate.

Certain anesthetics—especially ether, which is obsolete—irritate the respiratory tract, and thereby stimulate secretion from salivary, nasal, pharyngeal, and bronchial glands. If these secretions are sufficiently profuse, they can interfere with respiration. By blocking muscarinic receptors on secretory glands, atropine can help prevent excessive secretions. Fortunately, modern anesthetics are much less irritating than ether. The availability of these new anesthetics has greatly reduced the use of atropine as an anti-secretagogue during anesthesia.

Disorders of the Eye.

By blocking muscarinic receptors in the eye, atropine can cause mydriasis and paralysis of the ciliary muscle. Both actions can be of help during eye examinations and ocular surgery. The ophthalmic uses of atropine and other muscarinic antagonists are discussed in Chapter 103.

Bradycardia.

Atropine can accelerate heart rate in certain patients with bradycardia. Heart rate is increased because blockade of cardiac muscarinic receptors prevents the parasympathetic nervous system from slowing the heart.

Intestinal Hypertonicity and Hypermotility.

By blocking muscarinic receptors in the intestine, atropine can decrease both the tone and motility of intestinal smooth muscle. This can be beneficial in conditions characterized by excessive intestinal motility, such as mild dysentery and diverticulitis. When taken for these disorders, atropine can reduce both the frequency of bowel movements and associated abdominal cramps.

Muscarinic Agonist Poisoning.

Atropine is a specific antidote to poisoning by agents that activate muscarinic receptors. By blocking muscarinic receptors, atropine can reverse all signs of muscarinic poisoning. As discussed above, muscarinic poisoning can result from an overdose with medications that promote muscarinic activation (eg, bethanechol, cholinesterase inhibitors) or from ingestion of certain mushrooms.

Peptic Ulcer Disease.

Because it can suppress secretion of gastric acid, atropine has been used to treat peptic ulcer disease. Unfortunately, when administered in doses that are strong enough to block the muscarinic receptors that regulate secretion of gastric acid, atropine also blocks most other muscarinic receptors. Hence, treatment of ulcers is necessarily associated with a broad range of antimuscarinic side effects (dry mouth, blurred vision, urinary retention, constipation, and so on). Because of these side effects, atropine is not a first-choice drug for ulcer therapy. Rather, atropine is reserved for rare cases in which symptoms cannot be relieved with preferred medications (eg, antibiotics, histamine2 receptor antagonists, proton pump inhibitors).

Asthma.

By blocking bronchial muscarinic receptors, atropine can promote bronchial dilation, thereby improving respiration in patients with asthma. Unfortu-

nately, in addition to dilating the bronchi, atropine also causes drying and thickening of bronchial secretions, effects that can be harmful to patients with asthma. Furthermore, when given in the doses needed to dilate the bronchi, atropine causes a variety of antimuscarinic side effects. Because of the potential for harm, and because superior medicines are available, atropine has a very limited role in asthma therapy.

Biliary Colic.

Biliary colic is characterized by intense abdominal pain brought on by passage of a gallstone through the bile duct. This pain is usually treated with morphine. In some cases, atropine may be combined with morphine to relax biliary tract smooth muscle, thereby helping alleviate discomfort.

Adverse Effects

Most adverse effects of atropine and other anticholinergic drugs are the direct result of muscarinic receptor blockade. Accordingly, they can be predicted from your knowledge of muscarinic receptor function.

Xerostomia (Dry Mouth).

Blockade of muscarinic receptors on salivary glands can inhibit salivation, thereby causing dry mouth. Not only is this uncomfortable, it can impede swallowing. Patients should be informed that dryness can be alleviated by chewing gum, sucking on hard candy, and sipping fluids.

Blurred Vision and Photophobia.

Blockade of muscarinic receptors on the ciliary muscle and the sphincter of the iris can paralyze these muscles. Paralysis of the ciliary muscle focuses the eye for far vision, causing nearby objects to appear blurred. Patients should be forewarned about this effect and advised to avoid hazardous activities if vision is impaired.

Paralysis of the iris sphincter prevents constriction of the pupil, thereby rendering the eye unable to adapt to bright light. Patients should be advised to wear dark glasses if photophobia (intolerance to light) is a problem. Room lighting for hospitalized patients should be kept low.

Elevation of Intraocular Pressure.

Paralysis of the iris sphincter can cause intraocular pressure (IOP) to rise. The mechanism of this effect is discussed in Chapter 103 (Drugs for the Eye). Because they can raise IOP, anticholinergic drugs are contraindicated for patients with glaucoma, a disease characterized by abnormally high IOP. In addition, these drugs should be used with caution in patients who may not have glaucoma per se but for whom a predisposition to glaucoma may be present. Included in this group are all people older than 40.

Urinary Retention.

Blockade of muscarinic receptors in the urinary tract reduces pressure within the bladder and increases the tone of the urinary sphincter and trigone. These effects can produce urinary hesitancy or urinary retention. In the event of severe urinary retention, catheterization or treatment with a muscarinic agonist (eg, bethanechol) may be required. Patients should be advised that urinary retention can be minimized by voiding just prior to taking their medication.

Constipation.

Muscarinic blockade decreases the tone and motility of intestinal smooth muscle. The resultant delay in transit through the intestine can produce constipation. Patients should be informed that constipation can be minimized by increasing dietary fiber and fluids. A laxative may be needed if constipation is severe. Because of their ability to decrease smooth muscle tone, muscarinic antagonists are contraindicated for patients with intestinal atony, a condition in which intestinal tone is already low.

Anhidrosis.

Blockade of muscarinic receptors on sweat glands can produce anhidrosis (a deficiency or absence of sweat). Since sweating is necessary for cooling, people who cannot sweat are at risk of hyperthermia. Patients should be warned of this possibility and advised to avoid activities that might lead to overheating (eg, exercising on a hot day).

Tachycardia.

Blockade of cardiac muscarinic receptors eliminates parasympathetic influence on the heart. By removing the "braking" influence of parasympathetic nerves, anticholinergic agents can cause tachycardia (excessive heart rate). Caution must be exercised in patients with pre-existing tachycardia.

Asthma.

In patients with asthma, antimuscarinic drugs can cause *thickening and drying of bronchial secretions*, and can thereby cause bronchial plugging. Consequently, although muscarinic antagonists can be used to treat asthma, they can also be harmful.

Drug Interactions

A number of drugs that are not classified as muscarinic antagonists can nonetheless produce significant muscarinic blockade. Among these are antihistamines, phenothiazine antipsychotics, and tricyclic antidepressants. Because of their prominent anticholinergic actions, these drugs can greatly enhance the antimuscarinic effects of atropine and related agents. Accordingly, it is wise to avoid combined use of atropine with other drugs that can cause muscarinic blockade.

Preparations, Dosage, and Administration

General Systemic Therapy.

Atropine sulfate is available in 0.4-mg tablets (sold as Sal-Tropine) for oral administration, and in solution (0.05 to 1 mg/mL) for IM, IV, and subQ administration. The average adult dose is 0.5 mg.

AtroPen for Cholinesterase Inhibitor Poisoning.

The AtroPen is a pre-filled auto-injector indicated for IM therapy of poisoning with an organophosphate cholinesterase inhibitor (nerve agent or insecticide). Three strengths are available: 0.5 mg (for children weighing 15 to 40 pounds), 1 mg (for children 40 to 90 pounds), and 2 mg (for adults and children over 90 pounds). Injections are made into the lateral thigh, directly through clothing if necessary.

Ophthalmology.

Formulations for ophthalmic use are discussed in Chapter 103.

Anticholinergic Drugs for Overactive Bladder (Urge Incontinence)

Overactive Bladder: Characteristics and Overview of Treatment

Overactive bladder (OAB) is a disorder with four major symptoms: urinary urgency (a sudden, compelling desire to urinate), urinary frequency (voiding 8 or more times in 24 hours), nocturia (waking 2 or more times to void), and urge incontinence (involuntary urine leakage associated with a strong urge to void). In almost all cases, urge incontinence results from *involuntary contractions of the bladder detrusor* (the smooth muscle component of the bladder wall). These contractions are often referred to as detrusor instability or detrusor overactivity. Urge incontinence should not be confused with *stress incontinence*, defined as involuntary urine leakage caused by activities (eg, exertion, sneezing, coughing, laughter) that increase pressure within the abdominal cavity.

OAB is a common disorder, affecting up to one-third of Americans. However, relatively few (about 15%) seek medical help. The condition can develop at any age, but is most prevalent in the elderly. Among people ages 40 to 44, symptoms are reported by 3% of men and 9% of women. In comparison, among those 75 and older, symptoms are reported by 42% of men and 31% of women. Because urge incontinence, the most disturbing symptom, is both unpredictable and potentially embarrassing, many people with OAB curtail travel, social activities, and even work.

OAB can be treated with behavioral techniques and with drugs. Behavioral therapy can be highly effective—even more so than drugs—and hence should be tried first. Behavioral interventions include pelvic muscle exercises, scheduled voiding, education about bladder function, avoiding caffeine (a diuretic), and timing fluid intake appropriately. As a rule, drugs should be reserved for patients who don't respond adequately to nondrug measures.

Introduction to Anticholinergic Therapy of OAB

When drug therapy *is* indicated, *anticholinergic agents* (eg, oxybutynin, tolterodine) are preferred. These drugs block muscarinic receptors on the bladder detrusor, and thereby inhibit bladder contractions and the urge to void.

Unfortunately, drugs that block muscarinic receptors in the bladder can also block muscarinic receptors elsewhere, and hence can cause typical anticholinergic side effects. *Dry mouth* is the primary concern. Other possible effects include constipation, urinary retention, blurred vision, photophobia, tachycardia, and cognitive effects (confusion, hallucinations). All of these can be intensified by concurrent use of other drugs that have anticholinergic actions (eg, antihistamines, tricyclic antidepressants, phenothiazine antipsychotic agents).

Anticholinergic side effects can be reduced in at least three ways: (1) using long-acting formulations, (2) using drugs that don't cross the blood-brain barrier, and (3) using drugs that are selective for muscarinic receptors in the bladder. Long-acting formulations (eg, extended-release capsules, transdermal patches) reduce side effects by providing a steady but relatively low level of drug, thereby avoiding the high peak levels that can cause intense side effects. Drugs that can't cross the blood-brain barrier are unable to cause CNS effects.

What about drugs that are selective for muscarinic receptors in the bladder? To answer this question, we must first discuss muscarinic receptor subtypes. As noted in Chapter 13, there are five known muscarinic receptor subtypes. However, only three—designated M***1***, M***2***, and M***3***—have clearly identified functions. Locations of these receptor subtypes, and responses to their activation and blockade, are summarized in Table 14-2. As indicated, M***3*** receptors are the most widely distributed, being found in salivary glands, the bladder detrusor, GI smooth muscle, and the eye. M***2*** receptors are found only in the heart, and M***1*** receptors are found in salivary glands and the CNS. At each location, responses to receptor activation are the same as we discussed in Chapter 13—although, in that chapter, we didn't identify the receptors by subtype; rather, we simply called all of them *muscarinic*.

Muscarinic Subtype	Location	Response to Activation	Impact of Blockade
M_1	Salivary glands	Salivation	Dry mouth
	CNS	Enhanced cognition	Confusion, hallucinations
M_2	Heart	Bradycardia	Tachycardia
M_3	Salivary glands	Salivation	Dry mouth
	Bladder: detrusor	Contraction (increased pressure)	Relaxation (decreased pressure)
	GI smooth muscle	Increased tone and motility	Decreased tone and motility (constipation)
	Eye: Iris sphincter	Contraction (miosis)	Relaxation (mydriasis)
	Eye: Ciliary muscle	Contraction (accommodation)	Relaxation (blurred vision)
	Eye: Lachrymal gland	Tearing	Dry eyes

CNS = central nervous system, GI = gastrointestinal.

TABLE 14-2 Muscarinic Receptor Subtypes

With this background, we can consider how receptor selectivity might decrease anticholinergic side effects of drugs for OAB. To be beneficial, an anticholinergic agent must block muscarinic receptors in the bladder *detrusor*. That is, it must block the M***3*** receptor subtype. Because M***3*** receptors are also found in GI smooth muscle, the eye, and salivary glands, an M***3***-selective blocker will still have some unwanted anticholinergic effects, namely, constipation (from reducing bowel motility), blurred vision and photophobia (from preventing contraction of the ciliary muscle and iris sphincter), dry eyes (from blocking tear production), and *some* degree of dry mouth (from blocking salivary gland M***3*** receptors, while sparing salivary M***1*** receptors). What an M***3***-selective blocker will *not* do is cause tachycardia (because muscarinic re-

ceptors in the heart are the M2 type) or impairment of CNS function (because muscarinic receptors in the brain are primarily the M1 type).

Specific Anticholinergic Drugs for OAB

In the United States, we have five anticholinergic drugs approved specifically for OAB (Table 14-3). All five work by M3-muscarinic blockade, although most block M1 and M2 receptors as well. With all of these drugs, we want sufficient M3 blockade to reduce symptoms of OAB, but not so much as to cause urinary retention. It should be noted that clinical responses to these agents are relatively modest—about 30% over the response to placebo (which produces about a 30% response by itself). None of these drugs is useful for stress incontinence.

Drug	Formulation*	Dosage		Incidence of Dry Mouth
		Initial	Maximum	
Highly M_3 Selective				
Darifenacin				
Enablex	ER tablets	7.5 mg once daily	15 mg once daily	20% with 7.5 mg/day; 35% with 15 mg/day
Primarily M_3 Selective				
Oxybutynin				
Ditropan	Syrup	5 mg 2–3 times/day	5 mg 4 times/day	Dose-related; can exceed 70%
Ditropan	IR tablets	5 mg 2–3 times/day	5 mg 4 times/day	Dose-related; can exceed 70%
Ditropan XL	ER tablets	5 mg once daily	30 mg once daily†	Dose-related; can exceed 60%
Oxytrol	Transdermal patch	1 patch twice weekly (delivers 3 mg/day)	1 patch twice weekly	Low: 12% vs. 11% with placebo
Solifenacin				
VESIcare	Tablets	5 mg once daily	10 mg once daily	11% with 5 mg/day; 28% with 10 mg/day
Nonselective				
Tolterodine				
Detrol	IR tablets	1–2 mg twice daily	2 mg twice daily	35% with 2 mg twice daily

TABLE 14-3 Anticholinergic Drugs for Overactive Bladder

* ER = extended release, IR = immediate release.

† Titrate dose upward as needed and tolerated.

‡ Administer at least 1 hour before meals or on an empty stomach.

Oxybutynin.

Oxybutynin [Ditropan, Ditropan XL, Oxytrol] is an anticholinergic agent that acts primarily at M*3*-muscarinic receptors. The drug is approved only for OAB. Benefits derive from blocking M*3* receptors on the bladder detrusor.

Oxybutynin is available in four formulations. Two are short acting (syrup and immediate-release [IR] tablets) and two are long acting (transdermal patch and extended-release [ER] tablets). Anticholinergic side effects are less intense with the long-acting products.

Immediate-Release Tablets.

Oxybutynin IR tablets [Ditropan] can decrease the incidence of urinary urgency, urinary frequency, and urge incontinence. However, benefits are modest—and only somewhat greater than seen with placebo.

Oxybutynin is rapidly absorbed from the GI tract, achieving peak plasma levels about 1 hour after dosing. However, despite rapid absorption, absolute bioavailability is low (about 6%). Why? Because oxybutynin undergoes extensive first-pass metabolism—both in the gut wall and in the liver—primarily by CYP3A4, the 3A4 isozyme of cytochrome P450. One metabolite—*N*-desethyloxybutynin—is highly active, especially against muscarinic receptors in the salivary glands. Oxybutynin is very lipid soluble, and hence can penetrate the blood-brain barrier. The drug has a short half-life (2 to 3 hours), and hence multiple daily doses are required.

Anticholinergic side effects are common. The incidence of dry mouth is very high, in part because of muscarinic blockade by oxybutynin itself, and in part because of blockade by *N*-desethyloxybutynin. Other common side effects include constipation, tachycardia, urinary hesitancy, urinary retention, mydriasis, blurred vision, and dry eyes. In the CNS, cholinergic blockade can result in confusion, hallucinations, insomnia, and nervousness. In postmarketing reports of CNS effects, hallucinations and agitation were prominent among re-

ports involving pediatric patients, while hallucinations, confusion, and sedation were prominent among reports involving elderly patients. Combined use of oxybutynin with other anticholinergic agents (eg, antihistamines, tricyclic antidepressants, phenothiazine antipsychotics) can intensify all anticholinergic side effects.

Drugs that inhibit or induce CYP3A4 may alter oxybutynin blood levels, and may thereby either increase toxicity (inhibitors of CYP3A4) or reduce effectiveness (inducers of CYP3A4).

Immediate-release oxybutynin is available in 5-mg tablets. The usual dosage is 5 mg 2 or 3 times a day. The maximal dosage is 5 mg 4 times a day.

Syrup.

The basic and clinical pharmacology of oxybutynin syrup [Ditropan] is identical to that of the IR tablets. As with the IR tablets, the incidence of dry mouth and other anticholinergic side effects is high. The syrup contains 5 mg of oxybutynin/5 mL. The usual dosage is 5 mg 2 or 3 times a day. The maximal dosage is 5 mg 4 times a day.

Extended-Release Tablets.

Oxybutynin ER tablets [Ditropan XL] are as effective as the IR tablets and somewhat better tolerated. Although the incidence of dry mouth is reduced using ER tablets, it is nonetheless still high (about 60%). Other adverse effects include constipation (13%), dyspepsia (7%), blurred vision (8%), dry eyes (6%), and CNS effects: somnolence (12%), headache (10%), and dizziness (6%).

The ER tablets are available in three strengths: 5, 10, and 15 mg. The initial dosage is 5 mg once daily. Dosage may be raised weekly in 5-mg increments to a maximum of 30 mg/day. The dosing goal is to achieve a balance between symptom reduction and tolerability of anticholinergic side effects. The ER tablets have an insoluble shell that is eliminated intact in the feces. Patients should be informed of this fact.

Transdermal Patch.

The oxybutynin transdermal system [Oxytrol] contains 39 mg of oxybutynin and delivers 3.9 mg/day. Owing to its high lipid solubility, oxybutynin from

the patch is readily absorbed directly through the skin. A new patch is applied twice weekly to dry, intact skin of the abdomen, hip, or buttock, rotating the site with each change. Reduction of OAB symptoms is about the same as with the ER tablets.

Pharmacokinetically, the patch is unique in two ways. First, absorption is both slow and steady, and hence the patch produces low but stable blood levels of the drug. Second, transdermal absorption bypasses metabolism in the intestinal wall, and delays metabolism in the liver. As a result, levels of *N*-desethyloxybutynin, the active metabolite, are less than 20% of those achieved with oral therapy.

Transdermal oxybutynin is generally well tolerated. The most common side effect is application-site pruritus (itching), which develops in 15% of patients. The incidence of dry mouth is much lower than with the oral formulations (and only slightly higher than with placebo) presumably because (1) formation of *N*-desethyloxybutynin is low and (2) high peak levels of oxybutynin itself are avoided. Rates of constipation, blurred vision, and CNS effects are also low.

Darifenacin.

Of the anticholinergic agents used for OAB, darifenacin [Enablex] displays the greatest degree of M***3*** selectivity. As a result, the drug can reduce OAB symptoms while having no effect on M***1*** receptors in the brain or M***2*** receptors in the heart. However, darifenacin does block M***3*** receptors outside the bladder, and hence still can cause dry mouth, constipation, and other M***3***-related side effects.

Clinical benefits are similar to those of oxybutynin and tolterodine. On average, treatment decreases episodes of urge incontinence from 15/week down to 7/week (using 7.5 mg/day) and from 17/week down to 6/week (using 15 mg/day), compared with a decrease from 16/week down to 9/week with placebo. The bottom line? As with other drugs for OAB, responses are relatively modest, and only slightly greater than those seen with placebo.

Darifenacin is administered orally in ER tablets. Absorption is adequate (15% to 19%), and not affected by food. In the blood, darifenacin is 98% protein bound. The drug undergoes extensive hepatic metabolism, primarily by

CYP3A4. The resulting inactive metabolites are excreted in the urine (60%) and feces (40%). The drug's half-life is approximately 12 hours.

Darifenacin is relatively well tolerated. The most common side effect is dry mouth, which occurs in 35% of those taking 15 mg/day and 20% of those taking 7.5 mg/day, compared with only 8% of those taking placebo. In experimental animals, inhibition of salivation is less than that caused by oxybutynin, perhaps because darifenacin only blocks M***3*** receptors in salivary glands, permitting salivary M***1*** receptors to function normally. Constipation is also common, seen in 21% of those taking 15 mg/day and 15% of those taking 7.5 mg/day, compared with only 6% of those taking placebo. Other adverse effects include dyspepsia, gastritis, and headache. Darifenacin has little or no effect on memory, reaction time, word recognition, or cognition. The drug does not increase heart rate.

Levels of darifenacin can be raised significantly by strong inhibitors of CYP3A4. Among these are azole-type antifungal drugs (eg, ketoconazole, itraconazole), certain protease inhibitors used for HIV/AIDS (eg, ritonavir, nelfinavir), and clarithromycin (a macrolide antibiotic). If darifenacin is combined with any of these, darifenacin dosage must be kept low.

Darifenacin [Enablex] is available in 7.5- and 15-mg ER tablets, which should be swallowed whole with liquid. The initial dosage is 7.5 mg once daily. After 2 weeks, dosage may be doubled to 15 mg once daily. In patients with moderate liver impairment, and in those taking powerful inhibitors of CYP3A4, dosage should be kept low (7.5 mg/day or less). In patients with severe liver impairment, darifenacin should be avoided.

Solifenacin.

Solifenacin [VESIcare] is very similar to darifenacin, although it's not quite as M***3*** selective. In clinical trials, the drug reduced episodes of urge incontinence from 18/week down to 8/week (using 5 mg/day) and from 20/week down to 8/week (using 10 mg/day), compared with a decrease from 21/week down to 10/week with placebo—indicating that, like other drugs for OAB, solifenacin is only moderately more effective than placebo.

Solifenacin undergoes nearly complete absorption after oral dosing, achieving peak plasma levels in 3 to 6 hours. In the blood, the drug is highly (98%) pro-

tein bound. Like darifenacin, solifenacin undergoes extensive metabolism by hepatic CYP3A4. The resulting inactive metabolites are excreted in the urine (62%) and feces (23%). Solifenacin has a long half-life (about 50 hours), and hence can be administered just once a day.

The most common adverse effects are dry mouth (28% at 10 mg/day), constipation (13% at 10 mg/day), and blurred vision (5% at 10 mg/day). Dyspepsia, urinary retention, headache, and nasal dryness occur infrequently. At high doses (10 to 30 mg/day), solifenacin can prolong the QT interval, thereby posing a risk of a fatal dysrhythmia. Accordingly, caution is needed in patients with a history of QT prolongation and in those taking other QT-prolonging drugs. As with darifenacin, levels of solifenacin can be increased by strong inhibitors of CYP3A4 (eg, ketoconazole, ritonavir, clarithromycin).

Solifenacin [VESIcare] is available in 5- and 10-mg film-coated tablets, which should be swallowed intact with liquid. Dosing may be done with or without food. The initial dosage is 5 mg once daily. If treatment is well tolerated, the dosage can be doubled to 10 mg once daily. For patients with moderate hepatic impairment or severe renal impairment, and for those taking a powerful CYP3A4 inhibitor, dosage should not exceed 5 mg/day. For patients with severe hepatic impairment, solifenacin should be not be used.

Tolterodine.

Tolterodine [Detrol, Detrol LA] is a nonselective muscarinic antagonist approved only for OAB. Like oxybutynin, tolterodine is available in short- and long-acting formulations. Anticholinergic side effects are less intense with the long-acting form.

Immediate-Release Tablets.

In patients with OAB, tolterodine IR tablets [Detrol] can reduce the incidence of urge incontinence, urinary frequency, and urinary urgency. However, as with other drugs for OAB, benefits are modest.

Tolterodine is rapidly but variably absorbed from the GI tract. Plasma levels peak 1 to 2 hours after dosing. In most people, tolterodine undergoes extensive first-pass hepatic metabolism, primarily by CYP2D6 (the 2D6 isozyme of cytochrome P450), which converts much of the drug to an active metabolite.

In people who lack CYP2D6 (about 7% of the population), tolterodine is metabolized by CYP3A4, which does not produce an active metabolite. In all people, parent drug and metabolites are eliminated in the urine (77%) and feces (17%). Tolterodine has a relatively short half-life, and hence twice-daily dosing is required.

Anticholinergic side effects occur less often than with IR oxybutynin. At a dosage of 2 mg twice daily, the most common side effects are dry mouth (35% vs. 70% with IR oxybutynin), constipation (7%), and dry eyes (3%). Effects on the CNS—somnolence, vertigo, dizziness—occur infrequently. The incidence of tachycardia and urinary retention is less than 1%. Anticholinergic effects can be intensified by concurrent use of other drugs with anticholinergic actions (eg, antihistamines, tricyclic antidepressants, phenothiazine antipsychotics). Drugs that inhibit CYP3A4 (eg, erythromycin, ketoconazole) can raise levels of tolterodine.

Tolterodine IR tablets are available in 1- and 2-mg strengths. The initial dosage is 2 mg twice daily, taken with or without food. If this dosage is poorly tolerated, it should be reduced to 1 mg twice daily. A dosage of 1 mg twice daily should also be used by patients with significant hepatic or renal impairment, and for those taking an inhibitor of CYP3A4.

Extended-Release Capsules.

Tolterodine ER capsules [Detrol LA] are as effective as the IR tablets, and cause less dry mouth (23% vs. 35%). The incidence of other anticholinergic effects is about the same with both formulations. Detrol LA is available in 2- and 4-mg strengths. The recommended dosage is 4 mg once daily. As with the IR tablets, a lower dosage—2 mg once daily—should be used for patients with significant hepatic or renal impairment, and for those taking an inhibitor of CYP3A4.

Trospium.

Trospium [Sanctura, Sanctura XR] is a nonselective muscarinic blocker indicated only for OAB. Like oxybutynin and tolterodine, trospium is available in short- and long-acting formulations. Anticholinergic side effects are less intense with the long-acting form. Compared with other drugs for OAB, tro-

spium is notable for its low bioavailability, lack of CNS effects, and lack of metabolism-related interactions with other drugs.

Immediate-Release Tablets.

Trospium IR tablets [Sanctura] reduce episodes of urge incontinence from 27/week down to 12/week (compared with 30/week down to 16/week with placebo). Reductions in urinary frequency are minimal.

Trospium is a quaternary ammonium compound (always carries a positive charge), and hence crosses membranes poorly. Administration is oral, and absorption is poor (only 10%) and is greatly reduced (70% to 80%) by food. Plasma levels peak 3.5 to 6 hours after dosing, and decline with a half-life of 18 hours. Trospium does not undergo hepatic metabolism, and is eliminated unchanged in the urine.

Trospium IR tablets are generally well tolerated. The most common side effects are dry mouth (20% vs. 6% with placebo) and constipation (10% vs. 5%)—about the same as with long-acting oxybutynin and tolterodine. Rarely, the drug causes dry eyes and urinary retention. Owing to its positive charge, trospium cannot cross the blood-brain barrier, and hence is devoid of CNS effects.

No drug interaction studies have been performed. However, because trospium is eliminated by the kidneys, we can assume it may compete with other drugs that undergo renal tubular excretion. Among these are vancomycin (an antibiotic), metformin (a drug for diabetes), and digoxin and procainamide (both used for cardiac disorders). Because trospium is not metabolized, the drug is unlikely to influence hepatic metabolism of other agents.

Immediate-release trospium [Sanctura] is available in 20-mg tablets. The usual dosage is 20 mg twice daily, administered at least 1 hour before meals or on an empty stomach. For patients with severe renal impairment, the recommended dosage is 20 mg once daily at bedtime.

Extended-Release Capsules.

Trospium ER capsules [Sanctura XR] are as effective as the IR tablets, and cause less dry mouth (10% vs. 20%). The incidence of constipation and other

side effects is about the same. Extended-release trospium is available in 60-mg capsules for once-daily dosing.

Other Muscarinic Antagonists

Scopolamine.

Scopolamine is an anticholinergic drug with actions much like those of atropine, but with two exceptions: (1) whereas therapeutic doses of atropine produce mild CNS *excitation*, therapeutic doses of scopolamine produce *sedation*; and (2) scopolamine *suppresses emesis and motion sickness*, whereas atropine does not. Principal uses for scopolamine are motion sickness (see Chapter 79), production of cycloplegia and mydriasis for ophthalmic procedures (see Chapter 103), and production of preanesthetic sedation and obstetric amnesia.

Ipratropium Bromide.

Ipratropium [Atrovent] is an anticholinergic drug used to treat asthma, chronic obstructive pulmonary disease, and rhinitis caused by allergies or the common cold. The drug is administered by inhalation and systemic absorption is minimal. As a result, therapy is not associated with typical antimuscarinic side effects (dry mouth, blurred vision, urinary hesitancy, constipation, and so forth). Ipratropium is discussed at length in Chapter 75.

Antisecretory Anticholinergics.

Muscarinic blockers can be used to suppress gastric acid secretion in patients with peptic ulcer disease. However, since superior antiulcer drugs are available, and since anticholinergic agents produce significant side effects (dry mouth, blurred vision, urinary retention, and so forth), most of these drugs have been withdrawn. Today, only four agents—*glycopyrrolate* [Robinul], *mepenzolate* [Cantil], *methscopolamine* [Pamine], and *propantheline* [Pro-Banthine]—remain on the market. All four are administered orally, and one—glycopyrrolate—may also be given IM and IV.

Dicyclomine.

This drug is indicated for irritable bowel syndrome (spastic colon, mucous colitis) and functional bowel disorders (diarrhea, hypermotility). Administration may be oral (40 mg 4 times a day) or by IM injection (20 mg 4 times a day). Trade names include *Antispas, Bentyl*, and *Dibent*.

Pirenzepine and Telenzepine.

These drugs produce selective blockade of M***1*** muscarinic receptors—the subtype of muscarinic receptor involved in regulating the secretion of gastric acid. Both drugs can effectively suppress acid secretion in patients with peptic ulcer disease, but neither is currently available in the United States. Because these drugs are selective blockers of M***1*** muscarinic receptors, the incidence of dry mouth, blurred vision, and other typical antimuscarinic side effects is low.

Mydriatic Cycloplegics.

Five muscarinic antagonists—*atropine, homatropine, scopolamine, cyclopentolate*, and *tropicamide*—are employed to produce mydriasis and cycloplegia in ophthalmic procedures. These applications are discussed in Chapter 103.

Centrally Acting Anticholinergics.

Several anticholinergic drugs, including *trihexyphenidyl* [Artane] and *benztropine* [Cogentin], are used to treat Parkinson's disease and drug-induced parkinsonism. Benefits derive from blockade of muscarinic receptors in the CNS. The centrally acting anticholinergics and their use in Parkinson's disease are discussed in Chapter 21.

Toxicology of Muscarinic Antagonists

Sources of Antimuscarinic Poisoning.

Sources of poisoning include natural products (eg, *Atropa belladonna, Datura stramonium*), selective antimuscarinic drugs (eg, atropine, scopolamine), and other drugs with pronounced antimuscarinic properties (eg, antihistamines, phenothiazines, tricyclic antidepressants).

Symptoms.

Symptoms of antimuscarinic poisoning, which are the direct result of excessive muscarinic blockade, include dry mouth, blurred vision, photophobia, hyperthermia, CNS effects (hallucinations, delirium), and skin that is hot, dry, and flushed. Death results from respiratory depression secondary to blockade of cholinergic receptors in the brain.

Treatment.

Treatment consists of (1) minimizing intestinal absorption of the antimuscarinic agent and (2) administering an antidote. Absorption can be reduced by swallowing activated charcoal, which will adsorb the poison within the intestine, thereby preventing its absorption into the blood.

The most effective antidote to antimuscarinic poisoning is *physostigmine*, an inhibitor of acetylcholinesterase. By inhibiting cholinesterase, physostigmine causes acetylcholine to accumulate at all cholinergic junctions. As acetylcholine builds up, it competes with the antimuscarinic agent for receptor binding, thereby reversing excessive muscarinic blockade. The pharmacology of physostigmine is discussed in Chapter 15.

Warning.

It is important to differentiate between antimuscarinic poisoning, which often resembles psychosis (hallucinations, delirium), and an actual psychotic episode. We need to make the differential diagnosis because antipsychotic drugs, which have antimuscarinic properties of their own, will intensify symptoms if given to a victim of antimuscarinic poisoning. Fortunately, since a true psychotic episode is not ordinarily associated with signs of excessive muscarinic blockade (dry mouth, hyperthermia, dry skin, and so forth), differentiation is not usually difficult.

KEY POINTS

- Muscarinic agonists work through direct activation of muscarinic cholinergic receptors, thereby causing bradycardia; increased secretion from sweat, salivary, bronchial, and gastric glands; contraction of intestinal and bronchial smooth muscle; contraction of the bladder detrusor and relaxation of the

bladder trigone and sphincter; and, in the eye, miosis and accommodation for near vision.

- Bethanechol, the prototype of the muscarinic agonists, is used primarily to relieve urinary retention.
- Muscarinic agonist poisoning is characterized by profuse salivation, tearing, visual disturbances, bronchospasm, diarrhea, bradycardia, and hypotension.
- Muscarinic agonist poisoning is treated with atropine.
- Atropine, the prototype of the muscarinic antagonists (anticholinergic drugs), blocks the actions of acetylcholine (and all other muscarinic agonists) at muscarinic cholinergic receptors, and thereby (1) increases heart rate; (2) reduces secretion from sweat, salivary, bronchial, and gastric glands; (3) relaxes intestinal and bronchial smooth muscle; (4) causes urinary retention (by relaxing the bladder detrusor and contracting the trigone and sphincter); (5) acts in the eye to cause mydriasis and cycloplegia; and (6) acts in the CNS to produce excitation (at low doses) and delirium and hallucinations (at toxic doses).
- Applications of anticholinergic drugs include preanesthetic medication, ophthalmic examinations, reversal of bradycardia, treatment of overactive bladder (OAB), and management of muscarinic agonist poisoning.
- Anticholinergic drugs that are selective for M***3*** muscarinic receptors can still cause many anticholinergic side effects (eg, dry mouth, constipation, impaired vision), but will not slow heart rate (which is mediated by cardiac M***2*** receptors) and will be largely devoid of cognitive effects (which are mediated primarily by M***1*** receptors).
- Classic adverse effects of anticholinergic drugs are dry mouth, blurred vision, photophobia, tachycardia, urinary retention, constipation, and anhidrosis (suppression of sweating).
- Certain drugs—especially antihistamines, tricyclic antidepressants, and phenothiazine antipsychotics—have prominent antimuscarinic actions. These should be used cautiously, if at all, in patients receiving atropine or other muscarinic antagonists.

- The anticholinergic drugs used for OAB are only moderately effective: Symptom reduction is about 30% greater than with placebo therapy, which itself decreases symptoms by 30%.
- The short-acting anticholinergic drugs used for OAB cause more dry mouth and other anticholinergic side effects than do the long-acting drugs.
- Muscarinic antagonist poisoning is characterized by dry mouth, blurred vision, photophobia, hyperthermia, hallucinations and delirium, and skin that is hot, dry, and flushed.
- The best antidote for muscarinic antagonist poisoning is physostigmine, an inhibitor of acetylcholinesterase.

Summary of Major Nursing Implications*

BETHANECHOL

Preadministration Assessment

Therapeutic Goal

Treatment of nonobstructive urinary retention.

Baseline Data

Record fluid intake and output.

Identifying High-Risk Patients

Bethanechol is *contraindicated* for patients with peptic ulcer disease, urinary tract obstruction, intestinal obstruction, coronary insufficiency, hypotension, asthma, and hyperthyroidism.

Implementation: Administration

Route

Oral.

Administration

Advise patients to take bethanechol 1 hour before meals or 2 hours after to reduce gastric upset.

Because effects on the intestine and urinary tract can be rapid and dramatic, ensure that a bedpan or bathroom is readily accessible.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor fluid intake and output to evaluate treatment of urinary retention.

Minimizing Adverse Effects

Excessive muscarinic activation can cause salivation, sweating, urinary urgency, bradycardia, and hypotension. Monitor blood pressure and pulse rate. Observe for signs of muscarinic excess and report these to the physician. **Inform patients about manifestations of muscarinic excess and advise them to notify the prescriber if they occur.**

Management of Acute Toxicity

Overdose produces manifestations of excessive muscarinic stimulation (salivation, sweating, involuntary urination and defecation, bradycardia, severe hypotension). Treat with parenteral atropine and supportive measures.

ATROPINE AND OTHER MUSCARINIC ANTAGONISTS (ANTICHOLINERGIC DRUGS)

Preadministration Assessment

Therapeutic Goal

Atropine has many applications, including preanesthetic medication and treatment of bradycardia, biliary colic, intestinal hypertonicity and hypermotility, and muscarinic agonist poisoning.

Identifying High-Risk Patients

Atropine and other muscarinic antagonists are *contraindicated* for patients with glaucoma, intestinal atony, urinary tract obstruction, and tachycardia. Use with *caution* in patients with asthma.

Implementation: Administration

Routes

Atropine is administered PO, IV, IM, and subQ.

Administration

Dry mouth from muscarinic blockade may interfere with swallowing. **Advise patients to moisten the mouth by sipping water prior to oral administration.**

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Xerostomia (Dry Mouth).

Decreased salivation can dry the mouth. **Teach patients that xerostomia can be relieved by chewing gum, sucking on hard candy, and sipping fluids.**

Blurred Vision.

Paralysis of the ciliary muscle may reduce visual acuity. **Warn patients to avoid hazardous activities if vision is impaired.**

Photophobia.

Muscarinic blockade prevents the pupil from constricting in response to bright light. Keep hospital room lighting low to reduce visual discomfort. **Advise patients to wear sunglasses outdoors.**

Urinary Retention.

Muscarinic blockade in the urinary tract can cause urinary hesitancy or retention. **Advise patients that urinary retention can be minimized by voiding just prior to taking anticholinergic medication.** If urinary retention is

severe, catheterization or treatment with bethanechol (a muscarinic agonist) may be required.

Constipation.

Reduced tone and motility of the gut may cause constipation. **Advise patients that constipation can be reduced by increasing dietary fiber and fluids.** A laxative may be needed if constipation is severe.

Hyperthermia.

Suppression of sweating may result in hyperthermia. **Advise patients to avoid vigorous exercise in warm environments.**

Tachycardia.

Blockade of cardiac muscarinic receptors can accelerate heart rate. Monitor pulse and report significant increases.

Minimizing Adverse Interactions

Antihistamines, tricyclic antidepressants, and *phenothiazines* have prominent antimuscarinic actions. Combining these agents with atropine and other anticholinergic drugs can cause excessive muscarinic blockade.

Management of Acute Toxicity

Symptoms.

Overdose produces dry mouth, blurred vision, photophobia, hyperthermia, hallucinations, and delirium; the skin becomes hot, dry, and flushed. Differentiate muscarinic antagonist poisoning from psychosis!

Treatment.

Treatment centers on limiting absorption of ingested poison (eg, by giving activated charcoal to adsorb the drug) and administering physostigmine, an inhibitor of acetylcholinesterase.

15 Cholinesterase Inhibitors and Their Use in Myasthenia Gravis

Cholinesterase inhibitors are drugs that prevent the degradation of acetylcholine (ACh) by acetylcholinesterase (also known simply as cholinesterase [ChE]). By preventing the inactivation of ACh, the cholinesterase inhibitors enhance the actions of ACh released from cholinergic neurons. Hence, the cholinesterase inhibitors can be viewed as indirect-acting cholinergic agonists. Since cholinesterase inhibitors can intensify transmission at all cholinergic junctions (muscarinic, ganglionic, and neuromuscular), these drugs can elicit a broad spectrum of responses. Because they lack selectivity, cholinesterase inhibitors have limited therapeutic applications. Cholinesterase inhibitors are also known as *anticholinesterase agents*.

There are two basic categories of cholinesterase inhibitors: (1) *reversible inhibitors* and (2) *"irreversible" inhibitors*. The reversible inhibitors produce effects of moderate duration. In contrast, the irreversible inhibitors produce effects that are long lasting.

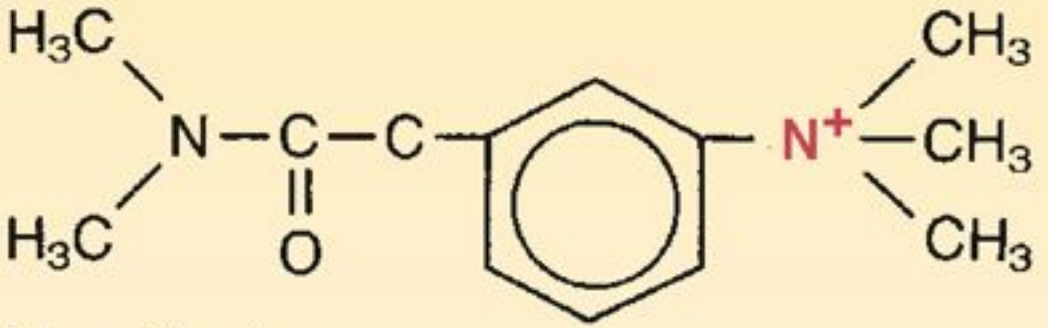
REVERSIBLE CHOLINESTERASE INHIBITORS

Neostigmine

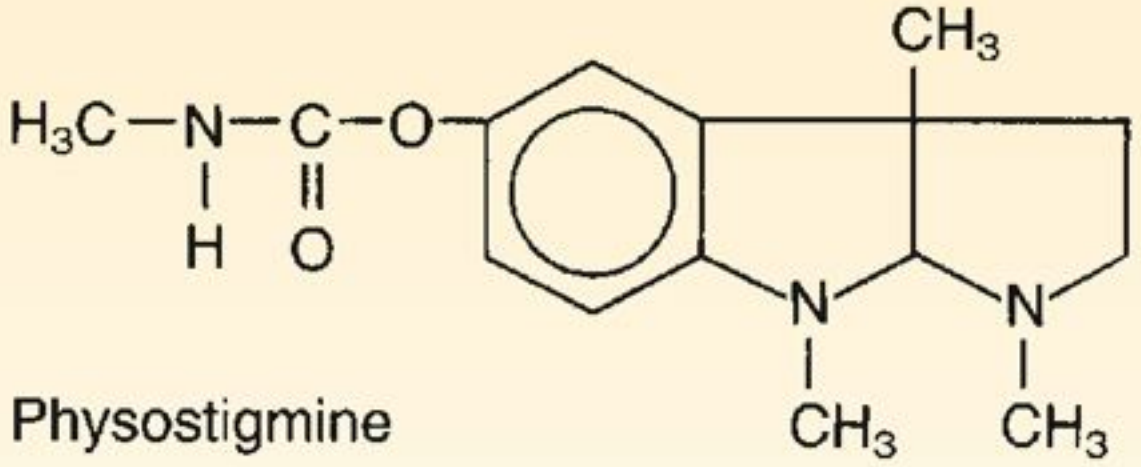
Neostigmine [Prostigmin] typifies the reversible cholinesterase inhibitors and will serve as our prototype for the group. The drug's principal indication is *myasthenia gravis*.

Chemistry

As indicated in Figure 15-1, neostigmine contains a quaternary nitrogen atom, and hence always carries a positive charge. Because of this charge, neostigmine cannot readily cross membranes, including those of the GI tract, blood-brain barrier, and placenta. Consequently, neostigmine is absorbed poorly following oral administration and has minimal effects on the brain and fetus.



Neostigmine



Physostigmine

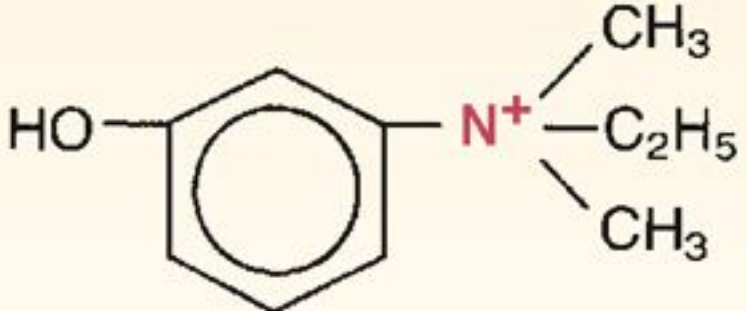


Figure 15-1 Structural formulas of reversible cholinesterase inhibitors. Note that neostigmine and edrophonium are quaternary ammonium compounds, but physostigmine is not. What does this difference imply about the relative abilities of these drugs to cross membranes, including the blood-brain barrier?

Mechanism of Action

Neostigmine and the other reversible cholinesterase inhibitors can be envisioned as poor substrates for ChE. As indicated in Figure 15-2, the normal function of ChE is to break down acetylcholine into choline and acetic acid. This process is termed a *hydrolysis* reaction because of the water molecule involved. As depicted in Figure 15-3A, hydrolysis of ACh takes place in two steps: (1) binding of ACh to the active center of ChE, followed by (2) splitting of ACh, which regenerates free ChE. The overall reaction between ACh and ChE is extremely fast. As a result, one molecule of ChE can break down a huge amount of ACh in a very short time.

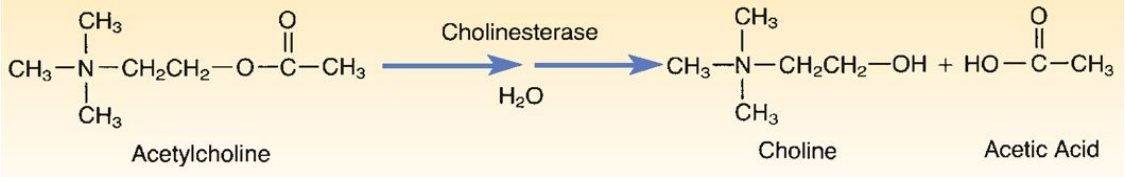


Figure 15-2 Hydrolysis of acetylcholine by cholinesterase.

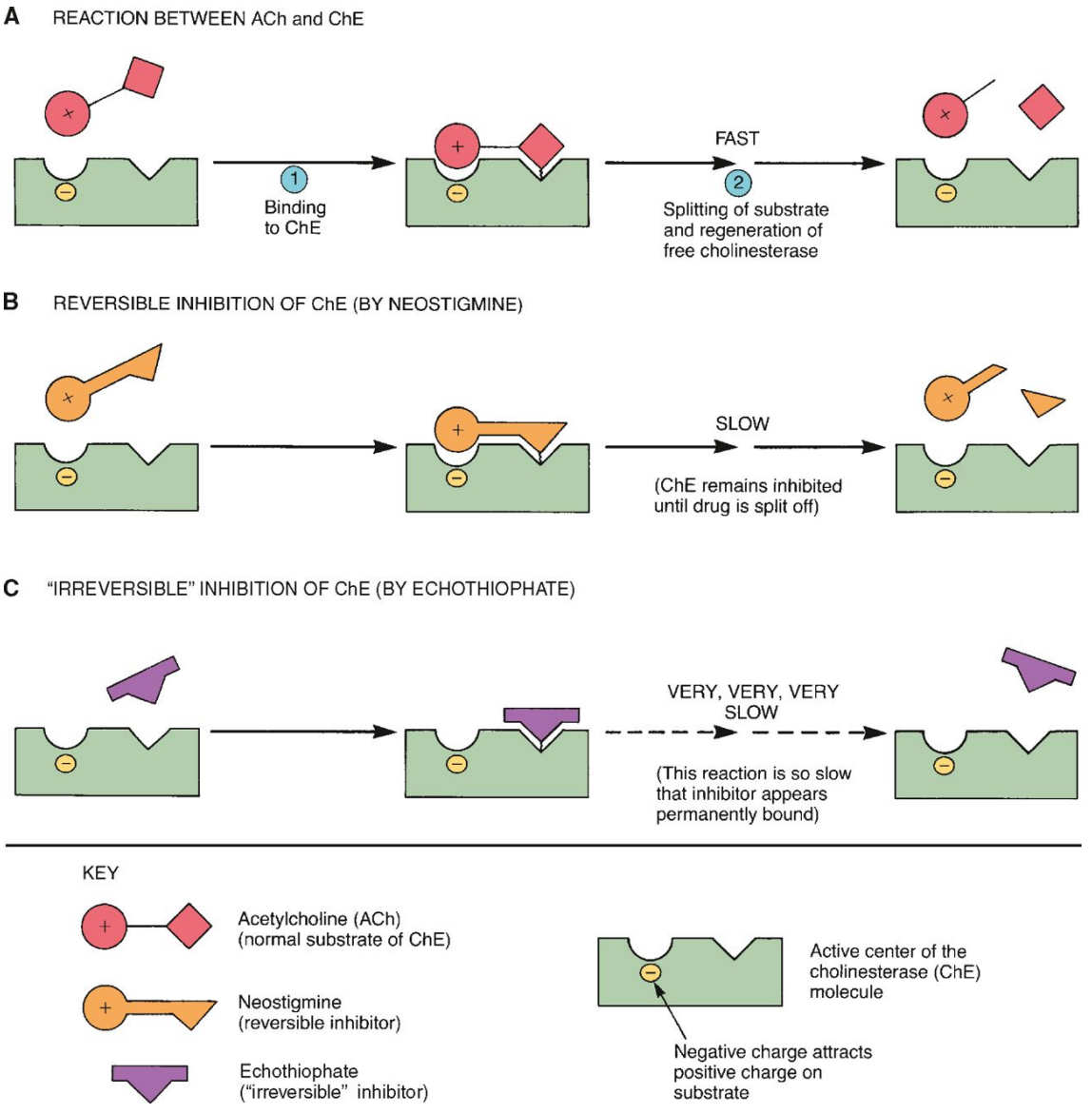


Figure 15-3 Inhibition of cholinesterase by reversible and "irreversible" inhibitors. (See text for details.)

As depicted in Figure 15-3*B*, the reaction between neostigmine and ChE is very similar to the reaction between ACh and ChE. The difference between the two reactions is simply that ChE splits neostigmine more slowly than it splits ACh. Hence, once neostigmine becomes bound to the active center of ChE, the drug remains in place for a relatively long time, thereby preventing ChE from cata-

lyzing the breakdown of ACh. ChE remains inhibited until it finally succeeds in splitting neostigmine off.

Pharmacologic Effects

By preventing inactivation of ACh, neostigmine and the other cholinesterase inhibitors can intensify transmission at virtually all junctions where ACh is the transmitter. In sufficient doses, cholinesterase inhibitors can produce skeletal muscle stimulation, activation of muscarinic receptors, ganglionic stimulation, and activation of cholinergic receptors in the central nervous system (CNS). However, when used *therapeutically,* cholinesterase inhibitors usually affect only muscarinic receptors on organs and nicotinic receptors of the neuromuscular junction (NMJ). Ganglionic transmission and CNS function are usually unaltered.

Muscarinic Responses.

Muscarinic effects of the cholinesterase inhibitors are identical to those of the direct-acting muscarinic agonists. By preventing breakdown of ACh, cholinesterase inhibitors can cause increased glandular secretions, increased tone and motility of GI smooth muscle, urinary urgency, bradycardia, bronchial constriction, miosis, and focusing of the lens for near vision.

Neuromuscular Effects.

The effects of cholinesterase inhibitors on skeletal muscle are dose dependent. At *therapeutic* doses, these drugs *increase* force of contraction. In contrast, *toxic* doses *reduce* force of contraction. Contractile force is reduced because excessive amounts of ACh at the NMJ keep the motor end-plate in a state of constant depolarization, thereby causing depolarizing neuromuscular blockade (see Chapter 16).

Central Nervous System.

Effects on the CNS vary with drug concentration. *Therapeutic* levels can produce mild *stimulation,* whereas *toxic* levels *depress* the CNS, including the areas that regulate respiration. However, it must be noted that, for CNS effects to occur, the inhibitor must first penetrate the blood-brain barrier, which some

cholinesterase inhibitors can do only when present in very high concentrations.

Pharmacokinetics

Neostigmine may be administered orally or by injection (IM, IV, subQ). Because neostigmine carries a positive charge, the drug is poorly absorbed following oral administration. Once absorbed, neostigmine can reach sites of action at the NMJ and peripheral muscarinic receptors, but cannot cross the blood-brain barrier to affect the CNS. Duration of action is 2 to 4 hours. Neostigmine is eliminated by enzymatic degradation: Cholinesterase, the enzyme that neostigmine inhibits, eventually converts neostigmine itself to an inactive product.

Therapeutic Uses

Myasthenia Gravis.

Myasthenia gravis is a major indication for neostigmine and several other reversible cholinesterase inhibitors. Treatment of myasthenia gravis is discussed separately later.

Reversal of Nondepolarizing Neuromuscular Blockade.

By causing accumulation of ACh at the NMJ, cholinesterase inhibitors can reverse the effects of nondepolarizing neuromuscular blocking agents (eg, pancuronium). This ability has two clinical applications: (1) reversal of neuromuscular blockade in postoperative patients and (2) treatment of overdose with a nondepolarizing neuromuscular blocker. When neostigmine is used to treat neuromuscular blocker overdose, artificial respiration must be maintained until muscle function has fully recovered. At the doses employed to reverse neuromuscular blockade, neostigmine is likely to elicit substantial muscarinic responses. If necessary, these can be reduced with atropine. It is important to note that cholinesterase inhibitors cannot be employed to counteract the effects of succinylcholine, a *depolarizing* neuromuscular blocker.

Adverse Effects

Excessive Muscarinic Stimulation.

Accumulation of ACh at muscarinic receptors can result in excessive salivation, increased gastric secretions, increased tone and motility of the GI tract, urinary urgency, bradycardia, sweating, miosis, and spasm of accommodation (focusing of the lens for near vision). If necessary, these responses can be suppressed with atropine.

Neuromuscular Blockade.

If administered in toxic doses, cholinesterase inhibitors can cause accumulation of ACh in amounts sufficient to produce depolarizing neuromuscular blockade. Paralysis of respiratory muscles can be fatal.

Precautions and Contraindications

Most of the precautions and contraindications regarding the cholinesterase inhibitors are the same as those for the direct-acting muscarinic agonists. These include (1) obstruction of the GI tract, (2) obstruction of the urinary tract, (3) peptic ulcer disease, (4) asthma, (5) coronary insufficiency, and (6) hyperthyroidism. The rationales underlying these precautions are discussed in Chapter 14. In addition to precautions related to muscarinic stimulation, cholinesterase inhibitors are contraindicated for patients receiving succinylcholine.

Drug Interactions

Muscarinic Antagonists.

The effects of cholinesterase inhibitors at muscarinic receptors are opposite to those of atropine (and other muscarinic antagonists). Consequently, cholinesterase inhibitors can be used to overcome excessive muscarinic blockade caused by atropine. Conversely, atropine can be used to reduce excessive muscarinic stimulation caused by cholinesterase inhibitors.

Nondepolarizing Neuromuscular Blockers.

By causing accumulation of ACh at the NMJ, cholinesterase inhibitors can reverse muscle relaxation induced with pancuronium and other nondepolarizing neuromuscular blocking agents.

Depolarizing Neuromuscular Blockers.

Cholinesterase inhibitors do not reverse the muscle-relaxant effects of succinylcholine, a depolarizing neuromuscular blocker. In fact, because cholinesterase inhibitors will decrease the breakdown of succinylcholine by cholinesterase, cholinesterase inhibitors will actually *intensify* neuromuscular blockade caused by succinylcholine.

Acute Toxicity

Symptoms.

Overdose with cholinesterase inhibitors causes *excessive muscarinic stimulation* and *respiratory depression*. (Respiratory depression results from a combination of depolarizing neuromuscular blockade and CNS depression.) The state produced by cholinesterase inhibitor poisoning is sometimes referred to as *cholinergic crisis*.

Treatment.

Intravenous *atropine* can alleviate the muscarinic effects of cholinesterase inhibition. Respiratory depression from cholinesterase inhibitors cannot be managed with drugs. Rather, treatment consists of mechanical ventilation with oxygen. Suctioning may be necessary if atropine fails to suppress bronchial secretions.

Preparations, Dosage, and Administration

Preparations.

Neostigmine [Prostigmin] is available as two salts: *neostigmine bromide* (for oral use) and *neostigmine methylsulfate* (for IM, IV, and subQ use). Neostigmine bromide is available in 15-mg tablets. Neostigmine methylsulfate is available in solution (0.25, 0.5, and 1 mg/mL).

Dosage and Administration.

Dosages for *myasthenia gravis* are highly individualized, ranging from 15 to 375 mg/day administered PO in divided doses every 3 to 4 hours. It is important to note that oral doses are much higher than parenteral doses.

To treat *poisoning by nondepolarizing neuromuscular blockers,* the initial dose is 0.5 to 2.0 mg administered by slow IV injection. Additional doses totaling a maximum of 5 mg may be given as required.

Other Reversible Cholinesterase Inhibitors

Physostigmine

The basic pharmacology of physostigmine is identical to that of neostigmine—except that physostigmine readily crosses membranes whereas neostigmine does not. Why? Because, in contrast to neostigmine, physostigmine is *not* a quaternary ammonium compound and hence does *not* carry a charge. Because physostigmine is uncharged, the drug crosses membranes with ease.

Physostigmine is the drug of choice for treating *poisoning by atropine and other drugs that cause muscarinic blockade* (eg, antihistamines, tricyclic antidepressants, phenothiazine antipsychotics). Physostigmine counteracts antimuscarinic poisoning by causing ACh to build up at muscarinic junctions. The accumulated ACh competes with the muscarinic blocker for receptor binding, and thereby reverses receptor blockade. Physostigmine is preferred to neostigmine for antimuscarinic poisoning because, lacking a charge, physostigmine is able to cross the blood-brain barrier to reverse muscarinic blockade in the CNS. The usual dose to treat antimuscarinic poisoning is 2 mg given by IM or slow IV injection.

Ambenonium, Edrophonium, and Pyridostigmine

These three drugs have pharmacologic effects much like those of neostigmine, our prototype cholinesterase inhibitor. One of these drugs—edrophonium—is noteworthy for its very brief duration of action. All three drugs are used for *myasthenia gravis.* Routes of administration and indications are summarized in Table 15-1.

Drugs for Alzheimer's Disease

Four cholinesterase inhibitors—*donepezil* [Aricept], *galantamine* [Razadyne], *rivastigmine* [Exelon], and *tacrine* [Cognex]—are approved for Alzheimer's disease, although one of them—tacrine—is rarely used. With all four, benefits de-

rive from inhibiting cholinesterase in the CNS. These drugs are discussed in Chapter 22.

"IRREVERSIBLE" CHOLINESTERASE INHIBITORS

The "irreversible" cholinesterase inhibitors are highly toxic. These agents are employed primarily as *insecticides*. During World War II, huge quantities of irreversible cholinesterase inhibitors were produced for possible use as *nerve agents,* but were never deployed. Today, there is concern that these agents might be employed as weapons of terrorism. The only clinical indication for the irreversible inhibitors is *glaucoma*.

Generic Name [Trade Name]	Routes	Myasthenia Gravis: Diagnosis	Myasthenia Gravis: Treatment	Glaucoma	Reversal of Nondepolarizing Neuromuscular Blockade	Antidote to Poisoning by Muscarinic Antagonists	Alzheimer's Disease
Reversible Inhibitors							
Neostigmine [Prostigmin]	PO, IM, IV, subQ		✓		✓		
Ambenonium [Mytelase]	PO		✓				
Pyridostigmine [Mestinon]	PO, IV		✓		✓		
Edrophonium [Tensilon, Enlon, Reversol]	IM, IV	✓			✓		
Physostigmine [Antilirium]	IM, IV					✓	
Donepezil [Aricept]	PO						✓
Galantamine [Razadyne]*	PO						✓
Rivastigmine [Exelon]	PO, transdermal						✓
Tacrine [Cognex]	PO						✓
Irreversible Inhibitor							
Echothiophate [Phospholine Iodide]	Topical			✓			

TABLE 15-1 Clinical Applications of Cholinesterase Inhibitors

* Formerly named Reminyl.

Basic Pharmacology

Chemistry

All irreversible cholinesterase inhibitors contain an atom of *phosphorus* (Fig. 15-4). Because of this phosphorus atom, the irreversible inhibitors are known as *organophosphate* cholinesterase inhibitors.

Almost all irreversible cholinesterase inhibitors are *highly lipid soluble*. As a result, these drugs are readily absorbed from all routes of administration. They can even be absorbed directly through the skin. Easy absorption, coupled with high toxicity, is what makes these drugs good insecticides—and gives them the potential for use as agents of chemical warfare. Once absorbed, the organophosphate inhibitors have ready access to all tissues and organs, including the CNS.

Mechanism of Action

The irreversible cholinesterase inhibitors bind to the active center of cholinesterase, thereby preventing the enzyme from hydrolyzing ACh. Although these drugs can be split from ChE, the splitting reaction takes place *extremely* slowly (see Fig. 15-3C). Hence, under normal conditions, their binding to ChE can be considered irreversible. Because binding is permanent, effects persist until new molecules of cholinesterase can be synthesized.

Although we normally consider the bond between irreversible inhibitors and cholinesterase permanent, this bond can, in fact, be broken. To break the bond, and thereby reverse the inhibition of cholinesterase, we must administer *pralidoxime* (see below).

Pharmacologic Effects

The irreversible cholinesterase inhibitors produce essentially the same spectrum of effects as the reversible inhibitors. The principal difference is that responses to irreversible inhibitors last a long time, whereas responses to reversible inhibitors are brief.

Therapeutic Uses

The irreversible cholinesterase inhibitors have only one indication: treatment of *glaucoma*. And for that indication, only one drug—echothiophate—is available. The limited indications for these drugs should be no surprise given their potential for toxicity. The use of echothiophate for glaucoma is discussed in Chapter 103 (Drugs for the Eye).

Toxicology

Sources of Poisoning.

Poisoning by organophosphate cholinesterase inhibitors is not uncommon. Agricultural workers have been poisoned by accidental ingestion of organophosphate insecticides and by absorption of these lipid-soluble compounds through the skin. In addition, because organophosphate insecticides are readily available to the general public, poisoning may occur accidentally or from attempted homicide or suicide. Exposure could also occur if these drugs were used as instruments of warfare or terrorism (see Chapter 109).

Symptoms.

Toxic doses of irreversible cholinesterase inhibitors produce *cholinergic crisis,* a condition characterized by *excessive muscarinic stimulation and depolarizing neuromuscular blockade*. Overstimulation of muscarinic receptors results in profuse secretions from salivary and bronchial glands, involuntary urination and defecation, laryngospasm, and bronchoconstriction. Neuromuscular blockade can result in paralysis, followed by death from apnea. Convulsions of CNS origin precede paralysis and apnea.

Treatment.

Treatment involves the following: (1) mechanical ventilation using oxygen, (2) giving *atropine* to reduce muscarinic stimulation, (3) giving *pralidoxime* to reverse inhibition of cholinesterase (primarily at the NMJ), and (4) giving *diazepam* to suppress convulsions.

Pralidoxime.

Pralidoxime is a specific antidote to poisoning by the irreversible (organophosphate) cholinesterase inhibitors; the drug is *not* effective against poisoning by reversible cholinesterase inhibitors. In poisoning by irreversible inhibitors, benefits derive from causing the inhibitor to dissociate from the active center of cholinesterase. Reversal is most effective at the NMJ. The drug is much less effective at reversing cholinesterase inhibition at muscarinic and ganglionic sites. Furthermore, since pralidoxime is a quaternary ammonium compound, it cannot cross the blood-brain barrier, and therefore cannot reverse cholinesterase inhibition in the CNS.

To be effective, pralidoxime must be administered soon after organophosphate poisoning has occurred. If too much time elapses, a process called *aging* takes place. In this process, the bond between the organophosphate inhibitor and cholinesterase increases in strength. Once aging has occurred, pralidoxime is unable to cause the inhibitor to dissociate from the enzyme. The time required for aging depends on the agent involved. For example, with a nerve agent called *soman,* aging occurs in just 2 minutes. In contrast, with a nerve agent called *tabun* (see Fig. 15-4), aging requires 13 hours.

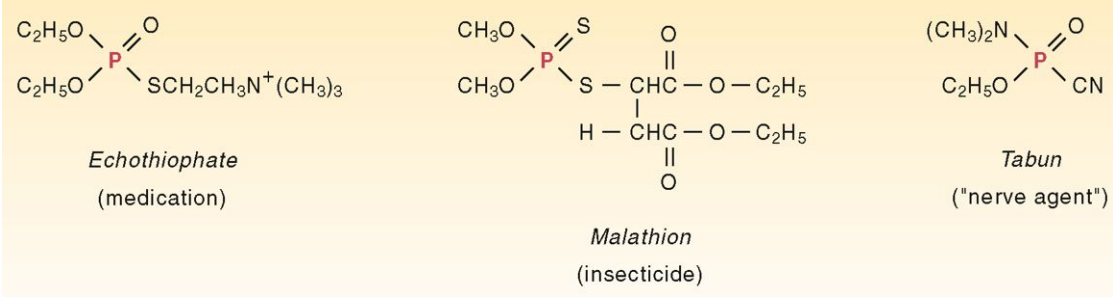


Figure 15-4 Structural formulas of "irreversible" cholinesterase inhibitors. Note that irreversible cholinesterase inhibitors contain an atom of phosphorus. Because of this atom, these drugs are known as organophosphate cholinesterase inhibitors. With the exception of echothiophate, all of these drugs are highly lipid soluble, and therefore move throughout the body with ease.

The usual dose for pralidoxime is 1 to 2 gm administered IV or IM. Intravenous doses should be infused slowly (over 20 to 30 minutes) to avoid hypertension. For prolonged treatment, dosing can be repeated every hour, or the drug can be given by continuous infusion (500 mg/hr). Pralidoxime is available alone under the trade name *Protopam,* and in combination with atropine under the trade name *DuoDote*.

MYASTHENIA GRAVIS

Pathophysiology

Myasthenia gravis (MG) is a neuromuscular disorder characterized by fluctuating muscle weakness and a predisposition to rapid fatigue. Common symptoms include ptosis (drooping eyelids), difficulty swallowing, and weakness of skeletal muscles. Patients with severe MG may have difficulty breathing owing to weakness of the muscles of respiration.

Symptoms of MG result from an autoimmune process in which the patient's immune system produces antibodies that attack nicotinic***M*** receptors on skeletal muscle. As a result, the number of functional receptors at the NMJ is reduced by 70% to 90%, thereby causing muscle weakness.

Treatment with Cholinesterase Inhibitors

Beneficial Effects.

Reversible cholinesterase inhibitors (eg, neostigmine) are the mainstay of therapy. By preventing ACh inactivation, anticholinesterase agents can intensify the effects of ACh released from motor neurons, and can thereby increase muscle strength. Cholinesterase inhibitors do not cure MG. Rather, they only produce symptomatic relief, and hence patients usually need therapy lifelong.

When working with a hospitalized patient, keep in mind that muscle strength may be insufficient to permit swallowing. Accordingly, you should assess the ability to swallow before giving oral medications. Assessment is accomplished by giving the patient a few sips of water. If the patient is unable to swallow the water, parenteral medication must be substituted for oral medication.

Side Effects.

Because cholinesterase inhibitors can inhibit acetylcholinesterase at any location, these drugs will cause ACh to accumulate at muscarinic junctions as well as at NMJs. If muscarinic responses are excessive, atropine may be given to suppress them. However, atropine should not be employed *routinely*. Why? Because the drug can mask the early signs (eg, excessive salivation) of overdose with anticholinesterase agents.

Dosage Adjustment.

In the treatment of MG, establishing an optimal dosage for cholinesterase inhibitors can be a challenge. Dosage determination is accomplished by administering a small initial dose followed by additional small doses until an optimal level of muscle function has been achieved. Important signs of improvement include increased ease of swallowing and increased ability to raise the eyelids. You can help establish a correct dosage by keeping records of (1) times of drug administration, (2) times at which fatigue occurs, (3) the state of muscle strength before and after drug administration, and (4) signs of excessive muscarinic stimulation.

To maintain optimal responses, patients must occasionally modify dosage themselves. To do this, they must be taught to recognize signs of undermedication (ptosis, difficulty in swallowing) and signs of overmedication (excessive salivation and other muscarinic responses). Patients may also need to modify dosage in anticipation of exertion. For example, they may find it necessary to take supplementary medication 30 to 60 minutes prior to such activities as eating and shopping.

Usual adult dosages for the three agents used to treat myasthenia gravis are

- *Ambenonium*—15 to 100 mg/day in divided doses
- *Neostigmine*—15 to 375 mg/day in divided doses
- *Pyridostigmine*—60 to 1500 mg/day in divided doses

Myasthenic Crisis and Cholinergic Crisis.

Myasthenic Crisis.

Patients who are inadequately medicated may experience myasthenic crisis, a state characterized by extreme muscle weakness (caused by insufficient ACh at the NMJ). Left untreated, myasthenic crisis can result in death from paralysis of the muscles of respiration. A cholinesterase inhibitor (eg, neostigmine) is used to relieve the crisis.

Cholinergic Crisis.

As noted, overdose with a cholinesterase inhibitor can produce cholinergic crisis. Like myasthenic crisis, cholinergic crisis is characterized by extreme muscle weakness or frank paralysis. In addition, cholinergic crisis is accom-

panied by signs of excessive muscarinic stimulation. Treatment consists of respiratory support plus atropine. The offending cholinesterase inhibitor should be withheld until muscle strength has returned.

Distinguishing Myasthenic Crisis from Cholinergic Crisis.

Because myasthenic crisis and cholinergic crisis share similar symptoms (muscle weakness or paralysis), but are treated very differently, it is essential to distinguish between them. A history of medication use or signs of excessive muscarinic stimulation are usually sufficient to permit a differential diagnosis. If these clues are inadequate, the differential diagnosis can be made by administering a challenging dose of *edrophonium,* an ultrashort-acting cholinesterase inhibitor. If edrophonium-induced elevation of ACh levels alleviates symptoms, the crisis is myasthenic. Conversely, if edrophonium intensifies symptoms, the crisis is cholinergic. Since the symptoms of cholinergic crisis will be made even worse by edrophonium, atropine and oxygen should be immediately available whenever edrophonium is used for this test.

Use of Identification by the Patient.

Because of the possibility of experiencing either myasthenic crisis or cholinergic crisis, and because both crises can be fatal, patients with MG should be encouraged to wear a Medic Alert bracelet or some other form of identification to inform emergency medical personnel of their condition.

KEY POINTS

- Cholinesterase inhibitors prevent breakdown of ACh by acetylcholinesterase, causing ACh to accumulate in synapses, which in turn causes activation of muscarinic receptors, nicotinic receptors in ganglia and the NMJ, and cholinergic receptors in the CNS.
- The major use of reversible cholinesterase inhibitors is treatment of myasthenia gravis. Benefits derive from accumulation of ACh at the NMJ.

- Secondary uses for reversible cholinesterase inhibitors are reversal of nondepolarizing neuromuscular blockade and treatment of glaucoma, Alzheimer's disease, and poisoning by muscarinic antagonists.
- Because physostigmine crosses membranes easily, this drug is the preferred cholinesterase inhibitor for treating poisoning by muscarinic antagonists.
- Irreversible cholinesterase inhibitors, also known as organophosphate cholinesterase inhibitors, are used primarily as insecticides. The only indication for these potentially toxic drugs is glaucoma.
- Most organophosphate cholinesterase inhibitors are highly lipid soluble. As a result, they can be absorbed directly through the skin and distribute easily to all tissues and organs.
- Overdose with cholinesterase inhibitors produces cholinergic crisis, characterized by depolarizing neuromuscular blockade plus signs of excessive muscarinic stimulation (hypersalivation, tearing, sweating, bradycardia, involuntary urination and defecation, miosis, and spasm of accommodation). Death results from respiratory depression.
- Poisoning by *reversible* cholinesterase inhibitors is treated with atropine (to reverse muscarinic stimulation) plus mechanical ventilation.
- Poisoning by *organophosphate* cholinesterase inhibitors is treated with atropine, mechanical ventilation, pralidoxime (to reverse inhibition of cholinesterase, primarily at the NMJ), and diazepam (to suppress seizures).

Summary of Major Nursing Implications*

REVERSIBLE CHOLINESTERASE INHIBITORS

Ambenonium

Donepezil

Edrophonium

Galantamine

Neostigmine

Physostigmine

Pyridostigmine

Rivastigmine

Tacrine

Preadministration Assessment

Therapeutic Goal

Cholinesterase inhibitors are used to treat myasthenia gravis, glaucoma, Alzheimer's disease, and poisoning by muscarinic antagonists and to reverse nondepolarizing neuromuscular blockade. Applications of individual agents are indicated in Table 15-1.

Baseline Data

Myasthenia Gravis.

Determine the extent of neuromuscular dysfunction by assessing muscle strength, fatigue, ptosis, and ability to swallow.

Identifying High-Risk Patients

Cholinesterase inhibitors are *contraindicated* for patients with mechanical obstruction of the intestine or urinary tract. Exercise *caution* in patients with peptic ulcer disease, bradycardia, asthma, or hyperthyroidism.

Implementation: Administration

Routes

These drugs are given orally, topically (PO, transdermal), and parenterally (IM, IV, subQ). Routes for individual agents are summarized in Table 15-1.

Administration and Dosage in Myasthenia Gravis

Administration.

Assess the patient's ability to swallow before giving oral medication. If swallowing is impaired, substitute a parenteral medication.

Optimizing Dosage.

Monitor for therapeutic responses (see below) and adjust the dosage accordingly. **Teach patients to distinguish between insufficient and excessive dosing so they can participate effectively in dosage adjustment.**

Reversing Nondepolarizing Neuromuscular Blockade

To reverse toxicity from overdose with a nondepolarizing neuromuscular blocking agent (eg, pancuronium), administer pyridostigmine or edrophonium IV. Support respiration until muscle strength has recovered fully.

Treating Muscarinic Antagonist Poisoning

Physostigmine is the drug of choice for this indication. The usual dose is 2 mg administered by IM or slow IV injection.

Implementation: Measures to Enhance Therapeutic Effects

Myasthenia Gravis

Promoting Compliance.

Inform patients that MG is not usually curable, and hence treatment is lifelong. Encourage patients to take their medication as prescribed and to play an active role in dosage adjustment.

Using Identification.

Because patients with MG are at risk of fatal complications (cholinergic crisis, myasthenic crisis), encourage them to wear a Medic Alert bracelet or similar identification to inform emergency medical personnel of their condition.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Myasthenia Gravis.

Monitor and record (1) times of drug administration; (2) times at which fatigue occurs; (3) state of muscle strength, ptosis, and ability to swallow; and (4) signs of excessive muscarinic stimulation. Dosage is increased or decreased based on these observations.

Monitor for *myasthenic crisis* (extreme muscle weakness, paralysis of respiratory muscles), which can occur when cholinesterase inhibitor dosage is insufficient. Manage with respiratory support and increased dosage.

Be certain to distinguish myasthenic crisis from cholinergic crisis. How? By observing for signs of excessive muscarinic stimulation, which will accompany cholinergic crisis but not myasthenic crisis. If necessary, these crises can be differentiated by giving *edrophonium,* which reduces symptoms of myasthenic crisis and intensifies symptoms of cholinergic crisis.

Minimizing Adverse Effects

Excessive Muscarinic Stimulation.

Accumulation of ACh at muscarinic receptors can cause profuse salivation, increased tone and motility of the gut, urinary urgency, sweating, miosis, spasm of accommodation, bronchoconstriction, and bradycardia. **Inform patients about signs of excessive muscarinic stimulation and advise them to notify the prescriber if these occur.** Excessive muscarinic responses can be managed with *atropine*.

Cholinergic Crisis.

his condition results from cholinesterase inhibitor overdose. Manifestations are skeletal muscle paralysis (from depolarizing neuromuscular blockade) and signs of excessive muscarinic stimulation (eg, salivation, sweating, miosis, bradycardia).

Manage with mechanical ventilation and atropine. Cholinergic crisis must be distinguished from myasthenic crisis.

16 Drugs That Block Nicotinic Cholinergic Transmission: Neuromuscular Blocking Agents and Ganglionic Blocking Agents

The drugs discussed in this chapter act through blockade of nicotinic cholinergic receptors. The *neuromuscular* blocking agents block nicotinic***M*** receptors at the neuromuscular junction. The *ganglionic* blocking agents block nicotinic***N*** receptors in autonomic ganglia. The neuromuscular blockers have important clinical applications. In contrast, the ganglionic blockers, once used widely for hypertension, have been largely replaced by newer drugs.

NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents prevent acetylcholine from activating nicotinic***M*** receptors on skeletal muscles, and thereby cause muscle relaxation. These drugs are given to produce muscle relaxation during surgery, endotracheal intubation, mechanical ventilation, and other procedures.

Control of Muscle Contraction

Before we discuss the neuromuscular blockers, we need to review physiologic control of muscle contraction. In particular, we need to understand *excitation-contraction coupling,* the process by which an action potential in a motor neuron leads to contraction of a muscle.

Basic Concepts: Polarization, Depolarization, and Repolarization

The concepts of *polarization, depolarization,* and *repolarization* are important to understanding both muscle contraction and the neuromuscular blocking drugs. In *resting* muscle there is uneven distribution of electrical charge across the inner and outer surfaces of the cell membrane. As shown in Figure 16-1, positive charges cover the outer surface of the membrane and negative charges cover the inner surface. Because of this uneven charge distribution, the resting membrane is said to be *polarized*.

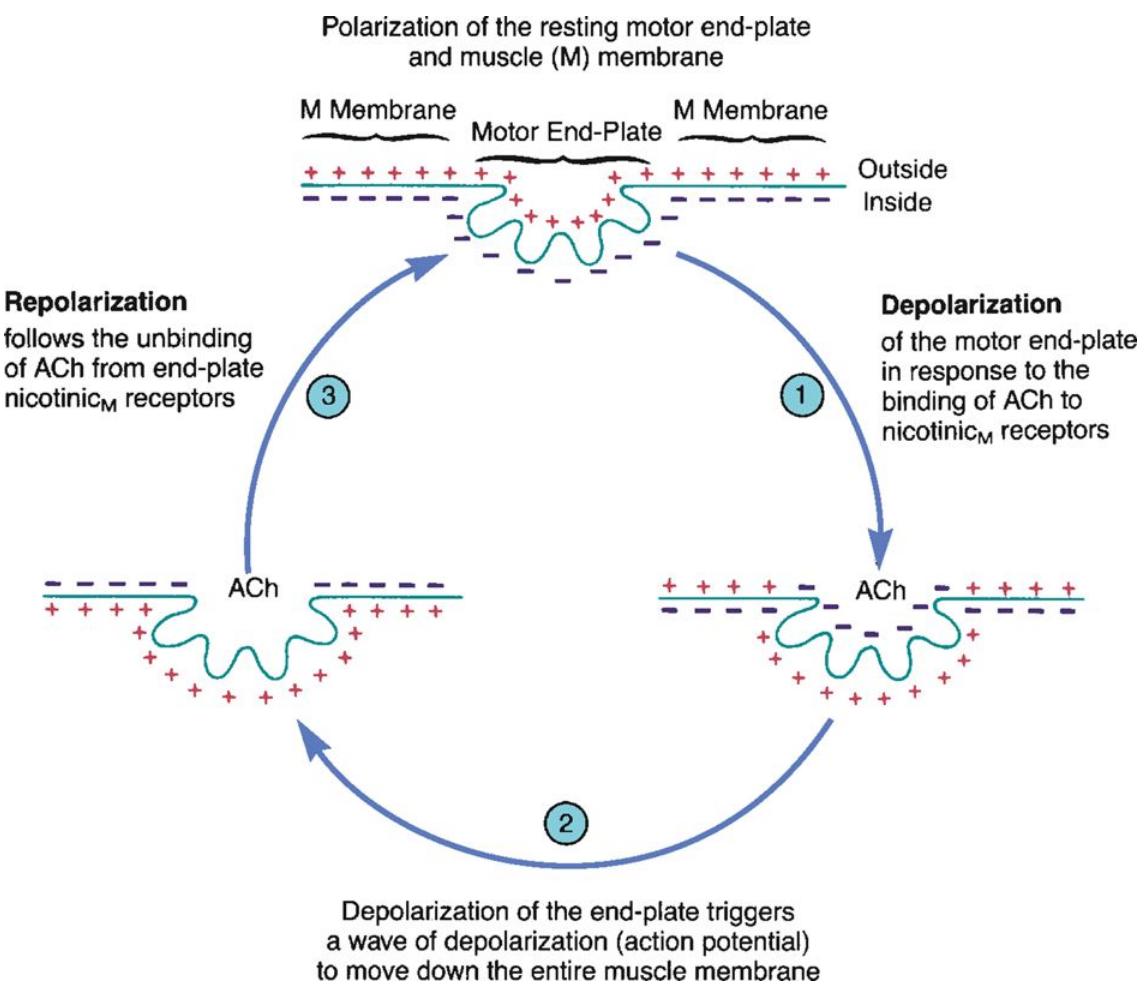


Figure 16-1 The depolarization-repolarization cycle of the motor end-plate and muscle membrane. (ACh acetylcholine.)

When the membrane *depolarizes,* positive charges move from outside to inside. So many positive charges move inward that the inside of the membrane becomes more positive than the outside (see Fig. 16-1).

Under physiologic conditions, depolarization of the muscle membrane is followed almost instantaneously by *repolarization*. Repolarization is accomplished by pumping positively charged ions out of the cell. Repolarization restores the original resting membrane state, with positive charges on the outer surface and negative charges on the inner surface.

Steps in Muscle Contraction

The steps leading to muscle contraction are summarized in Figure 16-2. The process begins with the arrival of an action potential at the terminal of a motor neuron, causing release of acetylcholine (ACh) into the subneural space. Acetylcholine then binds reversibly to nicotinic*M* receptors on the motor end-plate (a specialized region of the muscle membrane that contains the receptors for ACh) and causes the end-plate to *depolarize*. This depolarization initiates a muscle action potential (ie, a wave of depolarization that spreads rapidly over the entire muscle membrane), which in turn triggers the release of calcium from the sarcoplasmic reticulum (SR) of the muscle. This calcium permits the interaction of actin and myosin, thereby causing contraction. Very rapidly, ACh dissociates from the motor end-plate, the motor end-plate repolarizes, the muscle membrane repolarizes, and calcium is taken back up into the SR. Because there is no longer any calcium available to support the interaction of actin and myosin, the muscle relaxes.

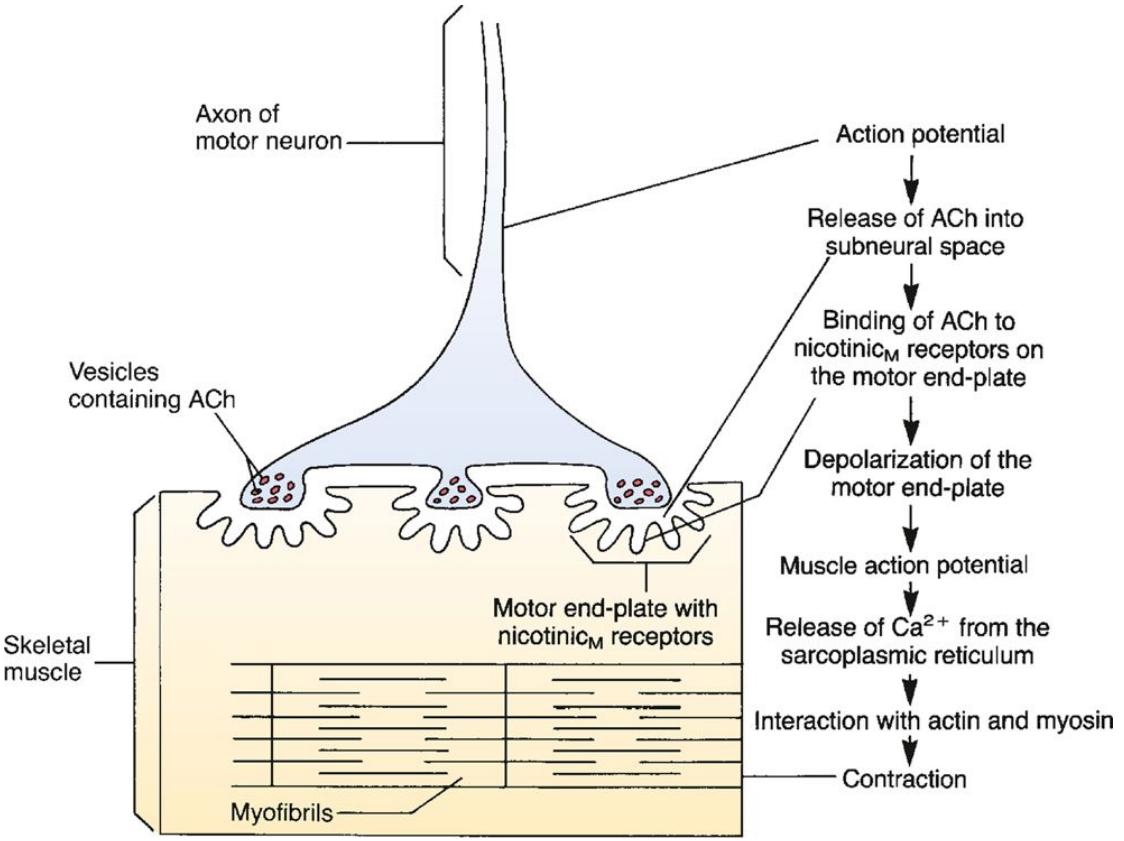


Figure 16-2 Steps in excitation-contraction coupling. (ACh acetylcholine.)

Sustained muscle contraction requires a continuous series of motor neuron action potentials. These action potentials cause repeated release of ACh, which causes repeated activation of nicotinic receptors on the motor end-plate. As a result, the end-plate goes through repeating cycles of depolarization and repolarization, which results in sufficient release of calcium to sustain contraction. If for some reason the motor end-plate fails to repolarize—that is, if the end-plate remains in a *depolarized* state—the signal for calcium release will stop, calcium will undergo immediate reuptake into the SR, and contraction will cease.

Classification of Neuromuscular Blockers

The neuromuscular blockers can be classified according to *mechanism of action* and *time course of action*. When classified by mechanism of action, these drugs fall into two categories: nondepolarizing agents and depolarizing agents. When classified by time course, these drugs fall into three categories: long acting, intermediate acting, and ultrashort acting.

Nondepolarizing Neuromuscular Blockers I: Tubocurarine

Tubocurarine is the oldest nondepolarizing neuromuscular blocker and will serve as our prototype for the group. However, please note that, although tubocurarine will be our prototype, the drug is no longer used in the United States. Why? Because it has been replaced by newer nondepolarizing blockers that lack certain undesirable properties of tubocurarine (see below).

The pharmacologic powers of tubocurarine were known to primitive hunters long before coming to the attention of modern scientists. Tubocurarine is one of several active principles found in *curare,* an arrow poison used for hunting by South American Indians. When shot into a monkey or other small animal, curare-tipped arrows cause relaxation (paralysis) of skeletal muscles. Death results from paralyzing the muscles of respiration.

The clinical utility of tubocurarine is based on the same action that is useful in hunting: production of skeletal muscle relaxation. Relaxation of skeletal

muscles is helpful in patients undergoing surgery, endotracheal intubation, mechanical ventilation, and other procedures.

Chemistry

Tubocurarine and all other neuromuscular blocking agents contain a *quaternary nitrogen* atom (Fig. 16-3). As a result, these drugs always carry a positive charge, and therefore cannot readily cross membranes.

The inability to cross membranes has three clinical consequences. First, neuromuscular blockers cannot be administered orally. Instead, they must all be administered parenterally (almost always IV). Second, these drugs cannot cross the blood-brain barrier, and hence have no effect on the central nervous system (CNS). Third, neuromuscular blockers cannot readily cross the placenta, and hence effects on the fetus are minimal.

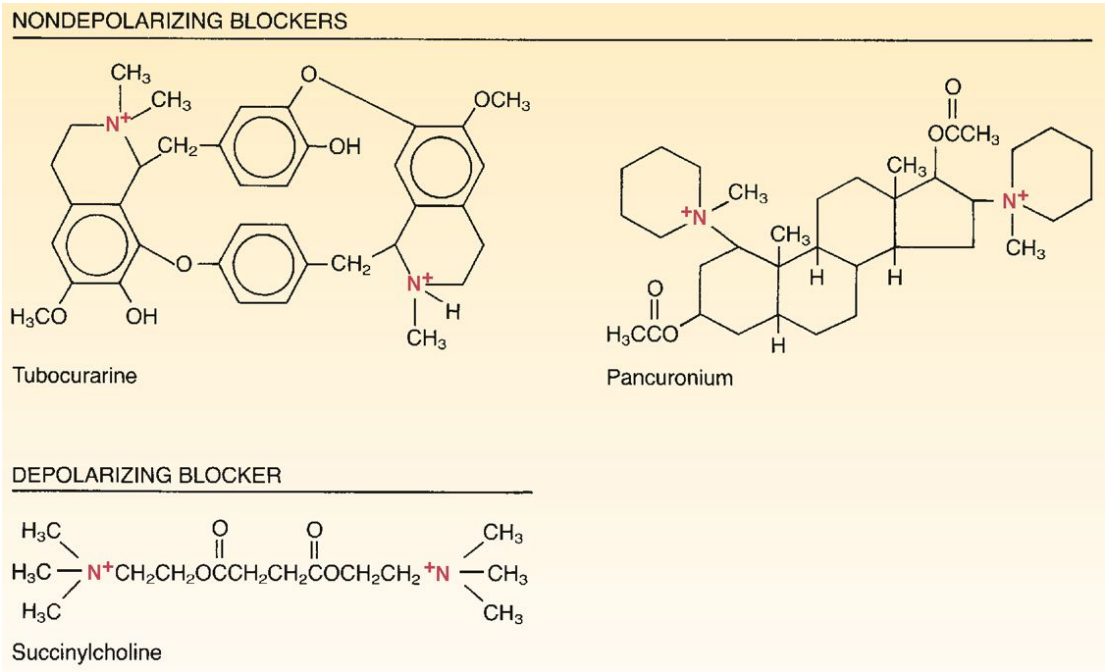


Figure 16-3 Structural formulas of representative neuromuscular blocking agents. Note that all of these agents contain quaternary nitrogen atoms and therefore cross membranes poorly. Consequently, they must be administered parenterally and have

little effect on the central nervous system or the developing fetus.

Mechanism of Action

Tubocurarine acts by competing with ACh for binding to nicotinic*M* receptors on the motor end-plate (Fig. 16-4). Since tubocurarine does not activate these receptors, binding does not result in contraction. Muscle relaxation persists as long as the amount of tubocurarine at the neuromuscular junction (NMJ) is sufficient to prevent receptor occupation by ACh. Muscle function can be restored by eliminating tubocurarine from the body or by increasing the amount of ACh at the NMJ.

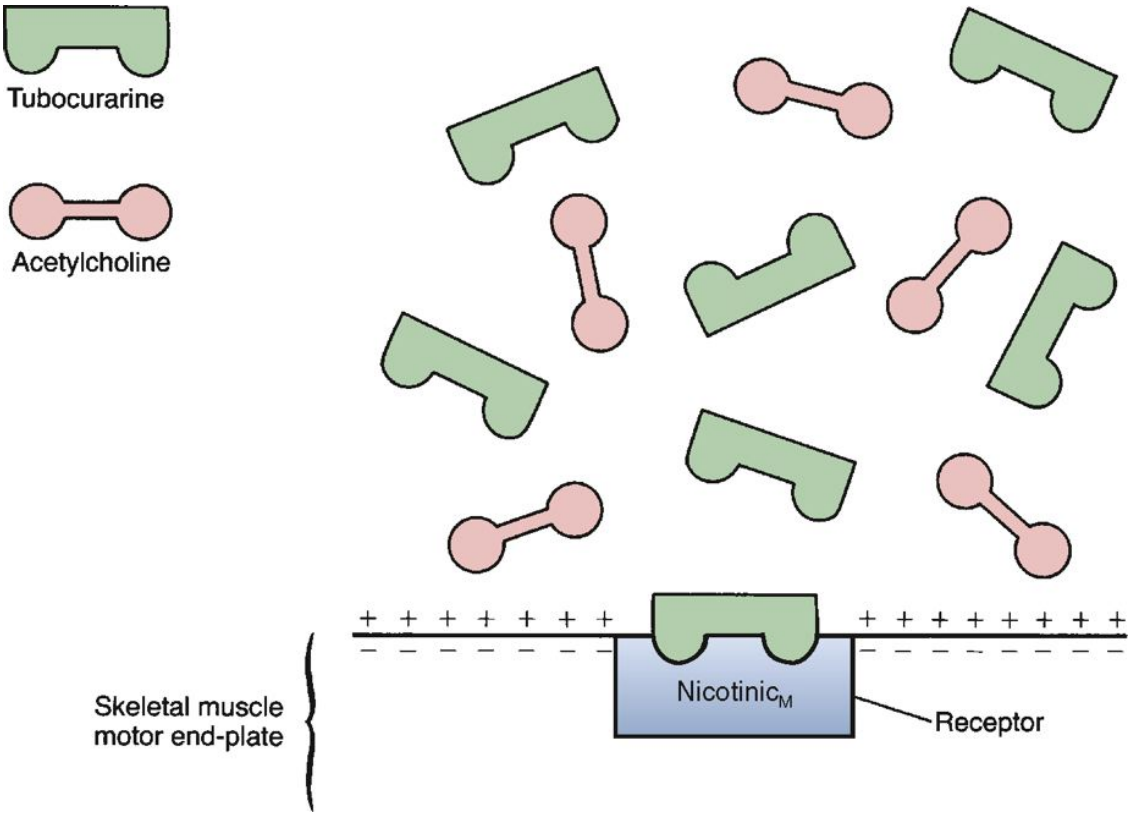


Figure 16-4 Mechanism of nondepolarizing neuromuscular blockade. Tubocurarine competes with acetylcholine (ACh) for binding to nicotinicM receptors on the motor end-plate. Binding of tubocurarine does not depolarize the end-plate, and therefore

does not cause contraction. At the same time, the presence of tubocurarine prevents ACh from binding to the receptor, hence contraction is prevented.

Pharmacologic Effects

Muscle Relaxation.

The primary effect of tubocurarine is relaxation of skeletal muscle, causing a state known as *flaccid paralysis*.

Although tubocurarine can paralyze all skeletal muscles, not all muscles are affected at once. The first to become paralyzed are the levator muscle of the eyelid and the muscles of mastication. Paralysis occurs next in muscles of the limbs, abdomen, and glottis. The last muscles affected are the muscles of respiration—the intercostals and diaphragm.

Hypotension.

Tubocurarine can lower blood pressure by two mechanisms: (1) release of histamine and (2) partial ganglionic blockade. Histamine lowers blood pressure by causing vasodilation. Ganglionic blockade lowers blood pressure by decreasing sympathetic tone to arterioles and veins. Tubocurarine suppresses ganglionic transmission by causing partial blockade of nicotinic***N*** receptors in autonomic ganglia.

Central Nervous System.

As noted, tubocurarine and the other neuromuscular blocking agents are unable to cross the blood-brain barrier. Consequently, these drugs have no effect on the CNS. Please note: *Neuromuscular blockers do not diminish consciousness or perception of pain—even when administered in doses that produce complete paralysis*.

Pharmacokinetics

Paralysis develops rapidly (in minutes) following IV injection. Peak effects persist 35 to 60 minutes and then decline. Complete recovery may take several *hours*. Tubocurarine is eliminated by a combination of hepatic metabolism and renal excretion.

Therapeutic Uses

Before being withdrawn from the market, tubocurarine was used for muscle relaxation during surgery, mechanical ventilation, endotracheal intubation, and electroconvulsive therapy. These applications are discussed later under *Therapeutic Uses of Neuromuscular Blockers*.

Adverse Effects

The principal adverse effects of tubocurarine concern the respiratory and cardiovascular systems.

Respiratory Arrest.

Paralysis of respiratory muscles can produce respiratory arrest. Because of this risk, facilities for artificial ventilation must be immediately available. Patients must be monitored closely and continuously. When tubocurarine is withdrawn, vital signs must be monitored until muscle function has fully recovered.

Cardiovascular Effects.

As noted, tubocurarine can cause *hypotension* secondary to histamine release and partial ganglionic blockade. In addition, the drug can cause *bradycardia, dysrhythmias,* and *cardiac arrest*. The mechanism underlying these latter effects is not clear.

Precautions and Contraindications

Myasthenia Gravis.

Neuromuscular blocking agents must be used with special care in patients with myasthenia gravis, a condition characterized by skeletal muscle weakness. The cause of weakness is a reduction in the number of nicotinic***M*** receptors on the motor end-plate. Because receptor number is reduced, neuromuscular blockade occurs readily. Also, doses that would have a minimal effect on others can produce complete paralysis in patients with myasthenia.

Accordingly, dosing must be done with great care. Myasthenia gravis and its treatment are discussed in Chapter 15.

Electrolyte Disturbances.

Responses to tubocurarine can be altered by electrolyte abnormalities. For example, low potassium levels can enhance paralysis, whereas high potassium levels can reduce paralysis. Because electrolyte status can influence the depth of neuromuscular blockade, it is important to maintain normal electrolyte balance.

Drug Interactions

Tubocurarine can interact with many other drugs. Interactions of primary interest are discussed below.

General Anesthetics.

All inhalation anesthetics produce some degree of skeletal muscle relaxation, and can thereby enhance the actions of tubocurarine and other neuromuscular blockers. Consequently, when general anesthetics and neuromuscular blockers are combined (as they often are), the dosage of the neuromuscular blocker should be reduced to avoid excessive neuromuscular blockade.

Antibiotics.

Several antibiotics can intensify responses to neuromuscular blockers. Among them are aminoglycosides (eg, gentamicin), tetracyclines, and certain other nonpenicillin antibiotics.

Cholinesterase Inhibitors.

Cholinesterase inhibitors can *decrease* the effects of tubocurarine and other *nondepolarizing* neuromuscular blockers. (As discussed later in the chapter, cholinesterase inhibitors have the opposite effect on responses to succinylcholine, a *depolarizing* neuromuscular blocker.)

How do cholinesterase inhibitors decrease the effects of tubocurarine? Recall that nondepolarizing blockers compete with ACh for binding to nicotinic***M*** receptors. By decreasing the degradation of ACh, cholinesterase inhibitors increase the amount of ACh available to compete with tubocurarine. As more ACh (and less tubocurarine) occupies nicotinic***M*** receptors, the degree of neuromuscular blockade declines.

The ability of cholinesterase inhibitors to decrease responses to nondepolarizing neuromuscular blockers has two clinical applications: (1) management of overdose with a nondepolarizing neuromuscular blocker and (2) reversal of neuromuscular blockade following surgery and other procedures.

Toxicology

Overdose with tubocurarine has three major effects: prolonged apnea, massive histamine release, and cardiovascular collapse. Apnea is managed with respiratory support plus a cholinesterase inhibitor (eg, neostigmine) to reverse neuromuscular blockade. Antihistamines are given to counteract released histamine. Cardiovascular toxicity must be assessed and treated as indicated.

Preparations, Dosage, and Administration

Tubocurarine is no longer used in the United States. For information on dosage and administration, refer to the sixth edition of this book.

Nondepolarizing Neuromuscular Blockers II: Others

Only five nondepolarizing blockers are currently approved for use in the United States. Several others—doxacurium [Nuromax], mivacurium [Mivacron], metocurine [Metubine], pipecuronium [Arduan], and tubocurarine—have recently been removed from the market.

Like tubocurarine, all neuromuscular blockers interact with acetylcholine at nicotinic***M*** receptors on the motor end-plate. Differences among the drugs relate primarily to time course of action (Table 16-1) and cardiovascular effects. With all of these agents, respiratory depression secondary to neuromuscular blockade is the major concern. Respiratory depression can be reversed by giving a cholinesterase inhibitor.

Generic Name	Route	Time to Maximum Paralysis (min)	Duration of Effective Paralysis (min)	Time to Nearly Full Spontaneous Recovery†
Long Acting				
Tubocurarine‡	IV, IM§	2–5	60–90	Hours
Intermediate Acting				
Atracurium [Tracrium]	IV	2–5	20–35	60–70 min
Cisatracurium [Nimbex]	IV	2–5	20–35	—
Pancuronium	IV	3–4	35–45	60–70 min
Rocuronium [Zemuron]	IV	1–3	20–40	—
Vecuronium [Norcuron]	IV	3–5	25–30	45–60 min
Ultrashort Acting				
Succinylcholine [Anectine, Quelicin]	IV, IM§	1	4–6	—

TABLE 16-1 Neuromuscular Blockers: Time Course of Action*

* Time course of action can vary widely with dosage and route of administration. The values presented are for an average adult dose administered as a single IV injection.

† Because spontaneous recovery can take a long time, recovery from the *nondepolarizing* agents (all of the drugs listed except succinylcholine) is often accelerated by giving a cholinesterase inhibitor.

‡ Tubocurarine is no longer available in the United States.

§ Intramuscular administration is rare.

Long-Acting Agents

Tubocurarine and all other long-acting agents—*doxacurium* [Nuromax], *metocurine* [Metubine], and *pipecuronium* [Arduan]—have been removed from the market. For information on these drugs, refer to the sixth edition of this book.

Intermediate-Acting Agents

Atracurium.

Atracurium [Tracrium] is approved for muscle relaxation during surgery, intubation, and mechanical ventilation. The drug can cause hypotension secondary to histamine release. Like succinylcholine, atracurium is eliminated primarily by *plasma cholinesterases,* not by the liver or kidneys. Hence, atracurium may be desirable for patients with renal or hepatic dysfunction, since these disorders will not prolong the drug's effects.

Cisatracurium.

Cisatracurium [Nimbex], a close relative of atracurium, is approved for muscle relaxation during surgery, intubation, and mechanical ventilation. Elimination is by spontaneous degradation, not by hepatic metabolism or renal excretion. Hence, like atracurium, cisatracurium would seem desirable for patients with kidney or liver dysfunction. Histamine release is minimal.

Pancuronium.

Pancuronium, formerly available as Pavulon, is approved for muscle relaxation during general anesthesia, intubation, and mechanical ventilation. The drug does not cause histamine release, ganglionic blockade, or hypotension. Vagolytic effects may produce tachycardia. Elimination is primarily renal.

Rocuronium.

Rocuronium [Zemuron] has a rapid onset and intermediate duration of action. The only neuromuscular blocker with a faster onset is succinylcholine. In contrast to succinylcholine, whose effects fade relatively quickly, rocuronium has effects that persist for 20 to 40 minutes. Rocuronium does not cause histamine release. Elimination is by hepatic metabolism. The drug is approved for muscle relaxation during intubation, surgery, and mechanical ventilation.

Vecuronium.

Vecuronium [Norcuron], an analog of pancuronium, is used for muscle relaxation during intubation and general anesthesia. The drug does not produce ganglionic or vagal block and does not release histamine. Consequently, cardiovascular effects are minimal. Vecuronium is excreted primarily in the bile, and hence paralysis may be prolonged in patients with liver dysfunction. Paralysis may also be prolonged in obese patients.

Short-Acting Agent: Mivacurium

Mivacurium [Mivacron] is the shortest acting *nondepolarizing* neuromuscular blocker. The only neuromuscular blocker with a shorter duration is succinylcholine, a *depolarizing* neuromuscular blocker. Paralysis with mivacurium is maximal 2 to 5 minutes after IV injection and persists only 10 to 15 minutes. Like the long-acting neuromuscular blockers, mivacurium is no longer available in the United States.

Depolarizing Neuromuscular Blockers: Succinylcholine

Succinylcholine, an ultrashort-acting drug, is the only depolarizing neuromuscular blocker in clinical use. This drug differs from the nondepolarizing blockers with regard to mechanism of action, mode of elimination, interaction with cholinesterase inhibitors, and management of toxicity.

Mechanism of Action

Succinylcholine produces a state known as *depolarizing neuromuscular blockade*. Like acetylcholine, succinylcholine binds to nicotinic***M*** receptors on the motor end-plate and thereby causes depolarization. This depolarization produces transient muscle contractions (fasciculations). Then, instead of dissociating rapidly from the receptor, succinylcholine remains bound, and thereby prevents the end-plate from repolarizing. That is, succinylcholine maintains the end-plate in a state of *constant depolarization*. Because the end-plate must repeatedly depolarize and repolarize to maintain muscle contraction, succinylcholine's ability to keep the end-plate depolarized causes paralysis (following the brief initial period of contraction). Paralysis persists until plasma levels of succinylcholine decline, thereby allowing the drug to dissociate from its receptors.

Pharmacologic Effects

Muscle Relaxation.

The muscle-relaxant effects of succinylcholine are much like those of tubocurarine: both drugs produce a state of flaccid paralysis. However, despite this similarity, there are two important differences: (1) paralysis from succinylcholine is preceded by transient contractions and (2) paralysis from succinylcholine abates much more rapidly.

Central Nervous System.

Like tubocurarine, succinylcholine has no effect on the CNS. The drug can produce complete paralysis without decreasing consciousness or the ability to feel pain.

Pharmacokinetics

Succinylcholine has an extremely short duration of action. Paralysis peaks about 1 minute after IV injection and fades completely 4 to 10 minutes later.

Paralysis is brief because succinylcholine is rapidly degraded by *pseudocholinesterase,* an enzyme present in plasma. (This enzyme is called pseudocholinesterase to distinguish it from "true" cholinesterase, the enzyme found at synapses where ACh is the transmitter.) Because of its presence in plasma, pseudocholinesterase is also known as *plasma cholinesterase*. In most individuals, pseudocholinesterase is highly active and can eliminate succinylcholine in minutes.

Therapeutic Uses

Succinylcholine is used primarily for muscle relaxation during endotracheal intubation, electroconvulsive therapy, endoscopy, and other short procedures. Because of its brief duration, succinylcholine is less desirable than the nondepolarizing blockers for use in prolonged procedures (ie, surgery and mechanical ventilation). Clinical applications are discussed further under *Therapeutic Uses of Neuromuscular Blockers*.

Adverse Effects

Prolonged Apnea in Patients with Low Pseudocholinesterase Activity.

A few people, because of their genetic makeup, produce a form of pseudocholinesterase that has extremely low activity. As a result, they are unable to degrade succinylcholine rapidly. If succinylcholine is given to these people, paralysis can persist for hours, rather than just a few minutes. Not surprisingly, succinylcholine is contraindicated for these individuals.

Patients suspected of having low pseudocholinesterase activity should be tested for this possibility before receiving full succinylcholine doses. Pseudocholinesterase activity can be assessed by direct measurement of a blood sample or by administering a tiny test dose of succinylcholine. If the test dose produces muscle relaxation that is unexpectedly intense and prolonged, pseudocholinesterase activity is probably low.

Malignant Hyperthermia.

Malignant hyperthermia is a rare and potentially fatal condition that can be triggered by succinylcholine, and by all inhalation anesthetics as well. The condition is characterized by muscle rigidity associated with a profound elevation of body temperature—sometimes to as high as 43°C. Temperature becomes elevated owing to excessive and uncontrolled metabolic activity in muscle, secondary to increased release of calcium from the SR. Left untreated, the condition can rapidly prove fatal. Malignant hyperthermia is a genetically determined reaction that has an incidence of about 1 in 25,000. Individuals with a family history of the reaction should not receive succinylcholine.

Treatment of malignant hyperthermia includes (1) immediate discontinuation of succinylcholine and the accompanying anesthetic, (2) cooling the patient with external ice packs and IV infusion of cold saline, and (3) administering intravenous *dantrolene,* a drug that stops heat generation by acting directly on skeletal muscle to reduce its metabolic activity. The pharmacology of dantrolene is discussed in Chapter 25 (Drugs for Muscle Spasm and Spasticity).

Postoperative Muscle Pain.

Between 10% and 70% of patients receiving succinylcholine experience postoperative muscle pain, most commonly in the neck, shoulders, and back. Pain

develops 12 to 24 hours after surgery and may persist several hours or even days. The cause may be the muscle contractions that occur during the initial phase of succinylcholine action.

Hyperkalemia.

Succinylcholine promotes release of potassium from tissues. Rarely, potassium release is sufficient to cause severe hyperkalemia. Death from cardiac arrest has resulted. Significant hyperkalemia is most likely in patients with major burns, multiple trauma, denervation of skeletal muscle, or upper motor neuron injury. Accordingly, the drug is contraindicated for these patients.

Drug Interactions

Cholinesterase Inhibitors.

These drugs *potentiate* (intensify) the effects of succinylcholine. How? By decreasing the activity of pseudocholinesterase, the enzyme that inactivates succinylcholine. Note that the effect of cholinesterase inhibitors on succinylcholine is opposite to the effect on *nondepolarizing* neuromuscular blockers.

Antibiotics.

The effects of succinylcholine, like those of tubocurarine, can be intensified by certain antibiotics. Among these are aminoglycosides, tetracyclines, and certain other nonpenicillin antibiotics.

Toxicology

Overdose can produce prolonged apnea. Since there is no specific antidote to succinylcholine poisoning, management is purely supportive. Recall that, with tubocurarine overdose, paralysis can be reversed with a cholinesterase inhibitor. Since cholinesterase inhibitors *delay* the degradation of succinylcholine, use of these agents would prolong—not reverse—succinylcholine toxicity.

Preparations, Dosage, and Administration

Succinylcholine chloride [Anectine, Quelicin] is available in solution and as a powder. The drug is usually administered IV but can also be given IM. Solu-

tions of succinylcholine are unstable and should be used within 24 hours. Multidose vials are stable for up to 2 weeks.

Dosage must be individualized and depends on the specific application. A typical adult dose for a brief procedure is 0.6 mg/kg, administered as a single IV injection. For prolonged procedures, succinylcholine may be administered by infusion at a rate of 2.5 to 4.3 mg/min.

Therapeutic Uses of Neuromuscular Blockers

The primary applications of the neuromuscular blocking agents are discussed below. No one agent is used for every application.

Muscle Relaxation During Surgery

Production of muscle relaxation during surgery offers two benefits. First, relaxation of skeletal muscles, especially those of the abdominal wall, makes the surgeon's work easier. Second, muscle relaxants allow us to decrease the dosage of the general anesthetic, thereby decreasing the risks associated with anesthesia. Before neuromuscular blockers became available, surgical muscle relaxation had to be achieved with the general anesthetic alone, often requiring high levels of anesthetic. (As noted earlier, inhalation anesthetics have muscle relaxant properties of their own.) By combining a neuromuscular blocker with the general anesthetic, we can achieve adequate surgical muscle relaxation with less anesthetic than was possible when paralysis had to be achieved with an anesthetic by itself. By allowing a reduction in anesthetic levels, neuromuscular blockers have decreased the risk of respiratory depression from anesthesia. In addition, because less anesthetic is administered, recovery from anesthesia occurs faster.

Whenever neuromuscular blockers are employed during surgery, it is very, very important that anesthesia be maintained at a level sufficient to produce unconsciousness. Recall that neuromuscular blockers do not enter the CNS, and therefore have no effect on hearing, thinking, or the ability to feel pain; all these drugs do is produce paralysis. Neuromuscular blockers are obviously and definitely not a substitute for anesthesia. It does not require much imagination to appreciate the horror of the surgical patient who is completely paralyzed from neuromuscular blockade yet fully awake because of inadequate an-

esthesia. Does this really happen? Yes. In fact, it happens in between 0.1% and 0.2% of surgeries in which neuromuscular blockers are used. Clearly, full anesthesia must be provided whenever surgery is performed on a patient who is under neuromuscular blockade.

With the agents in current use, full recovery from surgical neuromuscular blockade takes about an hour. (With the long-acting agents, which are no longer used, recovery could take several hours.) During the recovery period, patients must be monitored closely to ensure adequate ventilation. A patent airway should be maintained until the patient can swallow or speak. Recovery from the effects of *nondepolarizing* neuromuscular blockers (eg, tubocurarine) can be accelerated with a cholinesterase inhibitor.

Facilitation of Mechanical Ventilation

Some patients who require mechanical ventilation still have some spontaneous respiratory movements, which can fight the rhythm of the respirator. By suppressing these movements, neuromuscular blocking agents can reduce resistance to ventilation.

When neuromuscular blockers are used to facilitate mechanical ventilation, patients should be treated as if they were awake—even though they appear to be asleep. (Remember that the patient is paralyzed, and hence there is no way to assess state of consciousness.) Because the patient may be fully awake, steps should be taken to ensure comfort at all times. Furthermore, because neuromuscular blockade does not affect hearing, nothing should be said in the patient's presence that might be inappropriate for him or her to hear.

Being fully awake but completely paralyzed can be a stressful and generally horrific experience. Think about it. Accordingly, many clinicians do not recommend routine use of neuromuscular blockers during prolonged mechanical ventilation in intensive care units.

Adjunct to Electroconvulsive Therapy

Electroconvulsive therapy is an effective treatment for severe depression (see Chapter 32). Benefits derive strictly from the effects of electroshock on the brain; the convulsive movements that can accompany electroshock don't help relieve depression. Since convulsions per se serve no useful purpose, and since

electroshock-induced convulsions can be harmful, neuromuscular blockers are now used to prevent convulsive movements during electroshock therapy. Because of its short duration of action, succinylcholine is the preferred neuromuscular blocker for this application.

Endotracheal Intubation

An endotracheal tube is a large catheter that is inserted past the glottis and into the trachea to facilitate ventilation. Gag reflexes can fight tube insertion. By suppressing these reflexes, neuromuscular blockers can make intubation easier. Because of its short duration of action, succinylcholine is the preferred agent for this use.

Diagnosis of Myasthenia Gravis

An intermediate-acting neuromuscular blocker can be used to diagnose myasthenia gravis when safer diagnostic procedures have been inconclusive. To diagnose MG, a small test dose of the blocker is administered. Because the dose is too small to affect individuals who do not have MG, a significant reduction in muscle strength would be diagnostic of MG. If the test dose does decrease strength, neostigmine (a cholinesterase inhibitor) should be administered immediately; the resultant elevation in ACh at the NMJ will reverse neuromuscular blockade. It must be stressed that use of a neuromuscular blocker to diagnose myasthenia gravis is not without risk: If the patient does have MG, the challenging dose may be sufficient to cause pronounced respiratory depression. Consequently, facilities for artificial ventilation must be immediately available.

GANGLIONIC BLOCKING AGENTS

Ganglionic blocking agents produce a broad spectrum of pharmacologic effects. Because they lack selectivity, ganglionic blockers have limited applications. These drugs are used only to lower blood pressure—and then only under special circumstances. At this time, mecamylamine is the only ganglionic blocker available in the United States.

Mecamylamine

Mechanism of Action

Mecamylamine [Inversine] interrupts impulse transmission through ganglia of the autonomic nervous system. The drug blocks transmission by competing with ACh for binding to nicotinic***N*** receptors in autonomic ganglia. Because the nicotinic***N*** receptors of sympathetic and parasympathetic ganglia are the same, mecamylamine blocks transmission at *all* autonomic ganglia. By doing so, the drug can, in effect, shut down the entire autonomic nervous system, thereby depriving organs of autonomic regulation.

Pharmacologic Effects

Because mecamylamine acts by depriving organs of autonomic regulation, to predict the drug's effects, we need to know how the autonomic nervous system is affecting specific organs when the drug is given. That is, we need to know which branch of the autonomic nervous system is providing the predominant tone to specific organs. By knowing the source of predominant tone to an organ, and by knowing that ganglionic blockade will remove that tone, we can predict the effects that ganglionic blockade will produce.

Table 16-2 indicates (1) the major structures innervated by autonomic nerves, (2) the branch of the autonomic nervous system that provides the predominant tone to those structures, and (3) the responses to ganglionic blockade. As indicated, *the predominant autonomic tone to most organs is provided by the parasympathetic nervous system*. The sympathetic branch provides the predominant tone only to *sweat glands, arterioles,* and *veins*.

Since the parasympathetic nervous system provides the predominant tone to most organs, and since the parasympathetic nervous system works through muscarinic receptors to influence organ function, *most responses to ganglionic blockade resemble those produced by muscarinic antagonists*. These responses include dry mouth, blurred vision, photophobia, urinary retention, constipation, tachycardia, and anhidrosis.

In addition to their parasympatholytic effects, ganglionic blockers produce *hypotension*. The mechanism is blockade of sympathetic nerve traffic to arterioles and veins, which results in vasodilation.

Pharmacokinetics

Mecamylamine is well absorbed following oral administration. Effects begin within 2 hours and persist up to 12 hours. The drug is lipid soluble and hence crosses the placenta and blood-brain barrier with ease. Mecamylamine is eliminated unchanged in the urine.

Therapeutic Use

Mecamylamine is indicated for essential hypertension in selected patients. The drug is reserved for those rare cases in which blood pressure cannot be reduced with more desirable medications.

Adverse Effects

Mecamylamine can produce a broad spectrum of undesired effects, all the predictable consequence of generalized inhibition of the autonomic nervous system. Adverse effects fall into two major groups: (1) antimuscarinic effects, caused by parasympathetic blockade; and (2) hypotension, caused largely by sympathetic blockade.

Antimuscarinic Effects.

Blockade of *parasympathetic* ganglia produces typical antimuscarinic responses: dry mouth, blurred vision, photophobia, urinary retention, constipation, tachycardia, and anhidrosis. Antimuscarinic responses are discussed in detail in Chapter 14.

Orthostatic Hypotension.

Orthostatic hypotension, defined as a drop in blood pressure when we stand up, is the principal concern with this drug. The mechanism is dilation of veins, which causes blood to "pool" in veins when we move from a recumbent to an upright position. As a result of venous pooling, return of blood to the heart is greatly reduced, causing a reduction in cardiac output and a subsequent fall in blood pressure. Inform patients that orthostatic hypotension can be minimized by moving slowly when assuming an erect posture. Because hypotension can cause fainting, advise patients to sit or lie down if they become dizzy or lightheaded.

Overdose can cause a profound drop in blood pressure. If this occurs, pressure can be restored with a vasoconstrictor (eg, norepinephrine).

CNS Effects.

Because it readily crosses the blood-brain barrier, mecamylamine can cause CNS effects, including tremor, convulsions, and mental aberrations. However, these reactions are rare.

Location	Predominant Tone	Response to Ganglionic Blockade
Salivary glands	Parasympathetic	Dry mouth
Ciliary muscle	Parasympathetic	Blurred vision
Iris sphincter	Parasympathetic	Photophobia (from mydriasis)
Urinary bladder	Parasympathetic	Urinary retention
Gastrointestinal tract	Parasympathetic	Constipation
Heart	Parasympathetic	Tachycardia
Sweat glands	Sympathetic*	Anhidrosis
Arterioles	Sympathetic	Hypotension (from vasodilation)
Veins	Sympathetic	Orthostatic hypotension (from pooling of blood in veins secondary to venous dilation)

TABLE 16-2 Predominant Autonomic Tone and Responses to Ganglionic Blockade

* Sympathetic nerves to sweat glands release acetylcholine as their transmitter, which acts at muscarinic receptors on the sweat glands.

Preparations, Dosage, and Administration

Mecamylamine [Inversine] is available in 2.5-mg tablets for oral use. Dosing is begun at 2.5 mg twice daily, and then gradually increased until the target blood pressure is achieved. The average daily maintenance dose is 25 mg.

KEY POINTS

All of these key points apply to the *neuromuscular blocking* agents—not to ganglionic blocking agents.

- Sustained contraction of skeletal muscle results from repetitive activation of nicotinic***M*** receptors on the motor end-plate, causing the end-plate to go through repeating cycles of depolarization and repolarization.
- Neuromuscular blockers interfere with nicotinic***M*** receptor activation, and thereby cause muscle relaxation.
- Nondepolarizing neuromuscular blockers act by competing with ACh for binding to nicotinic***M*** receptors.
- Succinylcholine, the only depolarizing neuromuscular blocker in use, binds to nicotinic***M*** receptors, causing the end-plate to depolarize; the drug then remains bound, which keeps the end-plate from repolarizing.
- Neuromuscular blockers are used to produce muscle relaxation during surgery, endotracheal intubation, mechanical ventilation, and electroshock therapy.
- Neuromuscular blockers do not reduce consciousness or pain.
- The major adverse effect of neuromuscular blockers is respiratory depression.
- Cholinesterase inhibitors can reverse the effects of nondepolarizing neuromuscular blockers but will intensify the effects of succinylcholine.
- Succinylcholine can cause malignant hyperthermia, a life-threatening condition.
- Succinylcholine is eliminated by plasma cholinesterases. Accordingly, effects are greatly prolonged in patients with low plasma cholinesterase activity.
- All of the neuromuscular blockers are quaternary ammonium compounds, and therefore must be administered parenterally (almost always IV).

Summary of Major Nursing Implications*

NEUROMUSCULAR BLOCKING AGENTS

Atracurium

Cisatracurium

Pancuronium

Rocuronium

Succinylcholine

Vecuronium

Except where noted, the implications summarized below apply to all neuromuscular blocking agents.

Preadministration Assessment

Therapeutic Goal

Provision of muscle relaxation during surgery, endotracheal intubation, mechanical ventilation, electroconvulsive therapy, and other procedures.

Identifying High-Risk Patients

Use all neuromuscular blockers with *caution* in patients with myasthenia gravis.

Succinylcholine is *contraindicated* for patients with low pseudocholinesterase activity, a personal or familial history of malignant hyperthermia, or conditions that predispose to hyperkalemia (major burns, multiple trauma, denervation of skeletal muscle, upper motor neuron injury).

Implementation: Administration

Routes

Intravenous.

All neuromuscular blockers.

Intramuscular.

Only *succinylcholine*.

Administration

Neuromuscular blockers are dangerous drugs that should be administered by clinicians skilled in their use.

Implementation: Measures to Enhance Therapeutic Effects

Neuromuscular blockers do not affect consciousness or perception of pain. When used during surgery, these drugs must be accompanied by adequate anesthesia. When neuromuscular blockers are used for prolonged paralysis during mechanical ventilation, care should be taken to ensure comfort (eg, positioning the patient comfortably, moistening the mouth periodically). Because patients may be awake (but won't appear to be), conversations held in their presence should convey only information appropriate for them to hear.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Apnea.

All neuromuscular blockers can cause respiratory arrest. Facilities for intubation and mechanical ventilation should be immediately available.

Monitor respiration constantly during the period of peak drug action. When drug administration is discontinued, take vital signs at least every 17 minutes until recovery is complete.

A cholinesterase inhibitor can be used to reverse respiratory depression caused by *nondepolarizing* neuromuscular blockers, but not by succinylcholine, a *depolarizing* blocker.

Hypotension.

Some neuromuscular blockers can cause hypotension secondary to ganglionic blockade or release of histamine. Antihistamines may help counteract this effect.

Malignant Hyperthermia.

Succinylcholine can trigger malignant hyperthermia. Predisposition to this reaction is genetic. Assess for a family history of the reaction.

Hyperkalemia with Cardiac Arrest.

Succinylcholine can cause severe hyperkalemia resulting in cardiac arrest if given to patients with major burns, multiple trauma, denervation of skeletal muscle, or upper motor neuron injury. Accordingly, the drug is contraindicated for these people.

Muscle Pain.

Succinylcholine may cause muscle pain. **Reassure the patient that this response, although unpleasant, is not unusual.**

Minimizing Adverse Interactions

Antibiotics.

Certain antibiotics, including *aminoglycosides* and *tetracyclines*, can intensify neuromuscular blockade. Use them with caution.

Cholinesterase Inhibitors.

These drugs delay inactivation of *succinylcholine*, thereby greatly prolonging paralysis. Accordingly, cholinesterase inhibitors are contraindicated for patients receiving succinylcholine.

Adrenergic Drugs

17 Adrenergic Agonists

By definition, adrenergic agonists produce their effects by activating adrenergic receptors. Since the sympathetic nervous system acts through these same receptors, responses to adrenergic agonists and responses to stimulation of the sympathetic nervous system are very similar. Because of this similarity, adrenergic agonists are often referred to as *sympathomimetics*. Adrenergic agonists have a broad spectrum of indications, ranging from heart failure to asthma to preterm labor.

Learning about adrenergic agonists can be a challenge. To facilitate the process, our approach to these drugs has four stages. We begin with the general mechanisms by which drugs can activate adrenergic receptors. Next we establish an overview of the major adrenergic agonists, focusing on their receptor specificity and chemical classification. After that, we address the adrenergic receptors themselves; for each receptor type—alpha***1***, alpha***2***, beta***1***, beta***2***, and dopamine—we discuss the beneficial and harmful effects that can result from receptor activation. Finally, we integrate all of this information by discussing the characteristic properties of representative sympathomimetic drugs.

Please note that this chapter is intended only as an *introduction* to the adrenergic agonists. Our objective here is to discuss the basic properties of the sympathomimetic drugs and establish an overview of their applications and adverse effects. In later chapters, we will discuss the clinical applications of these agents in depth.

MECHANISMS OF ADRENERGIC RECEPTOR ACTIVATION

Drugs can activate adrenergic receptors by four basic mechanisms: (1) direct receptor binding, (2) promotion of norepinephrine (NE) release, (3) blockade of NE reuptake, and (4) inhibition of NE inactivation. Note that only the first mechanism is *direct*. With the other three, receptor activation occurs by an *indirect* process. Examples of drugs that act by these four mechanisms are presented in Table 17-1.

Mechanism of Stimulation	Examples
Direct Mechanism	
Binding to receptor to cause activation	Epinephrine
	Isoproterenol
	Ephedrine*
Indirect Mechanisms	
Promotion of NE release	Ephedrine*
	Amphetamines
Inhibition of NE reuptake	Cocaine
	Tricyclic antidepressants
Inhibition of MAO	MAO inhibitors

MAO = monoamine oxidase, NE = norepinephrine.

TABLE 17-1 Mechanisms of Adrenergic Receptor Activation

* Ephedrine is a mixed-acting drug that activates receptors directly and also promotes release of norepinephrine.

Direct Receptor Binding.

Direct interaction with receptors is the most common mechanism by which drugs activate peripheral adrenergic receptors. The direct-acting receptor stimulants produce their effects by binding to adrenergic receptors and mimicking the actions of natural transmitters (NE, epinephrine, dopamine). In this chapter, all of the drugs discussed activate receptors directly.

Promotion of NE Release.

By acting on terminals of sympathetic nerves to cause NE release, drugs can bring about activation of adrenergic receptors. Agents that activate receptors by this mechanism include the amphetamines and ephedrine. (Ephedrine can also activate adrenergic receptors directly.)

Inhibition of NE Reuptake.

Recall that reuptake of NE into terminals of sympathetic nerves is the major mechanism by which adrenergic transmission is terminated. By blocking NE reuptake, drugs can cause NE to accumulate within the synaptic gap, and can thereby increase receptor activation. Agents that act by this mechanism include cocaine and the tricyclic antidepressants (eg, imipramine).

Inhibition of NE Inactivation.

As discussed in Chapter 13, some of the NE in terminals of adrenergic neurons is subject to inactivation by monoamine oxidase (MAO). Hence, drugs that inhibit MAO can increase the amount of NE available for release, and can thereby enhance receptor activation. (It should be noted that, in addition to being present in sympathetic nerves, MAO is present in the liver and the intestinal wall. The significance of MAO at these other sites is considered later in the chapter.)

In this chapter, which is dedicated to *peripherally* acting sympathomimetics, practically all of the drugs discussed act exclusively by *direct* receptor activation. The only exception is *ephedrine,* an agent that works by a combination of direct receptor activation and promotion of NE release.

Most of the indirect-acting adrenergic agonists are used for their ability to activate adrenergic receptors in the central nervous system (CNS)—not for their effects in the periphery. The indirect-acting sympathomimetics (eg, amphetamine, cocaine) are mentioned here to emphasize that, although these agents are employed for effects on the brain, they can and will cause activation of adrenergic receptors in the periphery. Peripheral activation is responsible for certain toxicities of these drugs (eg, cardiac dysrhythmias, hypertension).

OVERVIEW OF THE ADRENERGIC AGONISTS

Chemical Classification: Catecholamines Versus Noncatecholamines

The adrenergic agonists fall into two major chemical classes: catecholamines and noncatecholamines. As discussed below, the catecholamines and noncatecholamines differ in three important respects: (1) oral usability, (2) duration of action, and (3) the ability to act in the CNS. Accordingly, if we know which category a particular adrenergic agonist belongs to, we will know three of its prominent features.

Catecholamines

The catecholamines are so named because they contain a *catechol* group and an *amine* group. A catechol group is simply a benzene ring that has hydroxyl groups on two adjacent carbons (Fig. 17-1). The amine component of the catecholamines is *ethylamine*. Structural formulas for each of the major catecholamines—epinephrine, norepinephrine, isoproterenol, dopamine, and dobutamine—are presented in Figure 17-1. Because of their chemistry, all catecholamines have three properties in common: (1) they cannot be used orally, (2) they have a brief duration of action, and (3) they cannot cross the blood-brain barrier.

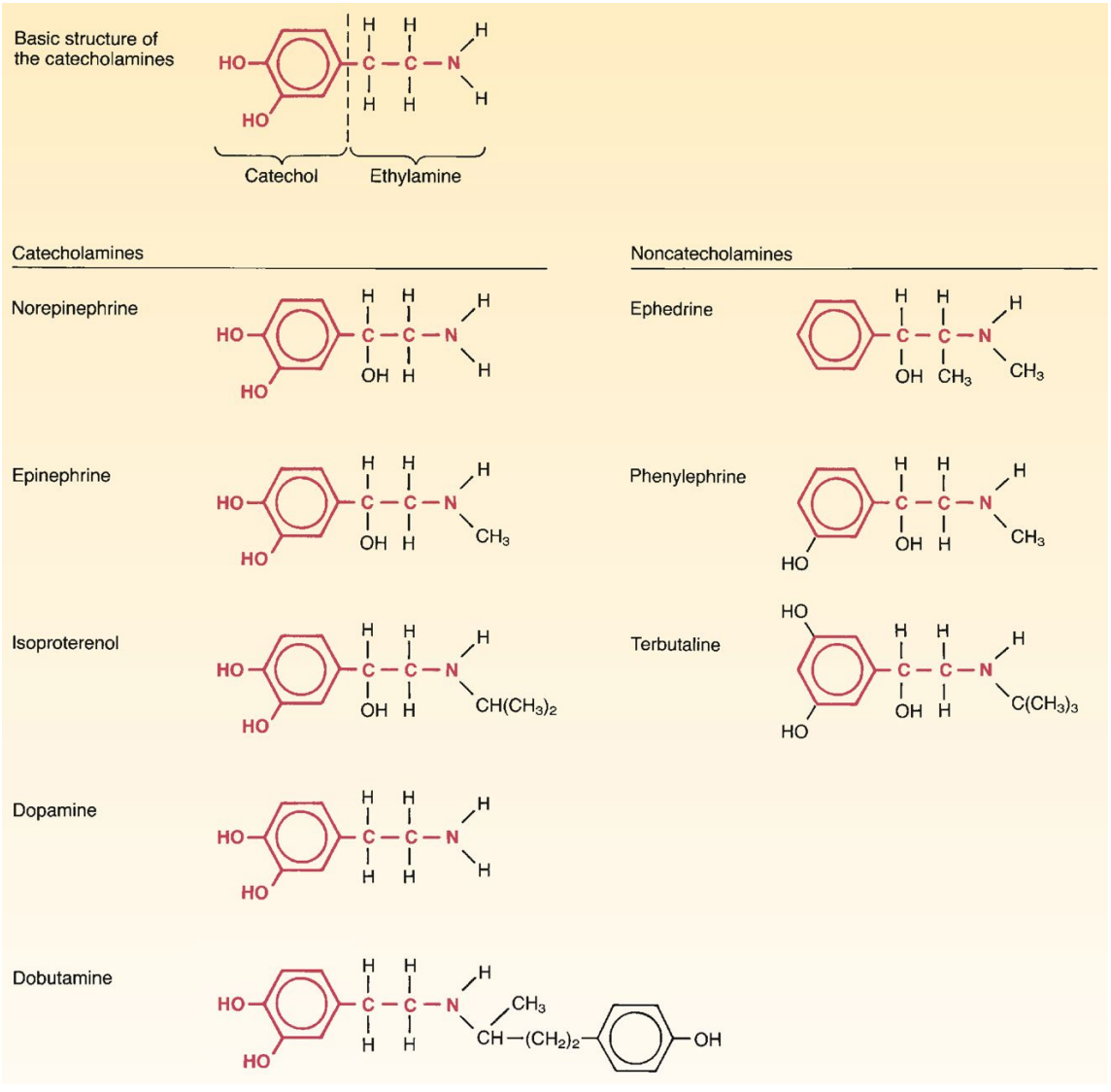


Figure 17-1 Structures of catecholamines and noncatecholamines. Catecholamines: Note that all of the catecholamines share the same basic chemical formula. Because of their biochemical properties, the catecholamines cannot be used orally, cannot cross the blood-brain barrier, and have short half-lives (owing to rapid inactivation by MAO and COMT). Noncatecholamines: Although structurally similar to catecholamines, noncatecholamines differ from catecholamines in three important ways: they

can be used orally; they can cross the blood-brain barrier; and, because they are not rapidly metabolized by MAO or COMT, they have much longer half-lives.

The actions of two enzymes—*monoamine oxidase* and *catechol-O-methyltransferase* (COMT)—explain why the catecholamines have short half-lives and cannot be used orally. MAO and COMT are located in the liver and the intestinal wall. Both enzymes are very active and quickly destroy catecholamines administered by any route. Because these enzymes are located in the liver and intestinal wall, catecholamines that are administered orally become inactivated before they can reach the systemic circulation. Hence, catecholamines are ineffective if given by mouth. Because of rapid inactivation by MAO and COMT, three catecholamines—norepinephrine, dopamine, and dobutamine—are effective only if administered by continuous infusion. Administration by other parenteral routes (eg, subQ, IM) will not yield adequate blood levels.

Catecholamines are polar molecules, and hence cannot cross the blood-brain barrier. (Recall from Chapter 4 that polar compounds penetrate membranes poorly.) The polar nature of the catecholamines is due to the hydroxyl groups on the catechol portion of the molecule. Because they cannot cross the blood-brain barrier, catecholamines have minimal effects on the CNS.

Be aware that catecholamine-containing solutions, which are colorless when first prepared, turn pink or brown over time. This pigmentation is caused by oxidation of the catecholamine molecule. As a rule, *catecholamine solutions should be discarded as soon as discoloration develops*. The only exception to this rule is dobutamine, which can be used up to 24 hours after the solution was made, even if discoloration appears.

Noncatecholamines

The noncatecholamines have ethylamine in their structure (see Fig. 17-1), but do not contain the catechol moiety that characterizes the catecholamines. In this chapter, we discuss three noncatecholamines: ephedrine, phenylephrine, and terbutaline.

The noncatecholamines differ from the catecholamines in three important respects. First, because they lack a catechol group, noncatecholamines are not substrates for COMT and are metabolized slowly by MAO. As a result, the

half-lives of noncatecholamines are much longer than those of catecholamines. Second, because they do not undergo rapid degradation by MAO and COMT, noncatecholamines can be given orally, whereas catecholamines cannot. Third, noncatecholamines are considerably less polar than catecholamines, and hence are more able to cross the blood-brain barrier.

Receptor Specificity

To understand the actions of individual adrenergic agonists, we need to know their receptor specificity. Since the sympathomimetic drugs differ widely with respect to the receptors they can activate, learning the receptor specificity of these drugs will take some effort.

Variability in receptor specificity among the adrenergic agonists can be illustrated with three drugs: terbutaline, isoproterenol, and epinephrine. Terbutaline is highly selective, acting at beta***2*** receptors only. Isoproterenol is less selective, acting at beta***1*** receptors and beta***2*** receptors. Epinephrine is less selective yet, acting at all four adrenergic receptor subtypes: alpha***1***, alpha***2***, beta***1***, and beta***2***.

The receptor specificities of the major adrenergic agonists are summarized in Table 17-2. In the upper part of the table, receptor specificity is presented in tabular form. In the lower part, the same information is presented schematically. By learning (memorizing) the content of Table 17-2, you will be well on your way toward understanding the pharmacology of the sympathomimetic drugs. Please note that the concept of receptor specificity is relative, not absolute. The ability of a drug to selectively activate certain receptors to the exclusion of others is dependent on dosage: at low doses, selectivity is maximal; as dosage increases, selectivity declines. For example, when terbutaline is administered in low to moderate doses, the drug is highly selective for beta***2***-adrenergic receptors. However, if the dosage is high, terbutaline will activate beta***1*** receptors as well. The information on receptor specificity in Table 17-2 refers to usual therapeutic doses. So-called selective agents will activate additional adrenergic receptors if the dosage is abnormally high.

THERAPEUTIC APPLICATIONS AND ADVERSE EFFECTS OF ADRENERGIC RECEPTOR ACTIVATION

In this section we discuss the responses—both therapeutic and adverse—that can be elicited with sympathomimetic drugs. Since many adrenergic agonists activate more than one type of receptor (see Table 17-2), it could be quite confusing if we were to talk about the effects of the sympathomimetics while employing specific drugs as examples. Consequently, rather than attempting to structure this presentation around representative drugs, we discuss the actions of the adrenergic agonists one receptor at a time. Our discussion begins with alpha*1* receptors, and then moves to alpha*2* receptors, beta*1* receptors, beta*2* receptors, and dopamine receptors. For each receptor type, we discuss both the therapeutic and adverse responses that can result from receptor activation.

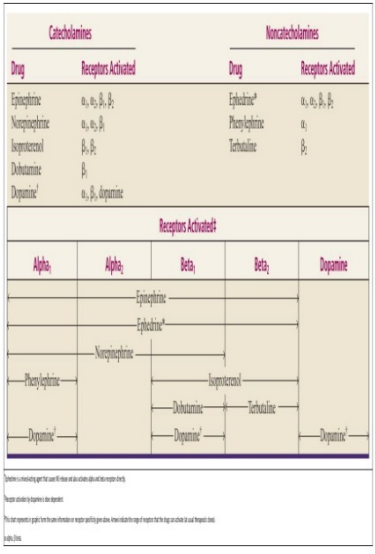


TABLE 17-2 Receptor Specificity of Representative Adrenergic Agonists

To understand the effects of any specific adrenergic agonist, all you need is two types of information: (1) the identity of the receptors at which the drug acts and (2) the effects produced by activating those receptors. Combining these two types of information will reveal a profile of drug action. This is the same approach to understanding neuropharmacologic agents that we discussed in Chapter 12.

Before you go deeper into this chapter, I encourage you (strongly advise you) to review Table 13-3. Since we are about to discuss the clinical consequences of adrenergic receptor activation, and since Table 13-3 summarizes the responses to activation of those receptors, the benefits of being familiar with Table 13-3 are obvious. If you choose not to memorize Table 13-3 now, at least be prepared to refer back to it as we discuss the consequences of receptor activation.

Clinical Consequences of Alpha*1* Activation

In this section we discuss the therapeutic and adverse effects that can result from activation of alpha*1*-adrenergic receptors. As shown in Table 17-2, drugs capable of activating alpha*1* receptors include epinephrine, NE, phenylephrine, ephedrine, and dopamine.

Therapeutic Applications of Alpha*1* Activation

Activation of alpha*1* receptors elicits two responses that can be of therapeutic use: (1) *vasoconstriction* (in blood vessels of the skin, viscera, and mucous membranes); and (2) *mydriasis*. Of the two, vasoconstriction is the one for which alpha*1* agonists are used most often. Using these drugs for mydriasis is relatively rare.

Hemostasis.

Hemostasis is defined as the arrest of bleeding, which alpha*1* agonists accomplish through vasoconstriction. Alpha*1* stimulants are given to stop bleeding primarily in the skin and mucous membranes. Epinephrine, applied topically, is the alpha*1* agonist used most for this purpose.

Nasal Decongestion.

Nasal congestion results from dilation and engorgement of blood vessels in the nasal mucosa. Drugs can relieve congestion by causing alpha*1*-mediated vasoconstriction. Specific alpha*1*-activating agents employed as nasal decongestants include phenylephrine (applied topically) and ephedrine (taken orally).

Adjunct to Local Anesthesia.

Alpha*1* agonists are frequently combined with local anesthetics to delay anesthetic absorption. The mechanism is alpha*1*-mediated vasoconstriction, which reduces blood flow to the site of anesthetic administration. Why delay anesthetic absorption? Because doing so prolongs anesthesia, allows a reduction in anesthetic dosage, and reduces the systemic effects that a local anesthetic might produce. The drug used most frequently to delay anesthetic absorption is epinephrine.

Elevation of Blood Pressure.

Because of their ability to cause vasoconstriction, alpha*1* agonists can elevate blood pressure in hypotensive patients. Please note, however, that alpha*1* agonists are not the primary therapy for hypotension. Rather, they are reserved for situations in which fluid replacement and other measures have failed to restore blood pressure to a satisfactory level.

Mydriasis.

Activation of alpha*1* receptors on the radial muscle of the iris causes mydriasis (dilation of the pupil), which can facilitate eye examinations and ocular surgery. Note that producing mydriasis is the only clinical use of alpha*1* activation that is not based on vasoconstriction.

Adverse Effects of Alpha*1* Activation

All of the adverse effects caused by alpha*1* activation result directly or indirectly from vasoconstriction.

Hypertension.

Alpha*1* agonists can produce hypertension by causing widespread vasoconstriction. Severe hypertension is most likely with parenteral administration. Accordingly, when alpha*1* agonists are given parenterally, cardiovascular status must be monitored continuously. Never leave the patient unattended.

Necrosis.

If the IV line employed to administer an alpha*1* agonist becomes extravasated, local seepage of the drug may result in necrosis (tissue death). The cause is lack of blood flow secondary to intense local vasoconstriction. If extravasa-

tion occurs, the area should be infiltrated with an alpha*1*-blocking agent (eg, phentolamine), which will counteract alpha*1*-mediated vasoconstriction, and thereby help minimize injury.

Bradycardia.

Alpha*1* agonists can cause reflex slowing of the heart. The mechanism is this: Alpha*1*-mediated vasoconstriction elevates blood pressure, which triggers the baroreceptor reflex, causing heart rate to decline. In patients with marginal cardiac reserve, the decrease in cardiac output may compromise tissue perfusion.

Clinical Consequences of Alpha*2* Activation

As discussed in Chapter 13, alpha*2* receptors in the periphery are located *presynaptically,* and their activation inhibits NE release. Several adrenergic agonists (eg, epinephrine, NE, ephedrine) are capable of causing alpha*2* activation. However, their ability to activate alpha*2* receptors in the periphery has little clinical significance. There are no therapeutic applications related to activation of peripheral alpha*2* receptors. Furthermore, activation of these receptors rarely causes significant adverse effects.

In contrast to alpha*2* receptors in the *periphery,* alpha*2* receptors in the *CNS* are of great clinical significance. By activating central alpha*2* receptors, we can produce two useful effects: (1) *reduction* of sympathetic outflow to the heart and blood vessels and (2) relief of severe pain. The central alpha*2* agonists used for effects on the heart and blood vessels, and the agents used to relieve pain, are discussed in Chapters 19 and 28, respectively.

Clinical Consequences of Beta*1* Activation

All of the clinically relevant responses to activation of beta*1* receptors result from activating beta*1* receptors in the *heart;* activation of renal beta*1* receptors is not associated with either beneficial or adverse effects. As indicated in Table 17-2, beta*1* receptors can be activated by epinephrine, NE, isoproterenol, dopamine, dobutamine, and ephedrine.

Therapeutic Applications of Beta*1* Activation

Cardiac Arrest.

By activating cardiac beta*1* receptors, drugs can initiate contraction in a heart that has stopped beating. It should be noted, however, that drugs are not the preferred treatment for cardiac arrest. Rather, drugs should be used only after more desirable procedures—mechanical thumping, direct-current cardioversion—have failed to restart the heart. When a beta*1* agonist is indicated, epinephrine—injected directly into the heart—is the preferred drug.

Heart Failure.

Heart failure is characterized by a reduction in the force of myocardial contraction, resulting in insufficient cardiac output. Because activation of beta*1* receptors in the heart has a positive inotropic effect (ie, increases the force of contraction), drugs that activate these receptors can improve cardiac performance.

Shock.

This condition is characterized by profound hypotension and greatly reduced tissue perfusion. The primary goal of treatment is to maintain blood flow to vital organs. By increasing heart rate and force of contraction, beta*1* stimulants can increase cardiac output and can thereby improve tissue perfusion.

Atrioventricular Heart Block.

Atrioventricular (AV) heart block is a condition in which impulse conduction from the atria to the ventricles is either impeded or blocked entirely. As a consequence, the ventricles are no longer driven at an appropriate rate. Since activation of cardiac beta*1* receptors can enhance impulse conduction through the AV node, beta*1* stimulants can help overcome AV block. It should be noted, however, that drugs are only a temporary form of treatment. For long-term management, a pacemaker is implanted.

Adverse Effects of Beta*1* Activation

All of the adverse effects of beta*1* activation result from activating beta*1* receptors in the heart; activating renal beta*1* receptors is not associated with untoward effects.

Altered Heart Rate or Rhythm.

Overstimulation of cardiac beta*1* receptors can produce *tachycardia* (excessive heart rate) and *dysrhythmias* (irregular heartbeat).

Angina Pectoris.

In some patients, drugs that activate beta*1* receptors can precipitate an attack of angina pectoris, a condition characterized by substernal pain in the region of the heart. Anginal pain occurs when cardiac oxygen supply (blood flow) is insufficient to meet cardiac oxygen needs. The most common cause of angina is coronary atherosclerosis (accumulation of lipids and other substances in coronary arteries). Since beta*1* agonists increase cardiac oxygen demand (by increasing heart rate and force of contraction), patients with compromised coronary circulation are at risk of an anginal attack.

Clinical Consequences of Beta*2* Activation

Therapeutic Applications of Beta*2* Activation

Therapeutic applications of beta*2* activation are limited to the *lungs* and *uterus*. Drugs used for their beta*2*-activating ability include ephedrine, epinephrine, isoproterenol, and terbutaline.

Asthma.

Asthma is a chronic condition characterized by inflammation and bronchoconstriction occurring in response to a variety of stimuli. During a severe attack, airflow can be reduced so much as to threaten life. Since drugs that activate beta*2* receptors in the lung promote bronchodilation, these drugs can help relieve or prevent asthma attacks.

For therapy of asthma, adrenergic agonists that are *selective for beta2 receptors* (eg, terbutaline) are preferred to less selective agents (eg, epinephrine, isoproterenol). This is especially true for patients who also suffer from *angina pectoris* or *tachycardia*. Why? Because drugs that can activate beta*1* receptors would aggravate these cardiac disorders.

Several of the beta*2* agonists used to treat asthma are administered by *inhalation*. This route is desirable in that it helps minimize adverse systemic effects.

It should be noted, however, that inhalation does not guarantee safety: Serious systemic toxicity can result from overdosing with inhaled sympathomimetics. Accordingly, patients must be warned against inhaling too much drug.

Delay of Preterm Labor.

Activation of beta*2* receptors in the uterus relaxes uterine smooth muscle. This action can be exploited to delay preterm labor.

Adverse Effects of Beta*2* Activation

Hyperglycemia.

The most important adverse response to beta*2* activation is hyperglycemia (elevation of blood glucose). The mechanism is activation of beta*2* receptors in the liver and skeletal muscles, which promotes breakdown of glycogen into glucose. As a rule, beta*2* agonists cause hyperglycemia only in patients with *diabetes;* in patients with normal pancreatic function, insulin release will maintain blood glucose at an appropriate level. If hyperglycemia develops in the diabetic patient, insulin dosage should be increased.

Tremor.

Tremor is the most common side effect of beta*2* agonists. It occurs because activation of beta*2* receptors in skeletal muscle enhances contraction. Tremor generally fades over time and can be minimized by initiating therapy at low doses.

Clinical Consequences of Dopamine Receptor Activation

Activation of peripheral dopamine receptors causes dilation of the vasculature of the kidneys. This effect is exploited in the treatment of *shock:* by dilating renal blood vessels, we can improve renal perfusion and can thereby reduce the risk of renal failure. *Dopamine* itself is the only drug available that can activate dopamine receptors. It should be noted that, when dopamine is given to treat shock, the drug also enhances cardiac performance (because it activates beta*1* receptors in the heart).

Multiple Receptor Activation: Treatment of Anaphylactic Shock

Pathophysiology of Anaphylaxis.

Anaphylactic shock is a manifestation of severe allergy. The reaction is characterized by *hypotension* (from widespread vasodilation), *bronchoconstriction,* and *edema of the glottis*. Although histamine contributes to these responses, symptoms are due largely to release of other mediators (eg, leukotrienes). Anaphylaxis can be triggered by a variety of substances, including bee venom, wasp venom, latex rubber, certain foods (eg, peanuts, shellfish), and certain drugs (eg, penicillins).

Treatment.

Epinephrine, injected IM, is the treatment of choice for anaphylactic shock. Benefits derive from activating three types of adrenergic receptors: alpha***1***, beta***1***, and beta***2***. By activating these receptors, epinephrine can reverse the most severe manifestations of the anaphylactic reaction. Activation of beta***1*** receptors increases cardiac output, thereby helping elevate blood pressure. Blood pressure is also increased because epinephrine promotes alpha***1***-mediated vasoconstriction. In addition to increasing blood pressure, vasoconstriction helps suppress glottal edema. By activating beta***2*** receptors, epinephrine can counteract bronchoconstriction. Individuals who are prone to severe allergic responses should carry an epinephrine auto-injector at all times (see Box 17-1). Antihistamines are not especially useful against anaphylaxis because histamine is only a minor contributor to the reaction.

PROPERTIES OF REPRESENTATIVE ADRENERGIC AGONISTS

Our aim in this section is to establish an overview of the adrenergic agonists. The information is presented in the form of "drug digests" that highlight characteristic features of representative sympathomimetic agents.

As noted, there are two keys to understanding individual adrenergic agonists: (1) knowledge of the receptors that the drug can activate and (2) knowledge of the therapeutic and adverse effects that receptor activation can elicit. By in-

tegrating these two types of information, you can easily predict the spectrum of effects that a particular drug can produce.

Unfortunately, knowing the effects that a drug is *capable* of producing does not always indicate how that drug is *actually used* in a clinical setting. Why? Because some adrenergic agonists are not used for all the effects they can produce. Norepinephrine, for example, can activate alpha***1*** receptors and can therefore produce mydriasis. However, although NE can produce mydriasis, the drug is not actually used for this purpose. Similarly, although isoproterenol is capable of producing uterine relaxation (through beta***2*** activation), isoproterenol is not employed clinically for this effect. Because receptor specificity is not always a predictor of the therapeutic applications of a particular adrenergic agonist, for each of the drugs discussed below, approved clinical applications are indicated.

Epinephrine

- *Receptor specificity:* alpha***1***, alpha***2***, beta***1***, beta***2***
- *Chemical classification:* catecholamine

Epinephrine [Adrenalin, others] was among the first adrenergic agonists employed clinically and can be considered the prototype of the sympathomimetic drugs. Because of its prototypic status, epinephrine is discussed in detail.

Therapeutic Uses

Epinephrine can activate all four subtypes of adrenergic receptors. As a consequence, the drug can produce a broad spectrum of beneficial sympathomimetic effects:

- Because it can cause alpha***1***-mediated vasoconstriction, epinephrine is used to (1) delay absorption of local anesthetics, (2) control superficial bleeding, and (3) elevate blood pressure. In the past, epinephrine-induced vasoconstriction was also used for nasal decongestion.
- Activation of alpha***1*** receptors on the iris can be used to produce mydriasis during ophthalmologic procedures.

- Because it can activate beta*1* receptors, epinephrine is used to (1) overcome AV heart block and (2) restore cardiac function in patients experiencing cardiac arrest.
- Activation of beta*2* receptors in the lung promotes bronchodilation, which can be useful in patients with asthma (although other drugs are preferred).
- Because it can activate a combination of alpha and beta receptors, epinephrine is the treatment of choice for anaphylactic shock.

BOX 17-1 THE EPIPEN: DON'T LEAVE HOME WITHOUT IT!

The EpiPen is an epinephrine auto-injector, the only one available in the United States. The device is indicated for emergency treatment of anaphylaxis, a life-threatening allergic reaction caused by severe hypersensitivity to insect venoms (eg, from bees, wasps, fire ants), certain foods (eg, peanuts, walnuts, shellfish), and certain drugs (especially penicillins). Every year, anaphylaxis kills about 6000 Americans: 125 who have food allergies, between 40 and 400 who have venom allergies, and over 5400 who have penicillin allergy. Could most of these deaths be avoided? Yes—through immediate injection of epinephrine. Unfortunately, many of the people at risk don't carry an epinephrine injector, and many of those who do aren't sure how to use it. So listen up: By encouraging highly allergic clients to carry an EpiPen, and by teaching them when and how to use it, you could well save someone's life.

EpiPen Description and Dosage

The EpiPen auto-injector is a single-use delivery device, featuring a spring-activated needle, designed for IM injection of epinephrine. Two strengths are available. The larger one, sold as EpiPen, delivers a 0.3-mg dose (for individuals weighing 66 pounds or more). The smaller one, sold as EpiPen Jr, delivers a 0.15-mg dose (for individuals between 33 and 66 pounds). If one injection fails to completely reverse symptoms, a second injection (using a second EpiPen) may be given. The EpiPen is available only by prescription.

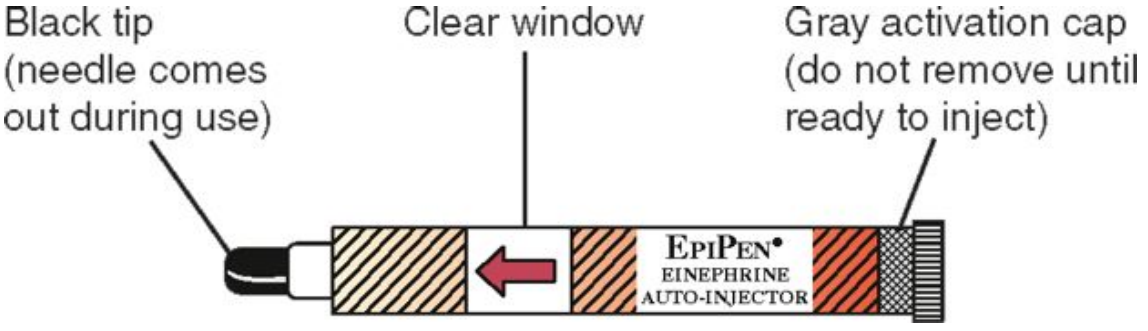
EpiPen Storage and Replacement

Epinephrine is sensitive to extreme heat and light, and hence the EpiPen should be stored at room temperature in a dark place. The factory-issue storage tube provides additional protection from UV light. Refrigeration can compromise the injection mechanism, and therefore should be avoided. If the epinephrine solution turns brown, if a precipitate forms, or if the expiration date has passed, the unit should be replaced. (The distributor offers a free service to remind patients when their EpiPen is about to expire.)

Who Should Carry an EpiPen and When Should They Use It?

Anyone who has experienced a severe, systemic allergic reaction should *always* carry at least one epinephrine auto-injector! Anaphylaxis can develop within minutes after allergen exposure. To prevent a full-blown reaction, epinephrine should be injected as soon as early symptoms appear (eg, swelling, shortness of breath). People who do not carry an EpiPen, and hence must wait for an emergency response team, greatly increase their risk of death.

What's the Self-Injection Procedure?

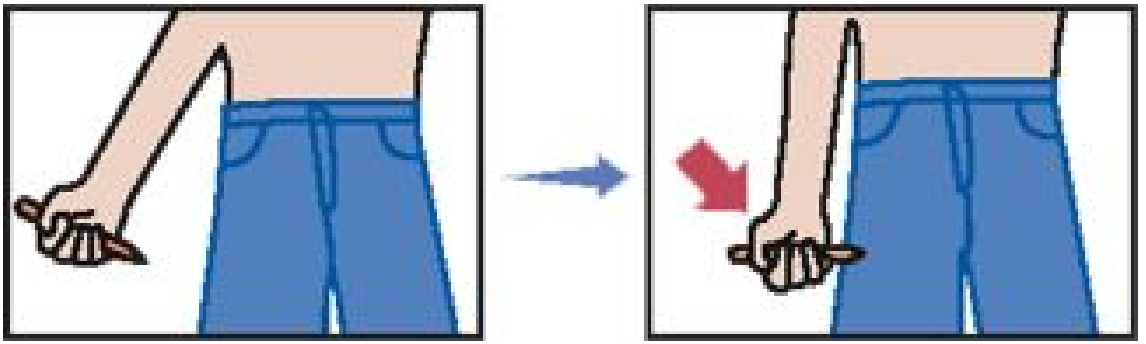


The EpiPen auto-injector is a tubular device with three prominent external features: a black tip (the needle comes out through this end), a clear window (for examining the epinephrine solution), and a gray cap (which prevents activation until being removed).

Injections are made into the outer thigh as follows:

1. Form a fist around the unit with the black tip pointing down.
2. With the free hand, pull off the gray activation cap.

3. Jab the device firmly into the outer thigh, at an angle perpendicular to the thigh, and hold it there for 10 seconds. (The injection may be made directly through clothing.)



4. Remove the unit and massage the area for 10 seconds to facilitate absorption.

To ensure the injection was made, examine the used EpiPen: If the needle is projecting through the black tip, the procedure was a success; if the needle is not projecting, jab the device in again. *Note:* The EpiPen contains 2 mL of epinephrine solution, but only 0.3 mL is actually injected. Hence, even after a successful injection, the device will not be empty.

What Should Be Done After the Injection?

Following epinephrine injection, it is important to get immediate medical attention. Why? Because (1) the effects of epinephrine begin to fade in 10 to 20 minutes and (2) anaphylactic reactions can be biphasic and prolonged. Accordingly, to ensure a good outcome, hospitalization (up to 6 hours) is recommended. Hospital staff should be informed that epinephrine has been injected, and should be shown the used EpiPen (to confirm the dosage). Prednisone may be given to manage delayed or persistent symptoms.

Does IM Epinephrine Have Side Effects?

Of course. The injection itself may cause discomfort, and the epinephrine may cause tachycardia, palpitations, and a feeling of nervousness. The drug may also cause sweating, dizziness, headache, nausea, and vomiting.

Pharmacokinetics

Absorption.

Epinephrine may be administered topically or by injection. The drug cannot be given orally because, as discussed, epinephrine and other catecholamines undergo destruction by MAO and COMT before reaching the systemic circulation. Following subQ injection, absorption is slow owing to epinephrine-induced local vasoconstriction. Absorption is more rapid following IM injection. When epinephrine is inhaled (to treat asthma), systemic absorption is usually minimal. However, if dosage is excessive, systemic absorption can be sufficient to cause toxicity.

Inactivation.

Epinephrine has a short half-life because of two processes: enzymatic inactivation and uptake into adrenergic nerves. The enzymes that inactivate epinephrine and other catecholamines are MAO and COMT.

Adverse Effects

Because it can activate the four major adrenergic receptor subtypes, epinephrine can produce multiple adverse effects.

Hypertensive Crisis.

Vasoconstriction secondary to excessive alpha***1*** activation can produce a dramatic increase in blood pressure. Cerebral hemorrhage can occur. Because of the potential for severe hypertension, patients receiving *parenteral* epinephrine must undergo continuous cardiovascular monitoring.

Dysrhythmias.

Excessive activation of beta***1*** receptors in the heart can produce dysrhythmias. Because of their sensitivity to catecholamines, hyperthyroid patients are at high risk for epinephrine-induced dysrhythmias.

Angina Pectoris.

By activating beta***1*** receptors in the heart, epinephrine can increase cardiac work and oxygen demand. If the increase in oxygen demand is big enough,

an anginal attack may ensue. Precipitation of angina is especially likely in patients with coronary atherosclerosis.

Necrosis Following Extravasation.

If an IV line containing epinephrine becomes extravasated, the resultant localized vasoconstriction may result in necrosis. Because of this possibility, patients receiving IV epinephrine should be monitored closely. If extravasation occurs, injury can be minimized by local injection of phentolamine, an alpha-adrenergic antagonist.

Hyperglycemia.

In diabetic patients, epinephrine can cause hyperglycemia. How? By causing breakdown of glycogen secondary to activation of beta*2* receptors in liver and skeletal muscle. If hyperglycemia develops, insulin dosage should be increased.

Drug Interactions

MAO Inhibitors.

As their name implies, MAO inhibitors suppress the activity of MAO. These drugs are used primarily to treat depression (see Chapter 32). Because MAO is one of the enzymes that inactivate epinephrine and other catecholamines, inhibition of MAO will prolong and intensify epinephrine's effects. As a rule, patients receiving an MAO inhibitor should not receive epinephrine.

Tricyclic Antidepressants.

Tricyclic antidepressants block the uptake of catecholamines into adrenergic neurons. Since neuronal uptake is one mechanism by which the actions of norepinephrine and other catecholamines are terminated, blocking uptake can intensify and prolong epinephrine's effects. Accordingly, patients receiving a tricyclic antidepressant may require a reduction in epinephrine dosage.

Concentration of Epinephrine Solution	Route of Administration
1% (1:100)	Oral inhalation
0.1% (1:1000)	Subcutaneous
	Intramuscular
	Intraspinal
0.01% (1:10,000)	Intravenous
	Intracardiac
0.001% (1:100,000)	In combination with local anesthetics

TABLE 17-3 Epinephrine Solutions: Concentrations for Different Routes of Administration

General Anesthetics.

Several inhalation anesthetics render the myocardium hypersensitive to activation by beta*1* agonists. When the heart is in this hypersensitive state, exposure to epinephrine and other beta*1* agonists can cause tachydysrhythmias.

Alpha-Adrenergic Blocking Agents.

Drugs that block alpha-adrenergic receptors can prevent receptor activation by epinephrine. Alpha blockers (eg, phentolamine) can be used to treat toxicity (eg, hypertension, local vasoconstriction) caused by excessive epinephrine-induced alpha activation.

Beta-Adrenergic Blocking Agents.

Drugs that block beta-adrenergic receptors can prevent receptor activation by epinephrine. Beta-blocking agents (eg, propranolol) can reduce adverse effects (eg, dysrhythmias, anginal pain) caused by epinephrine and other beta*1* agonists.

Preparations, Dosage, and Administration

Epinephrine [Adrenalin, EpiPen, Primatene Mist, others] is supplied in solution for administration by several routes: IV, IM, subQ, intracardiac, intraspin-

al, inhalation, and topical. As indicated in Table 17-3, the strength of the epinephrine solution employed depends on the route of administration. Note that solutions intended for *intravenous* administration are *less concentrated* than solutions intended for administration by most other routes. Why? Because *intravenous administration of a concentrated epinephrine solution can produce potentially fatal reactions* (severe dysrhythmias and hypertension). Therefore, *before you give epinephrine IV, check carefully to ensure that the concentration is appropriate!* Aspirate prior to IM or subQ injection to avoid inadvertent injection into a vein.

Patients receiving IV epinephrine should be monitored constantly. They should be observed for signs of excessive cardiovascular activation (eg, tachydysrhythmias, hypertension) and for possible extravasation of the IV line. If systemic toxicity develops, epinephrine should be discontinued; if indicated, an alpha-adrenergic blocker, a beta-adrenergic blocker, or both should be given to suppress symptoms. If an epinephrine-containing IV line becomes extravasated, administration should be discontinued and the region of extravasation infiltrated with an alpha-adrenergic blocker.

Treatment of anaphylaxis using the EpiPen auto-injector is discussed in Box 17-1.

Norepinephrine

- *Receptor specificity:* alpha***1***, alpha***2***, beta***1***
- *Chemical classification:* catecholamine

Norepinephrine [Levophed] is similar to epinephrine in several respects. With regard to receptor specificity, NE differs from epinephrine only in that NE does not activate beta***2*** receptors. Accordingly, NE can elicit all of the responses that epinephrine can—except those that are beta***2*** mediated. Because NE is a catecholamine, the drug is subject to rapid inactivation by MAO and COMT, and hence cannot be given orally. Adverse effects are nearly identical to those of epinephrine: tachydysrhythmias, angina, hypertension, and local necrosis upon extravasation. In contrast to epinephrine, NE does not promote hyperglycemia, a response that is beta***2*** mediated. As with epinephrine, responses to NE can be modified by MAO inhibitors, tricyclic antidepressants, general anesthetics, and adrenergic blocking agents.

Despite its similarity to epinephrine, NE has limited clinical applications. The only recognized indications are *hypotensive states* and *cardiac arrest*.

Norepinephrine is supplied in solution (1 mg/mL) for administration by IV infusion only. Never leave the patient unattended. Monitor cardiovascular status continuously. Take care to avoid extravasation.

Isoproterenol

- *Receptor specificity:* beta***1*** and beta***2***
- *Chemical classification:* catecholamine

Isoproterenol [Isuprel] differs significantly from NE and epinephrine in that isoproterenol acts only at beta-adrenergic receptors. Isoproterenol was the first beta-selective agent employed clinically and will serve as our prototype of the beta-selective adrenergic agonists.

Therapeutic Uses

Cardiovascular.

By activating beta***1*** receptors in the heart, isoproterenol can benefit patients with cardiovascular disorders. Specifically, it can help overcome AV heart block, restart the heart following cardiac arrest, and increase cardiac output during shock.

Asthma.

By activating beta***2*** receptors in the lung, isoproterenol can cause bronchodilation, thereby decreasing airway resistance. Following its introduction, isoproterenol became a mainstay of asthma therapy. However, because we now have even more selective beta-adrenergic agonists (ie, drugs that activate beta***2*** receptors only), use of isoproterenol for asthma has been abandoned.

Bronchospasm.

Although isoproterenol is no longer used for asthma, it *is* used to treat bronchospasm during anesthesia. Benefits derive from activating beta***2*** receptors in the lung.

Adverse Effects

Because isoproterenol does not activate alpha-adrenergic receptors, it produces fewer adverse effects than NE or epinephrine. The major undesired responses are cardiac. Excessive activation of beta*1* receptors in the heart can cause *tachydysrhythmias* and *angina pectoris*. In diabetic patients, isoproterenol can cause *hyperglycemia* (by promoting beta*2*-mediated glycogenolysis).

Drug Interactions

The major drug interactions of isoproterenol are nearly identical to those of epinephrine. Effects are enhanced by MAO inhibitors and tricyclic antidepressants and reduced by beta-adrenergic blocking agents. Like epinephrine, isoproterenol can cause dysrhythmias in patients receiving certain inhalation anesthetics.

Preparations and Administration

Isoproterenol hydrochloride [Isuprel] is available in solution (0.2 and 0.02 mg/mL) for parenteral administration.

When used to *stimulate the heart,* isoproterenol can be administered IV and IM and by intracardiac injection. The dosage for IM administration is about 10 times greater than the dosage employed by the other two routes.

When used to relieve *bronchospasm,* isoproterenol is administered IV.

Dopamine

- *Receptor specificity:* dopamine, beta*1*, and, at high doses, alpha*1*
- *Chemical classification:* catecholamine

Receptor Specificity

Dopamine (formerly available as Intropin) has *dose-dependent* receptor specificity. When administered in low therapeutic doses, dopamine acts on dopamine receptors only. At moderate therapeutic doses, dopamine activates beta*1* receptors in addition to dopamine receptors. And at very high doses, dopamine activates alpha*1* receptors along with beta*1* and dopamine receptors.

Therapeutic Uses

Shock.

The major indication for dopamine is shock. Benefits derive from effects on the heart and renal blood vessels. By activating beta*1* receptors in the heart, dopamine can increase cardiac output, thereby improving tissue perfusion. By activating dopamine receptors in the kidney, dopamine can dilate renal blood vessels, thereby improving renal perfusion. Success can be evaluated by monitoring output of urine.

Heart Failure.

Heart failure is characterized by reduced tissue perfusion secondary to reduced cardiac output. Dopamine can help alleviate symptoms by activating beta*1* receptors on the heart, which increases myocardial contractility, and thereby increases cardiac output.

Acute Renal Failure.

Because of its ability to increase renal blood flow and urine output, low-dose dopamine has long been used in efforts to preserve renal function in patients with evolving acute renal failure (ARF). However, we now have evidence that the drug is not effective: In patients with early ARF, dopamine failed to protect renal function, shorten hospital stays, or reduce the number of patients needing a kidney transplant. Accordingly, it would appear that it is time to abandon low-dose dopamine as a treatment for ARF.

Adverse Effects

The most common adverse effects of dopamine—*tachycardia, dysrhythmias,* and *anginal pain*—result from activation of beta*1* receptors in the heart. Because of its cardiac actions, dopamine is contraindicated for patients with tachydysrhythmias or ventricular fibrillation. Since high concentrations of dopamine cause alpha*1* activation, extravasation may result in *necrosis* from localized vasoconstriction; tissue injury can be minimized by local infiltration of phentolamine, an alpha-adrenergic blocking agent.

Drug Interactions

MAO inhibitors can intensify the effects of dopamine on the heart and blood vessels. If a patient is receiving an MAO inhibitor, the dosage of dopamine

must be reduced by at least 90%. Tricyclic antidepressants can also intensify dopamine's actions, but not to the extent seen with MAO inhibitors. Certain general anesthetics can sensitize the myocardium to stimulation by dopamine and other catecholamines, thereby creating a risk of dysrhythmias. Diuretics can complement the beneficial effects of dopamine on the kidney.

Preparations, Dosage, and Administration

Preparations.

Dopamine hydrochloride is supplied in aqueous solutions that range in concentration from 40 to 320 mg/mL.

Dosage.

Dopamine must be diluted prior to infusion. For treatment of *shock,* a dilution of 400 mcg/mL can be used. The recommended initial rate of infusion is 2 to 5 mcg/kg/min. If needed, the infusion rate can be gradually increased to a maximum of 20 to 50 mcg/kg/min.

Administration.

Dopamine is administered IV. Because of extremely rapid inactivation by MAO and COMT, the drug must be given by *continuous infusion*. A metering device is needed to control flow rate. Cardiovascular status must be closely monitored. If extravasation occurs, the infusion should be stopped and the affected area infiltrated with an alpha-adrenergic antagonist (eg, phentolamine).

Dobutamine

- *Receptor specificity:* beta***1***
- *Chemical classification:* catecholamine

Actions and Uses.

At therapeutic doses, dobutamine (formerly available as Dobutrex) causes selective activation of beta***1***-adrenergic receptors. The only indication for the drug is *heart failure*.

Adverse Effects.

The major adverse effect is *tachycardia*. Blood pressure and the electrocardiogram (ECG) should be monitored closely.

Drug Interactions.

Effects of dobutamine on the heart and blood vessels are intensified greatly by MAO inhibitors. Accordingly, in patients receiving an MAO inhibitor, dobutamine dosage must be reduced at least 90%. Concurrent use of tricyclic antidepressants may cause a moderate increase in the cardiovascular effects. Certain general anesthetics can sensitize the myocardium to stimulation by dobutamine, thereby increasing the risk of dysrhythmias.

Preparations, Dosage, and Administration.

Dobutamine hydrochloride is supplied in a concentrated solution (12.5 mg/mL in 20-mL vials), which must be diluted to at least 50 mL prior to use. Because of rapid inactivation by MAO and COMT, dobutamine is administered by continuous IV infusion. The usual rate is 2.5 to 10 mcg/kg/min.

Phenylephrine

- *Receptor specificity:* alpha***1***
- *Chemical classification:* noncatecholamine

Phenylephrine [Neo-Synephrine, others] is a selective alpha***1*** agonist. The drug can be administered locally to reduce nasal congestion and parenterally to elevate blood pressure. In addition, phenylephrine eye drops can be used to dilate the pupil. Also, phenylephrine can be coadministered with local anesthetics to retard anesthetic absorption.

Terbutaline

- *Receptor specificity:* beta***2***
- *Chemical classification:* noncatecholamine

Therapeutic Uses

Asthma.

Terbutaline [Brethine] can reduce airway resistance in asthma by causing beta***2***-mediated bronchodilation. Because terbutaline is "selective" for beta***2*** receptors, it produces much less activation of cardiac beta***1*** receptors than does isoproterenol. As a result, terbutaline and other beta***2***-selective agents have replaced isoproterenol for therapy of asthma. Remember, however, that receptor selectivity is only relative: If administered in large doses, terbutaline will lose selectivity and activate beta***1*** receptors as well as beta***2*** receptors. Accordingly, patients should be warned not to exceed recommended doses, since doing so may cause undesired cardiac stimulation. Preparations and dosages for asthma are presented in Chapter 75.

Delay of Preterm Labor.

By activating beta***2*** receptors in the uterus, terbutaline can relax uterine smooth muscle, thereby delaying labor. However, other drugs are preferred (see Chapter 63).

Adverse Effects

Adverse effects are minimal at therapeutic doses. *Tremor* is most common. If dosage is excessive, terbutaline can cause *tachycardia* by activating beta***1*** receptors in the heart.

Ephedrine

- *Receptor specificity:* alpha***1***, alpha***2***, beta***1***, beta***2***
- *Chemical classification:* noncatecholamine

Ephedrine is referred to as a *mixed-acting drug*, because it activates adrenergic receptors by direct *and* indirect mechanisms. *Direct* activation results from binding of the drug to alpha and beta receptors. *Indirect* activation results from release of NE from adrenergic neurons.

Owing to the development of more selective adrenergic agonists, uses for ephedrine are limited. By promoting beta***2***-mediated bronchodilation, ephedrine can benefit patients with *asthma*. By activating a combination of alpha and beta receptors, ephedrine can improve hemodynamic status in patients with *shock*. In the past, the drug was used for nasal decongestion.

Because ephedrine activates the same receptors as epinephrine, both drugs share the same adverse effects: hypertension, dysrhythmias, angina, and hyperglycemia. In addition, because ephedrine can cross the blood-brain barrier, it can act in the CNS to cause insomnia.

DISCUSSION OF ADRENERGIC AGONISTS IN OTHER CHAPTERS

All of the drugs presented in this chapter are discussed again in chapters that address specific applications. For example, the use of alpha*1* agonists to relieve nasal congestion is discussed in Chapter 76. Table 17-4 summarizes the chapters in which adrenergic agonists are discussed again.

Drug Class	Discussion Topic	Chapter
Alpha$_1$ Agonists	Nasal congestion	76
	Ophthalmology	103
Alpha$_2$ Agonists	Cardiovascular effects	19
	Pain relief	28
	Hypertension	46
	Ophthalmology	103
Beta$_1$ Agonists	Heart failure	47
Beta$_2$ Agonists	Asthma	75
	Preterm labor	63
Amphetamines	Basic pharmacology	36
	Attention-deficit/hyperactivity disorder	36
	Drug abuse	39
	Appetite suppression	81

TABLE 17-4 Discussion of Adrenergic Agonists In Other Chapters

KEY POINTS

- Adrenergic agonists are also known as sympathomimetics. Why? Because their effects mimic those caused by the sympathetic nervous system.
- Most adrenergic agonists act by direct activation of adrenergic receptors. A few act by indirect mechanisms: promotion of norepinephrine release, blockade of norepinephrine uptake, and inhibition of norepinephrine breakdown.
- Adrenergic agonists fall into two chemical classes: catecholamines and noncatecholamines.
- Agents in the catecholamine family cannot be taken orally (because of destruction by MAO and COMT), have a brief duration of action (because of destruction by MAO and COMT), and cannot cross the blood-brain barrier (because they are polar molecules).
- Adrenergic agonists that are noncatecholamines can be taken orally, have a longer duration than the catecholamines, and can cross the blood-brain barrier.
- Activation of alpha***1*** receptors causes vasoconstriction and mydriasis.
- Alpha***1*** agonists are used for hemostasis, nasal decongestion, and elevation of blood pressure, and as adjuncts to local anesthetics.
- Major adverse effects that can result from alpha***1*** activation are hypertension and local necrosis (if extravasation occurs).
- Activation of alpha***2*** receptors in the periphery is of minimal clinical significance. In contrast, drugs that activate alpha***2*** receptors in the CNS produce useful effects (see Chapters 19 and 28.
- All of the clinically relevant responses to activation of beta***1*** receptors result from activating beta***1*** receptors in the heart.
- Activation of cardiac beta***1*** receptors increases heart rate, force of contraction, and conduction through the AV node.
- Drugs that activate beta***1*** receptors can be used to treat heart failure, AV block, and cardiac arrest.

- Potential adverse effects from beta*1* activation are tachycardia, dysrhythmias, and angina.
- Drugs that activate beta*2* receptors are used primarily for asthma.
- Principal adverse effects from beta*2* activation are hyperglycemia (mainly in diabetic patients) and tremor.
- Activation of dopamine receptors dilates renal blood vessels, which helps maintain renal perfusion in shock.
- Epinephrine is a catecholamine that activates alpha*1*, alpha*2*, beta*1*, and beta*2* receptors.
- Epinephrine is the drug of choice for treating anaphylactic shock: By activating alpha*1*, beta*1*, and beta*2* receptors, epinephrine can elevate blood pressure, suppress glottal edema, and counteract bronchoconstriction.
- Epinephrine can also be used to control superficial bleeding, restart the heart after cardiac arrest, and delay absorption of local anesthetics.
- Epinephrine should not be combined with MAO inhibitors, and should be used cautiously in patients taking tricyclic antidepressants.
- Isoproterenol is a catecholamine that activates beta*1* and beta*2* receptors.
- Isoproterenol can be used to enhance cardiac performance (by activating beta*1* receptors) and to treat bronchospasm (by activating beta*2* receptors).
- Dopamine is a catecholamine whose receptor specificity is highly dose dependent: at low therapeutic doses, dopamine acts on dopamine receptors only; at moderate doses, dopamine activates beta*1* receptors in addition to dopamine receptors; and at high doses, dopamine activates alpha*1* receptors along with beta*1* receptors and dopamine receptors.
- Terbutaline is a noncatecholamine that produces selective activation of beta*2* receptors.
- Terbutaline can be used to treat asthma and delay preterm labor.
- Because terbutaline is “selective” for beta*2* receptors, it produces much less stimulation of the heart than does isoproterenol. Accordingly, terbutaline and related drugs have replaced isoproterenol for therapy of asthma.

Summary of Major Nursing Implications

EPINEPHRINE

Preadministration Assessment

Therapeutic Goal

Epinephrine has multiple indications. Major uses include treatment of *anaphylaxis* and *cardiac arrest*. Other uses include *control of superficial bleeding* and *delay of local anesthetic absorption*.

Identifying High-Risk Patients

Epinephrine must be used with *great caution* in patients with hyperthyroidism, cardiac dysrhythmias, organic heart disease, or hypertension. *Caution* is also needed in patients with angina pectoris or diabetes and in those receiving MAO inhibitors, tricyclic antidepressants, or general anesthetics.

Implementation: Administration

Routes

Topical, oral inhalation, and parenteral (IV, IM, subQ, intracardiac, intraspinal). Rapid inactivation by MAO and COMT prohibits oral use.

Administration

The concentration of epinephrine solutions varies according to the route of administration (see Table 17-3). To avoid serious injury, check solution strength to ensure that the concentration is appropriate for the intended route. Aspirate prior to IM and subQ administration to avoid inadvertent injection into a vein.

Epinephrine solutions oxidize over time, causing them to turn pink or brown. Discard discolored solutions.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

In patients receiving IV epinephrine, monitor cardiovascular status continuously.

Minimizing Adverse Effects

Cardiovascular Effects.

By stimulating the heart, epinephrine can cause *anginal pain, tachycardia,* and *dysrhythmias*. These responses can be reduced with a beta-adrenergic blocking agent (eg, propranolol).

By activating alpha***1*** receptors on blood vessels, epinephrine can cause intense vasoconstriction, which can result in *severe hypertension*. Blood pressure can be lowered with an alpha-adrenergic blocking agent (eg, phentolamine).

Necrosis.

If an IV line delivering epinephrine becomes extravasated, necrosis may result. Exercise care to avoid extravasation. If extravasation occurs, infiltrate the region with phentolamine to minimize injury.

Hyperglycemia.

Epinephrine may cause hyperglycemia in diabetic patients. If hyperglycemia develops, insulin dosage should be increased.

Minimizing Adverse Interactions

MAO Inhibitors and Tricyclic Antidepressants.

These drugs prolong and intensify the actions of epinephrine. Patients taking these antidepressants require a reduction in epinephrine dosage.

General Anesthetics.

When combined with certain general anesthetics, epinephrine can induce cardiac dysrhythmias. Dysrhythmias may respond to a beta***1***-adrenergic blocker.

DOPAMINE

Preadministration Assessment

Therapeutic Goal

Dopamine is used to improve hemodynamic status in patients with *shock* or *heart failure*. Benefits derive from enhanced cardiac performance and increased renal perfusion.

Baseline Data

Full assessment of cardiac, hemodynamic, and renal status is needed.

Identifying High-Risk Patients

Dopamine is *contraindicated* for patients with tachydysrhythmias or ventricular fibrillation. Use with *extreme caution* in patients with organic heart disease, hyperthyroidism, or hypertension, and in patients receiving MAO inhibitors. *Caution* is also needed in patients with angina pectoris and in those receiving tricyclic antidepressants or general anesthetics.

Implementation: Administration

Route

Intravenous.

Administration

Administer by continuous infusion, employing a metering device to control flow rate.

If extravasation occurs, stop the infusion immediately and infiltrate the region with an alpha-adrenergic antagonist (eg, phentolamine).

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor cardiovascular status continuously. Increased urine output is one index of success. Diuretics may complement the beneficial effects of dopamine on the kidney.

Minimizing Adverse Effects

Cardiovascular Effects.

By stimulating the heart, dopamine may cause *anginal pain, tachycardia,* or *dysrhythmias*. These reactions can be decreased with a beta-adrenergic blocking agent (eg, propranolol).

Necrosis.

If the IV line delivering dopamine becomes extravasated, necrosis may result. Exercise care to avoid extravasation. If extravasation occurs, infiltrate the region with phentolamine.

Minimizing Adverse Interactions

MAO Inhibitors.

Concurrent use of MAO inhibitors and dopamine can result in severe cardiovascular toxicity. If a patient is taking an MAO inhibitor, dopamine dosage must be reduced by at least 90%.

Tricyclic Antidepressants.

These drugs prolong and intensify the actions of dopamine. Patients receiving them may require a reduction in dopamine dosage.

General Anesthetics.

When combined with certain general anesthetics, dopamine can induce dysrhythmias. These may respond to a beta***1***-adrenergic blocker.

DOBUTAMINE

Preadministration Assessment

Therapeutic Goal

Improvement of hemodynamic status in patients with heart failure.

Baseline Data

Full assessment of cardiac, renal, and hemodynamic status is needed.

Identifying High-Risk Patients

Use with *great caution* in patients with organic heart disease, hyperthyroidism, tachydysrhythmias, or hypertension and in those taking an MAO inhibitor. *Caution* is also needed in patients with angina pectoris and in those receiving tricyclic antidepressants or general anesthetics.

Implementation: Administration

Route

Intravenous.

Administration

Administer by continuous IV infusion. Dilute concentrated solutions prior to use. Infusion rates usually range from 2.5 to 10 mcg/kg/min. Adjust the infusion rate on the basis of the cardiovascular response.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor cardiac function (heart rate, ECG), blood pressure, and urine output. When possible, monitor central venous pressure and pulmonary wedge pressure.

Minimizing Adverse Effects

Major adverse effects are *tachycardia* and *dysrhythmias*. Monitor the ECG and blood pressure closely. Adverse cardiac effects can be reduced with a beta-adrenergic antagonist.

Minimizing Adverse Interactions

MAO Inhibitors.

Concurrent use of an MAO inhibitor with dobutamine can cause severe cardiovascular toxicity. If a patient is taking an MAO inhibitor, dobutamine dosage must be reduced by at least 90%.

Tricyclic Antidepressants.

These drugs can prolong and intensify the actions of dobutamine. Patients receiving them may require a reduction in dobutamine dosage.

General Anesthetics.

When combined with certain general anesthetics, dobutamine can cause cardiac dysrhythmias. These may respond to a beta*1*-adrenergic antagonist.

18 Adrenergic Antagonists

The adrenergic antagonists cause direct blockade of adrenergic receptors. With one exception, all of the adrenergic antagonists produce *reversible* (competitive) blockade.

Unlike many adrenergic agonists, which act at alpha- *and* beta-adrenergic receptors, most adrenergic antagonists are more selective. As a result, the adrenergic antagonists can be neatly divided into two major groups: (1) *alpha-adrenergic blocking agents* (drugs that produce selective blockade of alpha-adrenergic receptors); and (2) *beta-adrenergic blocking agents* (drugs that produce selective blockade of beta receptors).* Members of these two groups are listed in Table 18-1.

Category	Drugs	Receptors Blocked
Alpha-Adrenergic Blocking Agents	Phenoxybenzamine	$alpha_1$, $alpha_2$
	Phentolamine	$alpha_1$, $alpha_2$
	Alfuzosin	$alpha_1$
	Doxazosin	$alpha_1$
	Prazosin	$alpha_1$
	Silodosin	$alpha_1$
	Terazosin	$alpha_1$
	Tamsulosin	$alpha_1$
Beta-Adrenergic Blocking Agents	Carteolol	$beta_1$, $beta_2$
	Nadolol	$beta_1$, $beta_2$
	Penbutolol	$beta_1$, $beta_2$
	Pindolol	$beta_1$, $beta_2$
	Propranolol	$beta_1$, $beta_2$
	Sotalol	$beta_1$, $beta_2$
	Timolol	$beta_1$, $beta_2$
	Carvedilol	$beta_1$, $beta_2$, $alpha_1$
	Labetalol	$beta_1$, $beta_2$, $alpha_1$
	Acebutolol	$beta_1$
	Atenolol	$beta_1$
	Betaxolol	$beta_1$
	Bisoprolol	$beta_1$
	Esmolol	$beta_1$
	Metoprolol	$beta_1$

TABLE 18-1 Receptor Specificity of Adrenergic Antagonists

Our approach to the adrenergic antagonists mirrors the approach we took with the adrenergic agonists. That is, we begin by discussing the therapeutic and adverse effects that can result from alpha- and beta-adrenergic blockade, after which we discuss the individual drugs that produce receptor blockade.

Remember that it is much easier to understand responses to the adrenergic drugs if you first understand the responses to activation of adrenergic receptors. Accordingly, if you have not yet mastered (memorized) Table 13-3, you should do so now (or at least be prepared to consult the table as we proceed).

ALPHA-ADRENERGIC ANTAGONISTS I: THERAPEUTIC AND ADVERSE RESPONSES TO ALPHA BLOCKADE

In this section we discuss the beneficial and adverse responses that can result from blockade of alpha-adrenergic receptors. Properties of individual alpha-blocking agents are discussed later.

Therapeutic Applications of Alpha Blockade

Most of the clinically useful responses to alpha-adrenergic antagonists result from blockade of alpha*1* receptors on blood vessels. Blockade of alpha*1* receptors in the bladder and prostate can help men with benign prostatic hyperplasia (BPH). Blockade of alpha*1* receptors in the eye and blockade of alpha*2* receptors have no recognized therapeutic applications.

Essential Hypertension.

Hypertension (high blood pressure) can be treated with a variety of drugs, including the alpha-adrenergic antagonists. Alpha antagonists lower blood pressure by blocking alpha*1* receptors on arterioles and veins, causing vasodilation. Dilation of arterioles reduces arterial pressure directly. Dilation of veins lowers arterial pressure by an indirect process: In response to venous dilation, return of blood to the heart decreases, thereby decreasing cardiac output, which in turn reduces arterial pressure. The role of alpha-adrenergic blockers in essential hypertension is discussed further in Chapter 46 (Drugs for Hypertension).

* Only two adrenergic antagonists—carvedilol and labetalol—act at alpha and beta receptors.

Reversal of Toxicity from Alpha*1* Agonists.

Overdose with an alpha-adrenergic agonist (eg, epinephrine) can produce *hypertension* secondary to excessive activation of alpha*1* receptors on blood vessels. When this occurs, blood pressure can be lowered by reversing the vasoconstriction with an alpha-blocking agent.

If an IV line containing an alpha agonist becomes extravasated, necrosis can occur secondary to intense local vasoconstriction. By infiltrating the region with phentolamine (an alpha-adrenergic antagonist), we can block the vasoconstriction and thereby prevent injury.

Benign Prostatic Hyperplasia.

BPH results from proliferation of cells in the prostate gland. Symptoms include dysuria, increased frequency of daytime urination, nocturia, urinary hesitance and intermittence, urinary urgency, a sensation of incomplete voiding, and a reduction in the size and force of the urinary stream. All of these symptoms can be improved with drugs that block alpha*1* receptors. Benefits derive from reduced contraction of smooth muscle in the bladder neck (trigone and sphincter) and prostatic capsule. BPH is discussed at length in Chapter 65.

Pheochromocytoma.

A pheochromocytoma is a catecholamine-secreting tumor derived from cells of the sympathetic nervous system. These tumors are usually located in the adrenal medulla. If secretion of catecholamines (epinephrine, norepinephrine) is sufficiently great, persistent hypertension can result. The principal cause of hypertension is activation of alpha*1* receptors on blood vessels, although activation of beta*1* receptors on the heart can also contribute. The preferred treatment is surgical removal of the tumor, but alpha-adrenergic blockers may also be employed.

Alpha-blocking agents have two roles in managing pheochromocytoma. First, in patients with inoperable tumors, alpha blockers are given chronically to suppress hypertension. Second, when surgery is indicated, alpha blockers are administered preoperatively to reduce the risk of acute hypertension during

the procedure. (The surgical patient is at risk because manipulation of the tumor can cause massive catecholamine release.)

Raynaud's Disease.

Raynaud's disease is a peripheral vascular disorder characterized by vasospasm in the toes and fingers. Prominent symptoms are local sensations of pain and cold. Alpha blockers can suppress symptoms by preventing alpha-mediated vasoconstriction. It should be noted, however, that although alpha blockers can relieve symptoms of Raynaud's disease, they are generally ineffective against other peripheral vascular disorders that involve inappropriate vasoconstriction.

Adverse Effects of Alpha Blockade

The most significant adverse effects of the alpha-adrenergic antagonists result from blockade of alpha***1*** receptors. Detrimental effects associated with alpha***2*** blockade are minor.

Adverse Effects of Alpha***1*** Blockade

Orthostatic Hypotension.

This is the most serious adverse response to alpha-adrenergic blockade. Orthostatic hypotension can reduce blood flow to the brain, thereby causing dizziness, lightheadedness, and even syncope (fainting).

The cause of hypotension is blockade of alpha receptors on *veins,* which reduces muscle tone in the venous wall. Because of reduced venous tone, blood tends to pool (accumulate) in veins when the patient assumes an erect posture. As a result, return of blood to the heart is reduced, which decreases cardiac output, which in turn causes blood pressure to fall.

Patients should be informed about symptoms of hypotension (lightheadedness, dizziness) and advised to sit or lie down if these occur. In addition, patients should be informed that orthostatic hypotension can be minimized by avoiding abrupt transitions from a supine or sitting position to an erect posture.

Reflex Tachycardia.

Alpha-adrenergic antagonists can increase heart rate by triggering the baroreceptor reflex. The mechanism is this: (1) blockade of vascular alpha*1* receptors causes vasodilation; (2) vasodilation reduces blood pressure; and (3) baroreceptors sense the reduction in blood pressure and, in an attempt to restore normal pressure, initiate a reflex increase in heart rate via the autonomic nervous system. If necessary, reflex tachycardia can be suppressed with a beta-adrenergic blocking agent.

Nasal Congestion.

Alpha blockade can dilate the blood vessels of the nasal mucosa, producing nasal congestion.

Inhibition of Ejaculation.

Since activation of alpha*1* receptors is required for ejaculation (see Table 13-3), blockade of these receptors can cause impotence. This form of drug-induced impotence is reversible and resolves when the alpha blocker is withdrawn.

The ability of alpha blockers to inhibit ejaculation can be a major reason for nonadherence to the prescribed regimen. If a patient deems the adverse sexual effects of alpha blockade unacceptable, a change in medication will be required. Because males may be reluctant to discuss such concerns, a tactful interview may be needed to discern if drug-induced impotence is discouraging drug use.

Sodium Retention and Increased Blood Volume.

By reducing blood pressure, alpha blockers can promote renal retention of sodium and water, thereby causing blood volume to increase. The steps in this process are as follows: (1) by reducing blood pressure, alpha*1* blockers decrease renal blood flow; (2) in response to reduced perfusion, the kidney excretes less sodium and water; and (3) the resultant retention of sodium and water increases blood volume. As a result, blood pressure is elevated, blood flow to the kidney is increased, and, as far as the kidney is concerned, all is well. Unfortunately, when alpha blockers are used to treat hypertension (which they often are), this compensatory elevation in blood pressure can negate beneficial effects. In order to prevent the kidney from “neutralizing” hy-

potensive actions, alpha-blocking agents are usually combined with a diuretic when used in patients with hypertension.

Adverse Effects of Alpha2 Blockade

The most significant adverse effect associated with alpha2 blockade is *potentiation of the reflex tachycardia that can occur in response to blockade of alpha1 receptors*. Why does alpha2 blockade intensify reflex tachycardia? Recall that peripheral alpha2 receptors are located presynaptically and that activation of these receptors inhibits norepinephrine release. Hence, if alpha2 receptors are blocked, release of norepinephrine will increase. Since the reflex tachycardia caused by alpha1 blockade is ultimately the result of increased firing of the sympathetic nerves to the heart, and since alpha2 blockade will cause each nerve impulse to release a greater amount of norepinephrine, alpha2 blockade will potentiate reflex tachycardia initiated by blockade of alpha1 receptors. Accordingly, drugs such as phentolamine, which block alpha2 as well as alpha1 receptors, cause greater reflex tachycardia than do drugs that block alpha1 receptors only.

ALPHA-ADRENERGIC ANTAGONISTS II: PROPERTIES OF INDIVIDUAL ALPHA BLOCKERS

Only seven alpha-adrenergic antagonists are employed clinically. Because the alpha blockers often cause postural hypotension, therapeutic uses are limited.

As indicated in Table 18-1, the alpha-adrenergic blocking agents can be subdivided into two major groups. One group—the *nonselective* alpha-blocking agents—contains drugs that block alpha1 and alpha2 receptors. Phentolamine is the prototype. The second group, represented by *prazosin,* contains drugs that produce *selective alpha1 blockade*.

Prazosin

Actions and Uses.

Prazosin [Minipress] is a competitive antagonist that produces selective blockade of alpha1-adrenergic receptors. The result is dilation of arterioles and veins, and relaxation of smooth muscle in the bladder neck (trigone and

sphincter) and prostatic capsule. Prazosin is approved only for hypertension. However, it can also benefit men with BPH.

Pharmacokinetics.

Prazosin is administered orally. Antihypertensive effects peak in 1 to 3 hours and persist for 10 hours. The drug undergoes extensive hepatic metabolism followed by excretion in the bile. Only 10% is eliminated in the urine. The half-life is 2 to 3 hours.

Adverse Effects.

Blockade of alpha***1*** receptors can cause *orthostatic hypotension, reflex tachycardia, inhibition of ejaculation,* and *nasal congestion*. The most serious of these is hypotension. Patients should be educated about the symptoms of hypotension (dizziness, lightheadedness) and advised to sit or lie down if they occur. Also, patients should be informed that orthostatic hypotension can be minimized by moving slowly when changing from a supine or sitting position to an upright position.

About 1% of patients lose consciousness 30 to 60 minutes after receiving their initial prazosin dose. This "first-dose" effect is the result of severe postural hypotension. To minimize the first-dose effect, the initial dose should be small (1 mg or less). Subsequent doses can be gradually increased with little risk of fainting. Patients who are starting treatment should be forewarned about the first-dose effect and advised to avoid driving and other hazardous activities for 12 to 24 hours. Administering the initial dose at bedtime eliminates the risk of a first-dose effect.

Preparations, Dosage, and Administration.

Prazosin hydrochloride [Minipress] is available in capsules (1, 2, and 5 mg) for oral use. The initial adult dosage for hypertension is 1 mg 2 or 3 times a day. The maintenance dosage is 6 to 15 mg/day taken in divided doses.

Terazosin

Actions and Uses.

Like prazosin, terazosin [Hytrin] is a selective, competitive antagonist at alpha*1*-adrenergic receptors. The drug is approved for hypertension and BPH.

Pharmacokinetics.

Peak effects develop 1 to 2 hours after oral dosing. The drug's half-life is prolonged (9 to 12 hours), allowing benefits to be maintained with just one dose a day. Terazosin undergoes hepatic metabolism followed by excretion in the bile and urine.

Adverse Effects.

Like other alpha-blocking agents, terazosin can cause *orthostatic hypotension, reflex tachycardia,* and *nasal congestion*. In addition, terazosin is associated with a high incidence (16%) of *headache*. As with prazosin, the first dose can cause profound hypotension. To minimize this first-dose effect, the initial dose should be administered at bedtime.

Preparations, Dosage, and Administration.

Terazosin [Hytrin] is available in tablets and capsules (1, 2, 5, and 10 mg). *Antihypertensive* therapy is initiated with a 1-mg dose, administered at bedtime to minimize the first-dose effect. Dosage can be gradually increased as needed and tolerated. The recommended dosage range for maintenance therapy is 1 to 5 mg once daily. Dosing for *benign prostatic hyperplasia* is similar to that for hypertension, except that the maintenance dosage is 10 mg/day for most men.

Doxazosin

Actions and Uses.

Doxazosin [Cardura] is a selective, competitive inhibitor of alpha*1*-adrenergic receptors. The drug is indicated for hypertension and BPH.

Pharmacokinetics.

Doxazosin is administered orally, and peak effects develop in 2 to 3 hours. The drug has a prolonged half-life (22 hours), so once-a-day dosing is adequate. In the blood, most (98%) of the drug is protein bound. Doxazosin undergoes extensive hepatic metabolism followed by biliary excretion.

Adverse Effects.

Like prazosin and terazosin, doxazosin can cause *orthostatic hypotension, reflex tachycardia,* and *nasal congestion*. As with prazosin and terazosin, the first dose can cause profound hypotension, which can be minimized by giving the initial dose at bedtime.

Preparations, Dosage, and Administration.

Doxazosin is available in two oral formulations: standard tablets (1, 2, 4, and 8 mg), marketed as Cardura, and sustained-release tablets (4 and 8 mg), marketed as Cardura XL. Cardura is approved for hypertension and BPH, whereas Cardura XL is approved for BPH only.

Dosage Using Cardura.

The initial dosage for hypertension or BPH is 1 mg once a day. The dosage may be gradually increased as needed, up to a maximum of 16 mg once daily for hypertension or 8 mg once daily for BPH.

Dosage Using Cardura XL.

The initial dosage (for BPH) is 4 mg once a day administered with breakfast. If needed, the dosage may be increased to 8 mg once daily 3 to 4 weeks later.

Tamsulosin

Actions and Uses.

Tamsulosin [Flomax] is an alpha***1***-adrenergic antagonist that causes "selective" blockade of alpha***1*** receptors on smooth muscle of the bladder neck (trigone and sphincter), prostatic capsule, and prostatic urethra; blockade of vascular alpha***1*** receptors is weak. The drug is approved only for BPH; it is not useful for hypertension. In men with BPH, tamsulosin increases urine flow rate and decreases residual urine volume. Maximum benefits develop within 2 weeks.

Pharmacokinetics.

Tamsulosin is administered orally, and absorption is slow. Food further decreases the rate and extent of absorption. The drug is metabolized in the liver and excreted in the urine.

Adverse Effects.

The most common adverse effects are *headache* (20%) and *dizziness* (15%). Between 8% and 18% of patients experience *abnormal ejaculation* (ejaculation failure, ejaculation decrease, retrograde ejaculation). In addition, the drug is associated with increased incidence of *infection*. Because relaxation of vascular smooth muscle is relatively weak, the risk of orthostatic hypotension is much lower than with most other alpha blockers.

Drug Interactions.

Combined use with cimetidine increases tamsulosin serum levels, which may cause toxicity. Combined use with hypotensive drugs—including sildenafil [Viagra] and related agents—may cause a significant reduction in blood pressure.

Preparations, Dosage, and Administration.

Tamsulosin [Flomax] is available in 0.4-mg capsules. The usual dosage is 0.4 mg once a day, administered 30 minutes after the same meal each day.

Alfuzosin

Actions and Uses.

Like tamsulosin, alfuzosin [Uroxatral] is an alpha***1*** blocker with selectivity for alpha***1*** receptors in the prostate and urinary tract. At recommended doses, blockade of alpha***1*** receptors on blood vessels is weak. Alfuzosin is indicated only for BPH. The drug is not useful in hypertension.

Pharmacokinetics.

Alfuzosin is formulated in extended-release tablets, and hence absorption is slow. Plasma levels peak 8 hours after dosing. Bioavailability is 49%. Alfuzosin undergoes extensive hepatic metabolism, primarily by CYP3A4, an isozyme of cytochrome P450. Most (70%) of each dose is eliminated in the feces as in-

active metabolites. A small fraction leaves unchanged in the urine. The drug's half-life is 10 hours.

In patients with moderate to severe hepatic impairment, alfuzosin levels increase three- to fourfold. Accordingly, the drug is contraindicated for these patients.

Adverse Effects.

Alfuzosin in generally well tolerated. The most common adverse effect is *dizziness* (5%). Syncope and clinically significant hypotension are rare. Unlike tamsulosin, alfuzosin does not interfere with ejaculation. Doses 4 times greater than recommended can prolong the QT interval, and might thereby pose a risk of ventricular dysrhythmias.

Drug Interactions.

Levels of alfuzosin are markedly raised by powerful inhibitors of CYP3A4. Among these are erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, and the HIV protease inhibitors, such as ritonavir. Concurrent use of alfuzosin with these drugs is contraindicated.

Although alfuzosin does not lower blood pressure much by itself, combining it with other hypotensive agents could produce a more dramatic reduction. Accordingly, such combinations should be used with caution. Drugs of concern include organic nitrates, antihypertensive agents, and the type 5 phosphodiesterase inhibitors used for impotence (eg, sildenafil [Viagra]).

Preparations, Dosage, and Administration.

Alfuzosin [Uroxatral] is available in 10-mg extended-release tablets. The recommended dosage is 10 mg once a day, taken immediately after the same meal each day.

Silodosin

Actions and Uses.

Silodosin [Rapaflo], approved in October 2008, is an alpha-adrenergic antagonist that selectively blocks alpha***1*** receptors in the prostate, bladder, and ur-

ethra. Blockade of vascular alpha receptors is weak. The drug is indicated only for BPH.

Adverse Effects.

Silodosin in generally well tolerated. However, like tamsulosin, silodosin can greatly reduce or eliminate release of semen during orgasm. Fortunately, this effect reverses when the drug is discontinued. Although blockade of vascular alpha receptors is usually minimal, silodosin *can* produce dizziness, lightheadedness, and nasal congestion.

Preparations Dosage, and Administration.

When silodosin becomes commercially available (sometime in 1009), the expected formulations are 4- and 8-mg capsules. The usual dosage is 8 mg once daily, but should be reduced to 4 mg once daily in men with moderate renal or hepatic impairment. Men with severe renal or hepatic impairment should not use the drug.

Phentolamine

Actions and Uses.

Like prazosin, phentolamine (formerly available as Regitine) is a competitive adrenergic antagonist. However, in contrast to prazosin, phentolamine blocks alpha***2*** receptors as well as alpha***1*** receptors. Phentolamine has two approved applications: (1) treatment of pheochromocytoma and (2) prevention of tissue necrosis following extravasation of drugs that produce alpha***1***-mediated vasoconstriction (eg, norepinephrine).

Adverse Effects.

Like prazosin, phentolamine can produce the typical adverse effects associated with alpha-adrenergic blockade: *orthostatic hypotension, reflex tachycardia, nasal congestion,* and *inhibition of ejaculation*. Because it blocks alpha***2*** receptors, *phentolamine produces greater reflex tachycardia than prazosin*. If reflex tachycardia is especially severe, heart rate can be reduced with a beta blocker. Since tachycardia can aggravate angina pectoris and myocardial infarction (MI), phentolamine is contraindicated for patients with either disorder.

Overdose can produce profound hypotension. If necessary, blood pressure can be elevated with *norepinephrine. Epinephrine* should *not* be used, because the drug can cause blood pressure to drop even further! Why? Because in the presence of alpha***1*** blockade, the ability of epinephrine to promote vasodilation (via activation of vascular beta***2*** receptors) may outweigh the ability of epinephrine to cause vasoconstriction (via activation of vascular alpha***1*** receptors). Further lowering of blood pressure is not a problem with norepinephrine because norepinephrine does not activate beta***2*** receptors.

Preparations, Dosage, and Administration.

Phentolamine is supplied in solution (5 mg/2 mL) for IM and IV administration. The dose for preventing hypertension during surgical excision of a *pheochromocytoma* is 5 mg (IM or IV) given 1 to 2 hours before surgery. To prevent *necrosis following extravasation* of IV norepinephrine, the region should be infiltrated with 5 to 10 mg of phentolamine diluted in 10 mL of saline.

Phenoxybenzamine

Actions and Uses.

Phenoxybenzamine [Dibenzyline] is an old drug that, like phentolamine, blocks alpha***1*** and alpha***2*** receptors. However, unlike all of the other alpha-adrenergic antagonists, phenoxybenzamine is a *noncompetitive* receptor antagonist. Hence, receptor blockade is *not reversible*. As a result, the effects of phenoxybenzamine are long lasting. (Responses to a single dose can persist for several days.) Effects subside as newly synthesized receptors replace the ones that have been irreversibly blocked. Phenoxybenzamine is approved only for *pheochromocytoma*.

Adverse Effects.

Like the other alpha-adrenergic antagonists, phenoxybenzamine can produce *orthostatic hypotension, reflex tachycardia, nasal congestion,* and *inhibition of ejaculation*. Reflex tachycardia is greater than that caused by prazosin and about equal to that caused by phentolamine.

If dosage is excessive, phenoxybenzamine, like phentolamine, will cause profound hypotension. Furthermore, since hypotension is the result of *irreversible*

alpha*1* blockade, it cannot be corrected with an alpha*1* agonist. To restore blood pressure, patients must be given IV fluids, which elevate blood pressure by increasing blood volume.

Preparations, Dosage, and Administration.

Phenoxybenzamine hydrochloride [Dibenzyline] is available in 10-mg tablets for oral use. The initial adult dosage is 10 mg twice a day. The dosage can be increased every other day until the desired level of alpha blockade (blood pressure control) has been achieved. The usual adult maintenance dosage is 20 to 40 mg given 2 or 3 times a day.

BETA-ADRENERGIC ANTAGONISTS I: THERAPEUTIC AND ADVERSE RESPONSES TO BETA BLOCKADE

In this section we consider the beneficial and adverse responses that can result from blockade of beta-adrenergic receptors. Properties of individual beta blockers are discussed later.

Therapeutic Applications of Beta Blockade

Practically all of the therapeutic effects of the beta-adrenergic antagonists result from blockade of beta*1* receptors in the heart. The major consequences of blocking these receptors are (1) reduced heart rate, (2) reduced force of contraction, and (3) reduced velocity of impulse conduction through the atrioventricular (AV) node. Because of these effects, beta blockers are useful in a variety of cardiovascular disorders.

Angina Pectoris.

Angina pectoris (paroxysmal pain in the region of the heart) occurs when oxygen supply (blood flow) to the heart is insufficient to meet cardiac oxygen demand. Anginal attacks can be precipitated by exertion, intense emotion, and other factors. Beta-adrenergic blockers are a mainstay of antianginal therapy. By blocking beta*1* receptors in the heart, these drugs decrease cardiac work. This brings oxygen demand back into balance with oxygen supply, and thereby prevents pain. Angina pectoris and its treatment are the subject of Chapter 50.

Hypertension.

For years, beta blockers were considered drugs of choice for hypertension. However, recent data indicate they are less beneficial than previously believed.

The exact mechanism by which beta blockers reduce blood pressure is not known. Older proposed mechanisms include reduction of cardiac output through blockade of beta***1*** receptors in the heart and suppression of renin release through blockade of beta***1*** receptors in the kidney (see Chapter 43 for a discussion of the role of renin in blood pressure control). More recently, we have learned that, with long-term use, beta blockers reduce peripheral vascular resistance, which could account for much of their antihypertensive effects. The role of beta-adrenergic blocking agents in hypertension is discussed further in Chapter 46.

Cardiac Dysrhythmias.

Beta-adrenergic blocking agents are especially useful for treating dysrhythmias that involve excessive electrical activity in the sinus node and atria. By blocking cardiac beta***1*** receptors, these drugs can (1) decrease the rate of sinus nodal discharge and (2) suppress conduction of atrial impulses through the AV node, thereby preventing the ventricles from being driven at an excessive rate. The use of beta-adrenergic blockers to treat dysrhythmias is discussed at length in Chapter 48.

Myocardial Infarction.

An MI is a region of myocardial necrosis caused by localized interruption of blood flow to the heart wall. Treatment with a beta blocker can reduce pain, infarct size, mortality, and the risk of reinfarction. To be effective, therapy with a beta blocker must commence soon after an MI has occurred, and should be continued for several years. The role of beta blockers in treating MI is discussed further in Chapter 52.

Heart Failure.

Beta blockers are now considered standard therapy for heart failure. This application is relatively new and may come as a surprise to some readers. Why?

Because, until recently, heart failure was considered an absolute *contraindication* to beta blockers. At this time, only three beta blockers—carvedilol, bisoprolol, and metoprolol—have been shown effective for heart failure. Use of beta blockers for heart failure is discussed at length in Chapter 47.

Hyperthyroidism.

Hyperthyroidism (excessive production of thyroid hormone) is associated with an increase in the sensitivity of the heart to catecholamines (eg, norepinephrine, epinephrine). As a result, normal levels of sympathetic activity to the heart can generate tachydysrhythmias and angina pectoris. Blockade of cardiac beta***1*** receptors suppresses these responses.

Migraine.

When taken prophylactically, beta-adrenergic blocking agents can reduce the frequency of migraine attacks. However, although beta blockers are effective as prophylaxis, these drugs are not able to abort a migraine headache once it has begun. The mechanism by which beta blockers prevent migraine is not known. Treatment of migraine and other headaches is the subject of Chapter 30.

Stage Fright.

Public speakers and other performers sometimes experience "stage fright." Prominent symptoms are tachycardia and sweating brought on by generalized discharge of the sympathetic nervous system. Beta blockers help by preventing beta***1***-mediated tachycardia.

Pheochromocytoma.

As discussed above, a pheochromocytoma secretes large amounts of catecholamines, which can cause excessive stimulation of the heart. Cardiac stimulation can be prevented by beta***1*** blockade.

Glaucoma.

Beta blockers are important drugs for treating glaucoma, a condition characterized by elevated intraocular pressure with subsequent injury to the optic nerve. The group of beta blockers used in glaucoma (see Table 103-2) is differ-

ent from the group of beta blockers discussed in this chapter. Glaucoma and its treatment are addressed in Chapter 103 (Drugs for the Eye).

Adverse Effects of Beta Blockade

Although therapeutic responses to beta blockers are due almost entirely to blockade of beta*1* receptors, adverse effects involve both beta*1* and beta*2* blockade. Consequently, the nonselective beta-adrenergic blocking agents (drugs that block beta*1* *and* beta*2* receptors) produce a broader spectrum of adverse effects than do the "cardioselective" beta-adrenergic antagonists (drugs that selectively block beta*1* receptors at usual therapeutic doses).

Adverse Effects of Beta*1* Blockade

All of the adverse effects of beta*1* blockade are the result of blocking beta*1* receptors in the heart. Blockade of renal beta*1* receptors is not a concern.

Bradycardia.

Blockade of cardiac beta*1* receptors can produce bradycardia (excessively slow heart rate). If necessary, heart rate can be increased using a combination of isoproterenol (a beta-adrenergic agonist) and atropine (a muscarinic antagonist). Isoproterenol competes with the beta blocker for cardiac beta*1* receptors, thereby promoting cardiac stimulation. By blocking muscarinic receptors on the heart, atropine prevents slowing of the heart by the parasympathetic nervous system.

Reduced Cardiac Output.

Beta*1* blockade can reduce cardiac output by decreasing heart rate and the force of myocardial contraction. Because they can decrease cardiac output, *beta blockers must be used with great caution in patients with heart failure or reduced cardiac reserve*. In both cases, any further decrease in cardiac output could result in insufficient tissue perfusion.

Precipitation of Heart Failure.

In some patients, suppression of cardiac function with a beta blocker can be so great as to cause heart failure. Patients should be informed about the early signs of heart failure (shortness of breath, night coughs, swelling of the ex-

tremities) and instructed to notify the prescriber if these occur. It is important to appreciate that, although beta blockers can precipitate heart failure, they are also used to *treat* heart failure.

AV Heart Block.

Atrioventricular heart block is defined as suppression of impulse conduction through the AV node. In its most severe form, AV block prevents *all* atrial impulses from reaching the ventricles. Because blockade of cardiac beta*1* receptors can suppress AV conduction, production of AV block is a potential complication of beta-blocker therapy. These drugs are contraindicated for patients with pre-existing AV block.

Rebound Cardiac Excitation.

Long-term use of beta blockers can sensitize the heart to catecholamines. As a result, if a beta blocker is withdrawn *abruptly,* anginal pain or ventricular dysrhythmias may develop. This phenomenon of increased cardiac activity in response to abrupt cessation of beta-blocker therapy is referred to as *rebound excitation.* The risk of rebound excitation can be minimized by withdrawing these drugs gradually (eg, by tapering the dosage over a period of 1 to 2 weeks). If rebound excitation occurs, dosing should be temporarily resumed. Patients should be warned against abrupt cessation of treatment. Also, they should be advised to carry an adequate supply of their beta blocker when traveling.

Adverse Effects of Beta*2* Blockade

Bronchoconstriction.

Blockade of beta*2* receptors in the lung can cause constriction of the bronchi. (Recall that activation of these receptors promotes bronchodilation.) For most people, the degree of bronchoconstriction is insignificant. However, when bronchial beta*2* receptors are blocked in patients with asthma, the resulting increase in airway resistance can be life threatening. Accordingly, *drugs that block beta2 receptors* are contraindicated for people with asthma. If these individuals must use a beta blocker, they should use an agent that is beta*1* selective (eg, metoprolol).

Inhibition of Glycogenolysis.

As noted in Chapter 13, epinephrine, acting at beta***2*** receptors in skeletal muscle and the liver, can stimulate glycogenolysis (breakdown of glycogen into glucose). Beta***2*** blockade will inhibit this process. Although suppression of beta***2***-mediated glycogenolysis is inconsequential for most people, interference with this process can be detrimental to patients with *diabetes*. Why? Because these people are especially dependent on beta***2***-mediated glycogenolysis as a way to overcome severe reductions in blood glucose levels (caused by overdosing with insulin). If the diabetic patient requires a beta blocker, a beta***1***-selective agent should be chosen.

BETA-ADRENERGIC ANTAGONISTS II: PROPERTIES OF INDIVIDUAL BETA BLOCKERS

The beta-adrenergic antagonists can be subdivided into three groups:

- *First-generation (nonselective) beta blockers* (eg, propranolol), which block beta***1*** *and* beta***2*** receptors
- *Second-generation (cardioselective) beta blockers* (eg, metoprolol), which produce selective blockade of beta***1*** receptors (at usual doses)
- *Third-generation (vasodilating) beta blockers* (eg, carvedilol), which act on blood vessels to cause dilation, but may produce nonselective or cardioselective beta blockade

Our discussion of the individual beta blockers focuses on two prototypes: propranolol and metoprolol. Properties of these and other beta blockers are summarized in Tables 18-2 and 18-3.

Generic Name	Trade Name	Receptors Blocked	ISA	Lipid Solubility	Half-Life (hr)	Route*	Maintenance Dosage in Hypertension†
First-Generation: Nonselective Beta Blockers							
Carteolol	Cartrol	$Beta_1$, $Beta_2$	++	Low	6	PO	2.5 mg once/day
Nadolol	Corgard	$Beta_1$, $Beta_2$	0	Low	20–24	PO	40 mg once/day
Penbutolol	Levatol	$Beta_1$, $Beta_2$	+	Moderate	5	PO	20 mg once/day
Pindolol	Visken	$Beta_1$, $Beta_2$	+++	Moderate	3–4	PO	10 mg twice/day
Propranolol (IR)	Inderal	$Beta_1$, $Beta_2$	0	High	3–5	PO, IV	60 mg twice/day
Propranolol (SR)	Inderal LA, InnoPran XL					PO	80 mg once/day
Sotalol	Betapace	$Beta_1$, $Beta_2$	0	High	12	PO	Not for hypertension
Timolol	Blocadren	$Beta_1$, $Beta_2$	0	Low	4	PO	20 mg twice/day
Second-Generation: Cardioselective Beta Blockers							
Acebutolol	Sectral	$Beta_1$	+	Moderate	3–4	PO	400 mg once/day
Atenolol	Tenormin	$Beta_1$	0	Low	6–9	PO, IV	50 mg once/day
Betaxolol	Kerlone	$Beta_1$	0	Low	14–22	PO	10 mg once/day
Bisoprolol	Zebeta	$Beta_1$	0	Moderate	9–12	PO	5 mg once/day
Esmolol	Brevibloc	$Beta_1$	0	Low	0.15	IV	Not for hypertension
Metoprolol (IR)	Lopressor	$Beta_1$	0	High	3–7	PO, IV	100 mg once/day
Metoprolol (SR)	Toprol XL					PO	100 mg once/day
Third-Generation: Beta Blockers with Vasodilating Actions							
Nebivolol	Bystolic	$Beta_1$	0	High	12–19	PO	20 mg once/day
Carvedilol (IR)	Coreg	$Beta_1$, $Beta_2$, $Alpha_1$	0	Moderate	5–11	PO	12.5 mg twice/day
Carvedilol (SR)	Coreg CR					PO	40 mg once/day
Labetalol	Normodyne, Trandate	$Beta_1$, $Beta_2$, $Alpha_1$	0	Low	6–8	PO, IV	300 mg twice/day

IR = immediate release, ISA = intrinsic sympathomimetic activity (partial agonist activity), SR = sustained release.

TABLE 18-2 Clinical Pharmacology of the Beta-Adrenergic Blocking Agents

	Hypertension	Angina Pectoris	Cardiac Dysrhythmias	Myocardial Infarction	Migraine Prophylaxis	Stage Fright	Heart Failure
Acebutolol	A	I	A				
Atenolol	A	A	I	A	I	I	
Betaxolol	A						
Bisoprolol	A	I	I				I
Carteolol	A	I					
Carvedilol	A	I		A			A
Esmolol		I	A				
Labetalol	A						
Metoprolol	A	A	I	A	I		A
Nadolol	A	A	I		I	I	
Nebivolol	A						I
Penbutolol	A						
Pindolol	A		I			I	
Propranolol	A	A	A	A	A	I	
Sotalol			A				
Timolol	A		I	A	A	I	

A = FDA-approved use, I = investigational use.

TABLE 18-3 Beta-Adrenergic Blocking Agents: Summary of Therapeutic Uses

* Beta blockers used for glaucoma are discussed in Chapter 103 (Drugs for the Eye).

Propranolol

Propranolol [Inderal, InnoPran], our prototype of the first-generation beta blockers, produces *nonselective* beta blockade. That is, it blocks both beta***1***- *and* beta***2***-adrenergic receptors. Propranolol was the first beta blocker to receive widespread clinical use and remains one of our most important beta-blocking agents.

Pharmacologic Effects

By blocking *cardiac* beta*1* receptors, propranolol can *reduce heart rate, decrease the force of ventricular contraction,* and *suppress impulse conduction through the AV node*. The net effect is a reduction in cardiac output.

By blocking *renal* beta*1* receptors, propranolol can *suppress secretion of renin*.

By blocking beta*2* receptors, propranolol can produce three major effects: (1) *bronchoconstriction* (through beta*2* blockade in the lung), (2) *vasoconstriction* (through beta*2* blockade on certain blood vessels), and (3) *reduced glycogenolysis* (through beta*2* blockade in skeletal muscle and liver).

Pharmacokinetics

Propranolol is *highly lipid soluble* and therefore can readily cross membranes. The drug is well absorbed following oral administration, but, because of extensive metabolism on its first pass through the liver, less than 30% of each dose reaches the systemic circulation. Because of its ability to cross membranes, propranolol is widely distributed to all tissues and organs, including the central nervous system (CNS). Propranolol is inactivated by hepatic metabolism, and the metabolites are excreted in the urine.

Therapeutic Uses

Practically all of the applications of propranolol are based on blockade of beta*1* receptors in the heart. The drug's most important indications are *hypertension, angina pectoris, cardiac dysrhythmias,* and *myocardial infarction*. The role of propranolol and other beta blockers in these disorders is discussed in Chapter 46 (Drugs for Hypertension), Chapter 50 (Drugs for Angina Pectoris), Chapter 48 (Antidysrhythmic Drugs), and Chapter 52 (Management of ST-Elevation Myocardial Infarction). Additional indications include *migraine headache* and *"stage fright."*

Adverse Effects

The most serious adverse effects result from blockade of beta*1* receptors in the heart and blockade of beta*2* receptors in the lung.

Bradycardia.

Beta*1* blockade in the heart can cause bradycardia. Heart rate should be assessed before each dose. If necessary, heart rate can be increased by administering atropine and isoproterenol.

AV Heart Block.

By slowing conduction of impulses through the AV node, propranolol can cause AV heart block. The drug is contraindicated for patients with pre-existing AV block (if the block is greater than first degree).

Heart Failure.

In patients with cardiac disease, suppression of myocardial contractility by propranolol can result in heart failure. Patients should be informed about the early signs of heart failure (shortness of breath, night coughs, swelling of the extremities) and instructed to notify the prescriber if these occur. Propranolol is generally contraindicated for patients with pre-existing heart failure (although other beta blockers are used to *treat* heart failure).

Rebound Cardiac Excitation.

Abrupt withdrawal of propranolol can cause rebound excitation of the heart, resulting in tachycardia and ventricular dysrhythmias. To avoid rebound excitation, propranolol should be withdrawn slowly (ie, by giving progressively smaller doses over 1 to 2 weeks). Patients should be warned against abrupt cessation of treatment. In addition, they should be advised to carry an adequate supply of propranolol when traveling.

Bronchoconstriction.

Blockade of beta*2* receptors in the lung can cause bronchoconstriction. As a rule, increased airway resistance is hazardous only to patients with asthma and other obstructive pulmonary disorders.

Inhibition of Glycogenolysis.

Blockade of beta*2* receptors in skeletal muscle and the liver can inhibit glycogenolysis. This effect can be dangerous for people with diabetes (see below).

CNS Effects.

Because of its lipid solubility, propranolol can readily cross the blood-brain barrier, and hence has ready access sites in the CNS. However, although propranolol is reputed to cause a variety of CNS reactions—depression, insomnia, nightmares, and hallucinations—recent evidence indicates that such reactions are very rare. Because of the possible risk of depression, prudence dictates avoiding propranolol in patients who already have this disorder.

Precautions, Warnings, and Contraindications

Severe Allergy.

Propranolol should be avoided in patients with a history of severe allergic reactions (anaphylaxis). Why? Recall that epinephrine, the drug of choice for anaphylaxis, relieves symptoms in large part by activating beta*1* receptors in the heart and beta*2* receptors in the lung. If these receptors are blocked by propranolol, the ability of epinephrine to act will be dangerously impaired.

Diabetes.

Propranolol can be detrimental to diabetic patients in two ways. First, by blocking beta*2* receptors in muscle and liver, propranolol can suppress glycogenolysis, thereby eliminating an important mechanism for correcting hypoglycemia (which can occur when insulin dosage is excessive). Second, by blocking beta*1* receptors, propranolol can suppress tachycardia, which normally serves as an early warning signal that blood glucose levels are falling too low. (When glucose drops below a safe level, the sympathetic nervous system is activated, causing an increase in heart rate.) By "masking" tachycardia, propranolol can delay awareness of hypoglycemia, thereby compromising the patient's ability to correct the problem in a timely fashion. Diabetic patients who are taking propranolol should be warned that tachycardia may no longer be a reliable indicator of hypoglycemia. In addition, they should be taught to recognize alternative signs (sweating, hunger, fatigue, poor concentration) that blood glucose is falling perilously low. Because of its ability to suppress glycogenolysis and mask tachycardia, propranolol must be used with caution by diabetic patients.

Cardiac, Respiratory, and Psychiatric Disorders.

Propranolol can exacerbate *heart failure, AV heart block, sinus bradycardia, asthma,* and *bronchospasm*. Accordingly, the drug is contraindicated for patients with these disorders. In addition, propranolol should be used with caution in patients with a history of *depression*.

Drug Interactions

Calcium Channel Blockers.

The cardiac effects of two calcium channel blockers—verapamil and diltiazem—are identical to those of propranolol: reduction of heart rate, suppression of AV conduction, and suppression of myocardial contractility. When propranolol and these drugs are used concurrently, there is a risk of excessive cardiac suppression.

Insulin.

As discussed above, propranolol can impede early recognition of insulin-induced hypoglycemia. In addition, propranolol can block glycogenolysis, the body's mechanism for correcting hypoglycemia.

Preparations, Dosage, and Administration

General Dosing Considerations.

Establishing an effective propranolol dosage is difficult for two reasons: (1) patients vary widely in their requirements for propranolol and (2) there is a poor correlation between blood levels of propranolol and therapeutic responses. The explanation for these observations is that responses to propranolol are dependent on the activity of the sympathetic nervous system. If sympathetic activity is high, then the dose needed to reduce receptor activation will be high too. Conversely, if sympathetic activity is low, then low doses will be sufficient to produce receptor blockade. Since sympathetic activity varies among patients, propranolol requirements vary also. Accordingly, the dosage must be adjusted by monitoring the patient's response, and not by relying on dosing information in a drug reference.

Preparations.

Propranolol hydrochloride [Inderal, InnoPran] is available in three oral formulations: (1) standard tablets (10 to 90 mg), (2) extended-release (ER) capsules (60 to 160 mg), and (3) solution (4 and 8 mg/mL). The drug is also available in solution (1 mg/mL) for IV administration.

Dosage.

For treatment of *hypertension,* the initial dosage is 40 mg twice a day (using standard tablets) or 80 mg once a day (using ER capsules). Usual maintenance dosages are 120 to 240 mg/day in two, three, or four divided doses (using standard tablets) or 80 to 160 mg once a day (using ER capsules).

For *angina pectoris,* the initial dosage is 80 mg once a day (using ER capsules). The usual maintenance dosage is 160 mg once a day (using ER capsules) or 80 to 320 mg/day in two, three, or four divided doses (using standard tablets).

Metoprolol

Metoprolol [Lopressor, Toprol XL], our prototype of the second-generation beta blockers, produce selective blockade of beta***1*** receptors in the heart. At usual therapeutic doses, the drug does not cause beta***2*** blockade. Please note, however, that selectivity for beta***1*** receptors is not absolute: At higher doses, metoprolol and the other "cardioselective" agents will block beta***2*** receptors as well. Because their effects on beta***2*** receptors are normally minimal, the cardioselective agents are not likely to cause bronchoconstriction or suppression of glycogenolysis. Accordingly, these drugs are preferred to the nonselective beta blockers for patients with asthma or diabetes.

Pharmacologic Effects.

By blocking cardiac beta***1*** receptors, metoprolol has the same impact on the heart as propranolol: it reduces heart rate, force of contraction, and conduction velocity through the AV node. Also like propranolol, metoprolol reduces secretion of renin by the kidney. In contrast to propranolol, metoprolol does not block bronchial beta***2*** receptors (at usual doses), and therefore does not increase airway resistance.

Pharmacokinetics.

Metoprolol is very lipid soluble and well absorbed following oral administration. Like propranolol, metoprolol undergoes extensive metabolism on its first pass through the liver. As a result, only 40% of an oral dose reaches the systemic circulation. Elimination is by hepatic metabolism and renal excretion.

Therapeutic Uses.

The primary indication for metoprolol is *hypertension*. The drug is also approved for *angina pectoris, heart failure,* and *myocardial infarction*.

Adverse Effects.

Major adverse effects involve the heart. Like propranolol, metoprolol can cause *bradycardia, reduced cardiac output, AV heart block,* and *rebound cardiac excitation following abrupt withdrawal*. Also, even though metoprolol is approved for *treating* heart failure, it can *cause* heart failure if used incautiously. In contrast to propranolol, metoprolol causes minimal bronchoconstriction and does not interfere with beta*2*-mediated glycogenolysis.

Precautions, Warnings, and Contraindications.

Like propranolol, metoprolol is contraindicated for patients with *sinus bradycardia* and *AV block greater than first degree*. In addition, it should be used with great care in patients with *heart failure*. Because metoprolol produces only minimal blockade of beta*2* receptors, the drug is safer than propranolol for patients with asthma or a history of severe allergic reactions. In addition, since metoprolol does not suppress beta*2*-mediated glycogenolysis, it can be used more safely than propranolol by patients with diabetes. Please note, however, that metoprolol, like propranolol, will "mask" tachycardia, thereby depriving the diabetic patient of an early indication that hypoglycemia is developing.

Preparations, Dosage, and Administration.

Metoprolol is available in standard tablets (50 and 100 mg) under the trade name Lopressor and in sustained-release tablets (25, 50, 100, and 200 mg) under the trade name Toprol XL. The drug is also available in solution (1 mg/mL) for IV administration. The initial dosage for *hypertension* is 100 mg/day in single or divided doses. Dosages for maintenance therapy range from 100

to 450 mg/day in divided doses. Intravenous administration is reserved for *myocardial infarction*.

Other Beta-Adrenergic Blockers

In the United States, 16 beta blockers are approved for cardiovascular disorders (hypertension, angina pectoris, cardiac dysrhythmias, MI). Principal differences among these drugs concern receptor specificity, pharmacokinetics, indications, side effects, intrinsic sympathomimetic activity, and the ability to cause vasodilation.

In addition to the agents used for cardiovascular disorders, there is a group of beta blockers used for glaucoma (see Chapter 103, Drugs for the Eye).

Properties of the beta blockers employed for cardiovascular disorders are discussed below.

Receptor Specificity.

With regard to receptor specificity, beta blockers fall into two groups: nonselective agents and cardioselective agents. The nonselective agents block beta***1*** *and* beta***2*** receptors, whereas the cardioselective agents block beta***1*** receptors only (at usual doses). Because of their limited side effects, the cardioselective agents are preferred for patients with asthma or diabetes. Two beta blockers—*labetalol* and *carvedilol*—differ from all the others in that they block *alpha*-adrenergic receptors in addition to beta receptors. The receptor specificity of individual beta blockers is indicated in Tables 18-1 and 18-2.

Pharmacokinetics.

Pharmacokinetic properties of the beta blockers are summarized in Table 18-2. The relative lipid solubility of these agents is of particular importance. The drugs with high solubility (eg, propranolol, metoprolol) have two prominent features: (1) they penetrate the blood-brain barrier with ease and (2) they are eliminated primarily by hepatic metabolism. Conversely, the drugs with low lipid solubility (eg, nadolol, atenolol) penetrate the blood-brain barrier poorly and are eliminated primarily by renal excretion.

Therapeutic Uses.

Principal indications for the beta-adrenergic blockers are *hypertension, angina pectoris,* and *cardiac dysrhythmias*. Other uses include prophylaxis of *migraine headache,* treatment of *myocardial infarction,* symptom suppression in individuals with *situational anxiety* (eg, stage fright), and treatment of *heart failure* (see Chapter 47). Approved and investigational uses of the beta blockers are summarized in Table 18-3.

Esmolol and *sotalol* differ from the other beta blockers in that they are not used for hypertension. Because of its very short half-life (15 minutes), *esmolol* is clearly unsuited for treating hypertension, which requires maintenance of blood levels throughout the day, every day, for an indefinite time. The only approved indication for esmolol is emergency IV therapy of *supraventricular tachycardia. Sotalol* is approved only for *ventricular dysrhythmias*. Esmolol and sotalol are discussed further in Chapter 48 (Antidysrhythmic Drugs).

Adverse Effects.

By blocking beta***1*** receptors in the heart, all of the beta blockers can cause *bradycardia, AV heart block,* and, rarely, *heart failure*. By blocking beta***2*** receptors in the lung, the nonselective agents can cause significant *bronchoconstriction* in patients with asthma or chronic obstructive pulmonary disease. In addition, by blocking beta***2*** receptors in the liver and skeletal muscle, the *nonselective* agents can *inhibit glycogenolysis,* thereby compromising the ability of diabetic patients to compensate for insulin-induced hypoglycemia. Because of their ability to block alpha-adrenergic receptors, *carvedilol* and *labetalol* can cause *postural hypotension*.

Although *CNS effects* (insomnia, depression) can occur with all beta blockers, these effects are rare, and are most likely with the highly lipid-soluble agents. Abrupt discontinuation of any beta blocker can produce *rebound cardiac excitation*. Accordingly, all beta blockers should be withdrawn slowly (by tapering the dosage over 1 to 2 weeks).

Intrinsic Sympathomimetic Activity (Partial Agonist Activity).

The term *intrinsic sympathomimetic activity* (ISA) refers to the ability of certain beta blockers—especially *pindolol*—to act as *partial agonists* at beta-adrenergic

receptors. (As discussed in Chapter 5, a partial agonist is a drug that, when bound to a receptor, produces a limited degree of receptor activation while preventing strong agonists from binding to that receptor to cause full activation.)

In contrast to other beta blockers, agents with ISA have very little effect on resting heart rate and cardiac output. When patients are at rest, stimulation of the heart by the sympathetic nervous system is low. If an ordinary beta blocker is given, it will block sympathetic stimulation, causing heart rate and cardiac output to decline. However, if a beta blocker has ISA, its own ability to cause limited receptor activation will compensate for blocking receptor activation by the sympathetic nervous system and, consequently, resting heart rate and cardiac output are not reduced.

Because of their ability to provide a low level of cardiac stimulation, beta blockers with ISA are preferred to other beta blockers for use in patients with bradycardia. Conversely, these agents should not be given to patients with myocardial infarction. Why? Because their ability to cause even limited cardiac stimulation can be detrimental.

Vasodilation.

The third-generation beta blockers—*carvedilol, labetalol,* and *nebivolol*—can dilate blood vessels. Two mechanisms are employed: Carvedilol and labetalol block vascular alpha***1*** receptors; nebivolol promotes synthesis and release of nitric oxide from the vascular epithelium. The exact clinical benefit of vasodilation by these drugs has not been clarified.

Dosage and Administration.

With the exception of esmolol, all of the beta blockers discussed in this chapter can be administered orally. Three drugs—*atenolol, labetalol,* and *propranolol*—may be given *intravenously* as well as orally. *Esmolol* is administered only by IV injection.

Maintenance dosages for hypertension are summarized in Table 18-2. For most beta blockers, dosing can be done just once a day. For the drugs with especially short half-lives, Twice-A-Day dosing is required (unless an extended-release formulation is available).

KEY POINTS

- Most beneficial responses to alpha blockers, including reduction of blood pressure in patients with hypertension, result from blockade of alpha***1*** receptors on blood vessels.
- Alpha blockers reduce symptoms of BPH by blocking alpha***1*** receptors in the bladder neck and prostatic capsule, which causes smooth muscle at those sites to relax.
- The major adverse effects of alpha blockers are *orthostatic hypotension* (caused by blocking alpha***1*** receptors on veins); *reflex tachycardia* (caused by blocking alpha***1*** receptors on arterioles); *nasal congestion* (caused by blocking alpha***1*** receptors in blood vessels of the nasal mucosa); and *inhibition of ejaculation* (caused by blocking alpha***1*** receptors in male sex organs).
- The first dose of an alpha blocker can cause fainting from profound orthostatic hypotension, the so-called first-dose effect.
- The alpha blockers used most frequently—prazosin, doxazosin, and terazosin—produce selective blockade of alpha***1*** receptors.
- Beta blockers produce most of their beneficial effects by blocking beta***1*** receptors in the heart, thereby reducing heart rate, force of contraction, and AV conduction.
- Principal indications for the beta blockers are cardiovascular: hypertension, angina pectoris, heart failure, and supraventricular tachydysrhythmias.
- Potential adverse effects from beta***1*** blockade are bradycardia, reduced cardiac output, AV block, and precipitation of heart failure (even though some beta blockers are used to treat heart failure).
- Potential adverse effects from beta***2*** blockade are bronchoconstriction (a concern for people with asthma) and reduced glycogenolysis (a concern for people with diabetes).

- Beta blockers can be divided into three groups: (1) first-generation agents (ie, nonselective beta blockers, such as propranolol, which block beta*1* and beta*2* receptors); (2) second-generation agents (ie, cardioselective beta blockers, such as metoprolol, which block beta*1* receptors only at usual doses); and (3) third-generation agents (ie, vasodilating beta blockers, which may be cardioselective or nonselective).
- Beta blockers can be hazardous to patients with severe allergies because they can block beneficial actions of epinephrine, the drug of choice for treating anaphylactic shock.
- Beta blockers can be detrimental to diabetic patients because they suppress glycogenolysis (an important mechanism for correcting insulin-induced hypoglycemia), and they suppress tachycardia (an early warning signal that glucose levels are falling too low).
- Combining a beta blocker with a calcium channel blocker can produce excessive cardiosuppression.
- Cardioselective beta blockers are preferred to nonselective beta blockers for patients with asthma or diabetes.

Summary of Major Nursing Implications*

ALPHA*1*-ADRENERGIC ANTAGONISTS

Alfuzosin

Doxazosin

Prazosin

Silodosin

Tamsulosin

Terazosin

Preadministration Assessment

Therapeutic Goal

Doxazosin, Prazosin, Terazosin.

Reduction of blood pressure in patients with *essential hypertension*.

Doxazosin, Terazosin, Alfuzosin, Silodosin, Tamsulosin.

Reduction of symptoms in patients with *benign prostatic hyperplasia*.

Baseline Data

Essential Hypertension.

Determine blood pressure and heart rate.

Benign Prostatic Hyperplasia.

Determine the degree of nocturia, daytime frequency, hesitance, intermittency, terminal dribbling (at the end of voiding), urgency, impairment of size and force of urinary stream, dysuria, and sensation of incomplete voiding.

Identifying High-Risk Patients

The only contraindication is hypersensitivity to these drugs.

Implementation: Administration

Route

Oral.

Administration

Instruct patients to take the initial dose at bedtime to minimize the "first-dose" effect. Except for *tamsulosin,* which is administered *after* eating, these drugs may be taken with food.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Essential Hypertension.

Evaluate by monitoring blood pressure.

Benign Prostatic Hyperplasia.

Evaluate for improvement in the symptoms listed above under *Baseline Data*.

Minimizing Adverse Effects

Orthostatic Hypotension.

Alpha***1*** blockade can cause postural hypotension. Inform patients about the symptoms of hypotension (dizziness, lightheadedness) and advise them to sit or lie down if these occur. Advise patients to move slowly when changing from a supine or sitting position to an upright posture.

First-Dose Effect.

The first dose may cause fainting from severe orthostatic hypotension. Forewarn patients about this effect and advise them to avoid driving and other hazardous activities for 12 to 24 hours after the initial dose. To minimize risk, advise patients to take the first dose at bedtime.

BETA-ADRENERGIC ANTAGONISTS

Acebutolol

Atenolol

Betaxolol

Bisoprolol

Carteolol

Carvedilol

Labetalol

Metoprolol

Nadolol

Nebivolol

Penbutolol

Pindolol

Propranolol

Timolol

Except where noted, the implications summarized here apply to all beta-adrenergic blocking agents.

Preadministration Assessment

Therapeutic Goal

Principal indications are *hypertension, angina pectoris, heart failure,* and *cardiac dysrhythmias*. Indications for individual agents are summarized in Table 18-3.

Baseline Data

All Patients.

Determine heart rate.

Hypertension.

Determine standing and supine blood pressure.

Angina Pectoris.

Determine the incidence, severity, and circumstances of anginal attacks.

Cardiac Dysrhythmias.

Obtain a baseline electrocardiogram (ECG).

Identifying High-Risk Patients

All beta blockers are *contraindicated* for patients with sinus bradycardia or AV heart block greater than first degree, and must be used with *great caution* in patients with heart failure. Use with *caution* (especially the nonselective agents) in patients with asthma, bronchospasm, diabetes, or a history of severe allergic reactions. Use all beta blockers with *caution* in patients with a history of depression and in those taking calcium channel blockers.

Implementation: Administration

Routes

Oral.

All beta blockers.

Intravenous.

Atenolol, labetalol, metoprolol, and propranolol.

Administration

For maintenance therapy of hypertension, administer one or more times daily (see Table 18-2 and text).

Warn patients against abrupt discontinuation of treatment.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Hypertension.

Monitor blood pressure and heart rate prior to each dose. Advise outpatients to monitor blood pressure and heart rate daily.

Angina Pectoris.

Advise patients to record the incidence, circumstances, and severity of anginal attacks.

Cardiac Dysrhythmias.

Monitor for improvement in the ECG.

Minimizing Adverse Effects

Bradycardia.

Beta*1* blockade can reduce heart rate. If bradycardia is severe, withhold medication and notify the physician. If necessary, administer atropine and isoproterenol to restore heart rate.

AV Heart Block.

Beta*1* blockade can decrease AV conduction. Do not give beta blockers to patients with AV block greater than first degree.

Heart Failure.

Suppression of myocardial contractility can cause heart failure. Inform patients about early signs of heart failure (shortness of breath, night coughs, swelling of the extremities), and instruct them to notify the prescriber if these occur.

Rebound Cardiac Excitation.

Abrupt withdrawal of beta blockers can cause tachycardia and ventricular dysrhythmias. Warn patients against abrupt discontinuation of drug use. Also, advise patients, when traveling, to carry an adequate supply of medication plus a copy of their prescription.

Postural Hypotension.

By blocking alpha-adrenergic receptors, *carvedilol* and *labetalol* can cause postural hypotension. Inform patients about signs of hypotension (lightheadedness, dizziness) and advise them to sit or lie down if these develop. Advise patients to move slowly when changing from a supine or sitting position to an upright posture.

Bronchoconstriction.

Beta*2* blockade can cause substantial airway constriction in patients with asthma. The risk of bronchoconstriction is much lower with the cardioselective agents than with the nonselective agents.

Effects in Diabetic Patients.

Beta*1* blockade can "mask" tachycardia, an early sign of hypoglycemia. Warn patients that tachycardia cannot be relied on as an indicator of impending hypoglycemia, and teach them to recognize other indicators (sweating, hunger, fatigue, poor concentration) that blood glucose is falling dangerously low. Beta*2* blockade can prevent glycogenolysis, an emergency means of increasing blood glucose. Patients may need to reduce their insulin dosage. Cardiose-

lective beta blockers are preferred to nonselective agents in patients with diabetes.

CNS Effects.

Rarely, beta blockers cause depression, insomnia, and nightmares. If these occur, it may be helpful to switch to a beta blocker with low lipid solubility (see Table 18-2).

Minimizing Adverse Interactions

Calcium Channel Blockers.

Two calcium channel blockers—verapamil and diltiazem—can intensify the cardiosuppressant effects of the beta blockers. Use the combination with caution.

Insulin.

Beta blockers can prevent the compensatory glycogenolysis that normally occurs in response to insulin-induced hypoglycemia. Diabetic patients may need to reduce their insulin dosage.

19 Indirect-Acting Antiadrenergic Agents

The indirect-acting antiadrenergic agents are drugs that prevent activation of peripheral adrenergic receptors, but they do so by mechanisms that do not involve direct interaction with peripheral receptors. There are two categories of indirect-acting antiadrenergic drugs. The first group—*adrenergic neuron-blocking agents*—consists of drugs that act within the terminals of sympathetic neurons to decrease norepinephrine (NE) release. The second group—*centrally acting alpha2* agonists—consists of drugs that act within the central nervous system (CNS) to reduce the outflow of impulses along sympathetic neurons. With both groups, the net result is reduced activation of peripheral adrenergic receptors. Hence, the pharmacologic effects of the indirect-acting adrenergic blocking agents are very similar to those of drugs that block adrenergic receptors directly.

ADRENERGIC NEURON-BLOCKING AGENTS

The adrenergic neuron-blocking agents act presynaptically to reduce the release of NE from sympathetic neurons. These drugs have very little effect on release of epinephrine from the adrenal medulla. Our discussion focuses on reserpine.

Reserpine

Reserpine is a naturally occurring compound prepared from the root of *Rauwolfia serpentina,* a shrub indigenous to India. Because of its source, reserpine is classified as a *Rauwolfia alkaloid*. The primary indication for reserpine is hypertension. The side effect of greatest concern is severe depression.

Mechanism of Action

Reserpine causes *depletion of NE from postganglionic sympathetic neurons*. By doing so, the drug can decrease activation of practically all adrenergic receptors. Hence, the effects of reserpine closely resemble those produced by a combination of alpha- and beta-adrenergic blockade.

Reserpine depletes NE in two ways. First, the drug acts on vesicles within the nerve terminal to cause displacement of stored NE, thereby exposing the transmitter to destruction by monoamine oxidase. Second, reserpine suppresses NE synthesis. How? By blocking the uptake of dopamine (the immediate precursor of NE) into presynaptic vesicles, which contain the enzymes needed to convert dopamine into NE (Fig. 19-1). A week or two may be required to produce maximal transmitter depletion.

In addition to its peripheral effects, reserpine can cause depletion of transmitters (serotonin, catecholamines) from neurons in the CNS. Depletion of these CNS transmitters underlies the most serious side effect of reserpine—deep emotional depression—and also explains the occasional use of reserpine in psychiatry.

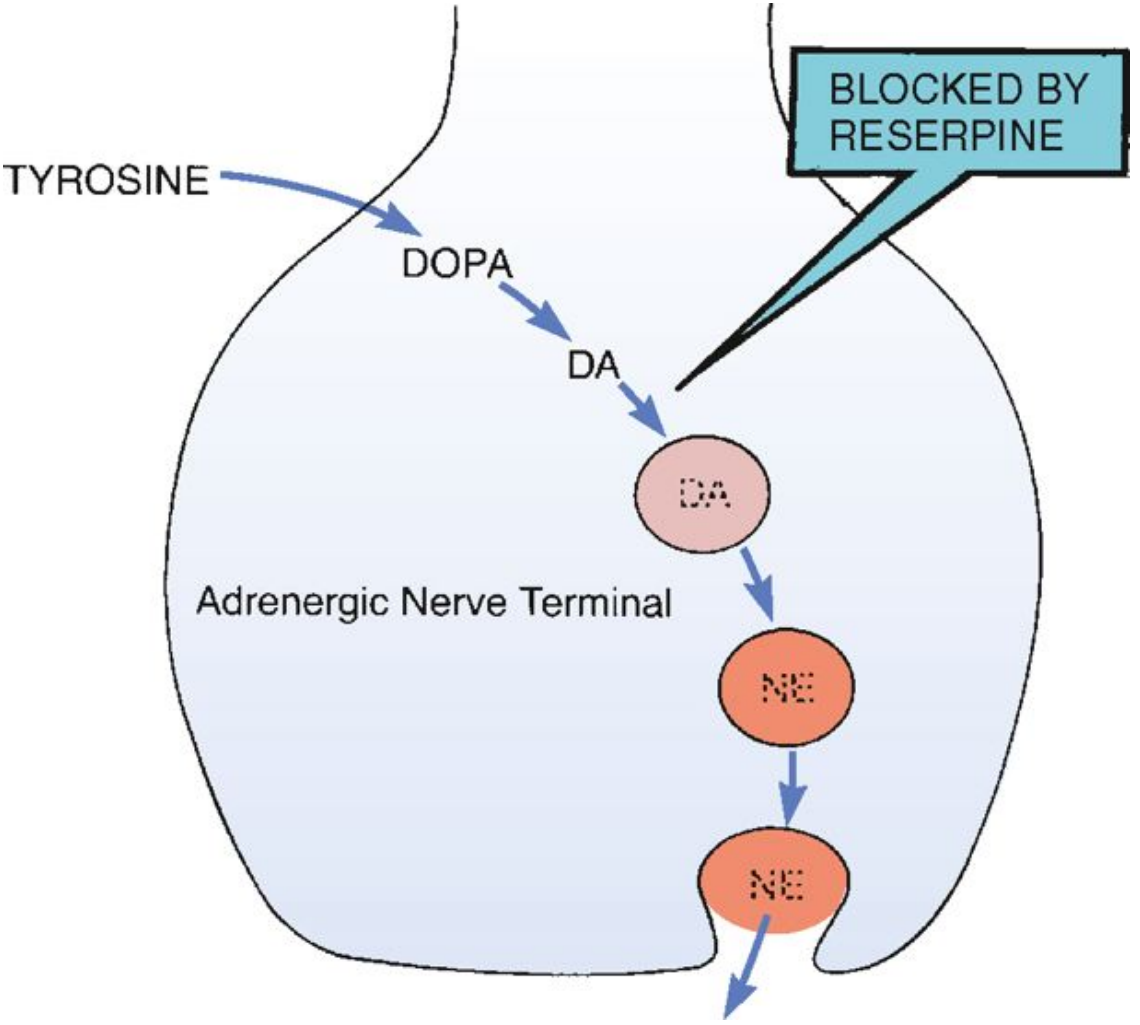


Figure 19-1 Mechanism of reserpine action. Reserpine depletes neurons of norepinephrine (NE) by two mechanisms. (1) As indicated in this figure, reserpine blocks the uptake of dopamine (DA) into vesicles, thereby preventing NE synthesis. (2) Reserpine also displaces NE from vesicles, thereby allowing degradation of NE by monoamine oxidase present in the nerve terminal (not shown).

Pharmacologic Effects

Peripheral Effects.

By depleting sympathetic neurons of NE, reserpine decreases the activation of alpha- and beta-adrenergic receptors. Decreased activation of beta receptors slows heart rate and reduces cardiac output. Decreased alpha activation promotes vasodilation. All three effects cause a *decrease in blood pressure*.

Effects on the CNS.

Reserpine produces sedation and a state of indifference to the environment. In addition, the drug can cause severe depression. These effects are thought to result from depletion of certain neurotransmitters (catecholamines, serotonin) from neurons in the brain.

Therapeutic Uses

Hypertension.

The principal indication for reserpine is hypertension. Benefits result from vasodilation and reduced cardiac output. Since these effects occur secondary to depletion of NE, and since transmitter depletion occurs slowly, full antihypertensive responses can take a week or more to develop. Conversely, when reserpine is discontinued, effects may persist for several weeks as the NE content of sympathetic neurons becomes replenished. Because its side effects can be severe, and because more desirable drugs are available (see Chapter 46), reserpine is not a preferred drug for hypertension.

Psychotic States.

Reserpine can be used to treat agitated psychotic patients, such as those suffering from certain forms of schizophrenia. However, since superior drugs are available, reserpine is rarely employed in psychotherapy.

Adverse Effects

Depression.

Reserpine can produce severe depression that may persist for months after the drug is withdrawn. Suicide has occurred. All patients should be informed about the risk of depression. Also, they should be educated about signs of depression (eg, early morning insomnia, loss of appetite, change in mood) and

instructed to notify the prescriber immediately if these develop. Because of the risk of suicide, patients who develop depression may require hospitalization. *Reserpine is contraindicated for patients with a history of depressive disorders*. The risk of depression can be minimized by keeping the dosage low (0.25 mg/day or less).

Cardiovascular Effects.

Depletion of NE from sympathetic neurons can result in *bradycardia, orthostatic hypotension,* and *nasal congestion*. Bradycardia is caused by decreased activation of beta***1*** receptors in the heart. Hypotension and nasal congestion result from decreased activation of alpha receptors on blood vessels. Patients should be informed that orthostatic hypotension, the most serious cardiovascular effect, can be minimized by moving slowly when changing from a seated or supine position to an upright position. In addition, patients should be advised to sit or lie down if lightheadedness or dizziness occurs.

GI Effects.

By mechanisms that are not understood, reserpine can stimulate several aspects of GI function. The drug can increase secretion of gastric acid, which may result in *ulcer formation*. In addition, reserpine can increase the tone and motility of intestinal smooth muscle, thereby causing *cramps* and *diarrhea*.

Preparations, Dosage, and Administration

Reserpine is available in 0.1- and 0.25-mg tablets, which may administered with food if GI upset occurs. The usual initial dosage for hypertension in adults is 0.5 mg/day for 1 to 2 weeks. The usual maintenance dosage is 0.1 to 0.25 mg/day.

Guanadrel and Guanethidine

Guanadrel [Hylorel] and guanethidine [Ismelin] are adrenergic neuron-blocking agents with actions similar to those of reserpine. However, in contrast to reserpine, these drugs cannot cross the blood-brain barrier, and hence do not cause adverse CNS effects. Nonetheless, they do have serious side effects: diarrhea and *severe* orthostatic hypotension. As a result, guanadrel and

guanethidine are considered last-choice options for hypertension, their only indication.

Guanadrel is available in 10- and 25-mg tablets. The usual initial adult dosage is 5 mg twice a day. Maintenance dosages range from 20 to 75 mg/day, given in divided doses.

Guanethidine has been voluntarily withdrawn from the U.S. market. For more information on this drug, refer to previous editions of this book.

CENTRALLY ACTING ALPHA2 AGONISTS

The drugs discussed in this section act within the CNS to reduce the firing of sympathetic neurons. These drugs are used primarily for hypertension.

Why are we discussing centrally acting drugs in a unit on peripheral nervous system pharmacology? Because the effects of these drugs are ultimately the result of decreased activation of alpha- and beta-adrenergic receptors in the periphery. That is, by inhibiting the firing of sympathetic neurons, the centrally acting agents decrease the release of NE from sympathetic nerves, and thereby decrease activation of peripheral adrenergic receptors. Hence, although these drugs act within the CNS, their effects are like those of the direct-acting adrenergic receptor blockers. Accordingly, it seems appropriate to discuss these agents in the context of peripheral nervous system pharmacology, rather than presenting them in the context of CNS drugs.

Clonidine

Clonidine [Catapres] is an *antihypertensive drug* that acts within the CNS. Except for rare instances of rebound hypertension, the drug is generally free of serious adverse effects. Because it is both effective and safe, clonidine is widely used. To treat hypertension, the drug is administered by mouth or by transdermal patch.

In addition to its use in hypertension, clonidine is used to relieve *severe pain of cancer*. To provide pain relief, the drug must be administered by epidural infusion. The preparation employed for this purpose is marketed under the trade name *Duraclon*. Because clonidine's analgesic pharmacology differs substantially from its antihypertensive pharmacology, the analgesic pharmacology is discussed separately in Chapter 28.

Mechanism of Antihypertensive Action

Clonidine is an alpha2-adrenergic agonist that causes "selective" activation of alpha2 receptors in the CNS—specifically, in brainstem areas associated with autonomic regulation of the cardiovascular system. By activating central alpha2 receptors, clonidine reduces sympathetic outflow to blood vessels and the heart.

Pharmacologic Effects

The most significant effects of clonidine occur in the heart and vascular system. By suppressing the firing of sympathetic nerves to the heart, clonidine can cause *bradycardia* and *a decrease in cardiac output*. By suppressing sympathetic regulation of blood vessels, the drug promotes *vasodilation*. The net result of cardiac suppression and vasodilation is *decreased blood pressure*. Blood pressure is reduced in both supine and standing subjects. (Note that the effect of clonidine on blood pressure is unlike that of the peripheral alpha-adrenergic blockers, which tend to decrease blood pressure only when the patient is standing.) Because the hypotensive effects of clonidine are not posture dependent, orthostatic hypotension is minimal.

Pharmacokinetics

Clonidine is very lipid soluble. As a result, the drug is readily absorbed following oral administration and is widely distributed throughout the body, including the CNS. Hypotensive responses begin 30 to 60 minutes after dosing and peak in 4 hours. Effects of a single dose may persist as long as 1 day. Clonidine is eliminated by a combination of hepatic metabolism and renal excretion.

Therapeutic Uses

Clonidine has two *approved* applications: treatment of hypertension (its main use) and relief of severe pain (see Chapter 28). *Investigational* uses include treatment of migraine; menopausal flushing; withdrawal from opioids, alcohol, and tobacco; and Tourette's syndrome, a CNS disease characterized by uncontrollable tics and verbal outbursts that are frequently obscene.

Adverse Effects

Drowsiness.

CNS depression is common. About 35% of patients experience drowsiness; an additional 8% experience outright sedation. These responses become less intense with continued drug use. Patients in their early weeks of treatment should be advised to avoid hazardous activities if alertness is impaired.

Xerostomia.

Xerostomia (dry mouth) is common, occurring in about 40% of patients. The reaction usually diminishes over the first 2 to 4 weeks of therapy. Although not dangerous, xerostomia can be annoying enough to discourage drug use. Patients should be advised that discomfort can be reduced by chewing gum, sucking on hard candy, and taking frequent sips of fluids.

Rebound Hypertension.

Rebound hypertension is characterized by a large increase in blood pressure occurring in response to abrupt clonidine withdrawal. This rare but serious reaction is caused by overactivity of the sympathetic nervous system, and can be accompanied by nervousness, tachycardia, and sweating. Left untreated, the reaction may persist for a week or more. If blood pressure climbs dangerously high, it should be lowered with a combination of alpha- and beta-adrenergic blocking agents. Rebound effects can be avoided by withdrawing clonidine slowly (over 2 to 4 days). Patients should be informed about rebound hypertension and warned not to discontinue clonidine without consulting the prescriber.

Use in Pregnancy.

Clonidine is embryotoxic in animals. Because of the possibility of fetal harm, clonidine is not recommended for pregnant women. Pregnancy should be ruled out before clonidine is given.

Other Adverse Effects.

Clonidine can cause a variety of adverse effects, including *constipation, impotence, gynecomastia,* and *adverse CNS effects* (eg, vivid dreams, nightmares, anxiety, depression). *Localized skin reactions* are common with transdermal clonidine patches.

Preparations, Dosage, and Administration

Preparations.

Clonidine hydrochloride is available in oral and transdermal formulations. *Oral clonidine* [Catapres] is available in 0.1-, 0.2-, and 0.3-mg tablets. *Transdermal clonidine* [Catapres-TTS] is available in 2.5-, 5-, and 7.5-mg patches that deliver 0.1, 0.2, and 0.3 mg/24 hr, respectively.

Dosage and Administration

Oral.

For treatment of hypertension, the initial adult dosage is 0.1 mg twice a day. The usual maintenance dosage is 0.2 to 0.6 mg/day administered in divided doses. By taking the majority of the daily dose at bedtime, daytime sedation can be minimized.

Transdermal.

Transdermal patches are applied to a region of hairless, intact skin on the upper arm or torso. A new patch is applied every 7 days.

Guanabenz and Guanfacine

The pharmacology of guanabenz [Wytensin] and guanfacine [Tenex] is very similar to that of clonidine. Like clonidine, both drugs activate brainstem alpha2-adrenergic receptors, and thereby reduce sympathetic outflow to the heart and blood vessels. The result is a reduction in cardiac output and blood pressure. Both drugs also share the major adverse effects of clonidine: sedation and dry mouth. In addition, both can cause rebound hypertension following abrupt withdrawal. Guanabenz is available in 4- and 8-mg tablets. Dosing is begun at 4 mg twice daily and can be increased to 32 mg twice daily. Guanfacine is available in 1- and 2-mg tablets. The usual dosage is 1 mg/day, taken at bedtime to minimize daytime sedation.

Methyldopa and Methyldopate

Methyldopa is an oral antihypertensive agent that lowers blood pressure by acting at sites within the CNS. Two side effects—hemolytic anemia and hepatic

necrosis—can be severe. Methyldopate, an intravenous agent, is nearly identical to methyldopa in structure and pharmacologic effects. In the discussion below, the term *methyldopa* is used in reference to both methyldopate and methyldopa itself.

Mechanism of Action

Methyldopa has a mechanism of action similar to that of clonidine. Like clonidine, methyldopa inhibits sympathetic outflow from the CNS by causing alpha*2* activation in the brain. However, methyldopa differs from clonidine in that methyldopa itself is not an alpha*2* agonist. Hence, before it can act, methyldopa must first be taken up into brainstem neurons, where it is then converted to methylnorepinephrine, a compound that *is* an effective alpha*2* agonist. Release of methylnorepinephrine results in alpha*2* activation.

Pharmacologic Effects

The most prominent response to methyldopa is a drop in blood pressure. The principal mechanism is vasodilation, not cardiosuppression. Vasodilation occurs because of reduced sympathetic traffic to blood vessels. At usual therapeutic doses, methyldopa does not decrease heart rate or cardiac output. Hence, hypotensive actions cannot be ascribed to cardiac depression. The hemodynamic effects of methyldopa are very much like those of clonidine: Both drugs lower blood pressure in supine and standing subjects, and both produce relatively little orthostatic hypotension.

Therapeutic Use

The only indication for methyldopa is *hypertension*. Methyldopa was one of the earliest antihypertensive agents available and remains in wide use. Methyldopate may be used for hypertensive crisis, but other drugs are preferred.

Adverse Effects

Positive Coombs' Test and Hemolytic Anemia.

A positive Coombs' test* develops in 10% to 20% of patients who take methyldopa chronically. The test usually turns positive between the 6th and 12th month of treatment. Of the patients who have a positive Coombs' test, only

a few (about 5%) develop hemolytic anemia. Coombs-positive patients who do not develop hemolytic anemia may continue methyl dopa treatment. However, if hemolytic anemia does develop, methyldopa should be withdrawn immediately. For most patients, hemolytic anemia resolves shortly after drug withdrawal, although the Coombs' test may remain positive for months. A Coombs' test should be performed prior to treatment and 6 to 12 months later. Blood counts (hematocrit, hemoglobin, or red cell count) should be obtained prior to treatment and periodically thereafter.

* The Coombs' test detects the presence of antibodies directed against the patient's own red blood cells. These antibodies can cause hemolysis (ie, red blood cell lysis).

Hepatotoxicity.

Methyldopa has been associated with hepatitis, jaundice, and, rarely, fatal hepatic necrosis. All patients should undergo periodic assessment of liver function. If signs of hepatotoxicity appear, methyldopa should be discontinued immediately. Liver function usually normalizes after drug withdrawal.

Other Adverse Effects.

Methyldopa can cause *xerostomia, sexual dysfunction, orthostatic hypotension,* and a variety of *CNS effects,* including drowsiness, reduced mental acuity, nightmares, and depression. These responses are not usually dangerous, but they can detract from adherence.

Preparations, Dosage, and Administration

Preparations.

Methyldopa is available in tablets (250 and 500 mg) for oral use. *Methyldopate* is available in solution (50 mg/mL) for IV use.

Oral Therapy.

For treatment of hypertension, the initial adult dosage is 250 mg 2 to 3 times a day. Daily maintenance dosages usually range from 0.5 to 2 gm administered in two to four divided doses.

Intravenous Therapy.

Methyldopate, administered by slow IV infusion, is indicated for hypertensive emergencies. However, since faster acting drugs are available, use of methyldopate is rare. Methyldopate for infusion should be diluted in 5% dextrose to a concentration of 10 mg/mL. The usual adult dose is 250 to 500 mg infused over 30 to 60 minutes. Dosing may be repeated every 6 hours as required.

KEY POINTS

- All of the drugs discussed in this chapter reduce activation of peripheral alpha- and beta-adrenergic receptors, but they do so by mechanisms other than direct receptor blockade.
- The principal indication for these drugs is hypertension.
- Reserpine acts by depleting NE from adrenergic neurons.
- Clonidine and methyldopa reduce sympathetic outflow to the heart and blood vessels by causing activation of alpha*2*-adrenergic receptors in the brainstem.
- The principal adverse effect of reserpine is depression.
- The principal adverse effects of clonidine are drowsiness and dry mouth. Rebound hypertension can occur if the drug is abruptly withdrawn.
- The principal adverse effects of methyldopa are hemolytic anemia and liver damage.
- The Coombs' test detects the presence of antibodies directed against the patient's own red blood cells. These antibodies can cause hemolysis (ie, red blood cell lysis).

Summary of Major Nursing Implications*

RESERPINE

Preadministration Assessment

Therapeutic Goal

Reduction of blood pressure in hypertensive patients.

Baseline Data

Determine blood pressure and heart rate.

Identifying High-Risk Patients

Reserpine is *contraindicated* for patients with active peptic ulcer disease or a history of depression.

Implementation: Administration

Route

Oral.

Administration

Administer with food to reduce gastric upset.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Full antihypertensive effects may take a week or more to develop. Monitor blood pressure to evaluate treatment.

Minimizing Adverse Effects

Depression.

Reserpine can cause profound depression. Inform patients about signs of depression (eg, early morning insomnia, loss of appetite, change in mood) and instruct them to notify the prescriber if these develop. Hospitalization may be required. Avoid reserpine in patients with a history of depression. To minimize the risk of depression, keep the dosage low (0.25 mg/day or less).

Orthostatic Hypotension.

Inform patients that orthostatic hypotension can be minimized by moving slowly when changing from a seated or supine position to an upright position. Advise patients to sit or lie down if dizziness or lightheadedness occurs.

CLONIDINE

Preadministration Assessment

Therapeutic Goal

Reduction of blood pressure in hypertensive patients.

Baseline Data

Determine blood pressure and heart rate.

Identifying High-Risk Patients

Clonidine is embryotoxic to animals and should not be used during pregnancy. Rule out pregnancy before initiating treatment.

Implementation: Administration

Routes

Oral, transdermal.

Administration

Oral.

Advise the patient to take the major portion of the daily dose at bedtime to minimize daytime sedation.

Transdermal.

Instruct the patient to apply transdermal patches to hairless, intact skin on the upper arm or torso, and to apply a new patch every 7 days.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor blood pressure.

Minimizing Adverse Effects

Drowsiness and Sedation.

Inform patients about possible CNS depression and warn them to avoid hazardous activities if alertness is impaired.

Xerostomia.

Dry mouth is common. Inform patients that discomfort can be reduced by chewing gum, sucking on hard candy, and taking frequent sips of fluids.

Rebound Hypertension.

Severe hypertension occurs rarely following abrupt clonidine withdrawal. Treat with a combination of alpha- and beta-adrenergic blockers. To avoid rebound hypertension, withdraw clonidine slowly (over 2 to 4 days). Inform patients about rebound hypertension and warn them against abrupt discontinuation of treatment.

METHYLDOPA

Preadministration Assessment

Therapeutic Goal

Reduction of blood pressure in hypertensive patients.

Baseline Data

Obtain baseline values for blood pressure, heart rate, blood counts (hematocrit, hemoglobin, or red cell count), Coombs' test, and liver function tests.

Identifying High-Risk Patients

Methyldopa is *contraindicated* for patients with active liver disease or a history of methyldopa-induced liver dysfunction.

Implementation: Administration

Routes

Oral.

For routine management of hypertension.

Intravenous.

For hypertensive emergencies.

Administration

Most patients on oral therapy require divided (two to four) daily doses. For some patients, blood pressure can be controlled with a single daily dose at bedtime.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor blood pressure.

Minimizing Adverse Effects

Hemolytic Anemia.

If hemolysis occurs, withdraw methyldopa immediately; hemolytic anemia usually resolves soon. Obtain a Coombs' test prior to treatment and 6 to 12 months later. Obtain blood counts (hematocrit, hemoglobin, or red cell count) prior to treatment and periodically thereafter.

Hepatotoxicity.

Methyldopa can cause hepatitis, jaundice, and fatal hepatic necrosis. Assess liver function prior to treatment and periodically thereafter. If liver dysfunction develops, discontinue methyldopa immediately. In most cases, liver function returns to normal soon.

V. CENTRAL NERVOUS SYSTEM DRUGS

Introduction

20 Introduction to Central Nervous System Pharmacology

The central nervous system (CNS) drugs—agents that act on the brain and spinal cord—are used widely for medical and nonmedical purposes. Medical applications include treatment of psychiatric disorders, suppression of seizures, relief of pain, and production of anesthesia. CNS drugs are used non-medically for their stimulant, depressant, euphoriant, and other "mind-altering" abilities.

Despite the widespread use of CNS drugs, knowledge of these agents is limited. Much of our ignorance stems from the anatomic and neurochemical complexity of the brain and spinal cord. (There are more than 50 billion neurons in the cerebral hemispheres alone.) Because of this complexity, we are a long way from fully understanding both the CNS itself and the drugs used to influence it.

TRANSMITTERS OF THE CNS

In contrast to the peripheral nervous system, in which only three compounds—acetylcholine, norepinephrine, and epinephrine—serve as neurotransmitters, the CNS contains at least 21 compounds that serve as neurotransmitters (Table 20-1). Furthermore, since there are numerous sites within the CNS for which no transmitter has been identified, it is clear that additional compounds, yet to be discovered, also mediate neurotransmission in the brain and spinal cord.

It is important to note that none of the compounds that are thought to be CNS neurotransmitters has actually been proved to serve this function. The reason for uncertainty lies with the technical difficulties involved in CNS research. However, although absolute proof may be lacking, the evidence supporting a neurotransmitter role for several compounds (eg, dopamine, norepinephrine, serotonin, enkephalins) is completely convincing.

Although much is known about the actions of CNS transmitters at various sites in the brain and spinal cord, it is not usually possible to relate these known actions in a precise way to behavioral or psychologic processes. For example, although we know the locations of specific CNS sites at which norepinephrine appears to act as a transmitter, and although we know the effect of norepinephrine at most of these sites (suppression of neuronal excitability), we do not know the precise relationship between suppression of neuronal excitability at each of these sites and the impact of that suppression on the overt function of the organism. This example illustrates the general state of our knowledge of CNS transmitter function: We have a great deal of detailed information about the biochemistry and electrophysiology of CNS transmitters, but we are as yet unable to assemble those details into a completely meaningful picture.

THE BLOOD-BRAIN BARRIER

As discussed in Chapter 4, the blood-brain barrier impedes the entry of drugs into the brain. Passage across the barrier is limited to lipid-soluble agents and to drugs that are able to cross by way of specific transport systems. Drugs that are protein bound and drugs that are highly ionized cannot cross.

From a therapeutic perspective, the blood-brain barrier is a mixed blessing. On the positive side, the barrier protects the brain from injury by potentially toxic substances. On the negative side, the barrier can be a significant obstacle to entry of therapeutic agents.

The blood-brain barrier is not fully developed at birth. Accordingly, infants are much more sensitive to CNS drugs than are older children and adults.

HOW DO CNS DRUGS PRODUCE THERAPEUTIC EFFECTS?

Although much is known about the biochemical and electrophysiologic effects of CNS drugs, in most cases we cannot state with certainty the relationship between these effects and production of beneficial responses. Why? In order to fully understand how a drug alters symptoms, we need to understand, at a biochemical and physiologic level, the pathophysiology of the disorder being treated. In the case of most CNS disorders, our knowledge is limited. That is, we do not fully understand the brain in either health or disease. Given our in-

complete understanding of the CNS itself, we must exercise caution when attempting to assign a precise mechanism for a drug's therapeutic effects.

Although we can't state with certainty how CNS drugs act, we do have sufficient data to permit formulation of plausible hypotheses. Consequently, as we study CNS drugs in the chapters that follow, proposed mechanisms of action are presented. Keep in mind, however, that these mechanisms are tentative, representing our best guess based on data available today. As we learn more, it is almost certain that these concepts will be modified, if not discarded entirely.

TABLE 20-1 Neurotransmitters of the CNS

Monoamines

Dopamine

Epinephrine

Norepinephrine

Serotonin

Amino Acids

Aspartate

GABA

Glutamate

Glycine

Purines

Adenosine

Adenosine monophosphate

Adenosine triphosphate

Opioid Peptides

Dynorphins

Endorphins

Enkephalins

Nonopioid Peptides

Neurotensin

Oxytocin

Somatostatin

Substance P

Vasopressin

Others

Acetylcholine

Histamine

GABA = gamma-aminobutyric acid.

ADAPTATION OF THE CNS TO PROLONGED DRUG EXPOSURE

When CNS drugs are taken chronically, their effects may differ from those produced during initial use. These altered effects are the result of adaptive changes that occur in the brain in response to prolonged drug exposure. The brain's ability to adapt to drugs can produce alterations in therapeutic effects and side effects. Adaptive changes are often beneficial, although they can also be detrimental.

Increased Therapeutic Effects.

Certain drugs used in psychiatry—antipsychotics and antidepressants—must be taken for several weeks before full therapeutic effects develop. It would appear that beneficial responses are delayed because they result from adaptive changes—and not from the direct effects of drugs on synaptic function. Hence, full therapeutic effects are not seen until the CNS has had time to modify itself in response to prolonged drug exposure.

Decreased Side Effects.

When CNS drugs are taken chronically, the intensity of side effects may decrease (while therapeutic effects remain undiminished). For example, phenobarbital (an antiseizure drug) produces sedation during the initial phase of therapy; however, with continued treatment, sedation declines while full protection from seizures is retained. Similarly, when morphine is given to control pain, nausea is a common side effect early on; however, as treatment contin-

ues, nausea diminishes while analgesic effects persist. Adaptations within the brain are believed to underlie these phenomena.

Tolerance and Physical Dependence.

Tolerance and physical dependence are special manifestations of CNS adaptation. *Tolerance* is defined as a decreased response occurring in the course of prolonged drug use. *Physical dependence* is defined as a state in which abrupt discontinuation of drug use will precipitate a withdrawal syndrome. Research indicates that the kinds of adaptive changes that underlie tolerance and dependence are such that, once they have taken place, continued drug use is required for the brain to function "normally." If drug use is stopped, the drug-adapted brain can no longer function properly, and hence a withdrawal syndrome ensues. The withdrawal reaction continues until the adaptive changes have had time to revert, thereby restoring the CNS to its pretreatment state.

DEVELOPMENT OF NEW PSYCHOTHERAPEUTIC DRUGS

Because of deficiencies in our knowledge of the neurochemical and physiologic changes that underlie mental disease, it is impossible to take a rational approach to the development of truly new (nonderivative) psychotherapeutic agents. History bears this out: Virtually all of the major advances in psychopharmacology have been happy accidents.

In addition to our relative ignorance about the neurochemical and physiologic correlates of mental illness, two other factors contribute to the difficulty in generating truly new psychotherapeutic agents. First, in contrast to many other diseases, we lack adequate animal models of mental illness. Accordingly, animal research is not likely to reveal new types of psychotherapeutic agents. Second, mentally healthy individuals cannot be used as subjects to assess potential psychotherapeutic agents. Why? Because most psychotherapeutic drugs either have no effect on healthy individuals or produce paradoxical effects.

Once a new drug has been stumbled upon, variations on that agent can be developed systematically. The following process can be employed: (1) structural analogs of the new agent are synthesized, (2) these analogs are run through biochemical and physiologic screening tests to determine whether or not they possess activity similar to that of the parent compound, and (3) after serious

toxicity has been ruled out, promising agents are tested in humans for possible psychotherapeutic activity. By following this procedure, it is possible to develop drugs that have fewer side effects than the original drug and perhaps even superior therapeutic effects. However, although this procedure may produce small advances, it is not likely to yield a major therapeutic breakthrough.

APPROACHING THE STUDY OF CNS DRUGS

Because our understanding of the CNS is less complete than our understanding of the peripheral nervous system, our approach to studying CNS drugs differs from the approach we took with peripheral nervous system agents. When we studied the pharmacology of the peripheral nervous system, we emphasized the importance of understanding transmitters and their receptors prior to embarking on a study of drugs. Since our knowledge of CNS transmitters is insufficient to allow this approach, rather than making a detailed examination of CNS transmitters before we study CNS drugs, we will discuss drugs and transmitters concurrently. Hence, for now, all that you need to know about CNS transmitters is that (1) there are a lot of them, (2) their precise functional roles are not clear, and (3) their complexity makes it difficult for us to know with certainty just how CNS drugs produce their effects.

KEY POINTS

- In the CNS, many compounds appear to act as neurotransmitters, whereas in the periphery, only three compounds act as neurotransmitters.
- As a rule, we do not understand with precision how CNS drugs produce their effects.
- The blood-brain barrier can protect the CNS from toxic substances, but can also block entry of medicines into the CNS.
- The CNS often undergoes adaptive changes during prolonged drug exposure. The result can be increased therapeutic effects, decreased side effects, tolerance, and physical dependence.

Drugs for Neurodegenerative Disorders

21 Drugs for Parkinson's Disease

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder first described in 1817 by Dr. James Parkinson, a London physician. The disease afflicts over 1 million Americans, making it second only to Alzheimer's disease as the most common degenerative disease of neurons. Cardinal symptoms are tremor, rigidity, postural instability, and slowed movement. In addition to these motor symptoms, most patients also experience nonmotor symptoms, especially autonomic disturbances, depression, psychosis, and dementia. As a rule, symptoms first appear in middle age and progress relentlessly. The underlying cause of motor symptoms is loss of dopaminergic neurons in the substantia nigra. Although there is no cure for motor symptoms, drug therapy can maintain functional mobility for years, and can thereby substantially prolong quality of life and life expectancy. The most effective drug for PD is levodopa, almost always given in combination with carbidopa. Unfortunately, as neurodegeneration progresses, levodopa eventually becomes ineffective.

PATHOPHYSIOLOGY THAT UNDERLIES MOTOR SYMPTOMS

Motor symptoms result from damage to the *extrapyramidal system,* a complex neuronal network that helps regulate movement. When extrapyramidal function is disrupted, *dyskinesias* (disorders of movement) result. The dyskinesias that characterize PD are tremor at rest, rigidity, postural instability, and bradykinesia (slowed movement). In severe PD, bradykinesia may progress to *akinesia*—complete absence of movement.

In people with PD, neurotransmission is disrupted primarily in the *striatum,* an important component of the extrapyramidal system. A simplified model of striatal neurotransmission is depicted in Figure 21-1*A*. As indicated, proper function of the striatum requires a balance between two neurotransmitters: *dopamine* and *acetylcholine* (ACh). Dopamine is an *inhibitory* transmitter; ACh is *excitatory*. According to the model, the neurons that release dopamine inhibit neurons that release gamma-aminobutyric acid (GABA, another inhibitory transmit-

ter). In contrast, the neurons that release ACh excite the neurons that release GABA. Movement is normal when the inhibitory influence of dopamine and the excitatory influence of ACh are in balance. Note that the neurons that supply dopamine to the striatum originate in the *substantia nigra*. Between 70% and 80% of these neurons must be lost before PD becomes clinically recognizable. This loss takes place over 5 to 20 years. Put another way, neuronal degeneration begins long before overt symptoms appear.

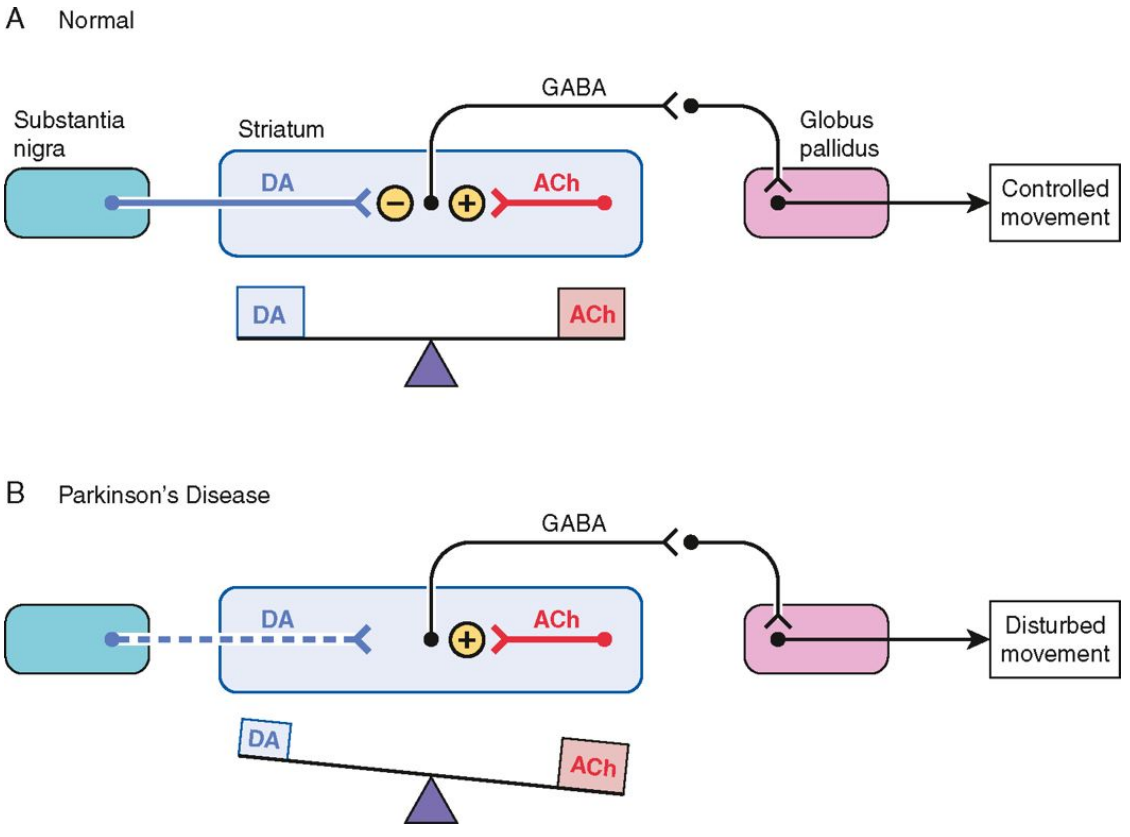


Figure 21-1 A model of neurotransmission in the healthy striatum and parkinsonian striatum. A, In the healthy striatum, dopamine (DA) released from neurons originating in the substantia nigra inhibits the firing of neurons in the striatum that release gamma-aminobutyric acid (GABA). Conversely, neurons located within the striatum, which release acetylcholine (ACh), excite the GABAergic neurons. Hence, under normal conditions,

the inhibitory actions of DA are balanced by the excitatory actions of ACh, and controlled movement results. B, In Parkinson's disease, the neurons that supply DA to the striatum degenerate. In the absence of sufficient DA, the excitatory effects of ACh go unopposed, and disturbed movement results.

In PD, there is an imbalance between dopamine and ACh in the striatum (Fig. 21-1*B*). As noted, the imbalance results from *degeneration of the neurons that supply dopamine to the striatum*. In the absence of dopamine, the excitatory influence of ACh goes unopposed, causing excessive stimulation of the neurons that release GABA. Overactivity of these GABAergic neurons contributes to the motor symptoms that characterize PD.

What causes degeneration of dopaminergic neurons? No one knows for sure. However, some evidence strongly implicates *alpha-synuclein*—a potentially toxic protein synthesized by dopaminergic neurons. Under normal conditions, alpha-synuclein is rapidly degraded. As a result, it doesn't accumulate and no harm occurs. Degradation of alpha-synuclein requires two other proteins: *parkin* and *ubiquitin*. (Parkin is an enzyme that catalyzes the binding of alpha-synuclein to ubiquitin. Once bound to ubiquitin, alpha-synuclein can be degraded.) If any of these proteins—alpha-synuclein, parkin, or ubiquitin—is defective, degradation of alpha-synuclein cannot take place. When this occurs, alpha-synuclein accumulates inside the cell, forming neurotoxic fibrils. At autopsy, these fibrils are visible as so-called Lewy bodies, which are characteristic of PD pathology. Failure to degrade alpha-synuclein appears to result from two causes: genetic vulnerability and toxins in the environment. Defective genes coding for all three proteins have been found in families with inherited forms of PD. In people with PD that is not inherited, environmental toxins may explain the inability to degrade alpha-synuclein.

As discussed in Chapter 31, movement disorders similar to those of PD can occur as side effects of antipsychotic drugs. These dyskinesias, which are referred to as *extrapyramidal side effects,* result from blockade of dopamine receptors in the striatum. This drug-induced parkinsonism can be managed with some of the drugs used to treat PD.

OVERVIEW OF MOTOR SYMPTOM MANAGEMENT

Therapeutic Goal

Ideally, treatment would reverse neuronal degeneration, or at least prevent further degeneration, and control symptoms. Unfortunately, the ideal treatment doesn't exist. Hence, the goal with current drugs is simply to improve the patient's ability to carry out activities of daily life. Drug selection and dosage are determined by the extent to which PD interferes with work, walking, dressing, eating, bathing, and other activities. Drugs benefit the patient primarily by improving bradykinesia, gait disturbance, and postural instability. Tremor and rigidity, although disturbing, are less disabling. It is important to note that drugs only provide symptomatic relief; they do not cure PD. Furthermore, there is no convincing proof that any current drug can delay disease progression.

Drugs Employed

Given the neurochemical basis of parkinsonism—too little striatal dopamine and too much ACh—the approach to treatment is obvious: give drugs that can restore the functional balance between dopamine and ACh. To accomplish this, two types of drugs are used: (1) *dopaminergic agents* (ie, drugs that directly or indirectly cause activation of dopamine receptors); and (2) *anticholinergic agents* (ie, drugs that block receptors for ACh). Of the two groups, dopaminergic agents are by far the more widely employed.

Drug	Mechanism of Action	Therapeutic Role
Dopamine Replacement		
Levodopa Levodopa/carbidopa	Levodopa undergoes conversion to DA in the brain and then activates DA receptors (carbidopa blocks destruction of levodopa in the periphery)	First-line drug, or supplement to a dopamine agonist
Dopamine Agonists		
Nonergot Derivatives Apomorphine Pramipexole Ropinirole	Directly activate DA receptors	First-line drugs, or supplements to levodopa; the oral nonergot derivatives—pramipexole and ropinirole—are preferred
Ergot Derivatives Bromocriptine Cabergoline		Apomorphine—a subQ nonergot agent—is reserved for rescue therapy during "off" times
COMT Inhibitors		
Entacapone Tolcapone	Inhibit breakdown of levodopa by COMT	Adjunct to levodopa to decrease "wearing off"; entacapone is more effective and safer than tolcapone
Dopamine Releaser		
Amantadine	Promotes release of DA from remaining dopaminergic neurons; may also block DA reuptake	Second- or third-line drug. May help reduce levodopa-induced dyskinesias
MAO-B Inhibitors		
Selegiline	Inhibit breakdown of DA by	Used in newly diagnosed

TABLE 21-1 Dopaminergic Agents for Parkinson's Disease

As shown in Table 21-1, dopaminergic drugs act by several mechanisms: levodopa promotes dopamine synthesis; the dopamine agonists activate dopamine receptors directly; inhibitors of monoamine oxidase-B (MAO-B) prevent dopamine breakdown; amantadine promotes dopamine release (and may also block dopamine reuptake); and the inhibitors of catechol-*O*-methyltransferase (COMT) enhance the effects of levodopa by blocking its degradation.

In contrast to the dopaminergic drugs, which act by multiple mechanisms, all of the anticholinergic agents share the same mechanism: blockade of muscarinic receptors in the striatum.

Clinical Guidelines

The American Academy of Neurology (AAN) has developed evidence-based guidelines for the treatment of Parkinson's disease. These guidelines were published in *Neurology* as five separate articles, released in 2002 and 2006. Their titles and release years are as follows:

- Initiation and Treatment for Parkinson Disease (Updated), 2002
- Diagnosis and Prognosis for New Onset Parkinson Disease, 2006
- Neuroprotective Strategies and Alternative Therapies for New Onset Parkinson Disease, 2006
- Evaluation and Treatment of Depression, Psychosis and Dementia in Parkinson Disease, 2006
- Medical and Surgical Treatment of Parkinson Disease with Motor Fluctuations and Dyskinesia, 2006

The recommendations below are based on this set of guidelines.

Drug Selection

Initial Treatment.

For patients with mild symptoms, treatment can be begin with selegiline, an MAO-B inhibitor that confers mild, symptomatic benefit. Rasagiline, an MAO-B inhibitor that was not available when the guidelines were published, would probably work just as well.

For patients with more severe symptoms, treatment should begin with either levodopa (combined with carbidopa) or a dopamine agonist. Levodopa is more effective than the dopamine agonists, but long-term use carries a higher risk of disabling dyskinesias. Hence, the choice must be tailored to the patient: If improving motor function is the primary objective, then levodopa is preferred; however, if drug-induced dyskinesias are a primary concern, then a dopamine agonist would be preferred.

Management of Motor Fluctuations.

Long-term treatment with levodopa or dopamine agonists is associated with two types of motor fluctuations: *"off" times* (loss of symptom relief) and *drug-induced dyskinesias* (involuntary movements). "Off" times can be reduced with three types of drugs: dopamine agonists, COMT inhibitors, and MAO-B inhibitors. Evidence of efficacy is strongest for entacapone (a COMT inhibitor) and rasagiline (an MAO-B inhibitor). The only drug recommended for dyskinesias is amantadine.

Neuroprotection.

To date, there is no definitive proof that any drug can protect dopaminergic neurons from progressive degeneration. According to the 2006 guidelines, there is insufficient evidence to support or refute the use of riluzole, coenzyme Q-10, pramipexole, ropinirole, rasagiline, or amantadine for neuroprotection. As for vitamin E, there is good evidence that the compound does *not* confer protection, and hence should not be taken for this purpose. Early treatment with two MAO-B inhibitors—rasagiline and selegiline—can delay *symptom* progression. However, we don't know if the delay is the result of protecting dopaminergic neurons, or simply the result of preventing dopamine destruction.

PHARMACOLOGY OF THE DRUGS USED FOR MOTOR SYMPTOMS

Levodopa

Levodopa was introduced in the 1960s, and has been a cornerstone of PD treatment ever since. Unfortunately, although the drug is highly effective, benefi-

cial effects diminish over time. The most troubling adverse effects are dyskinesias. To enhance effects, levodopa is almost always combined with carbidopa.

Use in Parkinson's Disease

Beneficial Effects.

Levodopa [Dopar, Larodopa] is the most effective drug for PD. At the beginning of treatment, about 75% of patients experience a 50% reduction in symptom severity. Levodopa is so effective, in fact, that a diagnosis of PD should be questioned if the patient fails to respond.

Full therapeutic responses may take several months to develop. Consequently, although the effects of levodopa can be significant, patients should not expect immediate improvement. Rather, they should be informed that beneficial effects are likely to increase steadily over the first few months.

In contrast to the dramatic improvements seen during initial therapy, long-term therapy with levodopa has been disappointing. Although symptoms may be well controlled during the first 2 years of treatment, by the end of 5 years the patient's ability to function may deteriorate to pretreatment levels. This probably reflects progression of the disease and not development of tolerance to levodopa.

Acute Loss of Effect.

Acute loss of effect occurs in two patterns: gradual loss and abrupt loss. Gradual loss—"wearing off"—develops near the end of the dosing interval, and simply indicates that drug levels have declined to a subtherapeutic value. Wearing off can be minimized in three ways: (1) shortening the dosing interval, (2) giving a drug that prolongs levodopa's plasma half-life (eg, entacapone), and (3) giving a direct-acting dopamine agonist.

Abrupt loss of effect, often referred to as the "on-off" phenomenon, can occur at any time during the dosing interval—even while drug levels are high. "Off" times may last from minutes to hours. Over the course of treatment, "off" periods are likely to increase in both intensity and frequency. Drugs that can help reduce "off" times are listed in Table 21-2. As discussed below, avoidance of high-protein meals may also help.

Drug	Drug Class
Drugs for "Off" Times	
Definitely Effective	
Entacapone	COMT inhibitor
Rasagiline	MAO-B inhibitor
Probably Effective	
Pramipexole	DA agonist
Ropinirole	DA agonist
Tolcapone	COMT inhibitor
Possibly Effective	
Apomorphine	DA agonist
Cabergoline	DA agonist
Selegiline	MAO-B inhibitor
Drug for Levodopa-Induced Dyskinesias	
Amantadine	DA-releasing agent

COMT = catechol-*O*-methyltransferase, DA = dopamine, MAO-B = type B monoamine oxidase.

TABLE 21-2 Drugs for Motor Complications of Levodopa Therapy

Mechanism of Action

Levodopa reduces symptoms by promoting synthesis of dopamine in the striatum (Fig. 21-2). Levodopa enters the brain via an active transport system that carries it across the blood-brain barrier. Once in the brain, the drug undergoes uptake into the few dopaminergic nerve terminals that remain in the striatum. Following uptake, levodopa, which has no direct effects of its own, is converted to dopamine, its active form. As dopamine, levodopa helps restore a proper balance between dopamine and ACh.

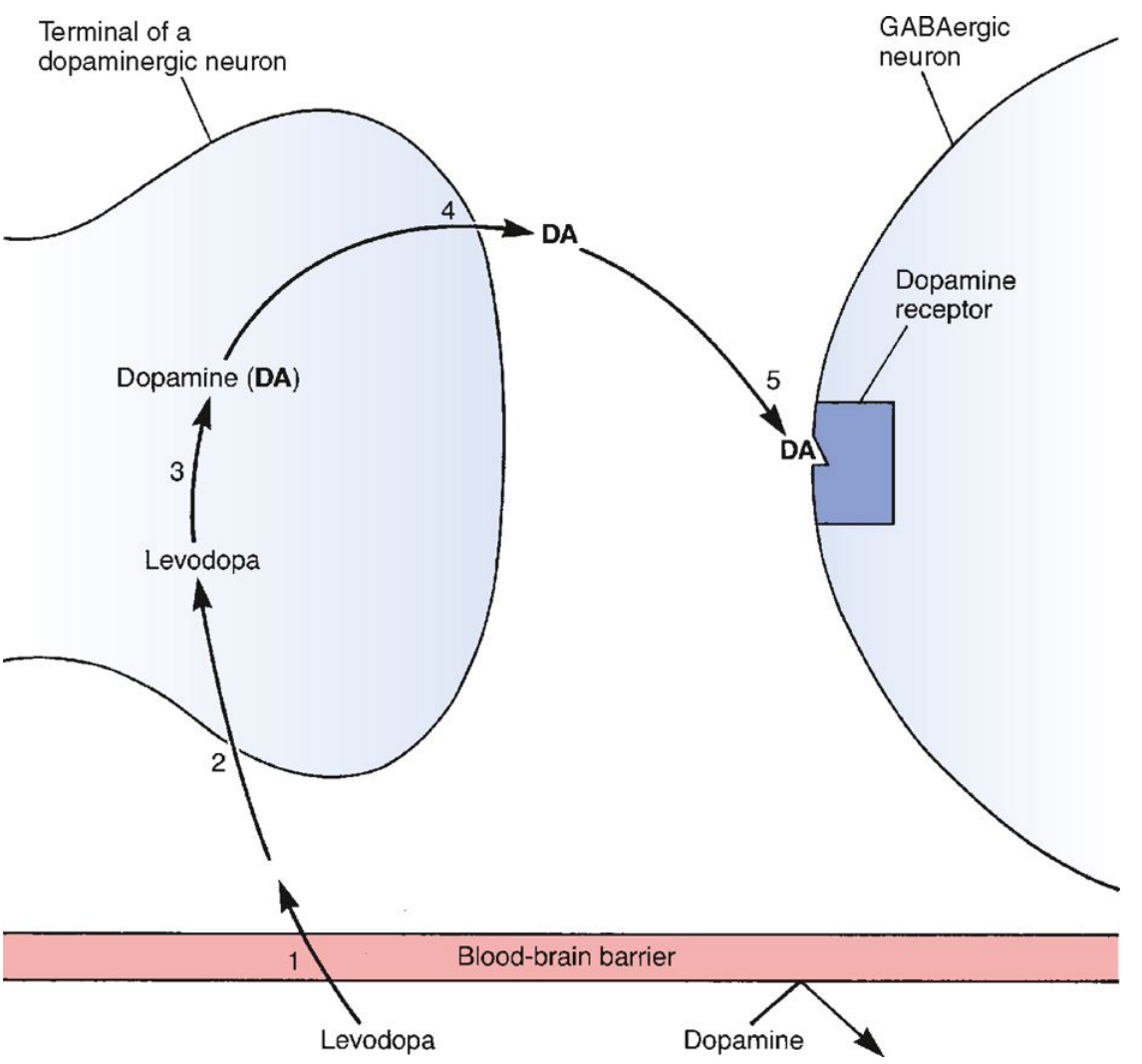


Figure 21-2 Steps leading to alteration of CNS function by levodopa. To produce its beneficial effects in PD, levodopa must be (1) transported across the blood-brain barrier; (2) taken up by dopaminergic nerve terminals in the striatum; (3) converted into dopamine; (4) released into the synaptic space; and (5) bound to dopamine receptors on striatal GABAergic neurons, causing them to fire at a slower rate. Note that dopamine itself is unable to cross the blood-brain barrier, and hence cannot be used to treat PD.

Conversion of levodopa to dopamine is depicted in Figure 21-3. As indicated, the enzyme that catalyzes the reaction is called a *decarboxylase* (because it removes a carboxyl group from levodopa). The activity of decarboxylases is enhanced by *pyridoxine* (vitamin B*6*).

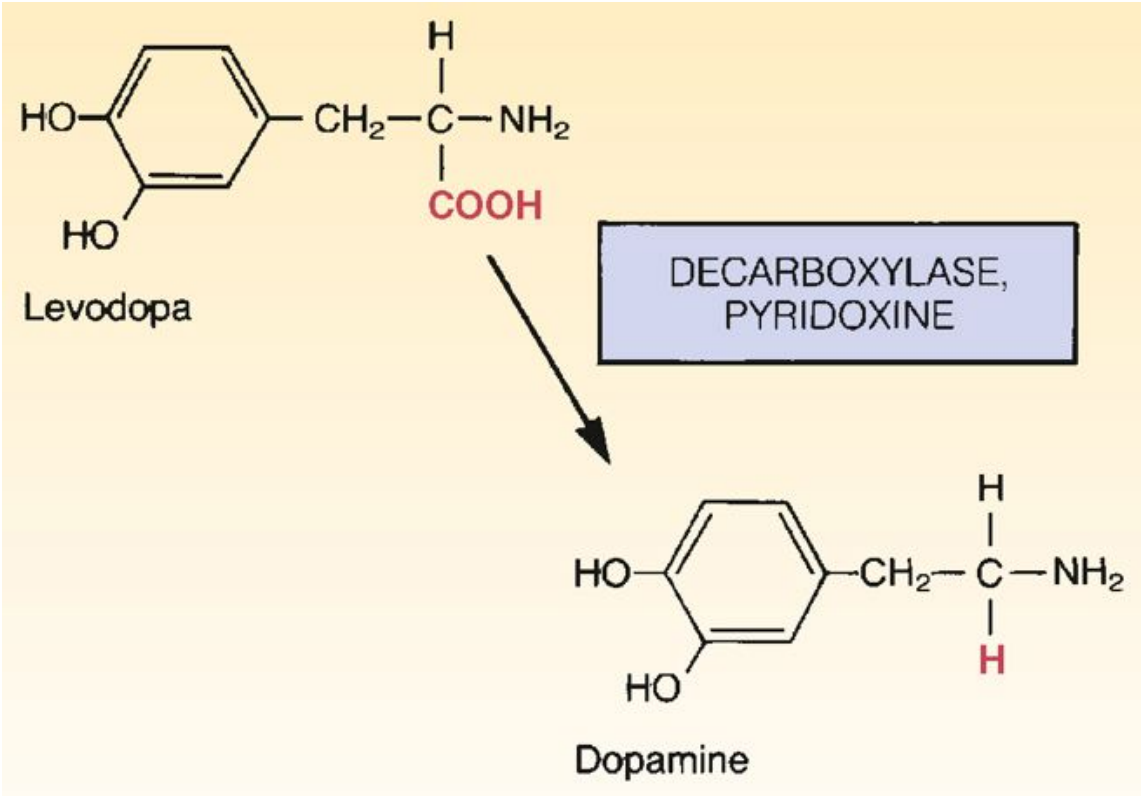


Figure 21-3 Conversion of levodopa to dopamine. Decarboxylases present in the brain, liver, and intestine convert levodopa into dopamine. Pyridoxine (vitamin B6) accelerates the reaction.

Why is PD treated with levodopa and not with dopamine itself? There are two reasons. First, dopamine cannot cross the blood-brain barrier (see Fig. 21-2). As noted, levodopa crosses the barrier by means of an active transport system; this system does not transport dopamine. Second, dopamine has such a short half-life in the blood that it would be impractical to use even if it could cross the blood-brain barrier.

Pharmacokinetics

Levodopa is administered orally and undergoes rapid absorption from the small intestine. Food delays absorption by slowing gastric emptying. Furthermore, since neutral amino acids compete with levodopa for intestinal absorption (and for transport across the blood-brain barrier as well), high-protein foods will reduce therapeutic effects.

Only a small fraction of each dose reaches the brain. The majority is metabolized in the periphery, primarily by *decarboxylase enzymes* and to a lesser extent by COMT. Peripheral decarboxylases convert levodopa into dopamine, an active metabolite. In contrast, COMT converts levodopa into an inactive metabolite. Like the enzymes that decarboxylate levodopa within the brain, peripheral decarboxylases work faster in the presence of pyridoxine. Because of peripheral metabolism, less than 2% of each dose enters the brain.

Adverse Effects

Most side effects of levodopa are dose dependent. The elderly, who are the primary users of levodopa, are especially sensitive to adverse effects.

Nausea and Vomiting.

Most patients experience nausea and vomiting early in treatment. The cause is activation of dopamine receptors in the chemoreceptor trigger zone (CTZ) of the medulla. Nausea and vomiting can be reduced by administering levodopa in low initial doses and with meals. (Food retards levodopa absorption, causing a decrease in peak plasma drug levels and a corresponding decrease in stimulation of the CTZ.) However, since administration with food can reduce therapeutic effects (by decreasing levodopa absorption), administration with meals should be avoided if possible. Giving additional carbidopa (without levodopa) can help reduce nausea and vomiting. Why carbidopa helps is unknown.

Dyskinesias.

Ironically, levodopa, which is given to *alleviate* movement disorders, actually *causes* movement disorders in many patients. About 80% develop involuntary movements within the first year. Some dyskinesias are just annoying (eg, head bobbing, tics, grimacing), whereas others can be disabling (eg, ballismus, choreoathetosis). These dyskinesias develop just before or soon after optimal levodopa dosage has been achieved. Dyskinesias can be managed in three

ways. First, the dosage of levodopa can be reduced. However, dosage reduction may allow PD symptoms to re-emerge. Second, we can give amantadine (see below), which can reduce dyskinesias in some patients. If these measures fail, the only remaining options are surgery and electrical stimulation (see Box 21-1).

Cardiovascular Effects.

Postural hypotension is common early in treatment. The underlying mechanism is unknown. Hypotension can be reduced by increasing intake of salt and water. An alpha-adrenergic agonist can also help.

Conversion of levodopa to dopamine in the periphery can produce excessive activation of beta***1*** receptors in the heart. *Dysrhythmias* can result, especially in patients with heart disease.

Psychosis.

Psychosis develops in about 20% of patients. Prominent symptoms are visual hallucinations, vivid dreams or nightmares, and paranoid ideation (fears of personal endangerment, sense of persecution, feelings of being followed or spied on). Activation of dopamine receptors is in some way involved. Symptoms can be reduced by lowering levodopa dosage, but this will reduce beneficial effects too.

Treatment of levodopa-induced psychosis with first-generation antipsychotics is problematic. Yes, these agents can decrease psychologic symptoms. However, they will also *intensify* symptoms of PD. Why? Because they block receptors for dopamine in the striatum. In fact, when first-generation antipsychotic agents are used for schizophrenia, the biggest problem is parkinsonian side effects, referred to as extrapyramidal symptoms (EPS).

Two second-generation antipsychotics—*clozapine* and *quetiapine*—have been used successfully to manage levodopa-induced psychosis. Unlike the first-generation antipsychotic drugs, clozapine and quetiapine cause little or no blockade of dopamine receptors in the striatum, and hence do not cause EPS. In patients taking levodopa, these drugs can reduce psychotic symptoms without intensifying symptoms of PD. Interestingly, the dosage of clozapine is only 25

mg/day, about 20 times lower than the dosage used for schizophrenia. Clozapine and quetiapine are discussed at length in Chapter 31.

Other Adverse Effects.

Levodopa may *darken sweat and urine;* patients should be informed about this harmless effect. The drug can *activate malignant melanoma* and consequently should be avoided in patients with undiagnosed skin lesions.

BOX 21-1 SURGICAL AND ELECTRICAL TREATMENTS FOR PARKINSON'S DISEASE

For patients with advanced Parkinson's disease (PD), levodopa therapy is far from ideal. Over time, the drug becomes less and less effective. Patients typically experience "off" times as well as drug-induced dyskinesias. For these patients, nondrug therapies may help. Potential options are deep brain stimulation, pallidotomy, and cell implants. Brain stimulation and pallidotomy have been very successful; cell implants have not.

Deep Brain Stimulation

Electrical stimulation of specific brain areas can improve motor symptoms in patients with PD. Three areas have been targeted: the subthalamic nucleus (STN), the globus pallidus internus, and the ventralis intermedius nucleus of the thalamus. Stimulation of the STN has produced the best results. Compared with pallidotomy, electrical stimulation has several advantages: it's reversible and adjustable, and, because brain tissue is not permanently damaged, it can be done bilaterally with low risk. On the other hand, electrical stimulation is very expensive. Several studies on STN stimulation have been conducted. One is described below.

In 1998, researchers reported that continuous, long-term electrical stimulation of the STN can improve symptoms in patients with advanced PD. This work was based on animal models of PD in which (1) motor symptoms were associated with abnormal neuronal activity in the STN and (2) electrical stimulation of the STN improved the symptoms. In patients with PD, electrodes were implanted *bilaterally* in the STN and then connected by a subcutaneous lead to a pulse generator implanted in the subclavicular region, much like a cardiac

pacemaker. The pulse generator was then programmed by telemetry to adjust stimulation parameters (eg, voltage, frequency). All patients in the study had advanced PD and all were experiencing "off" periods with levodopa.

Electrical stimulation produced substantial benefits during "off" times but only modest benefits during "on" times. During "off" times, there was a 60% improvement in motor function; bradykinesia, rigidity, tremor, and gait all improved. During "on" times, improvement was only 10%. Stimulation allowed all patients to become independent in most activities of daily living. On average, stimulation permitted a 50% reduction in levodopa dosage.

Adverse effects were generally mild, but serious sequelae of the neurosurgery are possible. Of the 20 patients in this study, 8 experienced transient CNS effects, including confusion, hallucinations, temporospatial disorientation, and abulia (lack of will; inability to make decisions). All symptoms resolved within 2 weeks of the surgery. Of much greater concern, the procedure carries a 2% to 8% risk of intracerebral hematoma. Accordingly, the procedure should be reserved for patients with advanced PD who are otherwise good candidates for surgery.

How does STN stimulation improve PD symptoms? The answer is unclear. One theory, based on animal studies, suggests that electrical stimulation may *inhibit* overactivity of neurons in the STN. The net result would be to *increase* excitatory input to the cerebral cortex.

Electrical stimulation is expensive. The surgery costs about $25,000. The pulse generator costs another $13,000. And every 3 to 5 years, additional costs arise when the batteries in the pulse generator must be replaced.

Pallidotomy

Posteroventral medial pallidotomy, or simply pallidotomy, is a neurosurgical procedure for destroying a region of the globus pallidus. As indicated in Figure 21-1, the globus pallidus, which helps regulate movement, receives input from the striatum. In patients with PD, striatal input to the globus pallidus is disrupted, causing the globus pallidus itself to malfunction. It has been argued that altered output from the globus pallidus underlies many of the symptoms of PD, including tremor, rigidity, and bradykinesia. The results of pallidotomy support this argument: For many patients with PD, *unilateral* destruction of

the posteroventral medial region of the globus pallidus produces a substantial improvement in symptoms. The most consistent benefit is a reduction in levodopa-induced dyskinesias. Motor control during levodopa "off" times also improves. In contrast, very little improvement is seen during levodopa "on" times. Following pallidotomy, about 50% of patients who previously needed help with activities of daily living are able to live independently. Pallidotomy may also permit a temporary reduction in levodopa dosage. Although complications of the procedure are generally mild, intracerebral hemorrhage is a potential and serious risk.

Because pallidotomy is irreversible, and because complications can be serious, the procedure should be limited to patients with intractable levodopa-induced dyskinesias and to patients who are disabled by levodopa "off" times. Furthermore, because brain tissue is permanently destroyed, pallidotomy is usually performed unilaterally—thereby leaving the other side of the brain intact, just in case something goes wrong.

Cell Implants

The objective with cell implants is to replace degenerated dopaminergic neurons. Implants have been tried with human adrenal cells and with fetal brain cells from humans and pigs. Human brain cells work best, and even then benefits are modest.

In 1995, researchers finally obtained definitive proof that transplanting fetal dopaminergic neurons into the brain can benefit a patient with PD. In this case study, the patient had severe parkinsonism that would no longer respond to drug therapy. Following the transplant, symptoms steadily improved over 3 months, eventually allowing the patient to perform all activities of daily living without assistance. The improvements were sustained for 15 months, at which time the patient died of a massive pulmonary embolism unrelated to the transplant. Autopsy revealed that the grafts not only took but had become seamlessly integrated into the surrounding tissue. This was the first clear demonstration of a correlation between graft survival and improvement of symptoms.

In 1999, a study done with 40 patients showed that fetal tissue transplants are only moderately effective, and then only in patients who are relatively young.

In this study, 20 patients received bilateral implants of dopamine-producing cells and 20 control patients received sham implants. Twelve months later, brain scans indicated cell survival in 60% of the treated patients, regardless of age. However, *functional* improvement was modest (30%) and occurred only in patients under 60 years old. In patients over 60, there was no motor improvement despite survival of the implants. Furthermore, although motor function improved in some younger patients, it was not enough to permit a reduction in levodopa dosage.

Drug Holidays

With long-term use of levodopa, adverse effects tend to increase and therapeutic effects tend to diminish. For some patients, the situation may improve following a "drug holiday," defined as a brief (eg, 10-day) interruption of treatment. When the holiday is successful, beneficial effects are achieved with lower doses. Because doses are lower, the incidence of dyskinesias and psychosis is lowered as well. Unfortunately, drug holidays do not eliminate "off" times.

Drug holidays are dangerous. Because drug withdrawal will immobilize the patient, the holiday must take place in a hospital. In addition to severe psychologic distress, immobilization presents a risk of deep vein thrombosis, aspiration pneumonitis, and decubitus ulcers.

Drug Interactions

Interactions between levodopa and other drugs can (1) increase beneficial effects of levodopa, (2) decrease beneficial effects of levodopa, and (3) increase toxicity from levodopa. Major interactions are summarized in Table 21-3. Several interactions are discussed immediately below; others are discussed later.

Drug Category	Drug	Mechanism of Interaction
Drugs that *increase* beneficial effects of levodopa	Carbidopa	Inhibits peripheral decarboxylation of levodopa
	Entacapone, tolcapone	Inhibit destruction of levodopa by COMT in the intestine and peripheral tissues
	Apomorphine, bromocriptine, cabergoline, pramipexole, ropinirole	Stimulate dopamine receptors directly, and thereby add to the effects of dopamine derived from levodopa
	Amantadine	Promotes release of dopamine
	Anticholinergic drugs	Block cholinergic receptors in the CNS, and thereby help restore the balance between dopamine and ACh
Drugs that *decrease* beneficial effects of levodopa	Pyridoxine (vitamin B_6)	Enhances destruction of levodopa by decarboxylases
	Antipsychotic drugs*	Block dopamine receptors in the striatum
Drugs that increase levodopa toxicity	MAO inhibitors	Inhibition of MAO increases the risk of severe levodopa-induced hypertension

ACh = acetylcholine, CNS = central nervous system, COMT = catechol-*O*-methyltransferase, MAO = monoamine oxidase.

TABLE 21-3 Major Drug Interactions of Levodopa

* First-generation antipsychotic agents block dopamine receptors in the striatum and thereby nullify the therapeutic effects of levodopa. Two second-generation antipsychotics—clozapine and quetiapine—do not block dopamine receptors in the striatum, and hence do not nullify the therapeutic effects of levodopa.

First-Generation Antipsychotic Drugs.

All of the first-generation antipsychotic drugs (eg, chlorpromazine, haloperidol) block receptors for dopamine in the striatum. As a result, they

can decrease therapeutic effects of levodopa. Accordingly, concurrent use of levodopa and these drugs should be avoided. As discussed above, two second-generation agents—clozapine and quetiapine—do not block dopamine receptors in the striatum, and hence can be used safely in patients with PD.

Monoamine Oxidase Inhibitors.

Levodopa can cause a hypertensive crisis if administered to an individual taking a *nonselective* inhibitor of monoamine oxidase (MAO). The mechanism is as follows: (1) Levodopa elevates neuronal stores of dopamine and norepinephrine (NE) by promoting synthesis of both compounds. (2) Because intraneuronal MAO serves to inactivate dopamine and NE, inhibition of MAO allows elevated neuronal stores of these transmitters to grow even larger. (3) Because both dopamine and NE promote vasoconstriction, release of these agents in supranormal amounts can lead to massive vasoconstriction, thereby causing blood pressure to rise dangerously high. To avoid hypertensive crisis, nonselective MAO inhibitors should be withdrawn at least 2 weeks prior to giving levodopa.

Anticholinergic Drugs.

As discussed above, excessive stimulation of cholinergic receptors contributes to the dyskinesias of PD. Therefore, by blocking these receptors, anticholinergic agents can enhance responses to levodopa.

Pyridoxine.

Pyridoxine (vitamin B***6***) stimulates decarboxylase activity. By accelerating decarboxylation of levodopa in the periphery, pyridoxine can decrease the amount of levodopa that reaches the central nervous system (CNS). As a result, therapeutic effects of levodopa are reduced. Patients should be informed about this interaction and instructed to avoid multivitamin preparations that contain pyridoxine.

Food Interactions

Meals with a high protein content can reduce therapeutic responses to levodopa. Why? Because neutral amino acids compete with levodopa for absorption from the intestine and for transport across the blood-brain barrier.

Hence, a high-protein meal can significantly reduce both the amount of levodopa absorbed and the amount transported into the brain. It has been suggested that a high-protein meal could trigger an abrupt loss of effect (ie, an "off" episode). Accordingly, patients should be advised to spread their protein consumption evenly throughout the day.

Preparations, Dosage, and Administration

Levodopa [Dopar, Larodopa] is available in tablets and capsules (100, 250, and 500 mg). To minimize adverse effects, especially drug-induced dyskinesias, dosage must be individualized. The usual initial dosage is 0.5 to 1.0 gm/day administered in two or more divided doses. The total daily dosage can be increased gradually to a maximum of 8 gm. Full therapeutic responses may take 6 months to develop.

Levodopa/Carbidopa

The combination of levodopa plus carbidopa is our most effective therapy for PD—much more effective than levodopa alone. Levodopa plus carbidopa is available under two trade names: *Sinemet* and *Paracopa*.

Mechanism of Action

Carbidopa is used to enhance the effects of levodopa. Carbidopa has no therapeutic effects of its own, and therefore is always used in conjunction with levodopa. Carbidopa inhibits decarboxylation of levodopa in the intestine and peripheral tissues, thereby making more levodopa available to the CNS. Carbidopa does not prevent the conversion of levodopa to dopamine by decarboxylases in the brain. Why? Because carbidopa is unable to cross the blood-brain barrier.

The impact of carbidopa is shown schematically in Figure 21-4, which compares the fate of levodopa in the presence and absence of carbidopa. In the absence of carbidopa, about 98% of levodopa is lost in the periphery, leaving only 2% available to the brain. Why is levodopa lost? Primarily because decarboxylases in the GI tract and peripheral tissues convert it to dopamine. When these decarboxylases are inhibited by carbidopa, only 90% of levodopa is lost in the periphery, leaving 10% for actions in the brain.

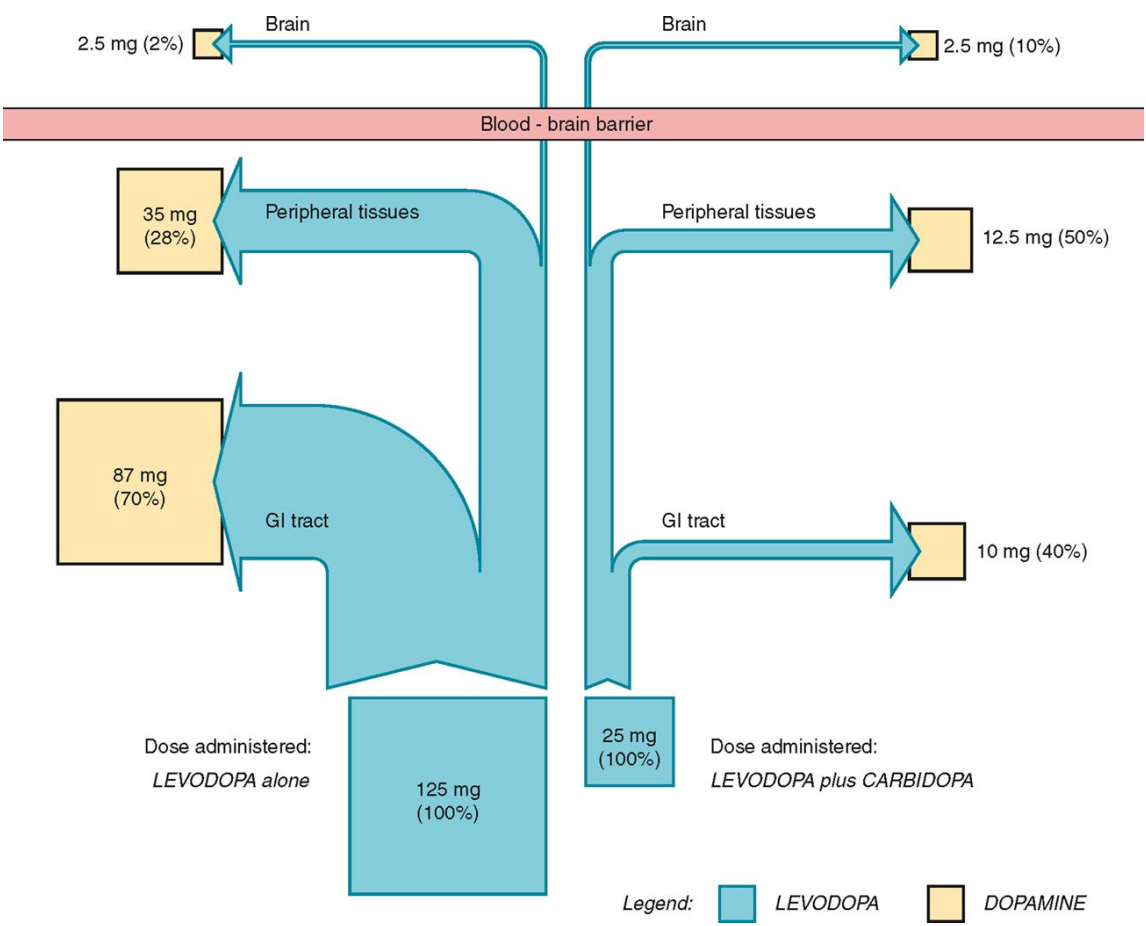


Figure 21-4 Fate of levodopa in the presence and absence of carbidopa. In the absence of carbidopa, 98% of an administered dose of levodopa is metabolized in intestinal and peripheral tissues—either by decarboxylases or COMT—leaving only 2% for actions in the brain. Hence, in order to deliver 2.5 mg of levodopa to the brain, the dose of levodopa must be large (125 mg). By inhibiting intestinal and peripheral decarboxylases, carbidopa increases the percentage of levodopa available to the brain. Hence, the dose needed to deliver 2.5 mg is greatly reduced (to 25 mg in this example). Since carbidopa cannot cross the blood-brain barrier, it does not suppress conversion of levodopa to dopamine in the brain. Furthermore, since carbidopa reduces peripheral production of dopamine (from 35 mg to 12.5 mg in this example),

peripheral toxicity (nausea, cardiovascular effects) is greatly reduced.

Advantages of Carbidopa

The combination of carbidopa plus levodopa is superior to levodopa alone in three ways:

- By increasing the fraction of levodopa available for actions in the CNS, carbidopa allows the dosage of levodopa to be reduced by about 75%. In the example in Figure 21-4, in order to provide 2.5 mg of dopamine to the brain, we must administer 125 mg of levodopa if carbidopa is absent, but only 25 mg if carbidopa is present.
- By reducing production of dopamine in the periphery, carbidopa reduces cardiovascular responses to levodopa as well as nausea and vomiting.
- By causing direct inhibition of decarboxylase, carbidopa obviates stimulation of decarboxylase by pyridoxine. As a result, carbidopa eliminates concern about decreasing the effects of levodopa by taking vitamin preparations that contain pyridoxine.

Disadvantages of Carbidopa

Carbidopa has no adverse effects of its own. Accordingly, any adverse responses from carbidopa/levodopa are the result of potentiating the effects of levodopa. When levodopa is combined with carbidopa, abnormal movements and psychiatric disturbances may occur sooner and may be more intense than when levodopa is employed alone.

Preparations, Dosage, and Administration

Therapy with levodopa plus carbidopa is almost always accomplished using a fixed-dose combination product, marketed as Sinemet or Paracopa. Under special circumstances, levodopa and carbidopa can be taken separately.

Levodopa/Carbidopa: Sinemet.

The Sinemet brand of levodopa/carbidopa is available in immediate-release (IR) and sustained-release (SR) tablets. The IR tablets are available in three strengths: (1) 10 mg carbidopa/100 mg levodopa, (2) 25 mg carbidopa/100 mg

levodopa, and (3) 25 mg carbidopa/250 mg levodopa. The SR tablets [Sinemet CR] are available in two strengths: 25 mg carbidopa/100 mg levodopa, and 50 mg carbidopa/200 mg levodopa. With either the IR or SR formulation, dosage is low initially and then gradually increased. The usual maximum is 800 mg of levodopa a day, administered in divided doses.

Levodopa/Carbidopa: Paracopa.

The Paracopa brand of levodopa/carbidopa was introduced in 2005. Paracopa products differ from Sinemet products in that Paracopa products are formulated to dissolve on the tongue and then be swallowed with saliva—a potential advantage for patients who, because of their PD, have difficulty swallowing tablets intact. Orally disintegrating Paracopa tablets are available in the same strengths as IR Sinemet tablets: 10 mg carbidopa/100 mg levodopa, 25 mg carbidopa/100 mg levodopa, and 25 mg carbidopa/250 mg levodopa. Dosage is the same as with Sinemet.

Carbidopa Alone.

Carbidopa without levodopa, available as *Lodosyn,* is available by special request for investigational use. This preparation is employed when dosages of levodopa and carbidopa must be titrated separately. Carbidopa is never used without levodopa.

Switching from Levodopa Alone to Levodopa/Carbidopa.

When patients who have been taking levodopa alone are switched to the combination of levodopa plus carbidopa, at least 8 hours should elapse between the last dose of levodopa and the first dose of the combination. This delay is needed to prevent excessive potentiation of residual levodopa by carbidopa. Also, when switching from levodopa alone to the combination, the total daily dose of levodopa must be reduced substantially: The dose of levodopa within the combination should be only 25% of the former dose. For patients who are not currently receiving levodopa, therapy can be initiated with either 10 mg carbidopa/100 mg levodopa or 25 mg carbidopa/100 mg levodopa, each taken 3 times a day.

Dopamine Agonists

Dopamine agonists are first-line drugs for PD. Beneficial effects result from direct activation of dopamine receptors in the striatum. For patients with mild or moderate symptoms, dopamine agonists are drugs of first choice. Although dopamine agonists are less effective than levodopa, they still have advantages. Specifically, in contrast to levodopa, they aren't dependent on enzymatic conversion to become active, aren't converted to potentially toxic metabolites, and don't compete with dietary proteins for uptake from the intestine or transport across the blood-brain barrier. In addition, when used long-term, dopamine agonists have a lower incidence of response failures and are less likely to cause disabling dyskinesias. However, dopamine agonists do cause more serious side effects—especially hallucinations, daytime sleepiness, and postural hypotension. As a result, these drugs are usually reserved for younger patients, who tolerate their side effects better than do the elderly.

At this time, five dopamine agonists are available. The dopamine agonists fall into two groups: derivatives of ergot (an alkaloid found in plants) and nonergot derivatives. The nonergot derivatives—*pramipexole, ropinirole,* and *apomorphine*—are highly selective for dopamine receptors. In contrast, the ergot derivatives—*bromocriptine* and *cabergoline*—activate serotonergic and alpha-adrenergic receptors as well. Because of their selectivity, the nonergot derivatives cause fewer side effects than the ergot derivatives, and hence are preferred.

Pramipexole

Actions and Uses.

Pramipexole [Mirapex] is a nonergot dopamine receptor agonist. The drug is used alone in early-stage PD, and combined with levodopa in advanced-stage PD. Pramipexole binds selectively to dopamine D***2*** and D***3*** receptor subtypes. Binding to D***2*** receptors underlies therapeutic effects. The significance of D***3*** binding is unknown. When used as monotherapy in early PD, pramipexole can produce significant improvement in motor performance. When combined with levodopa in advanced PD, the drug can reduce fluctuations in motor control and may permit a reduction in levodopa dosage. In both cases, maximal benefits take several weeks to develop. Compared with levodopa, pramipexole

is less effective at controlling motor symptoms of PD, but is also less likely to cause motor fluctuations.

In addition to its use in PD, pramipexole is approved for patients with moderate to severe *restless legs syndrome* (RLS), a sensorimotor disorder characterized by unpleasant leg sensations that create an urge to move the legs in an effort to ease discomfort. Symptoms are usually more intense in the evening and often disrupt sleep. People with severe RLS experience sleep loss, daytime exhaustion, and diminished quality of life.

Pharmacokinetics.

Pramipexole is rapidly absorbed and reaches peak plasma levels in 1 to 2 hours. Food reduces the speed of absorption but not the extent. Pramipexole undergoes wide distribution, and achieves a high concentration in red blood cells. The drug is eliminated unchanged in the urine.

Adverse Effects and Interactions.

Pramipexole can produce a variety of adverse effects. Most are the direct result of activating dopamine receptors. The most common effects seen when pramipexole is used *alone* are nausea (28%), dizziness (25%), daytime somnolence (22%), insomnia (17%), constipation (14%), weakness (14%), and hallucinations (9%). When the drug is *combined with levodopa,* many patients experience orthostatic hypotension (54%) and dyskinesias (47%), which are not seen when the drug is used by itself. In addition, the incidence of hallucinations nearly doubles, rising to 17%.

A few patients have experienced *sleep attacks* (overwhelming and irresistible sleepiness that comes on without warning). Sleep attacks can be a real danger for people who are driving (and a potential blessing for those in faculty meetings). Sleep attacks should not be equated with the normal sleepiness that occurs with dopaminergic agents. Patients who experience a sleep attack should inform their prescriber.

Rarely, pramipexole has been associated with pathologic gambling and other *compulsive, self-rewarding behaviors,* including binge eating, compulsive shopping, and hypersexuality. These behaviors are dose related, begin about 9 months after starting pramipexole, and reverse when the drug is discontin-

ued. Risk factors include relative youth, a family or personal history of alcohol abuse, and a personality trait called novelty seeking, characterized by impulsivity, a quick temper, and a low threshold for boredom. Before prescribing pramipexole, clinicians should screen patients for compulsive behaviors.

Cimetidine (a drug for peptic ulcer disease) can inhibit renal excretion of pramipexole, thereby increasing its blood level.

Preparations, Dosage, and Administration.

Pramipexole [Mirapex] is available in tablets (0.125, 0.25, 0.5, 1.0, and 1.5 mg) for oral dosing. Dosing may be done with food to reduce nausea. To minimize other adverse effects, dosage should be low initially and then gradually increased.

For patients with PD, the recommended starting dosage is 0.125 mg 3 times a day. This can be increased over 7 weeks to a maximum of 1.5 mg 3 times a day. In patients with significant renal impairment, dosage should be reduced.

For patients with RLS, dosing is done once daily, 2 to 3 hours before bedtime. The daily dosage is 0.125 mg initially, and can be gradually increased to a maximum of 0.5 mg.

Ropinirole

Actions, Uses, and Adverse Effects.

Ropinirole [Requip], a nonergot dopamine agonist, is similar to pramipexole with respect to receptor specificity, mechanism of action, and adverse effects. Like pramipexole, ropinirole is highly selective for D***2*** and D***3*** receptors, and both drugs share the same indications: PD and RLS. In patients with PD, ropinirole can be used as monotherapy (in early PD) and as an adjunct to levodopa (in advanced PD). In contrast to pramipexole, which is eliminated entirely by renal excretion, ropinirole is eliminated by hepatic metabolism. Some adverse effects are more common than with pramipexole. When ropinirole is used alone, the most common effects are nausea (60%), dizziness (40%), somnolence (40%), and hallucinations (5%). Rarely, sleep attacks occur. When ropinirole is combined with levodopa, the most important side effects are dyskinesias (34%), hallucinations (10%), and postural hypotension (2%). Note

that these occur less frequently than when pramipexole is combined with levodopa. Like pramipexole, ropinirole can promote compulsive gambling and other compulsive, self-rewarding behaviors. Animal tests indicate that ropinirole can harm the developing fetus. Accordingly, the drug should not be used during pregnancy.

Preparations, Dosage, and Administration.

Preparations and Administration. Ropinirole is available in immediate-release (IR) film-coated tablets (0.25, 0.5, 1, 2, 3, 4, and 5 mg), marketed as *Requip,* and in extended-release (ER) tablets (2, 4, and 8 mg), marketed as *Requip XL*. The drug may be taken with food to decrease nausea. Dosage should be low initially and then gradually increased.

Dosage in Parkinson's Disease.

With the IR tablets, dosing is begun at 0.25 mg 3 times a day, and can be increased over several months to a maximum of 8 mg 3 times a day. With the ER tablets, dosing is begun at 2 mg once a day, and can be increased over several months to a maximum of 24 mg once a day.

Dosage in Restless Legs Syndrome.

Dosing is done once daily, 1 to 3 hours before bedtime, using the IR tablets. The daily dosage is 0.25 mg initially, and can be gradually increased to a maximum of 4 mg.

Apomorphine

Actions and Therapeutic Use.

Apomorphine [Apokyn] is a nonergot dopamine agonist approved for acute, subQ treatment of hypomobility during "off" episodes in patients with advanced PD. Unlike other dopamine agonists, the drug is not indicated for routine PD management. When tested in patients experiencing at least 2 hours of "off" time a day, apomorphine produced a 62% improvement in PD rating scores, compared with no improvement in patients receiving placebo. Benefits were sustained during 4 weeks of use. Apomorphine is a derivative of

morphine, but is devoid of typical opioid effects (eg, analgesia, euphoria, respiratory depression).

Pharmacokinetics.

Apomorphine is highly lipophilic but undergoes extensive first-pass metabolism, and hence is ineffective when taken orally. After subQ injection, the drug undergoes rapid, complete absorption. Effects begin in 10 to 20 minutes and persist about 1 hour. The drug's half-life is about 40 minutes.

Adverse Effects.

The most common adverse effects are injection-site reactions (26%), hallucinations (14%), yawning (8%), drowsiness (7%), dyskinesias (7%), rhinorrhea (4%), and nausea and vomiting (4%). During clinical trials, there was a 4% incidence of serious cardiovascular events: angina, myocardial infarction, cardiac arrest, and/or sudden death. Postural hypotension and fainting occurred in 2% of patients. Like other dopamine agonists, apomorphine poses a risk of daytime sleep attacks. In addition, apomorphine can promote hypersexuality and enhanced erections (the drug is used in Europe to treat erectile dysfunction); rarely, apomorphine causes priapism (sustained, painful erection), possibly requiring surgical intervention.

Combined Use with an Antiemetic.

To prevent nausea and vomiting during clinical trials, nearly all patients were treated with an antiemetic, starting 3 days before the first dose of apomorphine. The antiemetic chosen was trimethobenzamide [Tigan, others]. Two classes of antiemetics *cannot* be used: serotonin receptor agonists (eg, ondansetron [Zofran]) and dopamine receptor antagonists (eg, prochlorperazine [Compazine]). Why? Because serotonin receptor agonists will increase the risk of serious postural hypotension, and dopamine receptor antagonists will decrease the effectiveness of apomorphine and most other drugs for PD. About half the trial participants discontinued the antiemetic at some point, but continued taking apomorphine.

Preparations, Dosage, and Administration.

Apomorphine [Apokyn] is available in 2-mL ampules and 3-mL cartridges, at a concentration of 10 mg/mL. Doses are given subQ. The 3-mL cartridges are used with the multidose injector pen provided. Only one dose is given for each "off" episode. In clinical trials, patients received an average of three doses a day. Doses should be low initially (1 to 2 mg) and then gradually increased (to a 6-mg maximum).

To control nausea and vomiting, package labeling states that all patients should take an antiemetic (eg, trimethobenzamide, 300 mg 3 times a day), starting 3 days before the first apomorphine dose. However, many patients find the antiemetic unnecessary, and discontinue it within a few days.

Ergot Derivatives: Bromocriptine and Cabergoline

Two ergot derivatives—bromocriptine and cabergoline—are employed for PD. Compared with the nonergot dopamine agonists, these drugs are much less well tolerated, and hence their use is limited. Of particular concern, the ergot derivatives have been associated with valvular heart injury. Because of this serious complication, a third ergot derivative—pergolide [Permax]—has been withdrawn. The side effect profile of the ergot derivatives differs from that of the nonergot agents because, in addition to activating dopamine receptors, the nonergot drugs activate serotonergic and alpha-adrenergic receptors as well.

Bromocriptine.

Bromocriptine [Parlodel], a derivative of ergot, is a direct-acting dopamine agonist. Beneficial effects result from activating dopamine receptors in the striatum. Responses are equivalent to those seen with pramipexole and ropinirole. Bromocriptine is used alone in early PD and in combination with levodopa in advanced PD. When combined with levodopa, bromocriptine can prolong therapeutic responses and reduce motor fluctuations. In addition, since bromocriptine allows the dosage of levodopa to be reduced, the incidence of levodopa-induced dyskinesias may be reduced too.

Adverse effects are dose dependent and seen in 30% to 50% of patients. Nausea is most common, occurring in over 50% of those treated. The most common dose-limiting effects are psychologic reactions (confusion, nightmares, agita-

tion, hallucinations, paranoid delusions). These occur in about 30% of patients and are most likely when the dosage is high. Like levodopa, bromocriptine can cause dyskinesias and postural hypotension. Rarely, bromocriptine causes retroperitoneal fibrosis, pulmonary infiltrates, a Raynaud-like phenomenon, and erythromelalgia (vasodilation in the feet, and sometimes hands, resulting in swelling, redness, warmth, and burning pain). In addition, the ergot derivatives have been associated with valvular heart injury. The probable cause is activation of serotonin receptors on heart valves.

Bromocriptine is available in 5-mg capsules [Parlodel] and 2.5-mg tablets [Parlodel SnapTabs]. The initial dosage is 1.25 mg twice daily, administered with meals. Dosage is gradually increased until the desired response has been achieved, or until side effects become intolerable. Maintenance dosages range from 30 to 100 mg/day.

Cabergoline.

Cabergoline [Dostinex] is used occasionally in PD, although it is not approved by the Food and Drug Administration for this disorder. According to the 2006 AAN guidelines, the drug is "possibly effective" for improving "off" times during levodopa therapy. The pharmacology of cabergoline, as well as its use in hyperprolactinemia, are discussed in Chapter 62 (Drug Therapy of Infertility).

COMT Inhibitors

Two COMT inhibitors are available: entacapone and tolcapone. With both drugs, benefits derive from inhibiting metabolism of levodopa in the periphery; these drugs have no direct therapeutic effects of their own. Entacapone is safer and more effective than tolcapone, and hence is preferred.

Entacapone

Actions and Therapeutic Use.

Entacapone [Comtan] is a selective, reversible inhibitor of COMT indicated only for use with levodopa. Like carbidopa, entacapone inhibits metabolism of levodopa in the intestine and peripheral tissues. However, the drugs inhibit different enzymes: carbidopa inhibits decarboxylases, whereas entacapone inhibits COMT. By inhibiting COMT, entacapone prolongs the half-life of le-

vodopa in blood, and thereby prolongs the time that levodopa is available to the brain. In addition, entacapone increases levodopa availability by a second mechanism: By inhibiting COMT, entacapone decreases production of levodopa metabolites that compete with levodopa for transport across the blood-brain barrier. In clinical trials, entacapone increased the half-life of levodopa by 50% to 75%, and thereby caused levodopa blood levels to be smoother and more sustained. As a result, "wearing off" was delayed and "on" times were extended. Entacapone may also permit a reduction in levodopa dosage.

Pharmacokinetics.

Entacapone is rapidly absorbed and reaches peak levels in 2 hours. Elimination is by hepatic metabolism followed by excretion in the feces and urine. The plasma half-life is 1.5 to 3.5 hours.

Adverse Effects.

Most adverse effects result from increasing levodopa levels, and some are caused by entacapone itself. By increasing levodopa levels, entacapone can cause dyskinesias, orthostatic hypotension, nausea, hallucinations, and sleep disturbances. These can be managed by decreasing levodopa dosage. Entacapone itself can cause vomiting, diarrhea, constipation, and yellow-orange discoloration of the urine.

Drug Interactions.

Because it inhibits COMT, entacapone can, in theory, increase levels of drugs metabolized by COMT. In addition to levodopa, these include methyldopa (an antihypertensive agent), dobutamine (an adrenergic agonist), and isoproterenol (a beta-adrenergic blocker). If entacapone is combined with these drugs, a reduction in their dosages may be needed.

Preparations, Dosage, and Administration.

Entacapone [Comtan], by itself, is available in 200-mg tablets. The recommended dosage is 200 mg taken with each dose of levodopa/carbidopa—to a maximum of 8 doses (1600 mg) a day.

As discussed below, entacapone is also available in fixed-dose combinations with levodopa/carbidopa, under the trade name *Stalevo*.

Tolcapone

Actions and Therapeutic Use.

Tolcapone [Tasmar] is a COMT inhibitor used only in conjunction with levodopa—and only if safer agents are ineffective or inappropriate. As with entacapone, benefits derive from inhibiting levodopa metabolism in the periphery, which prolongs levodopa availability. When given to patients taking levodopa, tolcapone improves motor function and may allow a reduction in levodopa dosage. For many patients, the drug reduces the "wearing off" effect that can occur with levodopa, thereby extending levodopa "on" times by as much as 2.9 hours a day. Unfortunately, although tolcapone is effective, it is also dangerous: Deaths from liver failure have occurred. Because it carries a serious risk, tolcapone should be reserved for patients who cannot be treated with safer drugs. Also, when tolcapone is used, treatment should be limited to 3 weeks in the absence of a beneficial response.

Pharmacokinetics.

Tolcapone is well absorbed following oral administration. Plasma levels peak 2 hours after dosing. In the blood, tolcapone is highly bound (over 99.9%) to plasma proteins, primarily albumin. The drug undergoes extensive hepatic metabolism followed by renal excretion. The plasma half-life is 2 to 3 hours.

Adverse Effects.

Liver Failure. Tolcapone can cause severe hepatocellular injury. At least three patients have died from acute, fulminant liver failure. Prior to treatment, patients should be fully apprised of the risks. Patients with pre-existing liver dysfunction should not take the drug. Patients taking tolcapone should be informed about signs of emergent liver dysfunction (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine) and instructed to report these immediately. If liver injury is diagnosed, tolcapone should be discontinued and never used again.

Laboratory monitoring of liver enzymes is required. Tests for serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be conducted prior to treatment and then throughout treatment as follows: every 2 weeks for the first year, every 4 weeks for the next 6 months, and every 8

weeks thereafter. If ALT or AST levels exceed the upper limit of normal, tolcapone should be discontinued. Monitoring may not prevent liver injury, but early detection and immediate drug withdrawal can minimize harm.

Other Adverse Effects.

By increasing the availability of levodopa, tolcapone can intensify levodopa-related effects, especially dyskinesias, orthostatic hypotension, nausea, hallucinations, and sleep disturbances; a reduction in levodopa dosage may be required. Tolcapone itself can cause diarrhea, hematuria, and yellow-orange discoloration of the urine. Abrupt withdrawal of tolcapone can produce symptoms that resemble neuroleptic malignant syndrome (fever, muscular rigidity, altered consciousness). In rats, large doses have caused renal tubular necrosis and tumors of the kidneys and uterus.

Preparations, Dosage, and Administration.

Tolcapone [Tasmar] is available in 100- and 200-mg tablets that may be taken with or without food. The usual dosage is 100 mg 3 times a day. The first dose should be administered in the morning along with levodopa/carbidopa. The next two doses are taken 6 and 12 hours later. If necessary, the dosage can be increased to 200 mg 3 times a day. However, elevations in ALT are more likely at the higher dosage.

Levodopa/Carbidopa/Entacapone

Levodopa, carbidopa, and entacapone are now available in fixed-dose combinations sold as *Stalevo*. As discussed above, both carbidopa and entacapone inhibit the enzymatic degradation of levodopa, and thereby enhance therapeutic effects. The triple combination is more convenient than taking levodopa/carbidopa and entacapone separately, and costs a little less too. Unfortunately, Stalevo is available only in immediate-release tablets and only in the following strengths:

- *Stalevo 50*—50 mg levodopa, 12.5 mg carbidopa, and 200 mg entacapone
- *Stalevo 75*—75 mg levodopa, 18.75 mg carbidopa, and 200 mg entacapone
- *Stalevo 100*—100 mg levodopa, 25 mg carbidopa, and 200 mg entacapone
- *Stalevo 150*—150 mg levodopa, 37.5 mg carbidopa, and 200 mg entacapone

• *Stalevo 125*—125 mg levodopa, 31.25 mg carbidopa, and 200 mg entacapone

Patients who need more flexibility in their regimen cannot be treated with Stalevo, nor can patients who require a sustained-release formulation. For each dose of Stalevo, only 1 tablet is taken. Also, since each tablet contains 200 mg of entacapone, and since patients should take no more than 1600 mg of entacapone a day, the daily limit for Stalevo is 8 tablets.

MAO-B Inhibitors

The MAO-B inhibitors—selegiline and rasagiline—are considered second- or third-line drugs for PD. When combined with levodopa, they can reduce the "wearing-off" effect, but benefits are modest.

Selegiline

Selegiline [Eldepryl, Carbex, Zelapar]—also known as deprenyl—was the first MAO inhibitor approved for PD. The drug may be used alone or in combination with levodopa. In both cases, improvement of motor function is modest. There is some evidence suggesting that selegiline may delay neurodegeneration, and hence may delay disease progression. However, conclusive proof of neuroprotection is lacking. Nonetheless, current guidelines suggest trying selegiline in newly diagnosed patients, just in case the drug *does* confer some protection.

Actions and Use.

Selegiline causes *selective*, *irreversible* inhibition of type B monoamine oxidase (MAO-B), the enzyme that inactivates dopamine in the striatum. Another form of MAO, known as MAO-A, inactivates NE and serotonin. As discussed in Chapter 32, nonselective inhibitors of MAO (ie, drugs that inhibit MAO-A *and* MAO-B) are used to treat depression—and pose a risk of hypertensive crisis as a side effect. Because selegiline is a selective inhibitor of MAO-B, the drug is not an antidepressant and, *at recommended doses,* poses little or no risk of hypertensive crisis.

Selegiline appears to benefit patients with PD in two ways. First, when used as an adjunct to levodopa, selegiline can suppress destruction of dopamine derived from levodopa. The mechanism is inhibition of MAO-B. By helping preserve dopamine, selegiline can prolong the effects of levodopa, and can

thereby decrease fluctuations in motor control. Unfortunately, these benefits decline dramatically within 12 to 24 months.

In addition to preserving dopamine, there is some hope that selegiline may delay the progression of PD. When used early in the disease, selegiline can delay the need for levodopa. This may reflect a delay in the progression of the disease, or it may simply reflect direct symptomatic relief from selegiline itself.

If selegiline does slow the progression of PD, what might be the mechanism? In experimental animals, selegiline can prevent development of parkinsonism following exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that causes selective degeneration of dopaminergic neurons. (Humans accidentally exposed to MPTP develop severe parkinsonism.) Neuronal degeneration is not caused by MPTP itself, but rather by a toxic metabolite. Formation of this metabolite is catalyzed by MAO-B. By inhibiting MAO-B, selegiline prevents formation of the toxic metabolite, and thereby protects against neuronal injury. If selegiline does retard progression of PD, this mechanism could explain the effect. That is, just as selegiline protects animals by suppressing formation of a neurotoxic metabolite of MPTP, the drug may retard progression of PD by suppressing formation of a neurotoxic metabolite of an as-yet unidentified compound.

Pharmacokinetics.

For treatment of PD, selegiline is available in two oral formulations (tablets and capsules) and in orally disintegrating tablets (ODTs).

Tablets and Capsules.

Selegiline in tablets and capsules [Eldepryl, Carbex] undergoes rapid GI absorption, travels to the brain, and quickly penetrates the blood-brain barrier. Irreversible inhibition of MAO-B follows. Selegiline undergoes hepatic metabolism followed by renal excretion. Two metabolites—l-*amphetamine* and l-*methamphetamine*—are CNS stimulants. These metabolites do not appear to have therapeutic effects, and they can be harmful. Because selegiline causes irreversible inhibition of MAO-B, effects persist until more MAO-B can be synthesized.

Orally Disintegrating Tablets.

Unlike selegiline in tablets and capsules, which is absorbed from the GI tract, selegiline in ODTs [Zelapar] is absorbed through the oral mucosa. As a result, bioavailability is higher than with tablets and capsules, and hence doses can be lower. Otherwise, the pharmacokinetics of selegiline in ODTs, tablets, and capsules are identical.

Adverse Effects.

When selegiline is used alone, the principal adverse effect is *insomnia,* presumably because of CNS excitation by amphetamine and methamphetamine. Insomnia can be minimized by administering the last daily dose no later than noon. Other adverse effects include orthostatic hypotension, dizziness, and GI symptoms. About 10% of patients taking selegiline ODTs experience irritation of the buccal mucosa.

Hypertensive Crisis.

Although selegiline is selective for MAO-B, high doses can inhibit MAO-A, and hence there is a risk of hypertensive crisis. As discussed in Chapter 32, when a patient is taking an MAO inhibitor, hypertensive crisis can be triggered by ingesting foods that contain tyramine and by taking certain drugs, including sympathomimetics. Accordingly, patients should be instructed to avoid these foods and drugs, both while taking selegiline and for 2 weeks after discontinuing it. For a full list of foods and drugs to avoid, see Chapter 32.

Drug Interactions.

Levodopa. When used with levodopa, selegiline can intensify adverse responses to levodopa-derived dopamine. These reactions—orthostatic hypotension, dyskinesias, and psychologic disturbances (hallucinations, confusion)—can be reduced by decreasing the dosage of levodopa.

Meperidine.

Like the nonselective MAO inhibitors, selegiline can cause a dangerous interaction with meperidine [Demerol]. Symptoms include stupor, rigidity, agitation, and hyperthermia. The combination should be avoided.

Fluoxetine.

Selegiline should not be combined with fluoxetine [Prozac]. The combination of a nonselective MAO inhibitor plus fluoxetine has been fatal. Although this interaction has not been reported with selegiline, prudence dictates caution. Accordingly, fluoxetine should be withdrawn at least 5 weeks before giving selegiline.

Preparations, Dosage, and Administration.

Tablets and Capsules. Selegiline [Eldepryl, Carbex] is available in 5-mg tablets and capsules. For treatment of PD, the usual dosage is 5 mg taken with breakfast and lunch, for a total of 10 mg a day. This dosage produces complete inhibition of MAO-B, and hence larger doses are unnecessary.

Orally Disintegrating Tablets.

Selegiline [Zelapar] is available in 1.25-mg ODTs. For patients with PD, treatment begins with 1.25 mg once a day for 6 weeks. If needed and tolerated, the dosage can then be raised to 2.5 mg once a day. Note that the maximum daily dose (2.5 mg) is 4 times lower than the maximum daily dose with tablets and capsules. Dosing should be done in the morning before breakfast, without liquid. Tablets are placed on the tongue, where they dissolve in seconds. Selegiline is then absorbed through the oral mucosa.

Transdermal System.

Selegiline is available in a transdermal system, marketed as *Emsam,* for treatment of major depressive disorder (see Chapter 32). Transdermal selegiline is not used for PD.

Rasagiline

Actions and Therapeutic Use.

Rasagiline [Azilect] was approved in 2006, making it the second MAO-B inhibitor for PD. Like selegiline, rasagiline is a selective, irreversible inhibitor of MAO-B. Benefits derive from preserving dopamine in the brain. The drug is approved for initial monotherapy of PD and for combined use with levodopa. As with selegiline, benefits are modest. Rasagiline is similar to selegiline in

most regards. The drugs differ primarily in that rasagiline is not converted to amphetamine or methamphetamine.

Pharmacokinetics.

Rasagiline is rapidly absorbed with a bioavailability of 36%. In the liver, the drug undergoes nearly complete metabolism by CYP1A2 (the 1A2 isozyme of cytochrome P450). Hepatic impairment and drugs that inhibit CYP1A2 will delay metabolism of rasagiline, causing blood levels of the drug to rise. In contrast to selegiline, rasagiline is not metabolized to amphetamine derivatives. Excretion is via the urine (62%) and feces (7%). The plasma half-life is 3 hours. However, because rasagiline causes irreversible inhibition of MAO-B, clinical effects persist until new MAO-B is synthesized.

Adverse Effects.

When used as monotherapy, rasagiline is generally well tolerated. The most common side effects are headache (14%), arthralgia (7%), dyspepsia (7%), depression (5%), flu-like symptoms (5%), and falls (5%). Unlike selegiline, rasagiline does not cause insomnia.

When rasagiline is combined with levodopa, side effects increase. The most common reactions are dyskinesias (18%), accidental injury (12%), nausea (12%), headache (11%), orthostatic hypotension (9%), constipation (9%), weight loss (9%), arthralgia (8%), and hallucinations (4%).

Like selegiline, rasagiline may pose a risk of hypertensive crisis (owing to inhibition of MAO-A), and hence patients should be instructed to avoid tyramine-containing foods and certain drugs, including sympathomimetic agents.

Rasagiline may increase the risk of malignant melanoma, a deadly cancer of the skin. Periodic monitoring is recommended.

Drug and Food Interactions.

Rasagiline has the potential to interact adversely with multiple drugs. Drugs that should be used with *caution* include

- *Levodopa*—Like selegiline, rasagiline can intensify adverse responses to levodopa-derived dopamine.

- *CYP1A2 Inhibitors*—Blood levels of rasagiline can be raised by ciprofloxacin and other drugs that inhibit CYP1A2, the hepatic enzyme that inactivates rasagiline.

Drugs and foods that are *contraindicated* include

- *MAO Inhibitors*—Combining rasagiline with another MAO inhibitor increases the risk of hypertensive crisis. At least 2 weeks should separate use of these drugs.
- *Sympathomimetics*—Sympathomimetics (eg, amphetamines, ephedrine, phenylephrine, pseudoephedrine) increase the risk of hypertensive crisis and must be avoided.
- *Tyramine-Containing Foods*—These agents increase the risk of hypertensive crisis and must be avoided.
- *Antidepressants*—Combining rasagiline with mirtazapine, selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors, and tricyclic antidepressants may pose a risk of hyperpyrexia and death. These drugs should be discontinued at least 14 days before starting rasagiline. Fluoxetine (an SSRI) should be discontinued at least 5 weeks before starting rasagiline.
- *Analgesics*—Combining rasagiline with meperidine, methadone, propoxyphene, or tramadol may pose a risk of serious reactions, including coma, respiratory depression, convulsions, hypertension, hypotension, and even death. At least 14 days should separate use of these drugs.
- *Dextromethorphan*—Combining rasagiline with dextromethorphan may pose a risk of brief episodes of psychosis and bizarre behavior.
- *Cyclobenzaprine*—This drug is structurally related to the tricyclic antidepressants, and hence should be avoided.

Preparations, Dosage, and Administration.

Rasagiline [Azilect] is available in 0.5- and 1-mg oral tablets.

For *monotherapy,* the usual dosage is 1 mg once a day, taken with or without food. For patients taking ciprofloxacin and other drugs that inhibit CYP1A2, the daily dosage should be reduced to 0.5 mg. For patients with mild hepatic

impairment, the daily dosage should be reduced to 0.5 mg. Patients with moderate to severe hepatic impairment should not use the drug.

For *adjunctive therapy* with levodopa, the dosage is 0.5 mg once a day initially, and may be increased to 1 mg once a day if needed. If the patient develops dopaminergic side effects, including dyskinesias or hallucinations, reducing the dosage of levodopa—not rasagiline—should be considered.

Amantadine

Actions and Uses.

Amantadine [Symmetrel] was developed as an antiviral agent (see Chapter 92), and was later found effective in PD. Possible mechanisms include inhibition of dopamine uptake, stimulation of dopamine release, blockade of cholinergic receptors, and blockade of glutamate receptors. Responses develop rapidly—often within 2 to 3 days—but are much less profound than with levodopa or the dopamine agonists. Furthermore, responses may begin to diminish within 3 to 6 months. Accordingly, amantadine is not considered a first-line agent. However, this drug may be helpful for managing dyskinesias caused by levodopa.

Adverse Effects.

Amantadine can cause adverse CNS effects (confusion, lightheadedness, anxiety) and peripheral effects that are thought to result from muscarinic blockade (blurred vision, urinary retention, dry mouth, constipation). All of these are generally mild when amantadine is used alone. However, if amantadine is combined with an anticholinergic agent, both the CNS and peripheral responses will be intensified.

Patients taking amantadine for 1 month or longer often develop *livedo reticularis,* a condition characterized by mottled discoloration of the skin. Livedo reticularis is a benign condition that gradually subsides following amantadine withdrawal.

Preparations, Dosage, and Administration.

Amantadine [Symmetrel] is supplied in 100-mg capsules and a syrup (10 mg/mL). The usual dosage is 100 mg twice daily. Because amantadine is eliminated primarily by the kidneys, dosage must be reduced in patients with renal impairment.

Amantadine often loses effectiveness after several months. If effects diminish, they can be restored by increasing the dosage or by interrupting treatment for several weeks.

Amantadine can enhance responses to levodopa and anticholinergic agents. When combined with these drugs, amantadine is administered in the same doses employed when taken alone.

Centrally Acting Anticholinergic Drugs

Anticholinergic drugs have been used in PD since 1867, making them the oldest medicines for this disease. These drugs alleviate symptoms by blocking muscarinic receptors in the striatum, thereby improving the functional imbalance between dopamine and ACh. Anticholinergic drugs can reduce tremor and possibly rigidity, but not bradykinesia. These agents are less effective than levodopa or dopamine agonists, but better tolerated. Today, anticholinergics are used as second-line therapy for tremor. They are most appropriate for younger patients with mild symptoms. Anticholinergics are generally avoided in the elderly, who are intolerant of CNS side effects (sedation, confusion, delusions, and hallucinations).

Although the anticholinergic drugs used today are somewhat selective for cholinergic receptors in the CNS, they can also block cholinergic receptors in the periphery. As a result, they can cause dry mouth, blurred vision, photophobia, urinary retention, constipation, and tachycardia. These effects are usually dose limiting. Blockade of cholinergic receptors in the eye may precipitate or aggravate glaucoma. Accordingly, intraocular pressure should be measured periodically. Peripheral anticholinergic effects are discussed fully in Chapter 14.

The anticholinergic agents used most often are *trihexyphenidyl* [Artane] and *benztropine* [Cogentin]. Doses are low initially and then gradually increased—until the desired response is achieved or until side effects become intolerable. For trihexyphenidyl, the initial dosage is 1.0 mg once a day, and the

maximum dosage is 2 mg 3 times a day. For benztropine, the initial dosage is 0.5 mg twice a day, and the maximum dosage is 2 mg twice a day. If anticholinergic drugs are discontinued abruptly, symptoms of parkinsonism may be intensified.

NONMOTOR SYMPTOMS AND THEIR MANAGEMENT

In addition to having characteristic motor symptoms, about 90% of patients with PD develop nonmotor symptoms, notably autonomic disturbances, depression, dementia, and psychosis.

Disruption of autonomic function can produce a variety of symptoms, including constipation, urinary incontinence, drooling, orthostatic hypotension, cold intolerance, and erectile dysfunction. The intensity of these symptoms increases in parallel with the intensity of motor symptoms. Constipation can be managed by getting regular exercise, maintaining adequate intake of fluid and fiber, and using a stool softener, such as docusate (see Chapter 78). Urinary incontinence can be controlled with oxybutynin and other peripherally acting anticholinergic drugs (see Chapter 14). Orthostatic hypotension can be managed by increasing intake of salt and fluid, and by treatment with fludrocortisone, a mineralocorticoid (see Chapter 59). Erectile function can be improved with sildenafil and other inhibitors of type 5 phosphodiesterase (see Chapter 65).

About 50% of PD patients develop depression, partly in reaction to having a debilitating disease, and partly because of the disease process itself. According to the 2006 AAN guidelines, only one drug—amitriptyline—has been proved effective in these patients. Unfortunately, amitriptyline, a tricyclic antidepressant, has anticholinergic effects that can exacerbate dementia, and antiadrenergic effects that can exacerbate orthostatic hypotension. Data for other antidepressants, including selective serotonin reuptake inhibitors and bupropion, are insufficient to prove or disprove efficacy in PD.

Dementia occurs in 40% of PD patients. The AAN guidelines recommend considering treatment with two drugs: donepezil and rivastigmine. Both drugs are cholinesterase inhibitors developed for Alzheimer's disease (Chapter 22). In patients with PD, these drugs can produce a modest improvement in cognit-

ive function, without causing significant worsening of motor symptoms, even though these drugs increase availability of acetylcholine at central synapses.

In patients with PD, psychosis is usually caused by the drugs taken to control motor symptoms. Most of these drugs—levodopa, dopamine agonists, amantadine, and anticholinergic drugs—can cause hallucinations. Therefore, if psychosis develops, dopamine agonists, amantadine, and anticholinergic drugs should be withdrawn, and the dosage of levodopa should be reduced to the lowest effective amount. If antipsychotic medication is needed, *first-generation* antipsychotics should be *avoided*. Why? Because all of these drugs block receptors for dopamine, and hence can intensify motor symptoms. Accordingly, the AAN guidelines recommend considering two second-generation antipsychotics: clozapine and quetiapine. Since clozapine can cause agranulocytosis, many clinicians prefer quetiapine. The guidelines recommend against routine use of olanzapine, another second-generation agent. The antipsychotic drugs are discussed in Chapter 31.

KEY POINTS

- Parkinson's disease is a neurodegenerative disorder that produces characteristic motor symptoms: tremor at rest, rigidity, postural instability, and bradykinesia.
- In addition to motor symptoms, PD can cause nonmotor symptoms, including autonomic dysfunction, depression, psychosis, and dementia.
- The primary pathology in PD is degeneration of neurons in the substantia nigra that supply dopamine to the striatum. The result is an imbalance between dopamine and ACh.
- Motor symptoms are treated primarily with drugs that directly or indirectly activate dopamine receptors. Drugs that block cholinergic receptors can also be used.
- Levodopa (combined with carbidopa) is the most effective treatment for motor symptoms.

- Levodopa relieves motor symptoms by undergoing conversion to dopamine in surviving nerve terminals in the striatum.
- The enzyme that converts levodopa to dopamine is called a decarboxylase.
- Acute loss of response to levodopa occurs in two patterns: gradual "wearing off," which develops at the end of the dosing interval, and abrupt loss of effect ("on-off" phenomenon), which can occur at any time during the dosing interval.
- The principal adverse effects of levodopa are nausea, dyskinesias, hypotension, and psychosis.
- First-generation antipsychotic drugs block dopamine receptors in the striatum, and can thereby negate the effects of levodopa. Two second-generation antipsychotics—clozapine and quetiapine—do not block dopamine receptors in the striatum, and hence can be used safely to treat levodopa-induced psychosis.
- Combining levodopa with a nonselective MAO inhibitor can result in hypertensive crisis.
- Because amino acids compete with levodopa for absorption from the intestine and for transport across the blood-brain barrier, high-protein meals can reduce therapeutic effects.
- Carbidopa enhances the effects of levodopa by preventing decarboxylation of levodopa in the intestine and peripheral tissues. Since carbidopa cannot cross the blood-brain barrier, it does not prevent conversion of levodopa to dopamine in the brain.
- Pramipexole, an oral nonergot dopamine agonist, is a first-line drug for motor symptoms. It can be used alone in early PD and combined with levodopa in advanced PD.
- Pramipexole and other dopamine agonists relieve motor symptoms by causing direct activation of dopamine receptors in the striatum.
- The major adverse effects of pramipexole—nausea, dyskinesia, postural hypotension, and hallucinations—result from excessive activation of dopamine receptors.

- Entacapone, a COMT inhibitor, is combined with levodopa to enhance levodopa's effects. The drug inhibits metabolism of levodopa by COMT in the intestine and peripheral tissues, thereby making more levodopa available to the brain.
- Selegiline and rasagiline enhance responses to levodopa by inhibiting MAO-B, the brain enzyme that inactivates dopamine.
- Anticholinergic drugs relieve symptoms of PD by blocking cholinergic receptors in the striatum.

Summary of Major Nursing Implications*

LEVODOPA/CARBIDOPA [SINEMET, PARACOPA]

Preadministration Assessment

Therapeutic Goal

The goal of treatment is to improve the patient's ability to carry out activities of daily living. Levodopa does not cure PD or delay its progression.

Baseline Data

Assess motor symptoms—bradykinesia, akinesia, postural instability, tremor, rigidity—and the extent to which they interfere with activities of daily living (ability to work, dress, bathe, walk, etc.).

Identifying High-Risk Patients

Levodopa is *contraindicated* for patients with malignant melanoma (it can activate this neoplasm) and for patients taking MAO inhibitors.

Exercise *caution* in patients with cardiac disease and psychiatric disorders.

Implementation: Administration

Route

Oral.

Administration

Motor symptoms may render self-medication impossible. Assist the patient with dosing when needed. If appropriate, involve family members in medicating outpatients.

Inform patients that levodopa may be taken with food to reduce nausea and vomiting. However, high-protein meals should be avoided.

If the patient has been taking levodopa alone, allow at least 8 hours between the last dose of levodopa and the first dose of levodopa/carbidopa. The dosage of levodopa in the combination should be reduced to no more than 25% of the dosage employed when levodopa was taken alone.

So that expectations may be realistic, **inform patients that benefits of levodopa may be delayed for weeks to months.** This knowledge will facilitate adherence.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Evaluate for improvements in activities of daily living and for reductions in bradykinesia, postural instability, tremor, and rigidity.

Managing Acute Loss of Effect

"Off" times can be reduced by combining levodopa/carbidopa with a dopamine agonist (eg, pramipexole), a COMT inhibitor (eg, entacapone), or an MAO-B inhibitor (eg, rasagiline). **Forewarn patients about possible abrupt loss of therapeutic effects and instruct them to notify the prescriber if this occurs. Avoiding high-protein meals may help.**

Minimizing Adverse Effects

Nausea and Vomiting.

Inform patients that nausea and vomiting can be reduced by taking levodopa with food. Instruct patients to notify the prescriber if nausea and

vomiting persist or become severe. Adding more carbidopa (without levodopa) can help reduce nausea and vomiting.

Dyskinesias.

Inform patients about possible levodopa-induced movement disorders (tremor, dystonic movements, twitching) and instruct them to notify the prescriber if these develop. Giving amantadine may help.

If the hospitalized patient develops dyskinesias, withhold levodopa and consult the prescriber about a possible reduction in dosage.

Dysrhythmias.

Inform patients about signs of excessive cardiac stimulation (palpitations, tachycardia, irregular heartbeat) and instruct them to notify the prescriber if these occur.

Orthostatic Hypotension.

Inform patients about symptoms of hypotension (dizziness, lightheadedness) and advise them to sit or lie down if these occur. Advise patients to move slowly when assuming an erect posture.

Psychosis.

Inform patients about possible levodopa-induced psychosis (visual hallucinations, vivid dreams, paranoia) and instruct them to notify the prescriber if these develop. Treatment with clozapine or quetiapine can help.

Minimizing Adverse Interactions

First-Generation Antipsychotic Drugs.

These can block responses to levodopa and should be avoided. Two second-generation antipsychotics—clozapine and quetiapine—can be used safely.

MAO Inhibitors.

Concurrent use of levodopa and a nonselective MAO inhibitor can produce severe hypertension. Withdraw nonselective MAO inhibitors at least 2 weeks before initiating levodopa.

Anticholinergic Drugs.

These can enhance therapeutic responses to levodopa, but they also increase the risk of adverse psychiatric effects.

High-Protein Meals.

Amino acids compete with levodopa for absorption from the intestine and for transport across the blood-brain barrier. **Instruct patients not to take levodopa/carbidopa with a high-protein meal.**

DOPAMINE AGONISTS

Apomorphine

Bromocriptine

Cabergoline

Pramipexole

Ropinirole

Preadministration Assessment

Therapeutic Goal

The goal of treatment is to improve the patient's ability to carry out activities of daily living. Dopamine agonists do not cure PD or delay its progression.

Apomorphine is reserved for rescue treatment of hypomobility during “off” episodes in patients with advanced PD.

Baseline Data

Assess motor symptoms—bradykinesia, akinesia, postural instability, tremor, rigidity—and the extent to which these interfere with activities of daily living (ability to work, dress, bathe, walk, etc.).

Identifying High-Risk Patients

Use *all dopamine agonists* with *caution* in elderly patients and in patients with psychiatric disorders. Use *pramipexole* with *caution* in patients with kidney dysfunction. Avoid *ropinirole* during pregnancy. Use *pramipexole* and *ropinirole* with *caution* in patients prone to compulsive behavior.

Implementation: Administration

Route

Oral.

Cabergoline, bromocriptine, pramipexole, ropinirole.

Subcutaneous.

Apomorphine.

Administration

Parkinsonism may render self-medication impossible. Assist the patient with dosing when needed. If appropriate, involve family members in medicating outpatients.

Inform patients that oral dopamine agonists may be taken with food to reduce nausea and vomiting.

To minimize adverse effects, dosage should be low initially and then gradually increased.

Reduce dosage of pramipexole in patients with significant renal dysfunction.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Evaluate for improvements in activities of daily living and for reductions in bradykinesia, postural instability, tremor, and rigidity.

Minimizing Adverse Effects

Nausea and Vomiting.

Inform patients that nausea and vomiting can be reduced by taking oral dopamine agonists with food. Instruct patients to notify the prescriber if nausea and vomiting persist or become severe. Instruct patients taking apomorphine to pretreat with trimethobenzamide [Tigan], an antiemetic.

Orthostatic Hypotension.

Inform patients about symptoms of hypotension (dizziness, lightheadedness) and advise them to sit or lie down if these occur. Advise patients to move slowly when assuming an erect posture.

Dyskinesias.

Inform patients about possible movement disorders (tremor, dystonic movements, twitching) and instruct them to notify the prescriber if these develop.

Hallucinations.

Forewarn patients that dopamine agonists can cause hallucinations, especially in the elderly, and instruct them to notify the prescriber if these develop.

Sleep Attacks.

Warn patients that *pramipexole, ropinirole,* and apomorphine may cause sleep attacks. Instruct patients that, if a sleep attack occurs, they should inform the prescriber and avoid potentially hazardous activities (eg, driving).

Fetal Injury.

Inform women of child-bearing age that ropinirole may harm the developing fetus, and advise them to use effective birth control. If pregnancy occurs, switching to a different dopamine agonist is advised.

Compulsive Behaviors.

Rarely, pramipexole and ropinirole may induce compulsive, self-rewarding behaviors, including compulsive gambling, binge eating, compulsive shopping, and hypersexuality. Risk factors include relative youth, a family or personal history of alcohol abuse, and a novelty-seeking personality. Before prescribing these drugs, clinicians should screen patient for compulsive behaviors.

22 Alzheimer's Disease

Alzheimer's disease (AD) is a devastating illness characterized by progressive memory loss, impaired thinking, neuropsychiatric symptoms (eg, hallucinations, delusions), and inability to perform routine tasks of daily living. AD affects about 5.1 million older Americans and kills about 100,000 each year, making it the fourth leading cause of death among adults. The annual cost of AD—over $80 billion—is exceeded only by the costs of heart disease and cancer. Major pathologic findings are degeneration of cholinergic neurons and the presence of neuritic plaques and neurofibrillary tangles. The neuronal damage in AD is irreversible, and hence the disease cannot be cured. Drugs in current use do little to relieve symptoms or prevent neuronal loss.

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

The underlying cause of AD is unknown. Scientists have discovered important pieces of the AD puzzle, but still don't know how they fit together. It may well be that AD results from a combination of factors, rather than from a single cause.

Degeneration of Neurons

Neuronal degeneration occurs in the hippocampus early in AD, followed later by degeneration of neurons in the cerebral cortex. The hippocampus serves an important role in memory. The cerebral cortex is central to speech, perception, reasoning, and other higher functions. As hippocampal neurons degenerate, short-term memory begins to fail. As cortical neurons degenerate, patients begin having difficulty with language. With advancing cortical degeneration, more severe symptoms appear. These include complete loss of speech, loss of bladder and bowel control, and complete inability for self-care. AD eventually destroys enough brain function to cause death.

Reduced Cholinergic Transmission

In patients with advanced AD, levels of acetylcholine (ACh) are 90% below normal. This dramatic loss contrasts with the small loss that occurs normally with age. Loss of ACh is significant for two reasons. First, ACh is an important trans-

mitter in the hippocampus and cerebral cortex, regions where neuronal degeneration occurs. Second, ACh is critical to forming memories, and its decline has been linked to memory loss. However, although loss of cholinergic function is clearly important, it cannot be the whole story. Why? Because in 1999, researchers reported that, in patients with *mild* AD, markers for cholinergic transmission are essentially normal. Hence, loss of cholinergic function cannot explain the cognitive deficits that occur early in the disease process.

Beta-Amyloid and Neuritic Plaques

Neuritic plaques, which form outside of neurons, are a hallmark of AD. These spherical bodies are composed of a central core of *beta-amyloid* (a protein fragment) surrounded by remnants of axons and dendrites. Neuritic plaques are seen mainly in the hippocampus and cerebral cortex. The relationship of neuritic plaques to the disease process is unknown.

In patients with AD, beta-amyloid is present in high levels and may contribute to neuronal injury. Several lines of evidence support this possibility: beta-amyloid can kill hippocampal cells grown in culture; it can release free radicals, which injure cells; it can disrupt potassium channels; and it may form channels in the cell membrane that permit excessive entry of calcium. Also, low doses of beta-amyloid cause vasoconstriction, and high doses cause permanent blood vessel injury (secondary to release of oxygen free radicals). By disrupting blood vessels, beta-amyloid could slowly starve neurons to death. Perhaps the strongest evidence linking beta-amyloid to AD is the observation that injection of the compound directly into the brains of rhesus monkeys produces pathology essentially identical to that of AD. Interestingly, beta-amyloid is harmful only to old monkeys; young monkeys are not affected. This may indicate that, as the brain ages, it produces substances that act in concert with beta-amyloid to permit neurotoxic effects.

Neurofibrillary Tangles and Tau

Like neuritic plaques, neurofibrillary tangles are a prominent feature of AD. These tangles, which form inside neurons, result when the orderly arrangement of microtubules becomes disrupted (Fig. 22-1). The underlying cause is production of an abnormal form of tau, a protein that, in healthy neurons, forms cross-bridges between microtubules, and thereby keeps their configur-

ation stable. In patients with AD, tau twists into paired helical filaments. As a result, the orderly arrangement of microtubules transforms into neurofibrillary tangles.

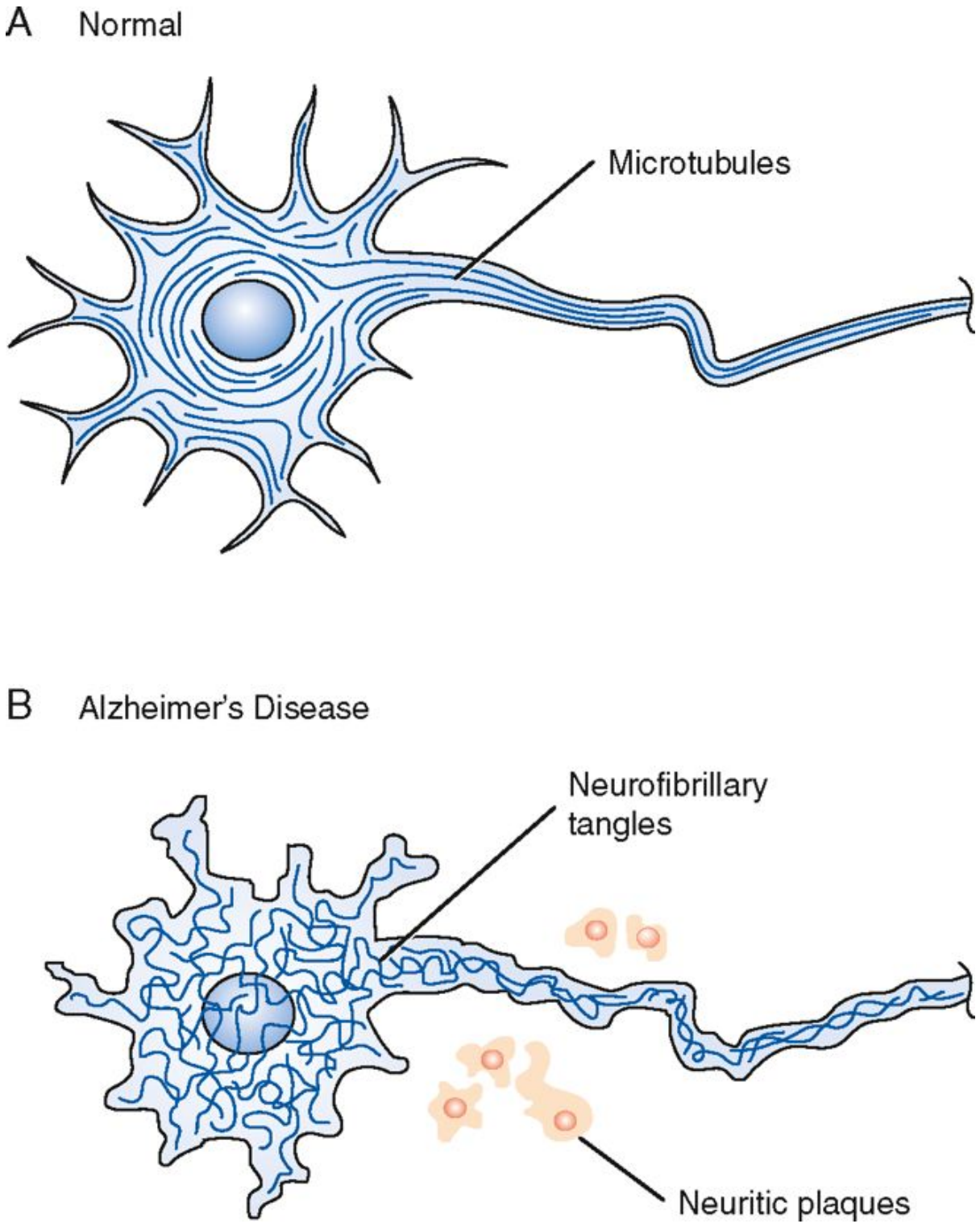

A Normal
Microtubules
B Alzheimer's Disease
Neurofibrillary tangles
Neuritic plaques

Figure 22-1 Histologic changes in Alzheimer's disease. Healthy neuron. B, Neuron affected by Alzheimer's disease, showing characteristic intracellular neurofibrillary tangles. Note also extracellular neuritic plaques.

Apolipoprotein E4

Apolipoprotein E (apoE), long known for its role in cholesterol transport, may also contribute to AD. Like some other proteins, apoE has more than one form. In fact, it has three forms, named apoE2, apoE3, and apoE4. (Don't ask what happened to apoE1.) Only one form—apoE4—is associated with AD. Genetic research has shown that individuals with one or two copies of the gene that codes for apoE4 are at increased risk for AD. In contrast, apoE2 seems protective.

What does apoE4 do? One possibility is that it promotes formation of neuritic plaques. ApoE4 binds quickly and tightly to beta-amyloid, causing this normally soluble substance to become insoluble, which could promote deposition of beta-amyloid in plaque.

It is important to note that apoE4 is neither necessary nor sufficient to cause AD. There are many people with AD who do not have the gene for apoE4. Conversely, in one study involving people who were 90 years old and homozygous for apoE4, 50% had not developed AD.

Endoplasmic Reticulum–Associated Binding Protein

The discovery of endoplasmic reticulum–associated binding protein (ERAB) adds another piece to the AD puzzle. Involvement of ERAB in AD is supported by several observations: ERAB is present in high concentration in the brains of patients with AD; ERAB is found in association with beta-amyloid, a compound with neurotoxic effects; high concentrations of ERAB enhance the neurotoxic effects of beta-amyloid; and the neurotoxic effects of beta-amyloid can be blocked by blocking the actions of ERAB.

Homocysteine

Elevated plasma levels of homocysteine are associated with an increased risk of AD. (Homocysteine is an amino acid formed from dietary methionine.) An elevation of 5 mmol/L appears to increase the risk by 40%; an elevation of 14

mmol/L appears to double the risk. How might homocysteine promote AD? One possibility is reduced blood flow secondary to blockage of cerebral blood vessels. (As discussed in Box 49-1, homocysteine is thought to accelerate atherosclerosis.) Another possibility is direct injury to nerve cells. Fortunately, even if homocysteine really does promote AD, the risk can be easily reduced: Levels of homocysteine can be lowered by eating foods rich in folic acid and vitamins B***6*** and B***12***, or by taking dietary supplements that contain these compounds.

RISK FACTORS, SYMPTOMS, AND DIAGNOSIS

Risk Factors

The major known risk factor for AD is advancing age. In 90% of patients, the age of onset is 65 years or older. After age 65, the risk of AD increases exponentially, doubling every 10 years. The only other known risk factor is a family history of AD. Being female *may* be a risk factor. However, the higher incidence of AD in women may occur simply because women live longer than men. Other possible risk factors include head injury, low educational level, production of apoE4, high levels of homocysteine, low levels of folic acid, and nicotine in cigarette smoke.

Symptoms

Alzheimer's is a disease in which symptoms progress relentlessly from mild to moderate to severe (Table 22-1). Symptoms typically begin after age 65, but may appear in people as young as 40. Early in the disease, patients begin to experience memory loss and confusion. They may be disoriented and get lost in familiar surroundings. Judgment becomes impaired and personality may change. As the disease progresses, patients have increasing difficulty with self-care. Between 70% and 90% eventually develop behavior problems (wandering, pacing, agitation, screaming). Symptoms may intensify in the evening, a phenomenon known as “sundowning.” In the final stages of AD, the patient is unable to recognize close family members or communicate in any way. All sense of identity is lost and the patient is completely dependent on others for survival. The time from onset of symptoms to death may be 20 years or longer, but is usually 4 to 8 years. Although there is no clearly effective therapy for

core symptoms, other symptoms (eg, incontinence, depression) can be treated. In addition, resources are available to help families cope with AD and prepare for future caregiving needs.

TABLE 22-1 Symptoms of Alzheimer's Disease

Mild Symptoms
Confusion and memory loss
Disorientation; getting lost in familiar surroundings
Problems with routine tasks
Changes in personality and judgment
Moderate Symptoms
Difficulty with activities of daily living, such as feeding and bathing
Anxiety, suspiciousness, agitation
Sleep disturbances
Wandering, pacing
Difficulty recognizing family and friends
Severe Symptoms
Loss of speech
Loss of appetite; weight loss
Loss of bladder and bowel control
Total dependence on caregiver

Diagnosis

Existing research criteria for diagnosis of AD—established in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and by the Alzheimer's Disease and Related Disorders Association (ADRDA)—are based on patient age and clinical evaluation (see Table 22-2). They do not involve any analytical tests. Hence, under these traditional criteria, a definitive diagnosis is possible only at autopsy, when the brain can be examined for characteristic neuritic plaques and neurofibrillary tangles. Prior to autopsy, diagnosis is done largely by exclusion. That is, when all other pos-

sible causes of dementia have been ruled out, a probable diagnosis of AD can be made.

TABLE 22-2 Diagnostic Criteria for Probable Alzheimer's Disease*

- Dementia is established by clinical examination, documented by mental status testing, and confirmed by neuropsychologic testing.
- Deficits are present in two or more cognitive areas (eg, memory, attention, language, personality, visuospatial functions).
- Cognitive deterioration is progressive.
- Cognitive deterioration occurs in the presence of a clear sensorium (ie, in the absence of delirium).
- Age of onset is between 40 and 90 years.
- The individual has no systemic or other illnesses that affect the brain and that can produce dementia.

* Established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and by the Alzheimer's Disease and Related Disorders Association (ADRDA).

In 2007, an international group of AD experts proposed new diagnostic criteria for AD that would add analytical technologies to the traditional measurements of cognitive and functional status. Specific tools would include structural magnetic resonance imaging (MRI), molecular neuroimaging with positron emission tomography (PET), and cerebrospinal fluid analyses. Using these tools, clinicians could evaluate patients for characteristic changes, including atrophy of brain areas as shown by MRI, altered patterns in a brain PET scan, and the presence of abnormal proteins in cerebrospinal fluid. Incorporating these advanced biochemical, structural, and metabolic measurements could significantly improve the early and accurate diagnosis of AD, and could thereby help both AD treatment and research.

DRUGS FOR COGNITIVE IMPAIRMENT

Ideally, the goal of treatment is to improve symptoms and reverse cognitive decline. Unfortunately, available drugs cannot do this. At best, drugs may retard loss of memory and cognition, and prolong independent function. However, for many patients, even these modest goals are elusive.

Five drugs are approved for treating Alzheimer's dementia, and none of them is very effective. Four of the drugs—donepezil, galantamine, rivastigmine, and tacrine—are cholinesterase inhibitors. The fifth drug—memantine—blocks neuronal receptors for NMDA (*N*-methyl-D-aspartate). In 2008, the American College of Physicians and the American Academy of Family Physicians reviewed published research on these drugs and released their findings in a clinical guideline: *Effectiveness of Cholinesterase Inhibitors and Memantine for Treating Dementia*. Their major conclusion? Treatment of dementia with these drugs can yield improvement that is statistically significant but clinically marginal. As one expert put it, benefits of these drugs are equivalent to losing half a pound after taking a weight-loss drug for 6 months: The loss may be statistically significant, but it lacks clinical significance. Given the modest benefits of these drugs, the guidelines do not recommend that all patients receive one, leaving the decision to the patient, family, and prescriber. The guidelines also conclude there is no proof that any of the five drugs is more effective than the others, and hence selection among them should be based on tolerability, ease of use, and cost. As for how long treatment should last, the guidelines note a lack of information on optimal treatment duration, as well as information that might guide treatment cessation. Properties of the cholinesterase inhibitors and memantine are summarized in Table 22-3.

Drug	Indication (AD Severity)	Dosing Schedule	Major Mode of Elimination	Comments
Cholinesterase Inhibitors*				
Donepezil [Aricept]	Mild to moderate	Once daily at bedtime	Metabolism by hepatic P450	
Rivastigmine [Exelon]	Mild to severe	*Oral:* Twice daily, with AM and PM meal *Patch:* Once daily	Metabolism by cholinesterase	Causes "irreversible" inhibition of cholinesterase. The patch is well tolerated because peak blood levels are low. The patch may be good for patients with difficulty swallowing.
Galantamine [Razadyne]	Mild to moderate	*Immediate-release:* Twice daily, with AM and PM meal *Extended-release:* Once daily	Metabolism by hepatic P450 and excretion by the kidneys	Reduce dosage in patients with *moderate* hepatic or renal impairment, and discontinue in patients with *severe* hepatic or renal impairment.
NMDA Antagonist				
Memantine [Namenda]	Moderate to severe	See text	Excretion by the kidneys	Reduce dosage in patients with

TABLE 22-3 Drugs for Cognitive Impairment

* Only three cholinesterase inhibitors are listed. A fourth agent—tacrine [Cognex]—is available, but rarely used owing to hepatotoxicity and inconvenient dosing.

Cholinesterase Inhibitors

The cholinesterase inhibitors were the first drugs approved by the Food and Drug Administration (FDA) to treat AD. In clinical trials, these drugs produced modest improvements in cognition, behavior, and function, and slightly delayed disease progression. Four cholinesterase inhibitors are currently available. However, only three are recommended: donepezil, galantamine, and rivastigmine. The fourth—tacrine—carries a significant risk of liver damage, and should be avoided.

Group Properties

Mechanism of Action.

Cholinesterase inhibitors prevent the breakdown of ACh by acetylcholinesterase (AChE), and thereby increase the availability of ACh at cholinergic synapses. In patients with AD, the result is enhanced transmission by central cholinergic neurons that have not yet been destroyed. Cholinesterase inhibitors do not cure AD, and they do not stop disease progression—although they may slow progression by a few months.

Therapeutic Effect.

All cholinesterase inhibitors are approved for patients with *mild to moderate* symptoms, and one agent—donepezil—is also approved for those with *severe* symptoms. Among patients with mild to moderate symptoms, only 25% to 30% respond. Among those who do respond, improvements are seen in quality of life and cognitive functions (eg, memory, thought, reasoning). However, these improvements are modest and short lasting. There is no convincing evidence of marked improvement or significant delay of disease progression. Nonetheless, although improvements are neither universal, dramatic, nor long lasting, and although side effects are common (see below), the benefits may still be worth the risks for some patients.

Adverse Effects.

By elevating ACh in the periphery, all cholinesterase inhibitors can cause typical cholinergic side effects. Gastrointestinal effects—*nausea, vomiting, dyspepsia, diarrhea*—occur often. *Dizziness* and *headache* are also common. Elevation of ACh at synapses in the lungs can cause *bronchoconstriction*. Accordingly, cholinesterase inhibitors should be used with caution in patients with asthma or chronic obstructive pulmonary disease (COPD). One drug—tacrine—carries a high risk of *liver injury,* and is used only rarely.

Drug Interactions.

Drugs that block cholinergic receptors (eg, first-generation antihistamines, tricyclic antidepressants, conventional antipsychotics) can reduce therapeutic effects, and should be avoided.

Dosage and Duration of Treatment.

Dosage should be carefully titrated, and treatment should continue as long as clinically indicated. The highest doses produce the greatest benefits—but also the most intense side effects. Accordingly, dosage should be low initially and then gradually increased to the highest tolerable amount. Treatment can continue indefinitely, or until side effects become intolerable or benefits are lost.

Properties of Individual Cholinesterase Inhibitors

Of the four cholinesterase inhibitors with FDA approval, only three—donepezil, galantamine, and rivastigmine—are widely used. These three drugs have not been directly compared with one another for efficacy. However, they appear to offer equivalent benefits. Accordingly, selection among them is based on side effects, ease of dosing, and cost.

Tacrine.

Tacrine [Cognex], introduced in 1993, was the first cholinesterase inhibitor approved for AD. The drug causes reversible inhibition of AChE. Benefits derive from increasing ACh concentrations at cholinergic synapses in the brain. Tacrine has two major drawbacks: (1) it can cause liver injury and (2) it must be administered 4 times a day (owing to a short half-life). Because of these drawbacks, tacrine is rarely used.

Tacrine is administered orally, and food decreases absorption. Bioavailability is low because of substantial first-pass metabolism. Blood levels peak in 2 hours, and decline with an elimination half-life of 3 hours. Tacrine crosses the blood-brain barrier with ease, and is retained in the central nervous system (CNS).

Tacrine carries a high risk of serious liver injury. Damage is monitored by assessing serum for elevations in alanine aminotransferase (ALT), an enzyme released from liver cells when they are injured. In 50% of patients taking tacrine, ALT levels are greater than 3 times the amount considered normal. Depending on the degree of ALT elevation and other indices of liver damage (eg, jaundice, elevation of serum bilirubin), tacrine must be given in reduced dosage or discontinued. In most patients, liver damage reverses after drug withdrawal. The recommended schedule for ALT measurement is every 2 weeks during weeks 4 through 16 of treatment, and every 3 months thereafter. If ALT levels exceed twice normal, more frequent monitoring is required. If ALT levels exceed 5 times normal, tacrine should be discontinued. Treatment can resume when ALT levels return to normal. If the patient develops clinical jaundice (defined here as bilirubin levels above 3 mg/mL), or if there are signs and symptoms of hypersensitivity (eg, rash, fever) in association with elevated ALT, tacrine should be immediately and permanently discontinued.

Tacrine is supplied in capsules (10, 20, 30, and 40 mg) for oral dosing. The drug must be taken 4 times a day, preferably between meals to enhance absorption. However, tacrine can be taken with meals if stomach upset occurs. Dosing is begun at 10 mg 4 times a day, and then gradually increased to a maximum of 40 mg 4 times a day, as tolerated. When treatment is resumed after temporary discontinuation, the original titration sequence should be repeated.

Donepezil.

Donepezil [Aricept, Aricept ODT], approved in 1996, was the second cholinesterase inhibitor for AD. Like tacrine, donepezil causes reversible inhibition of AChE—but is more selective for the form of AChE found in the brain than that found in the periphery. Therapeutic responses appear equal to those of tacrine. Like tacrine, donepezil does not affect the underlying disease process.

Donepezil is well absorbed following oral administration and undergoes metabolism by hepatic cytochrome P450 enzymes. Elimination is mainly in the urine and partly in the bile. Donepezil has a prolonged plasma half-life (about 60 hours), and hence can be administered just once a day.

Although donepezil is somewhat selective for brain cholinesterase, it can still cause peripheral cholinergic effects; nausea (11%) and diarrhea (10%) are most common. Bradycardia may also develop, especially in patients with predisposing heart disease. Unlike tacrine, donepezil is not hepatotoxic.

Donepezil is available in three oral formulations: standard tablets (5 and 10 mg), orally disintegrating tablets (5 and 10 mg), and a solution (1 mg/mL). With all three, dosing is done late in the evening, with or without food. The dosage is 5 mg once daily initially, and can be increased to 10 mg once daily.

Rivastigmine.

Rivastigmine [Exelon], released in 2000, is approved for AD and dementia of Parkinson's disease. Unlike tacrine and donepezil, which cause *reversible* inhibition of AChE, rivastigmine causes *irreversible* inhibition. As with tacrine and donepezil, benefits in AD are modest.

Rivastigmine is available in tablets and solution for oral dosing and a "patch" for transdermal dosing. Oral rivastigmine is well absorbed from the GI tract, especially in the presence of food. With the patch, blood levels are lower and more steady than with oral therapy. In contrast to other cholinesterase inhibitors, rivastigmine is converted to inactive metabolites by AChE, and not by P450 enzymes in the liver. The half-life is short—about 1.5 hours.

Like other cholinesterase inhibitors, rivastigmine can cause peripheral cholinergic side effects. With oral dosing, the most common cholinergic effects are nausea (47%), vomiting (31%), diarrhea (19%), abdominal pain (13%), and anorexia (17%). Significant weight loss (7% of initial weight) occurs in 18% to 26% of patients. By enhancing cholinergic transmission, rivastigmine can intensify symptoms in patients with peptic ulcer disease, bradycardia, sick sinus syndrome, urinary obstruction, and lung disease; caution is advised. Because blood levels are lower with transdermal dosing, the intensity of side effects is lower as well. In contrast to tacrine, rivastigmine is not hepatotoxic. Rivastig-

mine has no significant drug interactions—probably because it does not interact with hepatic drug-metabolizing enzymes.

Rivastigmine for *oral dosing* is available in tablets (1.5, 3, 4.5, and 6 mg) and solution (2 mg/mL). The initial dosage is 1.5 mg twice daily. The maximum dosage is 6 mg twice daily. All doses should be administered with food to enhance absorption and to reduce GI effects.

Rivastigmine patches for *transdermal dosing* are available in two strengths, delivering 4.6 mg/24 hr and 9.5 mg/24 hr. A single patch is applied once daily to the chest, upper arm, upper back, or lower back. The site should be changed daily, and not repeated for at least 14 days. Before a new patch is applied, the old one must be removed. If not, toxicity can result. (About 50% of the starting dose remains in the patch after 24 hours.) Bathing should not affect treatment. Patients should begin treatment with the 4.6-mg patch and, after 4 weeks, change to the 9.5-mg patch for maintenance. For patients transitioning from oral therapy, the first patch should be applied on the day after the last oral dose. These patients should start with the 4.6-mg patch (if their oral dose was below 6 mg a day) or the 9.5 mg-patch (if their oral dose was 6 to 12 mg/day).

Galantamine.

Galantamine [Razadyne, formerly named Reminyl], approved in 2001, is a reversible cholinesterase inhibitor indicated for mild to moderate AD. The drug is prepared by extraction from daffodil bulbs. In clinical trials, galantamine improved cognitive function, behavioral symptoms, quality of life, and ability to perform activities of daily living. However, as with other cholinesterase inhibitors, benefits were modest and short lasting.

Galantamine is rapidly and completely absorbed following oral administration. Protein binding in plasma is low. Elimination is by hepatic metabolism and renal excretion. Moderate to severe hepatic or renal impairment delays elimination and increases blood levels. In healthy adults, the half-life is about 7 hours.

The most common adverse effects are nausea (13% to 17%), vomiting (6% to 10%), diarrhea (6% to 12%), anorexia (7% to 9%), and weight loss (5%). Nausea and other GI complaints are greater than with donepezil, but less than with

oral rivastigmine. Like other cholinesterase inhibitors, galantamine can cause bronchoconstriction, and hence must be used with caution in patients with asthma or COPD. Unlike tacrine, galantamine is not hepatotoxic. Drugs that block cholinergic receptors (eg, first-generation antihistamines, tricyclic antidepressants, conventional antipsychotics) can reduce therapeutic effects, and hence should be avoided.

Galantamine is available in immediate-release (IR) tablets (4, 8, and 12 mg), extended-release (ER) capsules (8, 16, and 24 mg), and solution (4 mg/mL). With all formulations, dosage should be gradually titrated to minimize GI complaints. For the solution and IR tablets, dosing is begun at 4 mg twice daily (taken with the morning and evening meals); after a minimum of 4 weeks, dosage may be increased to 8 mg twice daily; and 4 weeks later, dosage may be increased again to 12 mg twice daily. For the ER capsules, dosing is begun at 8 mg once daily; after a minimum of 4 weeks, dosage may be increased to 16 mg once daily; and 4 weeks later, dosage may be increased to 24 mg once daily. With all formulations, dosage must be adjusted in patients with hepatic or renal impairment as follows: For those with moderate hepatic or renal impairment, the maximum dosage is 16 mg/day; for those with severe hepatic or renal impairment, galantamine should be avoided.

Memantine

Memantine [Namenda] is the first representative of a new class of drugs for AD, the NMDA (*N*-methyl-D-aspartate) receptor antagonists. Unlike the cholinesterase inhibitors, which are indicated for *mild to moderate* AD, memantine is indicated for *moderate to severe* AD. We don't yet know if memantine is more effective than the cholinesterase inhibitors, but we do know it's better tolerated. Although memantine helps treat symptoms of AD, there is no evidence that it modifies the underlying disease process. Memantine was approved by the FDA in 2003, but has been used in Germany since 1982.

Therapeutic Effects.

In patients with moderate to severe AD, memantine appears to confer modest benefits. For many patients, the drug can slow the decline in function, and, in some cases, it may actually cause symptoms to improve. In one study, pa-

tients taking memantine for 28 weeks scored higher on tests of cognitive function and day-to-day function than did those taking placebo, suggesting that memantine slowed functional decline. In another study, treatment with memantine plus donepezil (a cholinesterase inhibitor) was compared with donepezil alone. The result? After 24 weeks, those taking the combination showed less decline in cognitive and day-to-day function than those taking donepezil alone, suggesting that either (1) the two agents confer independent benefits or (2) they act synergistically to enhance each other's effects.

Mechanism of Action.

Memantine modulates the effects of glutamate (the major excitatory transmitter in the CNS) at NMDA receptors, which are believed to play a critical role in learning and memory. The NMDA receptor—a transmembrane protein with a central channel—regulates calcium entry into neurons. Binding of glutamate to the receptor promotes calcium influx.

Under healthy conditions, an action potential releases a burst of glutamate into the synaptic space. Glutamate then binds with the NMDA receptor, displaces magnesium from the receptor channel, and thereby permits calcium entry (Fig. 22-2A). Glutamate then quickly dissociates from the receptor, permitting magnesium to reblock the channel, and thereby prevents further calcium influx. The brief period of calcium entry constitutes a “signal” in the learning and memory process.

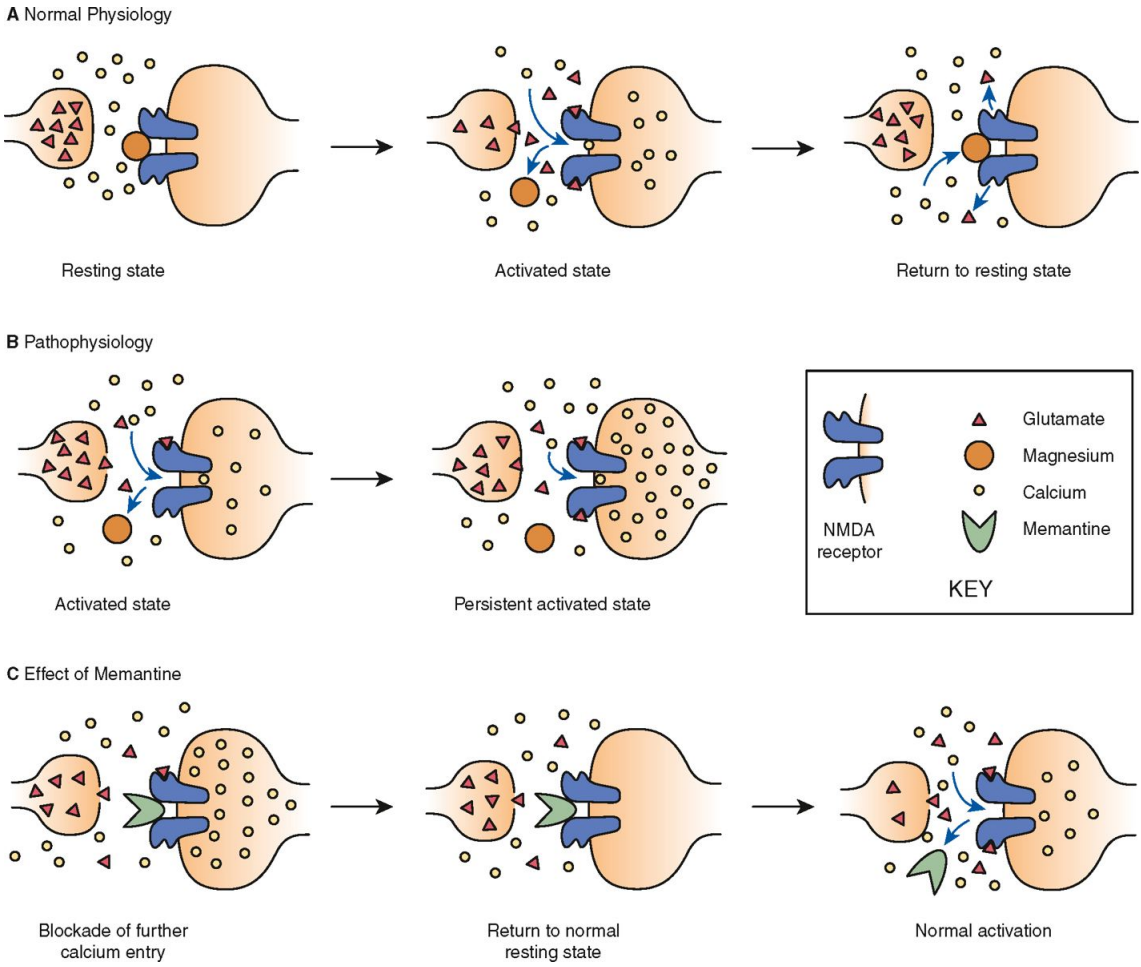


Figure 22-2 Memantine mechanism of action. A, Normal physiology. In the resting postsynaptic neuron, magnesium occupies the NMDA receptor channel, blocking calcium entry. Binding of glutamate to the receptor displaces magnesium, allowing calcium to enter. When glutamate dissociates from the receptor, magnesium returns to the channel and blocks further calcium inflow. The brief period of calcium entry constitutes a "signal" in the learning and memory process. B, Pathophysiology. Slow but steady leakage of glutamate from the presynaptic neuron keeps the NMDA receptor in a constantly activated state, thereby allowing excessive influx of calcium, which can impair memory and learning, and can eventually cause neuronal death. C, Effect

of memantine. Memantine blocks calcium entry when extracellular glutamate is low, and thereby stops further calcium entry, which allows intracellular calcium levels to normalize. When a burst of glutamate is released in response to an action potential, the resulting high level of glutamate is able to displace memantine, causing a brief period of calcium entry. Not shown: When glutamate diffuses away, memantine reblocks the channel, and thereby stops further calcium entry, despite continuing low levels of glutamate in the synapse.

Under pathologic conditions, there is slow but steady leakage of glutamate from the presynaptic neuron, and from surrounding glia too. As a result, the channel in the NMDA receptor is kept open, thereby allowing excessive influx of calcium (Fig. 22-2*B*). High intracellular calcium has two effects: (1) impaired learning and memory (because the "noise" created by excessive calcium overpowers the "signal" created when calcium enters in response to glutamate released by a nerve impulse); and (2) neurodegeneration (because too much intracellular calcium is toxic).

How does memantine help? It blocks calcium influx when extracellular glutamate is low, but permits calcium influx when extracellular glutamate is high. As shown in Figure 22-2*C*, when the glutamate level is low, memantine is able to occupy the NMDA receptor channel, and thereby block the steady entry of calcium. As a result, the level of intracellular calcium is able to normalize. Then, when a burst of glutamate is released in response to an action potential, the resulting high level of extracellular glutamate is able to displace memantine, causing a brief period of calcium entry. Because intracellular calcium is now low, normal signaling can occur. When glutamate diffuses away from the receptor, memantine reblocks the channel, and thereby stops further calcium entry, despite continuing low levels of glutamate in the synapse.

Pharmacokinetics.

Memantine is well absorbed following oral dosing, both in the presence and absence of food. Plasma levels peak in 3 to 7 hours. The drug undergoes little metabolism, and is excreted largely unchanged in the urine. The half-life is long—60 to 80 hours. Clearance is reduced in patients with renal impairment.

Adverse Effects.

Memantine is well tolerated. The most common side effects are *dizziness* (7%), *headache* (6%), *confusion* (6%), and *constipation* (5%). In clinical trials, the incidence of these effects was about the same as in patients taking placebo.

Drug Interactions.

In theory, combining memantine with another NMDA antagonist, such as amantadine [Symmetrel] or ketamine [Ketalar], could have an undesirable additive effect. Accordingly, such combinations should be used with caution.

Sodium bicarbonate and other drugs that alkalinize the urine can greatly decrease the renal excretion of memantine. Accumulation of the drug to toxic levels might result.

Dosage and Administration.

Memantine [Namenda] is available in tablets (5 and 10 mg) for oral use. The drug may be taken with or without food. Dosage is titrated as follows:

- 5 mg/day (5 mg once a day), for 1 week or more
- 10 mg/day (5 mg twice a day), for 1 week or more
- 15 mg/day (5 mg and 10 mg in separate doses), for 1 week or more
- 20 mg/day (10 mg twice a day), for maintenance

In patients with moderate renal impairment, a dosage reduction may be needed. In patients with severe renal impairment, memantine should be avoided.

OTHER DRUGS FOR ALZHEIMER'S DISEASE

Drugs for Neuropsychiatric Symptoms

Neuropsychiatric symptoms (eg, agitation, aggression, delusions, hallucinations) occur in more than 80% of people with AD. Although multiple drug classes—antipsychotics, cholinesterase inhibitors, mood stabilizers, antidepressants, anxiolytics, NMDA receptor antagonists—have been tried as treatment, very few are effective, and even then benefits are limited. There is convincing evidence that neuropsychiatric symptoms can be reduced with

two atypical antipsychotics: risperidone [Risperdal] and olanzapine [Zyprexa]. However, benefits are modest, and these drugs slightly increase mortality, mainly from cardiovascular and infectious causes. Cholinesterase inhibitors may also offer modest help. There is little or no evidence to show a benefit from conventional antipsychotics (eg, haloperidol, chlorpromazine), mood stabilizers (valproate, carbamazepine, lithium), or memantine. Although selective serotonin reuptake inhibitors (eg, fluoxetine [Prozac]) can help relieve depression, they do little to relieve neuropsychiatric symptoms.

Nonsteroidal Anti-inflammatory Drugs

Although nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, and aspirin, are no good for treating established AD, there is mounting evidence that, with long-term use, they may help *prevent* AD—or at least *delay* AD onset. The most convincing study to date, published in 2001, followed nearly 7000 patients for 7 years. All were over the age of 54 and all were taking prescription NSAIDs (eg, ibuprofen, naproxen)—but not aspirin, which is available without prescription. The results? Taking NSAIDs for 2 years or more—regardless of dosage—decreased the risk of developing AD by 80%. Taking NSAIDs for less than 2 years conferred little or no protection. Furthermore, NSAIDs were of no help if they were taken after symptoms of AD developed, or if they were taken during the 2-year interval prior to symptom onset. This suggests that there is a critical period—which ends 2 years before symptoms begin—during which NSAIDs can be of benefit. Accordingly, for NSAIDs to help, dosing must begin at least 4 years before symptoms would have started. Because protection is conferred at low doses as well as high doses, and because low doses are not anti-inflammatory, it would seem that protection against AD is not due to suppression of inflammation. Instead, there is evidence that NSAIDs may actually help by inhibiting production of Ab***42***, a specific form of beta-amyloid. Does *aspirin* protect against AD? Yes: Two recent studies suggest that long-term, low-dose aspirin protects against AD, although the degree of protection is not as great as with nonaspirin NSAIDs.

Ginkgo Biloba

In a 1997 study, an extract made from the leaves of the maidenhair tree (*Ginkgo biloba)* was able to stabilize or improve cognitive performance and social beha-

vior for 6 to 12 months in patients with uncomplicated AD. These benefits are about equal to those seen with tacrine. Patients in the study were given 120 mg/day of a standardized *Gingko biloba* extract containing 24% ginkgo flavonoids and 6% terpenoids, both of which have biologic activity. An equivalent extract—marketed as Ginkgold—is available commercially. *Ginkgo biloba* extracts have antioxidant, antiplatelet, and anti-inflammatory actions. The role of these actions in AD is unknown. Significant adverse effects with *Ginkgo biloba* are uncommon. However, because the extract can inhibit platelet aggregation, it may pose a risk of bleeding. Accordingly, combined use with antiplatelet drugs (eg, aspirin) or anticoagulants (eg, warfarin, heparin) should be done with caution. *Ginkgo biloba* is discussed further in Chapter 107.

Vitamin E and Selegiline

Treatment guidelines from the American Academy of Neurology, issued in 2001, recommend vitamin E and selegiline as optional treatments for AD. This recommendation is based on a 1997 paper that reported that vitamin E (1000 international units [IU] twice daily) and selegiline (5 mg twice daily) can slow disease progression in patients with moderately severe AD. Both drugs have antioxidant properties. The authors hypothesized that benefits derived from decreasing neuronal injury that can be caused by oxidative processes.

Unfortunately, the study had significant problems, and hence the authors' conclusions may not be valid. Most importantly, neither drug was able to slow cognitive decline—the hallmark of AD. Rather, the drugs slightly delayed the time to (1) institutionalization, (2) death, (3) progression to severe dementia, or (4) loss of the ability to perform certain activities of daily living (eg, eating, using the toilet). Since cognitive decline is a core characteristic of AD, and since the drugs did not retard cognitive decline, it is questionable that they altered the natural course of the disease. The authors' conclusions are further undermined by the observation that giving the drugs together did not yield additive benefits. In fact, benefits were somewhat lower when the drugs were combined.

A more recent study, published in 2005, showed vitamin E to be ineffective. In patients with mild cognitive impairment, treatment with high-dose vitamin E (2000 IU daily for 3 years) failed to delay progression to AD. The results of this

study, coupled with the questionable results of the 1997 study, strongly suggest that early intervention with vitamin E has no benefit.

Estrogen

Data from the Women's Health Initiative Memory Study show clearly that estrogen does *not* reduce the risk of dementia in older women. In fact, the risk is actually increased, albeit very slightly (23 extra cases per year for every 10,000 women taking estrogen plus progesterone). This new evidence is much stronger than data from earlier observational studies, which suggested that estrogen might delay or prevent dementia.

KEY POINTS

- Alzheimer's disease (AD) is a relentless illness characterized by progressive memory loss, impaired thinking, neuropsychiatric symptoms, and inability to perform routine tasks of daily living.
- The histopathology of AD is characterized by neuritic plaques, neurofibrillary tangles, and degeneration of cholinergic neurons in the hippocampus and cerebral cortex.
- Neuritic plaques are spherical, extracellular bodies that consist of a beta-amyloid core surrounded by remnants of axons and dendrites.
- In patients with AD, beta-amyloid is present in high levels and may contribute to neuronal injury.
- Neurofibrillary tangles result from production of a faulty form of tau, a protein that in healthy neurons serves to maintain the orderly arrangement of neurotubules.
- The major known risk factor for AD is advancing age.
- Alzheimer's dementia can be treated with cholinesterase inhibitors or memantine. Although these drugs produced statistically significant improvements in clinical trials, benefits in patients are marginal.

- Cholinesterase inhibitors (eg, donepezil) increase the availability of acetylcholine at cholinergic synapses, and thereby enhance transmission by cholinergic neurons that have not yet been destroyed by AD.
- Cholinesterase inhibitors produce modest improvements in cognition, behavior, and function in 30% to 60% of AD patients.
- Cholinesterase inhibitors do not cure AD, and they do not stop disease progression—although they may delay it for a short time.
- The efficacy of all cholinesterase inhibitors appears equal.
- By elevating ACh in the periphery, all cholinesterase inhibitors can cause typical cholinergic effects. Gastrointestinal effects—nausea, vomiting, dyspepsia, diarrhea—are most common.
- Drugs that block cholinergic receptors (eg, first-generation antihistamines, tricyclic antidepressants, conventional antipsychotics) can reduce responses to cholinesterase inhibitors.
- Memantine is the first representative of a new class of drugs for AD, the NMDA receptor antagonists. Benefits derive from modulating the effects of glutamate at NMDA receptors.
- Unlike cholinesterase inhibitors, which are approved for mild to moderate AD, memantine is approved for moderate to severe AD.
- Like the cholinesterase inhibitors, memantine has only modest beneficial effects.
- Memantine appears devoid of significant adverse effects.
- NSAIDs are no good for treating established AD, but, with long-term use, may protect against development of AD.

23 Drugs for Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory, autoimmune disorder that damages the myelin sheath of neurons in the central nervous system (CNS), causing a wide variety of sensory and motor deficits. Initially, most patients experience periods of acute clinical exacerbations (relapses) alternating with periods of complete or partial recovery (remissions). Over time, symptoms usually grow progressively worse—although the course of the disease is unpredictable and highly variable. Among young adults, MS causes more disability than any other neurologic disease. Nonetheless, most patients manage to lead fairly normal lives, and life expectancy is only slightly reduced.

Drug therapy of MS changed dramatically in 1993, the year the first disease-modifying agent was approved. Prior to this time, treatment was purely symptomatic. We had no drugs that could alter the disease process. By using disease-modifying drugs, we can now slow the progression of MS, decrease the frequency and intensity of relapses, and delay permanent neurologic loss. As a result, we can significantly improve prognosis, especially if treatment is started early.

OVERVIEW OF MS AND ITS TREATMENT

Pathophysiology

What's the Primary Pathology of MS?

The pathologic hallmark of MS is the presence of multifocal regions of inflammation and myelin destruction in the CNS. Because of demyelination, axonal conduction is slowed or blocked, giving rise to a host of neurologic signs and symptoms. As inflammation subsides, damaged tissue is replaced by astrocyte-derived filaments, forming scars known as *scleroses,* hence the disease name. It is important to note that, in addition to stripping off myelin, inflammation may injure the underlying axon, and may also damage oligodendrocytes, the cells that make CNS myelin. Axon injury can also occur in the *absence* of inflammation, and can be seen early in the course of the disease.

How Does Inflammation Occur?

The mechanism appears to be autoimmune: Cells of the immune system mistakenly identify components of myelin as being foreign, and hence mount an attack against them. For the attack to occur, circulating lymphocytes (T cells) and monocytes (macrophages) must adhere to the endothelium of CNS blood vessels, migrate across the vessel wall, and then initiate the inflammatory process. The end result is an inflammatory cascade that destroys myelin and may also injure the axonal membrane and nearby oligodendrocytes.

What Initiates the Autoimmune Process?

No one knows. The most likely candidates are genetics, environmental factors, and microbial pathogens. We suspect a *genetic link* for two reasons. First, the risk of MS for first-degree relatives of someone with the disease is 10 to 20 times higher than the risk for people in the general population. Second, the risk of MS differs for members of different races. For example, the incidence is highest among Caucasians (especially those of northern European descent), much lower among Asians, and nearly zero among Inuits (the indigenous people of the Arctic). We suspect *environmental factors* because the risk is not the same in all places: In the United States, MS is more common in northern states than in southern states; around the globe, MS is most common in countries that have a moderately cool climate, whether in the northern or southern hemisphere; and, as we move from the equator toward the poles, the incidence of MS increases. *Microbial pathogens* suspected of initiating autoimmunity include Epstein-Barr virus, human herpesvirus 6, and *Chlamydia pneumoniae*. The bottom line? *Multiple sclerosis appears to be a disease that develops in genetically vulnerable people following exposure to an environmental or microbial factor that initiates autoimmune activity*.

What Happens When an Acute Attack Is Over?

When inflammation subsides, some degree of recovery occurs, at least in the early stages of the disease. Three mechanisms are involved: (1) partial remyelination, (2) functional axonal compensation (axons redistribute their sodium channels from the nodes of Ranvier to the entire region of demyelination), and (3) development of alternative neuronal circuits that bypass the damaged region. Unfortunately, with recurrent episodes of demyelination, recov-

ery becomes less and less complete. Possible reasons include mounting astrocytic scarring, irreversible axonal injury, and the death of neurons and oligodendrocytes.

Does MS Injure the Myelin Sheath of Peripheral Neurons?

No. Myelin in the periphery is made by Schwann cells, whereas myelin in the CNS is made by oligodendrocytes. Although myelin produced by these two cell types is very similar, it is not identical. Because peripheral myelin differs somewhat from CNS myelin, the immune system does not identify peripheral myelin as foreign, and hence this myelin is spared.

Signs and Symptoms

People with MS can experience a wide variety of signs and symptoms. Depending on where CNS demyelination occurs, a patient may experience paresthesias (numbness, tingling, pins and needles), muscle or motor problems (weakness, clumsiness, ataxia, spasms, spasticity, tremors, cramps), visual impairment (blurred vision, double vision, blindness), bladder and bowel symptoms (incontinence, urinary urgency, urinary hesitancy, constipation), sexual dysfunction, disabling fatigue, emotional lability, depression, cognitive impairment, slurred speech, dysphagia, dizziness, vertigo, neuropathic pain, and more. The intensity of these symptoms is determined by the size of the region of demyelination. To quantify the impact of MS symptoms, most clinicians employ the Kurtzke Expanded Disability Status Scale (EDSS), an instrument that measures the impact of MS on nine different functional systems (eg, visual, sensory, cerebellar). The results are tabulated and reported on a scale from 0 to 10, with 0 representing no disability and 10 representing death. An EDSS of 4 or greater indicates difficulties with ambulation. Symptoms of MS are discussed further under *Drugs Used to Manage MS Symptoms*.

MS Subtypes

There are four subtypes of MS—relapsing-remitting, secondary progressive, primary progressive, and progressive-relapsing—defined by the clinical course the disease follows. Symptom patterns that characterize the MS subtypes are depicted in Figure 23-1.

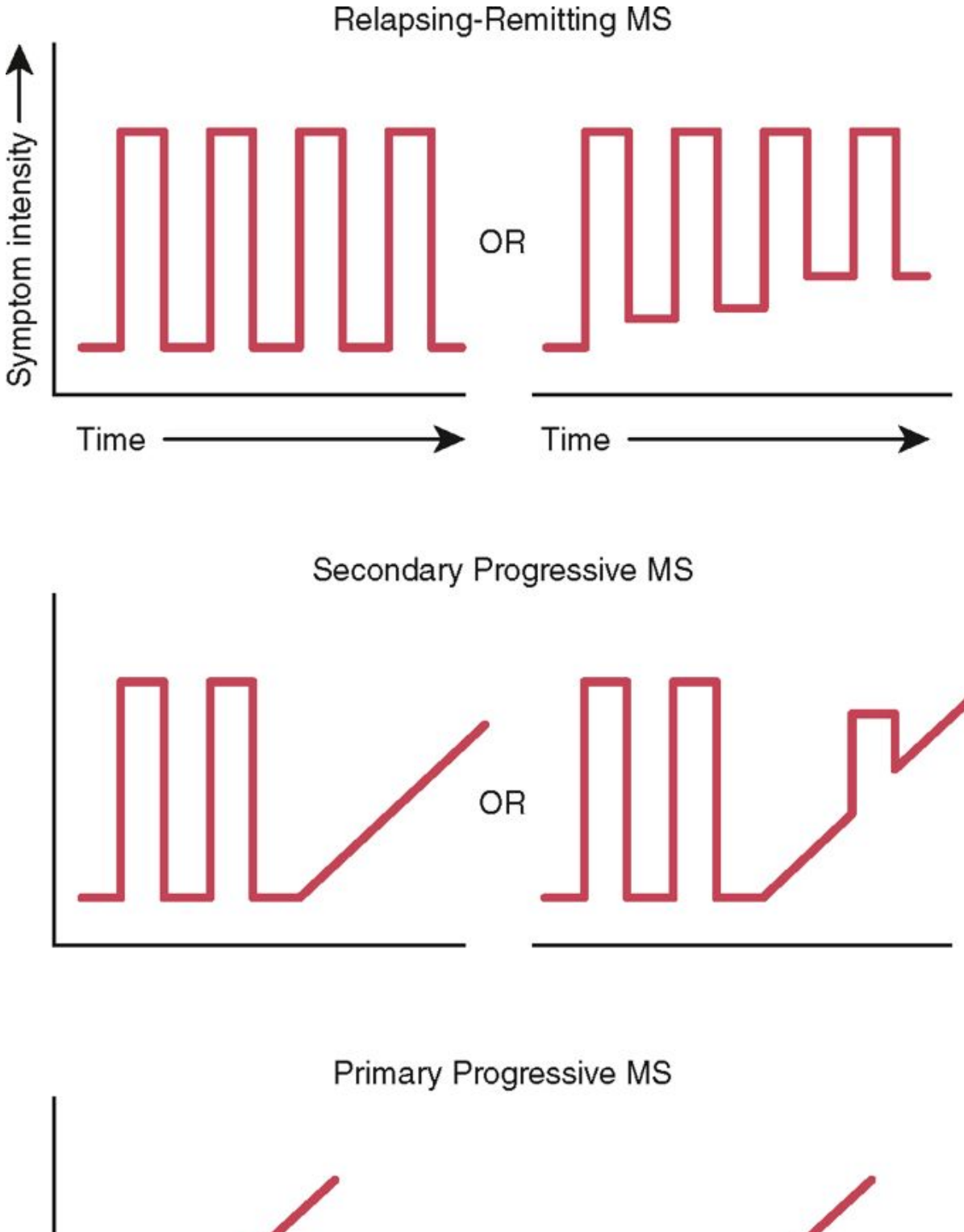

Relapsing-Remitting MS
Symptom intensity
OR
Time
Time
Secondary Progressive MS
OR
Primary Progressive MS

Figure 23-1 Symptom patterns that define the four subtypes of MS.

Relapsing-Remitting MS.

This subtype is characterized by recurrent, clearly defined episodes of neurologic dysfunction (relapses) separated by periods of partial or full recovery (remissions). Between 85% and 90% of patients have this form initially. Symptoms develop over several days, and then typically resolve within weeks. The average patient has two relapses every 3 years. Specific signs and symptoms during an attack depend on the size and location of CNS lesions, and hence vary from one attack to the next, and from one patient to another. The disease usually begins in the second or third decade of life, and affects twice as many women as men.

Secondary Progressive MS.

This subtype occurs when a patient with relapsing-remitting MS develops steadily worsening dysfunction—with or without occasional plateaus, acute exacerbations, or minor remissions. Within 10 to 20 years of symptom onset, about 50% of patients with relapsing-remitting MS develop secondary progressive MS.

Primary Progressive MS.

In this subtype, symptoms grow progressively more intense from the outset, although some patients may experience occasional plateaus or even temporary improvement. Clear remissions, however, do not occur. Only 10% of patients have this form of MS.

Progressive-Relapsing MS.

This subtype, which is rare, looks like primary progressive MS, but with acute exacerbations superimposed on the steady intensification of symptoms.

Diagnosis

Diagnosis of MS is based on clinical presentation supplemented with laboratory data. As a rule, we cannot diagnose MS on the basis of symptoms or signs or laboratory tests alone—for most patients, all three kinds of information are needed. In addition, because the signs, symptoms, and test results that suggest

MS can also suggest other disorders, a positive diagnosis cannot be made until all other possibilities have been ruled out. Diagnosis of MS is confounded by interpatient variability in symptoms and the course the disease follows.

In 1965, the following diagnostic criteria were introduced:

- There must be objective evidence of *two or more* clinical attacks lasting at least 24 hours each.
- The attacks must be *separated in time* by at least 1 month.
- The attacks must be *separated in space* (that is, the CNS damage underlying clinical symptoms must occur at different sites).
- There must be no better explanation for the attacks.

Since these criteria were introduced, additional diagnostic tools have become available. Important among these are magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) tests, and measurement of the visual evoked potential (VEP). All three tests can help confirm a suspected diagnosis of MS, but neither test, by itself, can provide definitive proof of the disease. Properties of these tests are as follows:

- MRI is the most sensitive way to image the brain. Sensitivity can be made even greater with gadolinium, an IV contrast agent. MRI is especially good for detecting areas of demyelination. However, it is important to note that, in some patients who have clinically definite MS, an MRI scan may fail to detect any lesions. Hence, a negative scan does not necessarily rule out MS. Conversely, because other disorders can produce a positive scan, a positive scan, by itself, does not prove the presence of MS, although it *can* help *confirm* a suspected case.
- Tests of CSF are used to assess immune activity within the CNS. Two tests are employed: measurement of immunoglobulin G (IgG) levels and measurement of oligoclonal IgG bands (OCBs), which indicate intrathecal production of antibodies. More than 90% of patients with MS have OCBs. However, as with MRI scans, other disorders can also produce positive test results—and negative results may be seen in some patients who *do* have MS. Accordingly, CSF analysis, by itself, can neither confirm nor rule out MS.

- The VEP test measures how quickly the brain responds to a visual stimulus, and hence indirectly measures conduction velocity in the optic nerve. In patients with MS, the VEP is delayed, indicating conduction velocity is slowed (owing to demyelination of the optic nerve). However, as with MRI scans and CSF tests, the VEP test is not specific for MS: Other disorders can produce positive results, and some patients with MS may get negative results.

Diagnostic criteria for MS were updated by the McDonald committee in 2001 and revised again in 2005 (Table 23-1). The latest criteria are still founded on the patient's clinical presentation, but also incorporate information from MRI scans, CSF tests, and VEP determinations. These criteria were designed to permit the earliest possible diagnosis of MS, and hence permit the earliest possible initiation of disease-modifying therapy.

Clinical Presentation	Additional Data Needed for a Diagnosis of MS
Two or more attacks *and* objective clinical evidence of 2 or more lesions	None
Two or more attacks *and* objective clinical evidence of 1 lesion	Proof of dissemination in space shown by *either* • MRI data indicating dissemination in space • Positive CSF* plus 2 or more MRI lesions consistent with MS • Another clinical attack implicating a different site
One attack *and* objective clinical evidence of 2 or more lesions	Proof of dissemination in time shown by *either* MRI *or* a second clinical attack
One attack *and* objective clinical evidence of 1 lesion (clinically isolated syndrome)	Proof of dissemination in space shown by *either* MRI *or* positive CSF* plus 2 or more MRI lesions consistent with MS *and* Proof of dissemination in time shown by *either* MRI *or* a second clinical attack
Insidious neurologic progression suggestive of MS but with no clear clinical attack	One year of disease progression (retrospectively or prospectively determined) *and* Two out of three of the following: • Positive brain MRI (9 T2-weighted lesions *or* 4 or more T2-weighted lesions combined with a positive VEP†)

TABLE 23-1 McDonald Criteria for Diagnosis of MS as Revised in 2005

* CSF = cerebrospinal fluid. A positive CSF test shows either oligoclonal bands different from those in serum or a raised IgG index.

† VEP = visual evoked potential. The test is positive if the VEP is delayed.

Drug Therapy Overview

In patients with MS, drugs are employed to (1) modify the disease process, (2) treat an acute relapse, and (3) manage symptoms. At this time, we have no drugs that can cure MS.

Disease-Modifying Therapy

Disease-modifying drugs can decrease the frequency and severity of relapses, reduce development of brain lesions, decrease future disability, and help maintain quality of life. In addition, they may prevent permanent damage to axons. However, it is important to note that, although these drugs can slow disease progression, they do not cure MS. Also, they do not work for all patients. Those with relapsing-remitting MS benefit most.

There are two main groups of disease-modifying drugs: *immunomodulators* and *immunosuppressants* (Table 23-2). The immunomodulators—interferon beta, glatiramer acetate, and natalizumab—are safer than mitoxantrone (the major immunosuppressant in use), and hence are generally preferred.

Generic Name	Trade Name	Route	Dose	Dosing Schedule	Annual Cost	Adverse Effects
IMMUNOMODULATORS						
Interferon Beta Preparations						
Interferon beta-1a	[Avonex]	IM	30 mcg	Once a week	$12,800	*All three preparations:* • Flu-like symptoms • Liver injury • Myelosuppression • Injection-site reactions
Interferon beta-1a	[Rebif]	subQ	44 mcg	3 times a week	$17,300	
Interferon beta-1b	[Betaseron]	subQ	250 mcg	Every other day	$13,100	
Other Immunomodulators						
Glatiramer acetate	[Copaxone]	subQ	20 mg	Once a day	$14,000	• Injection-site reactions • Postinjection reaction
Natalizumab	[Tysabri]	IV	300 mg	Every 4 weeks	$24,000	• Progressive multifocal leukoencephalopathy • Liver injury • Allergic reactions
IMMUNOSUPPRESSANT						
Mitoxantrone	[Novantrone]	IV	12 mg/m^2*	Every 3 months	$18,000	• Myelosuppression • Cardiotoxicity • Fetal harm

TABLE 23-2 Disease-Modifying Drugs for MS

* Maximum lifetime dose is 140 mg/m^2 (because of cardiotoxicity).

Relapsing-Remitting MS.

All patients with relapsing-remitting MS—regardless of age, frequency of attacks, or level of disability—should receive one of the immunomodulators:

- Interferon beta-1a [Avonex], for IM use

- Interferon beta-1a [Rebif], for subQ use
- Interferon beta-1b [Betaseron], for subQ use
- Glatiramer acetate [Copaxone], for subQ use
- Natalizumab [Tysabri], for IV use

Treatment should begin *as soon as possible* after relapsing-remitting MS has been diagnosed. Why? Because early treatment can help prevent axonal injury, and may thereby prevent permanent neurologic deficits.

Treatment should continue indefinitely. The principal reasons for stopping would be toxicity or a clear lack of effect. Unfortunately, if disease-modifying therapy is stopped, disease progression may return to the pretreatment rate.

If treatment with an immunomodulator fails to prevent severe relapses or disease progression, treatment with mitoxantrone (an immunosuppressant) should be considered. However, keep in mind that mitoxantrone can cause serious toxicity (eg, myelosuppression, heart damage), and hence should be reserved for patients who truly need it.

Secondary Progressive MS.

Interferon beta can benefit certain patients with secondary progressive MS, specifically, those who still experience acute relapses. For these people, interferon beta can reduce the severity and frequency of attacks, and can reduce development of MRI-detectable brain lesions. Whether *glatiramer* can help these patients is unclear.

Mitoxantrone can decrease clinical attack rate, reduce development of new brain lesions, and slow progression of disability. However, although the drug is effective, cardiotoxicity precludes long-term use.

Progressive-Relapsing MS.

Mitoxantrone is the only disease-modifying drug approved for this disorder. Unfortunately, benefits are generally modest.

Primary Progressive MS.

No disease-modifying therapy has been shown effective against this form of MS. However, ongoing studies with immunosuppressants (eg, methotrexate, azathioprine, cyclophosphamide) are encouraging.

Treating an Acute Episode (Relapse)

A short course of a *high-dose IV glucocorticoid* (eg, 500 mg to 1 gm of methylprednisolone daily for 3 to 5 days) is the preferred treatment of an acute relapse. Glucocorticoids suppress inflammation and can thereby reduce the severity and duration of a clinical attack. As discussed in Chapter 71, these drugs are very safe when used short term, elevation of blood glucose being the principal concern. By contrast, long-term exposure can cause osteoporosis and other serious adverse effects. Accordingly, frequent use (more than 3 times a year) or prolonged use (longer than 3 weeks at a time) should be avoided.

Acute relapse may also be treated with *IV gamma globulin*. This option can be especially helpful in patients intolerant of or unresponsive to glucocorticoids. Results have been good.

Drug Therapy of Symptoms

All four subtypes of MS share the same symptoms (eg, fatigue, spasticity, pain, bladder dysfunction, bowel dysfunction, sexual dysfunction). Accordingly, the drugs used for treatment are the same for all patients, regardless of MS subtype. Specific treatments are discussed below under *Drugs Used to Manage MS Symptoms*.

DISEASE-MODIFYING DRUGS: IMMUNOMODULATORS

Five immunomodulators are available: glatiramer acetate [Copaxone], natalizumab [Tysabri], and three preparations of interferon beta [Avonex, Rebif, Betaseron]. With the exception of natalizumab, all of these drugs are recommended as first-line therapy for patients with relapsing-remitting MS and for patients with secondary progressive MS who still experience acute exacerbations. Natalizumab is reserved for patients with relapsing-remitting MS who have not responded to at least one of the other four drugs. Why? Because, very rarely, natalizumab has been associated with a potentially fatal infection of the brain.

All of the *first-line* immunomodulators—glatiramer and the interferon beta preparations—appear equally effective, decreasing the relapse rate by about 30%. Because benefits are very similar, selection among these drugs is based primarily on patient and prescriber preference. If a particular drug is intolerable or ineffective, a different one should be tried. Natalizumab is more effective than the first-line drugs, decreasing the relapse rate by 68%, but is also more dangerous. As noted, although the immunomodulators can modify the course of MS, they do not cure the disease.

All of the immunomodulators are administered parenterally. The first-line agents are administered by self-injection (IM or subQ). Natalizumab is administered by IV infusion (in an approved infusion center). All five drugs are expensive: One year of treatment costs $12,000 to $24,000. Properties of these drugs are summarized in Table 23-2.

Interferon Beta Preparations

Description and Mechanism

Interferon beta is a naturally occurring glycoprotein with antiviral, antiproliferative, and immunomodulatory actions. Natural interferon beta is produced in response to viral invasion and other biologic inducers. In patients with MS, benefits are thought to derive primarily from inhibiting the migration of proinflammatory leukocytes across the blood-brain barrier, thereby preventing these cells from reaching neurons of the CNS.

Two forms of interferon beta are used clinically: *interferon beta-1a* [Avonex, Rebif] and *interferon beta-1b* [Betaseron]. Both forms are manufactured using recombinant DNA technology. Interferon beta-1a contains 166 amino acids plus glycoproteins, and is identical to natural human interferon beta with respect to amino acid content. Interferon beta-1b contains only 165 amino acids and has no glycoproteins, and hence differs somewhat from the natural compound. It should be noted that two preparations of interferon beta-1a are available, marketed as Avonex and Rebif. These products differ slightly in their glycoprotein content, and are administered by different routes (see below).

Therapeutic Use

All three interferon beta products are approved for relapsing forms of MS. These drugs can decrease the frequency and severity of attacks, reduce the number and size of MRI-detectable lesions, and delay the progression of disability. Benefits with Rebif and Betaseron may be somewhat greater than with Avonex, perhaps because Avonex is given less frequently and in lower dosage (see below).

In addition to its use in relapsing MS, interferon beta-1b [Betaseron] is approved for patients with secondary progressive MS.

Adverse Effects and Drug Interactions

Interferon beta is generally well tolerated, although side effects are common.

Flu-like Reactions.

Flu-like reactions occur often. Symptoms include headache, fever, chills, malaise, muscle aches, and stiffness. Fortunately, these diminish over time, despite continued interferon beta use. Symptoms can be minimized by (1) starting with a low dose and then slowing titrating up to the full dose, and (2) giving an analgesic-antipyretic medication (ie, acetaminophen; ibuprofen or another nonsteroidal anti-inflammatory drug).

Hepatotoxicity.

Interferon beta can injure the liver, typically causing an asymptomatic increase in circulating liver enzymes. Very rarely, patients develop hepatitis or even liver failure. To monitor for hepatotoxicity, liver function tests (LFTs) should be performed at baseline, 1 month later, then every 3 months for 1 year, and every 6 months thereafter. If LFTs indicate significant liver injury, a temporary reduction in dosage or interruption of treatment is indicated. When liver function returns to normal, treatment can resume, but careful monitoring is required. Interferon beta should be used with caution in patients who abuse alcohol, use hepatotoxic medications, or have active liver disease or a history of liver disease.

Myelosuppression.

Interferon beta can suppress bone marrow function, thereby decreasing production of all blood cell types. To monitor for myelosuppression, complete

blood counts should be obtained at baseline, every 3 months for 1 year, and every 6 months thereafter.

Injection-Site Reactions.

Subcutaneous injection (of Rebif or Betaseron) can cause pain, erythema (redness), bumps, and itching. Physical measures to reduce discomfort include rotating the injection site, applying ice (briefly) before and after the injection, and applying a warm, moist compress after the injection. Oral diphenhydramine [Benadryl] or topical hydrocortisone can reduce persistent itching and erythema. However, *continuous* use of topical hydrocortisone should be avoided, owing to a risk of skin damage. Very rarely, subQ injections have caused local necrosis. Intramuscular injection (of Avonex) can cause discomfort and bruising.

Depression.

It is unclear whether interferon beta promotes depression. Early studies showed an increased risk of depression, suicidal ideation, and suicide attempts. However, later studies have not confirmed these observations.

Neutralizing Antibodies.

Like all other foreign proteins, interferon beta is immunogenic, and hence can stimulate production of antibodies against itself. If present in sufficiently high titers, these neutralizing antibodies can decrease clinical benefits.

Drug Interactions.

Exercise caution when combining interferon beta with other drugs that can suppress the bone marrow or cause liver injury.

Preparations, Dosage, and Administration

Avonex (Interferon Beta-1a for IM Use).

Avonex is available in pre-filled, single-use syringes (30 mcg/0.5 mL) and as a powder (30 mcg/0.5 mL when reconstituted with sterile water). The dosage is 30 mcg IM once a week. Store *pre-filled syringes* at 36°F to 46°F (2°C to 8°C). Store the *powder* at 36°F to 46°F (2°C to 8°C) or, if refrigeration is unavailable,

store at or below 77°F (25°C) for up to 30 days. Injections are made late in the day so that flu-like symptoms occur during sleep.

Rebif (Interferon Beta-1a for SubQ Use).

Rebif is available in pre-filled, single-use syringes containing either 8.8 mcg/0.2 mL, 22 mcg/0.5 mL, or 44 mcg/0.5 mL. Injections are made subQ 3 times a week, preferably in late afternoon or evening, at least 48 hours apart, and on the same days each week (eg, Monday, Wednesday, Friday). Dosage is titrated as follows: 8.8 mcg/dose for weeks 1 and 2; 22 mcg/dose for weeks 3 and 4; and 44 mcg/dose thereafter. Store Rebif refrigerated at 36°F to 46°F (2°C to 8°C) or, if refrigeration is unavailable, at or below 25°C (77°F) for up to 30 days.

Betaseron (Interferon Beta-1b for SubQ Use).

Betaseron is supplied as a powder (0.3 mg) in single-use vials. Just prior to use, the drug is reconstituted to form a 0.25-mg/mL solution. Doses are given subQ every other day. Dosage is titrated as follows: 0.0625 mg/dose for weeks 1 and 2; 0.125 mg/dose for weeks 3 and 4; 0.1875 mg/dose for weeks 4 and 5; and 0.25 mg/dose thereafter. Store the powder at room temperature. Following reconstitution, the drug solution may be stored up to 3 hours refrigerated.

Glatiramer Acetate

Therapeutic Use.

Glatiramer acetate [Copaxone], also known as *copolymer-1,* is used for long-term therapy of relapsing-remitting MS. Like interferon beta, glatiramer can reduce the frequency and severity of relapses, decrease MRI-detectable lesions, and delay the progression of disability. Glatiramer requires more frequent injections than interferon beta, and is less well tolerated.

Description and Mechanism.

Glatiramer is a polypeptide composed of a random sequence of four amino acids: L-alanine, L-glutamate, L-lysine, and L-tyrosine. The drug is similar in structure to myelin basic protein, a component of the axonal myelin sheath. In patients with MS, the drug promotes a "T-cell shift." That is, it decreases production of proinflammatory TH1 cells and increases production of anti-in-

flammatory TH2 cells. The anti-inflammatory cells migrate across the blood-brain barrier at sites of inflammation, and then suppress the inflammatory attack on myelin.

Adverse Effects and Drug Interactions.

Glatiramer is generally well tolerated. *Injection-site* reactions—pain, erythema, pruritus (itching), induration (pitting)—are most common. Unlike interferon beta, glatiramer does *not* cause flu-like symptoms, myelosuppression, or liver toxicity. About 10% of patients experience a self-limited *postinjection reaction*—characterized by flushing, palpitations, severe chest pain, anxiety, laryngeal constriction, and urticaria—that typically lasts 15 to 20 minutes. No specific treatment is indicated. Safety in pregnancy or breast-feeding has not been established. No significant interactions with other MS drugs have been observed.

Preparations, Dosage, and Administration.

Glatiramer acetate [Copaxone] is available in single-use, pre-filled syringes that contain 20 mg/mL glatiramer plus 40 mg of mannitol. The recommended dosage is 20 mg (1 mL) once a day, injected subQ into the arm, abdomen, hip, or thigh. Store under refrigeration at 36°F to 46°F (2°C to 8°C).

Natalizumab

Natalizumab [Tysabri], a recombinant monoclonal antibody, was introduced in 2004 and then withdrawn a few months later, in response to three reports of progressive multifocal leukoencephalopathy (PML), a severe infection of the brain. The drug was re-introduced in 2006, but with protective restrictions on who can prescribe, dispense, administer, and receive it.

Therapeutic Uses

Natalizumab is approved for two autoimmune diseases: multiple sclerosis and Crohn's disease (an inflammatory disorder of the bowel). Because of the risk of PML, natalizumab is a second-line choice for both conditions.

Multiple Sclerosis.

Natalizumab is approved only for *monotherapy* of *relapsing forms of MS*. In the AFFIRM trial, which compared natalizumab with placebo, natalizumab reduced the annualized rate of relapse by 68%, and reduced the number of new or enlarging brain lesions by 83%. These benefits are superior to those seen with interferon beta or glatiramer. However, owing to the risk of PML, natalizumab should be reserved for patients who have not responded to at least one of the first-line agents, and should not be combined with other disease-modifying drugs. Safety and efficacy beyond 2 years of use has not been established, nor have safety and efficacy in patients with chronic progressive MS.

Crohn's Disease.

Natalizumab is approved for induction and maintenance therapy of moderate to severe Crohn's disease in patients who have been unresponsive to or intolerant of other therapies, including inhibitors of tumor necrosis factor (TNF)-alpha. In clinical trials, benefits of the drug were modest. Natalizumab must not be combined with TNF-alpha inhibitors or with immunosuppressants (eg, cyclophosphamide, azathioprine, methotrexate). Crohn's disease and its treatment are discussed at length in Chapter 79.

Mechanism of Action

In patients with MS and Crohn's disease, natalizumab prevents circulating leukocytes (T cells and monocytes) from leaving the vasculature, and thereby prevents these cells from migrating to sites where they can do harm. In order to exit the vasculature, activated leukocytes must first adhere to the vascular endothelium, a process that requires the interaction of two types of molecules: (1) *integrins* (adhesion molecules) expressed on the surface of leukocytes and (2) *integrin receptors* expressed on cells of the vascular epithelium. Natalizumab binds with integrin molecules on leukocytes, and thereby renders these cells unable to bind with integrin receptors on the capillary wall. As a result, the leukocytes cannot cross the capillary wall, and hence are unable to exit the vasculature to reach their sites of inflammatory action. In patients with MS, natalizumab prevents activated leukocytes from crossing the blood-brain barrier. In patients with Crohn's disease, the drug prevents leukocytes from crossing capillaries that deliver blood to the GI tract.

Adverse Effects

Natalizumab is generally well tolerated. The most common reactions are headache and fatigue. Other common reactions include abdominal discomfort, arthralgia, depression, diarrhea, gastroenteritis, urinary tract infections, and lower respiratory tract infections. The most serious effects are PML, liver injury, and hypersensitivity reactions.

Progressive Multifocal Leukoencephalopathy.

Shortly after natalizumab was released, there were three reports of PML, a severe infection of the CNS caused by reactivation of the JC virus, an opportunistic pathogen resistant to all available drugs. Two of the infected patients died. All three were taking natalizumab in combination with another immunosuppressant (azathioprine or interferon beta). As of August 2008, more than 25,000 patients had received natalizumab, and only two additional cases of PML had been confirmed. Surprisingly, both new cases were in patients taking natalizumab as monotherapy. (Presumably, PML is made possible by natalizumab-mediated immunosuppression, and hence combining natalizumab with another immunosuppressant increases the risk.) In addition to immunosuppressant drugs, the risk of PML is increased by HIV/AIDS and other conditions that compromise cell-mediated immunity.

To reduce the risk of PML, natalizumab is available only through the *TOUCH Prescribing Program*. Patients, prescribers, infusion nurses, infusion centers, and pharmacies associated with infusion centers must all register with the program. In addition, prescribers and patients must understand the risks of natalizumab, including PML and other opportunistic infections—and patients must be screened for PML prior to each infusion.

Hepatotoxicity.

Like interferon beta, natalizumab can injure the liver. Patients should be informed about signs of liver injury—jaundice, nausea, vomiting, fatigue, darkening of the urine—and instructed to report these immediately. If significant liver injury is diagnosed, natalizumab should be discontinued.

Hypersensitivity Reactions.

Natalizumab can cause a variety of allergic reactions, manifesting as hives, itching, chest pain, dizziness, chills, rash, flushing, and hypotension. Severe reactions (eg, anaphylaxis) usually develop within 2 hours of infusion onset, but can also develop later. The risk of a severe reaction is increased by the presence of neutralizing antibodies. If a severe reaction develops, natalizumab should be discontinued and never used again.

Neutralizing Antibodies.

Antibodies against natalizumab develop in about 6% of patients. These antibodies greatly decrease the efficacy of natalizumab and increase the risk of hypersensitivity and infusion reactions.

Drug Interactions

As noted, *immunosuppressants* increase the risk of PML and other opportunistic infections. Accordingly, these drugs should be discontinued at least 3 months before natalizumab is started.

Preparations, Dosage, and Administration

Natalizumab [Tysabri] is supplied in single-use vials (300 mg/15 mL) for dilution in 100 mL of 0.9% sodium chloride injection. Administration is by IV infusion, done over a 1-hour span. The dosage for MS and Crohn's disease is 300 mg every 4 weeks. Patients should be observed during the infusion and for 1 hour after. If any signs of hypersensitivity develop, the infusion should cease immediately. Before natalizumab can be administered, everyone involved with the drug—patients, physicians, pharmacists, infusion nurses, and infusion centers—must be registered with the TOUCH Prescribing Program. Natalizumab vials should be stored cold (36°F to 46°F [2°C to 8°C]), but not frozen.

DISEASE-MODIFYING DRUGS: IMMUNOSUPPRESSANTS

At this time, only one immunosuppressant—mitoxantrone—is approved by the Food and Drug Administration (FDA) for treating MS. Mitoxantrone is more toxic than the immunomodulators and produces greater immune suppression. Another immunosuppressant—cyclophosphamide—is also employed, but is not approved for MS.

Mitoxantrone

Mitoxantrone [Novantrone], originally used for cancer (see Chapter 101), was approved for MS in October 2000. The drug poses a significant risk of toxicity, and hence is generally reserved for patients who cannot be treated with safer agents.

Therapeutic Use

Mitoxantrone is approved for decreasing neurologic disability and clinical relapses in patients with

- Worsening relapsing-remitting MS
- Secondary progressive MS
- Progressive-relapsing MS

For these patients, the drug may delay the time to relapse and the time to disability progression. In addition, it may decrease the number of new MRI-detectable lesions. Mitoxantrone is *not* effective against primary progressive MS, and hence should not be used for this disorder.

Mechanism of Action

Mitoxantrone is a cytotoxic drug that binds with DNA and inhibits topoisomerase II. These actions inhibit DNA and RNA synthesis, and promote cross-linking and breakage of DNA strands. In cell culture, mitoxantrone is toxic to all cells, whether dividing or not. However, in clinical practice, the drug appears especially toxic to tissues with a high percentage of actively dividing cells (bone marrow, hair follicles, GI mucosa). In patients with MS, mitoxantrone suppresses production of immune system cells (B lymphocytes, T lymphocytes, and macrophages), and thereby decreases autoimmune destruction of myelin. Additional protection may derive from reducing antigen presentation and reducing production of cytokines (eg, interleukin-2, TNF-alpha, interferon gamma) that participate in the immune response.

Pharmacokinetics

Following IV infusion, mitoxantrone undergoes rapid, widespread distribution. Elimination occurs slowly, primarily by hepatic metabolism and biliary

excretion. In patients with liver dysfunction, clearance of the drug is reduced, thereby increasing the risk of toxicity. Accordingly, mitoxantrone should not be given to patients with liver disease. To assess liver status, LFTs should be performed at baseline and prior to each infusion. If LFTs are abnormal, the drug should be withheld.

Adverse Effects

Mitoxantrone can cause a variety of adverse effects. Myelosuppression, cardiotoxicity, and fetal injury are the greatest concerns.

Myelosuppression.

Toxicity to the bone marrow cells (myelosuppression) can decrease production of platelets and all blood cells. Loss of neutrophils, which is maximal 10 to 14 days after dosing, increases the risk of *severe infection*. Patients should be advised to avoid contact with people who have infections, and should report signs of infection (fever, chills, cough, hoarseness) immediately. Also, patients should not be immunized with a live virus vaccine (because the vaccine itself could cause infection). To guide mitoxantrone use, complete blood counts should be obtained at baseline, before each infusion, 10 to 14 days after each infusion, and whenever signs of infection develop. Dosing should not be done if the neutrophil count is below 1500 cells/mm^3.

Cardiotoxicity.

Mitoxantrone can cause irreversible injury to the heart, manifesting as a reduced left ventricular ejection fraction (LVEF) or outright heart failure. Injury may become apparent during treatment, or months to years after drug use has ceased. Cardiotoxicity is directly related to the cumulative lifetime dose. Risk increases significantly if the cumulative dose exceeds 140 mg/m^2, and hence the total should not exceed this amount. Mitoxantrone should not be given to patients with cardiac impairment. Accordingly, LVEF should be determined prior to the first dose, and, if the LVEF is less than 50%, mitoxantrone should be withheld. During treatment, LVEF should be measured before every dose and whenever signs of heart failure develop (eg, peripheral edema, fatigue, shortness of breath).

Fetal Harm.

Mitoxantrone has the potential for fetal harm, and is classified in FDA Pregnancy Risk Category D. In animal studies, extremely low doses were associated with growth retardation and premature delivery. To date, teratogenicity of mitoxantrone has not been proved. However, since mitoxantrone has the same mechanism as known teratogens, its teratogenicity can be inferred. Women of child-bearing age should avoid becoming pregnant, and pregnancy should be ruled out before each dose. If pregnancy occurs, counseling about possible termination of pregnancy should be offered.

Other Adverse Effects.

Because mitoxantrone is especially toxic to tissues with a high percentage of dividing cells, it can cause reversible hair loss and injury to the GI mucosa, resulting in stomatitis and GI distress. The drug can also cause nausea, vomiting, menstrual irregularities (eg, amenorrhea), and symptoms of allergy (itching, rash, hypotension, shortness of breath). In addition, mitoxantrone can impart a harmless, blue-green tint to the urine, skin, and sclera; patients should be forewarned. Very rarely, patients taking mitoxantrone for MS have developed acute myelogenous leukemia, although a cause-and-effect relationship has not been established.

Monitoring Summary

To minimize risk, we need to

- Perform complete blood counts at baseline, before each dose, and 10 to 14 days after each dose.
- Perform LFTs at baseline and before each dose.
- Perform a pregnancy test before each dose.
- Determine LVEF before each dose and whenever signs of heart failure develop.

Preparations, Dosage, and Administration

Mitoxantrone [Novantrone] is available in solution (2 mg/mL) in 10-, 12.5-, and 15-mL multi-use vials. For patients with MS, the dosage is 12 mg/m^2 every

3 months, infused IV over 5 to 30 minutes. The maximum lifetime cumulative dose is 140 mg/m2. Before infusing, dilute each dose with at least 50 mL of normal saline or 5% dextrose in water; then administer into a free-flowing IV line. Extravasation can cause severe local injury. Accordingly, if extravasation occurs, discontinue the infusion immediately and restart in a different vein. Don't mix mitoxantrone with other drugs.

Cyclophosphamide

Cyclophosphamide [Cytoxan, Neosar], originally developed for cancer (see Chapter 101), is used off-label to treat refractory MS. In one trial, high-dose cyclophosphamide prevented disease progression and, for many patients, produced a marked improvement in EDSS scores. Furthermore, these improvements persisted at least 15 months. Benefits appear to result from decreasing the number and activity of lymphocytes. Side effects, which can be severe, include bone marrow suppression, acute hemorrhagic cystitis, alopecia, and intense nausea and vomiting.

DRUGS USED TO MANAGE MS SYMPTOMS

Multiple sclerosis is associated with an array of potentially debilitating symptoms. Accordingly, effective management is essential for maintaining productivity and quality of life. However, despite the importance of symptom management, the discussion below is brief. Why? Because all of the drugs employed are discussed at length in other chapters. For more details on symptom management, the web site of the National Multiple Sclerosis Society—*www.nationalmssociety.org*—is a good resource.

Bladder Dysfunction

Bladder dysfunction is very common, occurring in up to 90% of patients. The underlying cause is disruption of nerve traffic in areas of the CNS that control the bladder detrusor muscle and bladder sphincter. (Recall that coordinated contraction of the detrusor and relaxation of the sphincter are required for normal voiding.) Three types of bladder dysfunction may be seen: detrusor hyperreflexia, detrusor-sphincter dyssynergia, and flaccid bladder. All three can be successfully managed.

Detrusor hyperreflexia results from decreased inhibition of the bladder reflex and manifests as urinary frequency, urinary urgency, nocturia, and incontinence. Relief is accomplished with anticholinergic drugs, which relax the detrusor and thereby permit a normal volume of urine to accumulate before bladder emptying. Options include *tolterodine* [Detrol], *oxybutynin* [Ditropan, Oxytrol], *darifenacin* [Enablex], and *solifenacin* [VESIcare].

Detrusor-sphincter dyssynergia is characterized by a lack of synchronization between detrusor contraction and sphincter relaxation. The result is difficulty initiating or stopping urination, and incomplete bladder emptying. Some patients respond to *alpha-adrenergic blocking agents,* such as phenoxybenzamine [Dibenzyline], tamsulosin [Flomax], or terazosin [Hytrin], all of which promote sphincter relaxation. However, most patients require intermittent or continuous catheterization.

In patients with *flaccid bladder,* there is a loss of reflex detrusor contraction, resulting in impaired bladder emptying. In some cases, the condition responds to *bethanechol* [Urecholine], a muscarinic agonist that directly stimulates the detrusor. However, as with detrusor-sphincter dyssynergia, many patients require intermittent or continuous catheterization.

Bowel Dysfunction

Constipation is relatively common, whereas fecal incontinence is relatively rare. Constipation can be managed by increasing dietary fiber and fluids, taking fiber supplements, performing regular exercise, and, if needed, using a bulk-forming laxative, such as *psyllium* [Metamucil]. Rapid relief can be achieved by instilling a mini-enema, sold under the name Enemeez. The product consists of docusate sodium (a stool softener) in a soft-soap base composed of polyethylene glycol and glycerin. Fecal incontinence can be managed by establishing a regular bowel routine and, if needed, using a bulk-forming laxative (to improve stool consistency) and/or using an anticholinergic agent (eg, hyoscyamine) to reduce bowel motility. Be aware, however, that excessive slowing of bowel motility can result in constipation.

Fatigue

Fatigue develops in up to 90% of patients. The underlying cause is unknown. Regular exercise can help. The most common drug therapies are *amantadine* [Symmetrel] and *modafinil* [Provigil]. Both are generally well tolerated. *Methylphenidate* [Ritalin] and *amphetamine mixture* [Adderall] are the next options. *Selective serotonin reuptake inhibitors (SSRIs)* can reduce fatigue, and hence are a good choice for patients who are also depressed.

Depression

Depression is seen in about 70% of MS patients. In these people, depression may be reactive—that is, it may be an emotional response to having a chronic, progressive, disabling disease—or it may be the result of MS-induced injury to neurons that help regulate mood. Depression can be treated with antidepressant drugs and with counseling. For drug therapy, the *SSRIs*, such as fluoxetine [Prozac] and sertraline [Zoloft], can elevate mood, but often seem to increase fatigue. In contrast, *bupropion* [Wellbutrin], which has stimulant properties, can relieve depression and may help fight fatigue. The *tricyclic antidepressants,* such as amitriptyline (formerly available as Elavil) and nortriptyline [Pamelor], can treat pain, sleep disturbances, and incontinence (owing to detrusor hyperreflexia) in addition to improving mood.

Spasticity

Spasticity can range in severity from mild muscle tightness to painful muscle spasms, usually in the legs. Clinically significant spasticity occurs in more than 40% of patients. Interestingly, for some patients, spasticity can be beneficial: By making the legs more rigid, spasticity can facilitate standing and walking.

Spasticity can be managed with drug therapy and with nondrug measures (physical therapy, stretching, regular exercise). The drugs used most are *baclofen* [Lioresal] and *tizanidine* [Zanaflex]. However, dosage must be carefully controlled. Why? Because high doses of either agent can exacerbate MS-related muscle weakness. Tizanidine causes less weakness than baclofen, but poses a risk of liver injury, sedation, and dry mouth. Alternatives to baclofen and tizanidine include *diazepam* [Valium] and *botulinum toxin* [Botox]. Intrathecal infusion of baclofen is a very effective option, but is also very invasive.

Sexual Dysfunction

Among MS patients, sexual dysfunction may affect as many as 91% of men and 72% of women. Among men, erectile dysfunction is the most common complaint. Among women, complaints include vaginal dryness, reduced libido, and decreased vaginal and clitoral sensation. Possible causes of sexual dysfunction include depression, side effects of drugs, and injury to neurons of the lower spinal cord. Erectile dysfunction can be treated with *sildenafil* [Viagra], *vardenafil* [Levitra], and other inhibitors of phosphodiesterase type 5 (see Chapter 65). Vaginal dryness can be managed with a water-soluble personal lubricant (eg, K-Y Jelly); petroleum jelly (Vaseline) should be avoided. There are no drugs proved to enhance vaginal sensation, clitoral sensation, or libido.

Neuropathic Pain

Neuropathic pain results from injury to neurons (in contrast to nociceptive pain, which results from injury to peripheral tissues.) Neuropathic pain responds poorly to traditional analgesics, but often does respond to certain antiepileptic drugs and antidepressants. The antiepileptic drugs employed include *carbamazepine* [Tegretol], *gabapentin* [Neurontin], and *oxcarbazepine* [Trileptal]. The antidepressants employed, all from the tricyclic family, include *nortriptyline* [Pamelor], *imipramine* [Tofranil], and *amitriptyline* (formerly available as Elavil). Please note that pain relief with antidepressants occurs even in patients who are *not* depressed, and hence is not simply the result of elevating mood.

Ataxia and Tremor

Ataxia (loss of coordination) and tremor are relatively common and often disabling. Unfortunately, they are also largely unresponsive to treatment. Drugs that may offer some relief include *clonazepam* [Klonopin], *primidone* [Mysoline], and *propranolol* [Inderal]. A physical therapist can provide gait training, and an occupational therapist can provide equipment to help maintain independence.

Cognitive Dysfunction

About 50% of people with MS experience cognitive dysfunction at some time in the course of the disease. Fortunately, only 5% to 10% experience dysfunction

severe enough to significantly interfere with daily living. Memory impairment is the most common problem. Other problems include impaired concentration, reasoning, and problem solving. Cognitive impairment is caused in part by demyelination of CNS neurons, and in part by depression, anxiety, stress, and fatigue. By protecting against demyelination, disease-modifying drugs can decrease the degree of cognitive loss. *Donepezil* [Aricept], a cholinesterase inhibitor developed for Alzheimer's disease, may offer modest benefits, as may *memantine* [Namenda], an NMDA receptor blocker developed for Alzheimer's disease (see Chapter 22).

Dizziness and Vertigo

Dizziness and vertigo result from lesions in CNS pathways that provide a sense of equilibrium. Both symptoms are relatively common, and can be reduced with several drugs. Among these are *meclizine* [Antivert, Dramamine] (a drug for motion sickness) and *ondansetron* [Zofran] (a powerful antiemetic).

KEY POINTS

- Multiple sclerosis is a chronic, inflammatory, autoimmune disorder that damages the myelin sheath of neurons in the CNS. Because of demyelination, axonal conduction is slowed or blocked, giving rise to a host of sensory and motor deficits. When inflammation subsides, some degree of recovery occurs, at least in the early stage of the disease.
- In addition to stripping off myelin, inflammation may injure the underlying axon, and may also injure nearby oligodendrocytes, the cells that make CNS myelin.
- What causes MS? There is general agreement that MS develops in genetically vulnerable people following exposure to an environmental or microbial factor that initiates autoimmune activity.
- There are four subtypes of MS: relapsing-remitting (the most common form), secondary progressive, primary progressive, and progressive-relapsing.
- Diagnosis of MS is based on clinical presentation supplemented by laboratory data (eg, MRI scans, CSF tests, and VEP determinations). A positive diagnosis

requires objective evidence of two or more clinical attacks separated in time and space.

- In patients with MS, drugs are employed to (1) modify the disease process, (2) treat acute relapses, and (3) manage symptoms. We have no drugs to cure MS.
- Disease-modifying drugs can decrease the frequency and severity of relapses, reduce development of brain lesions, decrease future disability, and help maintain quality of life. In addition, they may prevent permanent damage to axons.
- There are two main groups of disease-modifying drugs: immunomodulators and immunosuppressants.
- The immunomodulators—interferon beta, glatiramer acetate, and natalizumab—are much safer than mitoxantrone (the only FDA-approved immunosuppressant for MS), and hence are generally preferred.
- All patients with relapsing-remitting MS should receive an immunomodulator—interferon beta, glatiramer acetate, or natalizumab—beginning as soon as possible after diagnosis and continuing indefinitely.
- Interferon beta and glatiramer are equally effective, but less effective than natalizumab.
- Interferon beta and glatiramer are administered by self-injection (IM or subQ), whereas natalizumab is administered by IV infusion.
- Interferon beta is generally well tolerated, although side effects—flu-like reactions, liver injury, myelosuppression, injection-site reactions—are relatively common.
- Glatiramer is less well tolerated than interferon beta, and requires more frequent injections.
- The most common side effects of glatiramer are injection-site reactions (pain, erythema, pruritus, induration), and the most disturbing side effect is brief but severe chest pain after the injection. Unlike interferon beta, glatiramer does not cause flu-like symptoms, myelosuppression, or liver toxicity.

- Natalizumab can cause progressive multifocal leukoencephalopathy (PML), a severe CNS infection caused by reactivation of the JC virus. To reduce the risk of PML, natalizumab must not be combined with other immunosuppressant drugs, must not be given to patients with HIV/AIDS and other conditions that compromise cell-mediated immunity, and must be used in accord with the TOUCH Prescribing Program.
- Mitoxantrone is the only immunosuppressant currently approved for MS.
- Mitoxantrone suppresses immune function more strongly than the immunomodulators, but is also more toxic. Accordingly, the drug is generally reserved for patients who are unresponsive to or intolerant of an immunomodulator.
- In patients with MS, mitoxantrone suppresses production of immune system cells, and thereby decreases autoimmune destruction of myelin.
- The major side effects of mitoxantrone are myelosuppression, cardiotoxicity, and fetal injury.
- The risk of cardiotoxicity from mitoxantrone increases significantly if the lifetime cumulative dose exceeds 140 mg/m2, and hence the total dose should not exceed this amount.
- A short course of high-dose IV glucocorticoids (eg, methylprednisolone) is the preferred treatment for an acute MS relapse. Intravenous gamma globulin is an option.

Summary of Major Nursing Implications*

INTERFERON BETA

Interferon beta-1a [Avonex, Rebif]

Interferon beta-1b [Betaseron]

Preadministration Assessment

Therapeutic Goal

All preparations of beta interferon are used to decrease the frequency and severity of relapses and slow disease progression in patients with relapsing forms of MS. In addition, *interferon beta-1b* [Betaseron] is used to treat secondary progressive MS.

Baseline Data

Obtain baseline LFTs and complete blood counts.

Identifying High-Risk Patients

Exercise *caution* in patients who abuse alcohol, in those with active liver disease or a history of liver disease, and in those taking drugs that can cause liver injury or suppress the bone marrow.

Implementation: Administration

Routes

Intramuscular.

Avonex (interferon beta-1a).

Subcutaneous.

Rebif (interferon beta-1a), Betaseron (interferon beta-1b).

Administration

For all three formulations of interferon beta, teach patients how to self-inject, and advise them to rotate the injection site.

Avonex.

Instruct patients to inject Avonex IM once a week.

Rebif.

Instruct patients to inject Rebif subQ 3 times a week, preferably in the late afternoon or evening, at least 48 hours apart, and on the same days each week (eg, Monday, Wednesday, Friday).

Betaseron.

Instruct patients to reconstitute powdered Betaseron just prior to use, and to inject it subQ every other day.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Indices of success include a reduction in the frequency and intensity of relapses, a reduction in new MRI-detectable lesions, and improvement in the EDSS score.

Minimizing Adverse Effects

Flu-like Reactions.

Flu-like reactions—headache, fever, chills, malaise, muscle aches, stiffness—are common early in therapy, but later diminish. To minimize symptoms, begin therapy with low doses, and then slowly titrate to full doses. **Inform patients that symptoms can be reduced by taking an analgesic-antipyretic medication (ie, acetaminophen; ibuprofen or another nonsteroidal anti-inflammatory drug).**

Hepatotoxicity.

Interferon beta can cause liver injury. To monitor for hepatotoxicity, obtain LFTs at baseline, 1 month later, then every 3 months for 1 year, and every 6 months thereafter. If LFTs indicate significant injury, interferon should be given in reduced dosage or discontinued. When liver function returns to normal, treatment can resume with careful monitoring.

Myelosuppression.

Interferon beta can decrease production of all blood cell types. To monitor for myelosuppression, obtain complete blood counts at baseline, every 3 months for 1 year, and every 6 months thereafter.

Injection-Site Reactions.

Subcutaneous injection (of Rebif or Betaseron) can cause pain, erythema, bumps, and itching. **Inform patients that they can reduce discomfort by physical measures—rotating the injection site, applying ice (briefly) before and after the injection, and applying a warm moist compress—and that they can reduce persistent itching and erythema with oral diphenhydramine [Benadryl] or topical hydrocortisone. Instruct patients to avoid continuous exposure to topical hydrocortisone owing to a risk of skin damage. Forewarn patients that IM injection (of Avonex) can cause discomfort and bruising.**

Minimizing Adverse Interactions

Hepatotoxic and Myelosuppressant Drugs.

Exercise caution when combining interferon beta with other drugs that can suppress the bone marrow or cause liver injury.

GLATIRAMER ACETATE

Preadministration Assessment

Therapeutic Goal

The goal is to decrease the frequency and severity of relapses and slow disease progression in patients with relapsing-remitting MS.

Implementation: Administration

Route

Subcutaneous.

Administration

Teach patients how to self-inject the drug (subQ) into the arm, abdomen, hip, or thigh. Advise patients to store glatiramer under refrigeration at 36°F to 46°F (2°C to 8°C).

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Indices of success include a reduction in the frequency and intensity of relapses, a reduction in new MRI-detectable lesions, and improvement in the EDSS score.

Minimizing Adverse Effects

Injection-Site Reactions.

Forewarn patients that glatiramer may cause pain, erythema, pruritus, and induration at the injection site.

Immediate Postinjection Reaction.

Forewarn patients that glatiramer may cause an uncomfortable and disturbing set of systemic symptoms—flushing, palpitations, chest pain, anxiety, laryngeal constriction, urticaria—that may persist for 15 to 20 minutes after the injection. No specific intervention is needed.

NATALIZUMAB

Preadministration Assessment

Therapeutic Goal

Natalizumab is used to either (1) decrease the frequency and severity of relapses and slow disease progression in patients with relapsing forms of MS who have failed to respond to at least one other immunomodulating drug or (2) treat patients with moderate to severe Crohn's disease who have been unresponsive to or intolerant of other therapies, including inhibitors of TNF-alpha.

Baseline Data

Obtain an MRI scan of the brain at baseline and every 6 months thereafter. Obtain a baseline evaluation for PML.

Identifying High-Risk Patients

Natalizumab is *contraindicated* for patients with PML, for patients taking immunosuppressant drugs, and for patients with HIV/AIDS and other conditions that compromise cell-mediated immunity.

Implementation: Administration

Route

Intravenous

Administration

Dilute concentrated natalizumab in 100 mL of 0.9% sodium chloride injection and infuse over a 1-hour span. If any signs of hypersensitivity develop, stop the infusion immediately.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Indices of success include a reduction in the frequency and intensity of relapses, a reduction in new MRI-detectable lesions, and improvement in the EDSS score.

Minimizing Adverse Effects

Progressive Multifocal Leukoencephalopathy.

Natalizumab increases the risk of PML, a severe infection of the CNS with no effective treatment. To reduce the risk of PML, do not give natalizumab to patients taking immunosuppressants or to patients with HIV/AIDS and other conditions that compromise cell-mediated immunity. Screen for PML prior to each infusion. All patients, prescribers, infusion nurses, infusion centers, and pharmacies associated with infusion centers must register with the *TOUCH Prescribing Program* and must comply with its provisions.

Hepatotoxicity.

Natalizumab can injure the liver. **Inform patients about signs of liver injury—jaundice, nausea, vomiting, fatigue, darkening of the urine—and**

instruct them to report these immediately. Discontinue natalizumab if significant liver injury is diagnosed.

Hypersensitivity Reactions.

Natalizumab can cause severe hypersensitivity reactions (eg, anaphylaxis), usually within 2 hours of starting the infusion. Monitor patients for a reaction during the infusion and for 1 hour after. If a severe reaction develops, discontinue natalizumab and never use it again.

Drug Interactions

Immunosuppressants increase the risk of PML and other opportunistic infections, and hence should be discontinued at least 3 months before starting natalizumab.

MITOXANTRONE

Preadministration Assessment

Therapeutic Goal

The goal is to decrease the frequency and severity of relapses and slow disease progression in patients with secondary progressive MS, progressive-relapsing MS, and worsening relapsing-remitting MS.

Baseline Data

Obtain a pregnancy test, LFTs, complete blood counts, and LVEF determination.

Identifying High-Risk Patients

Mitoxantrone is *contraindicated* during pregnancy and for patients with abnormal LFTs or an LVEF below 50%.

Implementation: Administration

Route

Intravenous.

Administration

Infuse over 5 to 30 minutes through a free-flowing IV line. If extravasation occurs, discontinue the infusion immediately and restart in a different vein. Don't mix mitoxantrone with other drugs.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Indices of success include a reduction in the frequency and intensity of relapses, a reduction in new MRI-detectable lesions, and improvement in the EDSS score.

Monitoring Summary

Perform complete blood counts before each dose, 10 to 14 days after each dose, and whenever signs of infection develop.

Perform liver function tests before each dose.

Perform a pregnancy test before each dose.

Determine LVEF before each dose and whenever signs of heart failure develop.

Minimizing Adverse Effects

Myelosuppression.

Mitoxantrone can decrease production of platelets and all blood cells. Neutrophil loss increases the risk of severe infection, and hence the drug should be withheld if the neutrophil count has dropped below 1500 cells/mm***3*** **Advise patients to avoid contact with people who have infections, and instruct them to report signs of infection (fever, chills, cough, hoarseness) immediately.** Do not give patients a live virus vaccine.

Cardiotoxicity.

Mitoxantrone can cause irreversible injury to the heart, manifesting as a reduced LVEF or outright heart failure. Cardiotoxicity is directly related to the cumulative lifetime dose, which must not exceed 140 mg/m***2***. Withhold mitoxantrone if the LVEF drops below 50%. **Inform patients about symptoms of**

heart failure (eg, shortness of breath, fatigue, peripheral edema) and instruct them to report these immediately.

Fetal Harm.

Mitoxantrone is classified in FDA Pregnancy Risk Category D, and hence must not be used during pregnancy. Rule out pregnancy before each infusion. **Warn women of child-bearing age to avoid pregnancy. If pregnancy occurs, offer counseling about possible pregnancy termination.**

Urine and Tissue Discoloration.

Forewarn patients that mitoxantrone can impart a harmless, blue-green tint to the urine, skin, and sclera.

Neurologicl Drugs

24 Drugs for Epilepsy

The term *epilepsy* refers to a group of disorders characterized by excessive excitability of neurons in the central nervous system (CNS). This abnormal neuronal activity can produce a variety of symptoms, ranging from brief periods of unconsciousness to violent convulsions.

In the United States, about 2.3 million people have epilepsy. Every year, 150,000 new cases are diagnosed. The incidence is highest during the first year of life and in the elderly. Between 60% and 70% of patients can be rendered seizure free with drugs. Unfortunately, this means that 30% to 40% cannot.

The terms *seizure* and *convulsion* are not synonymous. *Seizure* is a general term that applies to all types of epileptic events. In contrast, *convulsion* has a more limited meaning, applying only to abnormal motor phenomena, for example, the jerking movements that occur during a tonic-clonic (grand mal) attack. Accordingly, although all convulsions may be called seizures, it is not correct to call all seizures convulsions. Absence seizures, for example, manifest as brief periods of unconsciousness, which may or may not be accompanied by involuntary movements. Since not all epileptic seizures involve convulsions, we will refer to the agents used to treat epilepsy as *antiepileptic drugs* (AEDs), rather than anticonvulsants.

SEIZURE GENERATION

Seizures are initiated by synchronous, high-frequency discharge from a group of hyperexcitable neurons, called a *focus*. A focus may result from several causes, including congenital defects, hypoxia at birth, head trauma, and cancer. Seizures result when discharge from a focus spreads to other brain areas, thereby recruiting normal neurons to discharge abnormally along with the focus.

The overt manifestations of any particular seizure disorder depend on the location of the seizure focus and the neuronal connections to that focus. (The connections to the focus determine the brain areas to which seizure activity can

spread.) If seizure activity invades a very limited part of the brain, a partial or local seizure occurs. In contrast, if seizure activity spreads to a large portion of the brain, a generalized seizure develops.

An experimental procedure referred to as *kindling* may explain how a focal discharge is eventually able to generate a seizure. Experimental kindling is performed by implanting a small electrode into the brain of an animal. The electrode is used to deliver localized stimuli for a brief interval once a day. When stimuli are first administered, no seizures result. However, after repeated once-a-day delivery, these stimuli eventually elicit a seizure. If brief, daily stimulations are continued long enough, spontaneous seizures will begin to occur.

The process of kindling may tell us something about seizure development in humans. For example, kindling may account for the delay that can take place between injury to the head and eventual development of seizures. Furthermore, kindling may explain why the seizures associated with some forms of epilepsy become more frequent as time passes. Also, the progressive nature of kindling suggests that early treatment might prevent seizure disorders from becoming more severe over time.

TYPES OF SEIZURES

Seizure can be divided into two broad categories: *partial (focal) seizures* and *generalized seizures*. In partial seizures, seizure activity begins focally in the cerebral cortex and usually undergoes limited spread to adjacent cortical areas. In generalized seizures, focal seizure activity is conducted widely throughout both hemispheres. As a rule, partial seizures and generalized seizures are treated with different drugs (Table 24-1).

	Drugs Used for Treatment	
Seizure Type	**Traditional AEDs**	**Newer AEDs**
Partial		
Simple partial, complex partial, and secondarily generalized	Carbamazepine	Oxcarbazepine
	Phenytoin	Gabapentin
	Valproic acid	Lamotrigine
	Phenobarbital	Levetiracetam
	Primidone	Pregabalin
		Topiramate
		Tiagabine
		Zonisamide
Primary Generalized		
Tonic-clonic	Carbamazepine	Lamotrigine
	Phenytoin	Levetiracetam
	Valproic acid	Topiramate
	Phenobarbital	
	Primidone	
Absence	Ethosuximide	Lamotrigine
	Valproic acid	
Myoclonic	Valproic acid	Lamotrigine
		Levetiracetam
		Topiramate

TABLE 24-1 Drugs for Specific Types of Seizures

Partial Seizures

Partial seizures fall into three groups: simple partial seizures, complex partial seizures, and partial seizures that evolve into secondarily generalized seizures.

Simple Partial Seizures.

These seizures manifest with discrete symptoms that are determined by the brain region involved. Hence, the patient may experience discrete motor symptoms (eg, twitching thumb), sensory symptoms (eg, local numbness; auditory, visual, or olfactory hallucinations), autonomic symptoms (eg, nausea, flushing, salivation, urinary incontinence), or psychoillusory symptoms (eg, feelings of unreality, fear, or depression). Simple partial seizures are distinguished from complex partial seizures in that there is *no loss of consciousness*. These seizures persist for 20 to 60 seconds.

Complex Partial Seizures.

These seizures are characterized by *impaired consciousness* and lack of responsiveness. At seizure onset, the patient becomes motionless and stares with a fixed gaze. This state is followed by a period of *automatism,* in which the patient performs repetitive, purposeless movements, such as lip smacking or hand wringing. Seizures last 45 to 90 seconds.

Secondarily Generalized Seizures.

These seizures begin as simple or complex partial seizures, and then evolve into generalized tonic-clonic seizures. Consciousness is lost. These seizures last 1 to 2 minutes.

Generalized Seizures

Generalized seizures may be convulsive or nonconvulsive. As a rule, they produce immediate loss of consciousness. The major generalized seizures are discussed briefly below.

Tonic-Clonic Seizures (Grand Mal).

In tonic-clonic seizures, neuronal discharge spreads throughout both hemispheres of the cerebral cortex. These seizures manifest as major convulsions, characterized by a period of muscle rigidity (tonic phase) followed by synchronous muscle jerks (clonic phase). Tonic-clonic seizures often cause urination, but not defecation. Convulsions may be preceded by a loud cry, caused by forceful expiration of air across the vocal cords. Tonic-clonic seizures are accompanied by marked impairment of consciousness and are followed by a period of CNS depression, referred to as the *postictal state*. The seizure itself lasts 90 seconds or less.

Absence Seizures (Petit Mal).

Absence seizures are characterized by loss of consciousness for a brief time (10 to 30 seconds). Seizures usually involve mild, symmetric motor activity (eg, eye blinking) but may occur with no motor activity at all. The patient may experience hundreds of absence attacks a day. Absence seizures occur primarily in children and usually cease during the early teens.

Atonic Seizures.

These seizures are characterized by sudden loss of muscle tone. If seizure activity is limited to the muscles of the neck, “head drop” occurs. However, if the muscles of the limbs and trunk are involved, a “drop attack” can occur, causing the patient to suddenly collapse. Atonic seizures occur mainly in children.

Myoclonic Seizures.

These seizures consist of sudden muscle contractions that last for just 1 second. Seizure activity may be limited to one limb (focal myoclonus) or it may involve the entire body (massive myoclonus).

Status Epilepticus.

Status epilepticus (SE) is defined as a seizure that persists for 30 minutes or longer. There are several types of SE, including generalized convulsive SE, absence SE, and myoclonic SE. Generalized convulsive SE, which can be life threatening, is discussed later.

Febrile Seizures.

Fever-associated seizures are common among children ages 6 months to 5 years. Febrile seizures typically manifest as generalized tonic-clonic convulsions of short duration. Children who experience these seizures are *not* at high risk of developing epilepsy later in life.

Mixed Seizures: Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy that usually develops during the preschool years. The syndrome is characterized by developmental delay and a mixture of partial and generalized seizures. Seizure types include partial, atonic, tonic, generalized tonic-clonic, and atypical absence. In children with LGS, seizures are often very difficult to treat.

HOW ANTIEPILEPTIC DRUGS WORK

We have long known that AEDs can (1) suppress discharge of neurons within a seizure focus and (2) suppress propagation of seizure activity from the focus to other areas of the brain. However, until recently we did not know how these effects were achieved. It now appears that AEDs act through four basic mechanisms: suppression of sodium influx, suppression of calcium influx, blockade of receptors for glutamate, and potentiation of gamma-aminobutyric acid (GABA).

Suppression of Sodium Influx.

Before discussing AED actions, we need to review sodium channel physiology. Neuronal action potentials are propagated by influx of sodium through sodium channels, which are gated pores in the cell membrane that control sodium entry. For sodium influx to occur, the channel must be in an *activated state*. Immediately following sodium entry, the channel goes into an *inactivated state,* during which further sodium entry is prevented. Under normal circumstances, the inactive channel very quickly returns to the activated state, thereby permitting more sodium entry and propagation of another action potential.

Several AEDs, including phenytoin, carbamazepine, valproic acid, and lamotrigine, reversibly bind to sodium channels while they are in the inactivated

state, and thereby prolong channel inactivation. By delaying return to the active state, these drugs decrease the ability of neurons to fire at high frequency. As a result, seizures that depend on high-frequency discharge are suppressed.

Suppression of Calcium Influx.

In axon terminals, influx of calcium through voltage-gated calcium channels promotes transmitter release. Hence, drugs that block these calcium channels can suppress transmission. Several AEDs, including valproic acid and ethosuximide, act by this mechanism.

Antagonism of Glutamate.

Glutamic acid (glutamate) is the primary excitatory transmitter in the CNS. The compound works through two receptors, known as (1) NMDA receptors (*N*-methyl-D-aspartate receptors) and (2) AMPA receptors (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors). Two drugs—felbamate and topiramate—block the actions of glutamate at NMDA and AMPA receptors, and thereby suppress neuronal excitation.

Potentiation of GABA.

Several AEDs potentiate the actions of GABA, an inhibitory neurotransmitter that is widely distributed throughout the brain. By augmenting the inhibitory influence of GABA, these drugs decrease neuronal excitability and thereby suppress seizure activity. Drugs increase the influence of GABA by several mechanisms. Benzodiazepines and barbiturates enhance the effects of GABA by mechanisms that involve direct binding to GABA receptors. Gabapentin promotes GABA release. Tiagabine inhibits GABA reuptake, and vigabatrin inhibits the enzyme that degrades GABA, and thereby increases GABA availability.

BASIC THERAPEUTIC CONSIDERATIONS

Therapeutic Goal and Treatment Options

The goal in treating epilepsy is to reduce seizures to an extent that enables the patient to live a normal or near-normal life. Ideally, treatment should eliminate seizures entirely. However, this may not be possible without causing intol-

erable side effects. Therefore, we must balance the desire for complete seizure control against the acceptability of side effects.

Epilepsy may be treated with drugs or with nondrug therapies. As noted, drugs can benefit 60% to 70% of patients. This means that, of the 2.3 million Americans with epilepsy, between 690,000 and 920,000 *cannot* be treated successfully with drugs. For these people, nondrug therapy may well help. Three options exist: neurosurgery, vagus nerve stimulation, and the ketogenic diet. Of the three, neurosurgery has the best success rate. All three nondrug therapies are discussed in Box 24-1.

Diagnosis and Drug Selection

Control of seizures requires proper drug selection. As indicated in Table 24-1, many AEDs are selective for specific seizure disorders. Phenytoin, for example, is useful for treating tonic-clonic and partial seizures but not absence seizures. Conversely, ethosuximide is active against absence seizures but does not work against tonic-clonic or partial seizures. Only one drug—valproic acid—appears effective against practically all forms of epilepsy. Since most AEDs are selective for certain seizure disorders, effective treatment requires a proper match between the drug and the seizure. To make this match, the seizure type must be accurately diagnosed.

Making a diagnosis requires physical, neurologic, and laboratory evaluations along with a thorough history. The history should determine the age at which seizures began, the frequency and duration of seizure events, precipitating factors, and times when seizures occur. Physical and neurologic evaluations may reveal signs of head injury or other disorders that could underlie seizure activity, although in many patients the physical and neurologic evaluations may be normal. An electroencephalogram (EEG) is essential for diagnosis. Other diagnostic tests that may be employed include computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI).

Very often, patients must try several AEDs before a regimen that is both effective and well tolerated can be established. Initial treatment should be done with just one AED. If this drug fails, it should be discontinued and a different AED should be tried. If this second drug fails, two options are open: (1) treatment with a third AED alone, or (2) treatment with a combination of AEDs.

Drug Evaluation

Once an AED has been selected, a trial period is needed to determine its effectiveness. During this time there is no guarantee that seizures will be controlled. Until seizure control is certain, the patient should be warned not to participate in driving and other activities that could be hazardous should a seizure occur.

During the process of drug evaluation, adjustments in dosage are often needed. No drug should be considered ineffective until it has been tested in sufficiently high dosage and for a reasonable time. Knowledge of plasma drug levels can be a valuable tool for establishing dosage and evaluating the effectiveness of a specific drug.

BOX 24-1 NONDRUG THERAPIES FOR EPILEPSY: NEUROSURGERY, VAGUS NERVE STIMULATION, AND THE KETOGENIC DIET

Neurosurgery: The Cure That's Rarely Used

For patients with temporal lobe epilepsy, surgery is highly effective, yet used only rarely. Despite advances in drug therapy, surgical intervention remains the only *cure* for epilepsy. (Although drugs can control symptoms, they don't offer a cure.) The safety and efficacy of surgery have been documented in literally hundreds of papers. Among patients with forms of epilepsy that can be treated surgically, the procedure can render between 70% and 90% seizure free—and, even when seizures do continue, their frequency is often decreased. This degree of success is all the more remarkable when we consider that, in order to qualify for surgery, candidates must first be proved refractory to drugs. Put another way, surgery is only performed on patients who have epilepsy that is especially hard to treat. Yet, despite its proven efficacy, surgery remains grossly underutilized: Each year, only 500 surgeries are performed, although more than 20,000 patients are eligible. This is especially unfortunate because, among people who are refractory to drugs, surgery can greatly improve seizure control, thereby improving quality of life, along with attendance at work and at school.

Temporal lobe surgery is not without risk. Between 5% and 10% of patients experience adverse effects, including infection, visual field defects, memory loss, and paralysis. The death rate is very low—only 0.2%. Prior to surgery, patients undergo a battery of tests designed to locate the seizure focus as well as nearby areas associated with language and other critical functions. This information allows the surgeon to remove as little tissue as possible, thereby minimizing disruption of normal brain function.

Vagus Nerve Stimulation: Fighting Impulses with Impulses

The vagus nerve stimulator (VNS) is the first medical device for reducing seizures. The only commercial VNS available—the VNS Therapy System (formerly known as the NeuroCybernetic Prosthesis System)—received FDA approval in 1997. The system is intended for use in conjunction with drugs by patients with severe, uncontrolled seizures. Responses to vagal stimulation develop slowly: Initial responses usually occur in 3 months, and full responses take even longer to develop.

The heart of the VNS is a small, programmable pulse generator that is implanted under the collarbone, much like a cardiac pacemaker. Subcutaneous leads connect the generator to the left branch of the vagus nerve in the neck. Stimulation is typically applied for 30 seconds every 5 minutes around the clock. When needed, stimulation parameters (voltage, frequency, duration) can be adjusted externally by the physician. By holding a small magnet over the generator, patients can activate the device manually if they feel a seizure coming on. In addition, patients can use the magnet to turn the generator off. VNS batteries last 3 to 5 years. Replacement is done in an outpatient procedure that takes 30 to 60 minutes.

In clinical trials, some patients responded dramatically and most showed at least some improvement. However, with a few patients, seizures *increased*. Specific results were as follows:

- In 26% of patients, seizure frequency decreased by 25% to 50%.
- In 11% of patients, seizure frequency decreased by more than 75%.
- In one patient, seizures stopped entirely.
- In 6% of patients, seizure frequency increased.

Vagal stimulation does not eliminate the need for drugs—but it can permit a simpler regimen. Up to 50% of patients can decrease the number of drugs they are taking (eg, two instead of three; one instead of two). Please note, however, that stimulation does *not* permit a reduction in dosage of the drugs that remain.

Vagal stimulation is well tolerated by most patients, although side effects occur often. During stimulation, patients experience hoarseness (100%), coughing (50%), voice alteration (73%), and shortness of breath (25%). In addition, there is a 2% to 3% risk of infection at the implant site. Stimulation does not cause cognitive effects and, perhaps surprisingly, does not cause autonomic effects (eg, bradycardia, GI disturbances, hypotension).

How does vagal stimulation decrease seizure frequency? No one knows. What we do know is that vagal fibers project to the brainstem, and from there to areas of the brain involved in seizure generation. When we stimulate the vagus, the resultant impulses in some way interrupt or prevent abnormal neuronal firing.

In 2005, the VNS Therapy System was approved for treating depression. This application is discussed in Chapter 32.

The Ketogenic Diet: It's Tough but It Works

The ketogenic diet for epilepsy can decrease seizure frequency, but it's hard to implement and potentially dangerous. The diet was introduced in the 1920s, but fell out of use when AEDs became available. Today, the diet is under renewed study as a way to control seizures when drug therapy fails. Because the diet is both difficult and hazardous, close medical supervision is essential.

The ketogenic diet has two cornerstones: high intake of fat and very low intake of carbohydrates. Fats—usually butter or heavy cream—comprise 80% of daily calories. In contrast, the carbohydrate allowance is very low—so low, in fact, that the sugar in a dose of valproic acid [Depakene] syrup would exceed the daily limit. With strict adherence to the diet, ketosis develops in a few days. However, with just a minor deviation from the diet (eg, ingestion of two cookies), ketosis will be lost in hours.

How does a high-fat, low-carbohydrate diet reduce seizures? By causing *ketoacidosis*. Because carbohydrate availability is low, the body burns fat to meet its needs. Burning fat produces large amounts of ketone bodies (beta-hydroxybutyric acid, acetoacetic acid, acetone), whose presence creates a state of ketoacidosis. For reasons that are unclear, ketoacidosis can decrease seizures in some patients.

The principal candidates for dietary therapy are children under the age of 10 who have not responded to AEDs. Depending on the child, the ketogenic diet may be very effective, moderately effective, or ineffective. In older clinical trials, about one-third of children became seizure free and were able to discontinue AEDs; one-third showed some improvement but still required AEDs; and one-third failed to benefit at all. Results of a more recent trial, released in 2008, indicated that, in treatment-resistant children, the diet can decrease seizure frequency by more than 50%. These results are of special interest in that this was the first randomized controlled trial to evaluate the diet's efficacy.

Adverse effects of the diet are considerable. The most consistent—and obvious—is elevation of blood cholesterol. In one study, cholesterol levels rose from a mean of 170 mg/dL to 245 mg/dL. In another study, five children developed severe hypercholesterolemia, with an average level of 367 mg/dL. Since cholesterol contributes to coronary artery disease (CAD), and since CAD is known to begin early in life, elevation of cholesterol is a significant drawback. Other adverse effects include poor linear growth, poor weight gain, kidney stones, dehydration, acidosis, constipation, and vomiting.

Maintenance of a seizure frequency chart is important for evaluating treatment. The chart should be kept by the patient or a family member and should contain a complete record of all seizure events. This record will enable the prescriber to determine if treatment has been effective. The nurse should teach the patient how to create and use a seizure frequency chart.

Monitoring Plasma Drug Levels

Monitoring plasma levels of AEDs is common. Safe and effective levels have been firmly established for most AEDs (Table 24-2). Measurement of these levels can help guide dosage adjustments.

Drug	Product Name	Daily Dosing	Daily Maintenance Dosage		Target Serum Level* (mcg/mL)	Induces Hepatic Drug Metabolism
			Adults (mg)	Children (mg/kg)		
Traditional AEDs						
Carbamazepine	Tegretol	3 times	600–1800	10–35	4–12	Yes
	Tegretol-XR	Twice				
	Carbatrol	Twice				
Ethosuximide	Zarontin	1 or 2 times	750	15–40	40–100	No
Phenobarbital	Generic only	1 or 2 times	60–120	3–6	15–45	Yes
Phenytoin	Phenytoin, prompt	2 or 3 times	200–300	4–8	10–20	Yes
	Dilantin Infatab	2 or 3 times				
	Dilantin Suspension	2 or 3 times				
	Phenytoin, extended	Once				
	Dilantin Kapseals	Once				
	Phenytek	Once				
Primidone	Mysoline	3 or 4 times	500–750	10–25	5–15†	Yes
Valproic acid	Depakene	3 or 4 times	750–3000	15–45	40–100	No
	Depakote	3 or 4 times				
	Depakote ER	Twice				
	Stavzor	2 or 3 times				
Newer AEDs						
Gabapentin	Neurontin	3 times	1200–3600	25–50	12–20	No
Lamotrigine	Lamictal	Twice	400‡§	5‡§	3–14	No
Levetiracetam	Keppra	Twice	2000–3000	40–100	10–40	No
Oxcarbazepine	Trileptal	Twice	900–2400	30–46	3–40	No¶
Pregabalin	Lyrica	2 or 3 times	150–600	ND	ND	No
Tiagabine	Gabitril Filmtabs	2 to 4 times	16–32	0.4§	ND	No
Topiramate	Topamax	Twice	100–400	3–9	5–25	No
Zonisamide	Zonegran	1 or 2 times	200–400	4–12	10–40	No

TABLE 24-2 Clinical Pharmacology of the Oral Antiepileptic Drugs (AEDs)

* ND = not determined.

† Target serum level is 5 to 15 mcg/mL for primidone itself, and 15 to 40 mcg/mL for phenobarbital derived from primidone.

‡ Dosage must be decreased in patients taking valproic acid.

§ Dosage must be increased in patients taking drugs that induce hepatic drug-metabolizing enzymes.

¶ Oxcarbazepine does not induce enzymes that metabolize AEDs, but does induce enzymes that metabolize other kinds of drugs.

Monitoring plasma drug levels is especially helpful when treating major convulsive disorders (eg, tonic-clonic seizures). Since these seizures can be dangerous, and since delay of therapy may allow the condition to worsen, rapid control of seizures is desirable. However, because these seizures occur infrequently, a long time may be needed to establish control if clinical outcome is relied on as the only means of determining an effective dosage. By adjusting initial doses on the basis of plasma drug levels (rather than on the basis of seizure control), we can readily achieve drug levels that are likely to be effective, thereby increasing our chances of establishing control quickly.

Measurements of plasma drug levels are not especially important for determining effective dosages for absence seizures. Why? Because absence seizures occur very frequently (up to several hundred a day), and hence observation of the patient is the best means for establishing an effective dosage: if seizures stop, dosage is sufficient; if seizures continue, more drug is needed.

In addition to serving as a guide for dosage adjustment, knowledge of plasma drug levels can serve as an aid to (1) monitoring patient adherence, (2) determining the cause of lost seizure control, and (3) identifying causes of toxicity, especially in patients taking more than one drug.

Promoting Patient Adherence

Epilepsy is a chronic condition that requires regular and continuous therapy. As a result, seizure control is highly dependent on patient adherence. In fact, it is estimated that nonadherence accounts for about 50% of all treatment failures. Accordingly, promoting adherence should be a priority for all members of the healthcare team. Measures that can help include

- Educating patients and families about the chronic nature of epilepsy and the importance of adhering to the prescribed regimen.
- Monitoring plasma drug levels so as to encourage and evaluate adherence.
- Deepening patient and family involvement by having them maintain a seizure frequency chart.

Withdrawing Antiepileptic Drugs

Some forms of epilepsy undergo spontaneous remission, and hence discontinuing treatment may at some time be appropriate. Unfortunately, there are no firm guidelines to indicate the most appropriate time to withdraw AEDs. However, once the decision to discontinue treatment has been made, agreement does exist on how drug withdrawal should be accomplished. The most important rule is that *AEDs be withdrawn slowly* (over a period of 6 weeks to several months). Failure to gradually reduce dosage is a frequent cause of SE. If the patient is taking two drugs to control seizures, they should be withdrawn sequentially, not simultaneously.

Suicide Risk with Antiepileptic Drugs

In 2008, the Food and Drug Administration (FDA) warned that AEDs may increase suicidal thoughts and behavior. By analyzing data from 199 placebo-controlled studies involving 11 different AEDs, the FDA found that, compared with patients taking a placebo, patients taking AEDs had *twice* the risk of suicidal thoughts and behaviors (0.43% vs. 0.22%). The reason underlying the increased risk is unknown. Of note, risk was higher among patients taking AEDs for epilepsy than among patients taking these drugs for other conditions, such as migraine, neuropathic pain, or psychiatric illness. Risk may rise within 1 week of starting AEDs and may continue for 24 weeks or more. Although the analysis was limited to 11 drugs, the FDA believes the results probably apply to *all* AEDs. Accordingly, all patients using these drugs should be monitored for increased anxiety, agitation, mania, and hostility—signs that may indicate the emergence or worsening of depression, and an increased risk of suicidal thoughts or behaviors. Patients, families, and caregivers should be alerted to these signs and advised to report them immediately.

CLASSIFICATION OF ANTIEPILEPTIC DRUGS

The AEDs can be grouped into two major categories: *traditional AEDs* and *newer AEDs*. The traditional group has six major members, the last of which—valproic acid—was approved in 1978. The group of newer AEDs has eight major members, all of which were approved in 1993 or later. As summarized in Table 24-3, both groups have their advantages and disadvantages. For example, clinical experience with the older AEDs is more extensive than with the newer ones, and the older drugs cost less. Both facts make the older drugs attractive. However, the older AEDs also have drawbacks, including troublesome side effects and complex drug interactions. Of importance, drugs in both groups appear equally effective—although few direct comparisons have been made. The bottom line? Neither group is clearly superior to the other. Hence, when selecting an AED, drugs in both groups should be considered.

	Drug Group	
Area of Comparison	**Traditional AEDs***	**Newer AEDs†**
Efficacy	Well established	Equally good (probably), but less well established
Clinical experience	Extensive	Less extensive
Therapeutic niche	Well established	Evolving
Tolerability	Less well tolerated	Better tolerated
Pharmacokinetics	Often complex	Less complex
Drug interactions	Extensive, owing to induction of drug-metabolizing enzymes	Limited; no induction of drug-metabolizing enzymes
Safety in pregnancy	Less safe	Safer
Cost	Less expensive	More expensive

TABLE 24-3 Comparison of Traditional and Newer Antiepileptic Drugs

* Carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproic acid.

† Gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide.

TRADITIONAL ANTIEPILEPTIC DRUGS

The traditional AEDs have been in use for many years. Antiseizure properties of phenobarbital, the oldest member of the group, were demonstrated in 1912. Even the youngest member—valproic acid—has been in use for over three decades. Because of this extensive clinical experience, the efficacy and therapeutic niche of the traditional AEDs are well established. As a result, these drugs are prescribed more widely than the newer AEDs. In the discussion below, we focus on six of the traditional AEDs: phenytoin, carbamazepine, valproic acid, ethosuximide, phenobarbital, and primidone. The group has other members, but they are less important.

Although familiarity makes the traditional AEDs appealing, these drugs do have drawbacks. In general, they are less well tolerated than the newer AEDs, and they pose a greater risk to the developing fetus. Furthermore, owing to effects on drug-metabolizing enzymes (either induction or inhibition), they have complex interactions with other drugs, including other AEDs.

Phenytoin

Phenytoin [Dilantin, Phenytek] is our most widely used AED, despite having tricky kinetics and troublesome side effects. The drug is active against partial seizures as well as primary generalized tonic-clonic seizures. Phenytoin is of historic importance in that it was the first drug to suppress seizures without depressing the entire CNS. Hence, phenytoin heralded the development of selective medications that could treat epilepsy while leaving most CNS functions undiminished.

Mechanism of Action

At the concentrations achieved clinically, phenytoin causes selective inhibition of sodium channels. Specifically, the drug slows recovery of sodium channels from the inactive state back to the active state. As a result, entry of sodium into neurons is inhibited, and hence action potentials are suppressed. Blockade of sodium entry is limited to neurons that are hyperactive. As a res-

ult, the drug suppresses activity of seizure-generating neurons while leaving healthy neurons unaffected.

Pharmacokinetics

Phenytoin has unusual pharmacokinetics that must be accounted for in therapy. Absorption varies substantially among patients. In addition, because of saturable kinetics, small changes in dosage can produce disproportionately large changes in serum drug levels. As a result, a dosage that is both effective and safe is difficult to establish.

Absorption.

Absorption varies between the different oral formulations of phenytoin. With some—Dilantin Infatab, Dilantin Suspension, phenytoin (prompt)—absorption is relatively fast, whereas with others—Dilantin Kapseals, Phenytek, phenytoin (extended)—absorption is delayed and prolonged.

In the past, there was concern that absorption also varied between preparations of phenytoin made by different manufacturers. However, it is now clear that all FDA-approved equivalent products have equivalent bioavailability. As a result, switching from one brand of phenytoin to another produces no more variability than switching between lots of phenytoin produced by the same manufacturer.

Metabolism.

The capacity of the liver to metabolize phenytoin is very limited. As a result, the relationship between dosage and plasma levels of phenytoin is unusual. Doses of phenytoin needed to produce therapeutic effects are only slightly smaller than the doses needed to saturate the hepatic enzymes that metabolize phenytoin. Consequently, if phenytoin is administered in doses only slightly greater than those needed for therapeutic effects, the liver's capacity to metabolize the drug will be overwhelmed, causing plasma levels of phenytoin to rise dramatically. This unusual relationship between dosage and plasma levels is illustrated in Figure 24-1*A*. As you can see, once plasma levels have reached the therapeutic range, small changes in dosage produce large changes in drug levels. As a result, small increases in dosage can cause toxicity, and small decreases can cause therapeutic failure. This relationship

makes it difficult to establish and maintain a dosage that is both safe and effective.

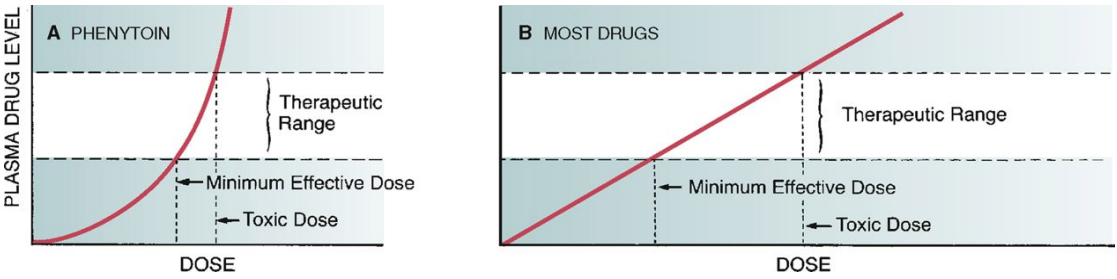


Figure 24-1 Relationship between dose and plasma level for phenytoin compared with most other drugs. A, Within the therapeutic range, small increments in phenytoin dosage produce sharp increases in plasma drug levels. This relationship makes it difficult to maintain plasma phenytoin levels within the therapeutic range. B, Within the therapeutic range, small increments in dosage of most drugs produce small increases in drug levels. With this relationship, moderate fluctuations in dosage are unlikely to result in either toxicity or loss of therapeutic effects.

Figure 24-1*B* indicates the relationship between dosage and plasma levels that exists for most drugs. As indicated, this relationship is *linear,* in contrast to the nonlinear relationship that exists for phenytoin. Accordingly, for most drugs, if the patient is taking doses that produce plasma levels that are within the therapeutic range, small deviations from that dosage produce only small deviations in plasma drug levels. Because of this relationship, for most drugs it is relatively easy to maintain plasma levels that are safe and effective.

Because of saturation kinetics, the half-life of phenytoin varies with dosage. At low doses, the half-life is relatively short—about 8 hours. However, at higher doses, the half-life becomes prolonged—in some cases up to 60 hours. Why? Because, at higher doses, there is more drug present than the liver can process. As a result, metabolism is delayed, causing the half-life to increase.

Therapeutic Uses

Epilepsy.

Phenytoin can be used to treat all major forms of epilepsy except absence seizures. The drug is especially effective against tonic-clonic seizures, and is a drug of choice for treating these seizures in adults and older children. (Carbamazepine is preferred to phenytoin for treating tonic-clonic seizures in young children.) Although phenytoin can be used to treat simple and complex partial seizures, the drug is less effective against these seizures than against tonic-clonic seizures. Phenytoin can be administered IV to treat generalized convulsive SE, but other drugs are preferred.

Cardiac Dysrhythmias.

Phenytoin is active against certain types of dysrhythmias. Antidysrhythmic applications are discussed in Chapter 48.

Adverse Effects

Effects on the CNS.

Although phenytoin acts on the CNS in a relatively selective fashion to suppress seizures, the drug is not completely devoid of CNS side effects—especially when dosage is excessive. At therapeutic levels (10 to 20 mcg/mL), sedation and other CNS effects are mild. At plasma levels above 20 mcg/mL, toxicity can occur. Nystagmus (continuous back-and-forth movements of the eyes) is relatively common. Other manifestations of excessive dosage include sedation, ataxia (staggering gait), diplopia (double vision), and cognitive impairment.

Gingival Hyperplasia.

Gingival hyperplasia (excessive growth of gum tissue) is characterized by swelling, tenderness, and bleeding of the gums. This effect occurs in about 20% of patients. Gingival hyperplasia can be minimized by good oral hygiene, including dental flossing and gum massage. Patients should be taught these techniques and encouraged to practice them. In some cases, gingival hyperplasia is so great as to require gingivectomy (surgical removal of excess gum tissue).

Skin Rash.

Between 2% and 5% of patients develop a morbilliform (measles-like) rash. Rarely, morbilliform rash progresses to toxic epidermal necrolysis or Stevens-Johnson syndrome, an inflammatory skin disease characterized by red macules, papules, and tubercles. If a rash develops, phenytoin should be stopped.

Effects in Pregnancy.

Phenytoin is a teratogen in animals and humans. In animals, the drug can cause cleft palate, hydrocephalus, renal defects, and micromelia (small or shortened limbs). In humans, phenytoin can cause cleft palate, heart malformations, and *fetal hydantoin syndrome,* characterized by growth deficiency, motor or mental deficiency, microcephaly, craniofacial distortion, positional deformities of the limbs, hypoplasia of the nails and fingers, and impaired neurodevelopment. Accordingly, phenytoin should be used during pregnancy only if the benefits of seizure control outweigh the risk to the fetus.

Phenytoin can decrease synthesis of vitamin K–dependent clotting factors, and can thereby cause *bleeding tendencies in newborns*. The risk of neonatal bleeding can be decreased by giving the mother prophylactic vitamin K for 1 month prior to and during delivery, and to the infant immediately after delivery.

Cardiovascular Effects.

When phenytoin is administered by IV injection (to treat SE), cardiac dysrhythmias and hypotension may result. These dangerous responses can be minimized by injecting phenytoin slowly and in dilute solution.

Other Adverse Effects.

Hirsutism (overgrowth of hair in unusual places) can be a disturbing response, especially in young women. Interference with vitamin D metabolism may cause *rickets* and *osteomalacia* (softening of the bones). Interference with vitamin K metabolism can lower prothrombin levels, thereby causing *bleeding tendencies in newborns*. Very rarely, *liver damage* occurs, probably because of drug allergy.

Drug Interactions

Phenytoin interacts with a large number of drugs. The more important interactions are discussed below.

Interactions Resulting from Induction of Hepatic Drug-Metabolizing Enzymes.

Phenytoin stimulates synthesis of hepatic drug-metabolizing enzymes. As a result, phenytoin can decrease the effects of other drugs, including *oral contraceptives, warfarin* (an anticoagulant), and *glucocorticoids* (anti-inflammatory/immunosuppressive drugs). Because avoiding pregnancy is desirable while taking antiseizure medications, and because phenytoin can decrease the effectiveness of oral contraceptives, women should increase the contraceptive dosage, or switch to an alternative form of contraception.

Drugs That Increase Plasma Levels of Phenytoin.

Since the therapeutic range of phenytoin is narrow, slight increases in phenytoin levels can cause toxicity. Consequently, caution must be exercised when phenytoin is used with drugs that can increase its level. Drugs known to elevate phenytoin levels include *diazepam* (an antianxiety agent and AED), *isoniazid* (a drug for tuberculosis), *cimetidine* (a drug for gastric ulcers), and *alcohol* (when taken acutely). These agents increase phenytoin levels by reducing the rate at which phenytoin is metabolized. *Valproic acid* (an AED) elevates levels of free phenytoin by displacing phenytoin from binding sites on plasma proteins.

Drugs That Decrease Plasma Levels of Phenytoin.

Carbamazepine, phenobarbital, and alcohol (when used chronically) can accelerate the metabolism of phenytoin, thereby decreasing its level. Breakthrough seizures can result.

CNS Depressants.

The depressant effects of *alcohol, barbiturates, and other CNS depressants* will add with those of phenytoin. Advise patients to avoid alcohol and all other drugs with CNS-depressant actions.

Preparations, Dosage, and Administration

Preparations.

Phenytoin [Dilantin, Phenytek] is available in solution for injection and in four oral formulations: (1) 50-mg chewable tablets, marketed as *Dilantin Infatab;* (2) a 25-mg/mL oral suspension, marketed as *Dilantin-125;* (3) 100-mg prompt-acting capsules (generic only); and (4) 30- and 100-mg extended-release capsules, marketed as *Dilantin, Dilantin Kapseals,* and *Phenytek*. Phenytoin products made by different manufacturers have equivalent bioavailability. Hence, although switching between products from different manufacturers was a concern in the past, it is not a concern today.

Dosage.

Dosing is highly individualized. Initial doses are usually given twice daily. Once a maintenance dosage has been established, once-a-day dosing is often possible (using extended-release capsules). For *adults,* a typical initial dosage is 150 mg twice a day; maintenance dosages usually range between 200 and 300 mg/day. For *children,* a typical initial dosage is 2.5 mg/kg twice a day; maintenance dosages usually range between 4 and 8 mg/kg/day.

Plasma drug levels are often monitored as an aid to dosage determination. *The dosing objective is to produce levels between 10 and 20 mcg/mL*. Levels below 10 mcg/mL are too low to control seizures; levels above 20 mcg/mL produce toxicity. Because phenytoin has a relatively narrow therapeutic range (between 10 and 20 mcg/mL), and because of the nonlinear relationship between phenytoin dosage and phenytoin plasma levels, *once a safe and effective dosage has been established, the patient should adhere to it rigidly*.

When treatment is discontinued, dosage should be reduced gradually. Abrupt withdrawal may precipitate seizures.

Administration.

Oral preparations may cause gastric discomfort. Patients should be informed that gastric upset can be reduced by administering phenytoin with or immediately after a meal. Patients using the oral suspension should shake it well before dispensing, since failure to do so can result in uneven dosing.

Intravenous administration is used to treat generalized convulsive SE. *It is imperative that infusions be performed slowly* (no faster than 50 mg/min). Why?

Because rapid administration can cause cardiovascular collapse. Phenytoin should not be added to an existing IV infusion, since mixing phenytoin with other solutions is likely to produce a precipitate. Solutions of phenytoin are highly alkaline and can cause local venous irritation. Irritation can be reduced by flushing the IV needle or catheter with sterile saline immediately after completing the infusion.

Carbamazepine

Carbamazepine [Tegretol, Tegretol-XR, Carbatrol, Epitol, Equetro] is a cornerstone of epilepsy therapy. The drug is active against partial seizures and tonic-clonic seizures but not absence seizures.

Mechanism of Action

Carbamazepine suppresses high-frequency neuronal discharge in and around seizure foci. The mechanism appears to be the same as that of phenytoin: delayed recovery of sodium channels from their inactivated state.

Pharmacokinetics

Absorption of carbamazepine is delayed and variable. Peak levels are achieved in 4 to 12 hours. Overall bioavailability is about 80%. The drug distributes well to tissues.

Elimination is by hepatic metabolism. Carbamazepine is unusual in that its half-life decreases as therapy progresses. During the initial phase of treatment, the half-life is about 40 hours. The half-life decreases to about 15 hours with continued treatment. Why? Because carbamazepine, like phenytoin and phenobarbital, induces hepatic drug-metabolizing enzymes; by increasing its own metabolism, carbamazepine causes its own half-life to decline.

Therapeutic Uses

Epilepsy.

Carbamazepine is effective against tonic-clonic, simple partial, and complex partial seizures. Because the drug causes fewer adverse effects than phenytoin and phenobarbital, it is often preferred to these agents. Many prescribers

consider carbamazepine the drug of first choice for partial seizures. Carbamazepine is not effective against absence, myoclonic, or atonic seizures.

Bipolar Disorder.

Carbamazepine can provide symptomatic control in patients with bipolar disorder (manic-depressive illness), and is often effective in patients who are refractory to lithium. The role of carbamazepine in bipolar disorder is discussed in Chapter 33.

Trigeminal and Glossopharyngeal Neuralgias.

A neuralgia is a severe, stabbing pain that occurs along the course of a nerve. Carbamazepine can reduce neuralgia associated with the trigeminal and glossopharyngeal nerves. The mechanism is unknown. It should be noted that, although carbamazepine can reduce pain in these specific neuralgias, it is not generally effective as an analgesic, and is not indicated for other kinds of pain.

Adverse Effects

CNS Effects.

In contrast to phenytoin and phenobarbital, carbamazepine has minimal effects on cognitive function. This is a primary reason for selecting carbamazepine over these other drugs.

Carbamazepine can cause a variety of *neurologic effects,* including visual disturbances (nystagmus, blurred vision, diplopia), ataxia, vertigo, unsteadiness, and headache. These reactions are common during the first weeks of treatment, affecting 35% to 50% of patients. Fortunately, tolerance usually develops with continued use. These effects can be minimized by initiating therapy at low doses and giving the largest portion of the daily dose at bedtime.

Hematologic Effects.

Carbamazepine-induced bone marrow suppression can cause *leukopenia, anemia,* and *thrombocytopenia*. However, serious reactions are rare. Thrombocytopenia and anemia, which have an incidence of 5%, respond to drug discontinuation. Leukopenia, which has an incidence of 10%, is usually transient and

subsides even with continued drug use; accordingly, carbamazepine should not be withdrawn unless the white blood cell count drops below 3000/mm3.

Fatal *aplastic anemia* has occurred during carbamazepine therapy. This reaction is extremely rare, having an incidence of 1 in 200,000. Very few cases have been reported since 1964, and in many of these, a direct cause-and-effect relationship could not be established.

To reduce the risk of serious hematologic effects, complete blood counts should be performed before treatment and periodically thereafter. Patients with pre-existing hematologic abnormalities should not use this drug. Patients should be informed about manifestations of hematologic abnormalities (fever, sore throat, pallor, weakness, infection, easy bruising, petechiae) and instructed to notify the prescriber if these occur.

Birth Defects.

Carbamazepine may be teratogenic. In humans, the drug is associated with an increased risk of neural tube defects. In mice, it has caused cleft palate, dilated cerebral ventricles, and growth retardation. Because it can harm the fetus, carbamazepine is classified in FDA Pregnancy Risk Category D, and hence should be used only if the benefits of seizure control are deemed to outweigh risks to the fetus.

Hypo-Osmolarity.

Carbamazepine can inhibit renal excretion of water, apparently by promoting secretion of antidiuretic hormone. Water retention can reduce the osmolarity of blood and other body fluids, thereby posing a threat to patients with heart failure. Periodic monitoring of serum sodium content is recommended.

Dermatologic Effects.

Carbamazepine has been associated with several dermatologic effects, including morbilliform rash (10% incidence), photosensitivity reactions, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Mild reactions can often be treated with prednisone (an anti-inflammatory agent) or an antihistamine. Severe reactions—SJS and TEN—necessitate drug withdrawal.

A major risk factor for severe skin reactions is a genetic variation known as *human leukocyte antigen (HLA)-B*1502,* which occurs primarily in people of Asian descent. Among people with the variant gene, about 5% develop SJS or TEN when taking carbamazepine. Accordingly, to reduce the risk of severe reactions, the FDA recommends that, before receiving carbamazepine, patients of Asian descent be tested for HLA-B*1502. Of note, this is the first time that the FDA has recommended genetic screening for a major drug.

Drug-Drug and Drug-Food Interactions

Induction of Drug-Metabolizing Enzymes.

Carbamazepine is an effective inducer of hepatic drug-metabolizing enzymes. By promoting synthesis of these enzymes, carbamazepine can increase the rate at which it and other drugs are inactivated. Accelerated inactivation of *oral contraceptives* and *warfarin* is of particular concern.

Phenytoin and Phenobarbital.

Both phenytoin and phenobarbital are effective inducers of hepatic drug metabolism. Hence, if either drug is taken with carbamazepine, induction of metabolism is likely to be greater than with carbamazepine alone. Accordingly, phenytoin and phenobarbital can further accelerate the metabolism of carbamazepine, thereby decreasing its effects.

Grapefruit Juice.

As discussed in Chapter 6, grapefruit juice can inhibit the metabolism of many drugs, thereby causing their plasma levels to rise. Grapefruit juice can increase peak and trough levels of carbamazepine by 40%. Accordingly, patients taking the drug should be advised to avoid grapefruit juice.

Preparations, Dosage, and Administration

Carbamazepine [Tegretol, Tegretol-XR, Carbatrol, Epitol, Equetro] is available in immediate-release tablets (200 mg), sold as *Tegretol* and *Epitol;* chewable tablets (100 mg), sold as *Tegretol;* extended-release tablets (100, 200, and 400 mg), sold as *Tegretol-XR;* extended-release capsules (200 and 300 mg), sold as *Carbatrol* and *Equetro;* and an oral suspension (20 mg/mL), sold as *Tegretol*. The

drug should be administered with meals to reduce gastric upset. Administering the largest portion of the daily dose at bedtime can help reduce adverse CNS effects. Carbamazepine suspension should not be administered with other liquid-formulation medicines.

Therapy is initiated with small doses (100 to 200 mg twice a day) to minimize side effects. Dosage is then increased gradually (every 1 to 3 weeks) until seizure control is achieved. Maintenance dosages for *adults* range from 600 to 1800 mg/day, administered in divided doses. Maintenance dosages for *children* range from 10 to 35 mg/kg/day, administered in divided doses.

Valproic Acid

Valproic acid [Depakene, Depakote, Depacon, Stavzor] is an important AED used widely to treat all major seizure types. Serious adverse effects are limited to rare cases of severe hepatotoxicity and pancreatitis, both of which can be fatal. In addition to its use in epilepsy, valproic acid is used for bipolar disorder and prevention of migraine.

Nomenclature

Valproic acid is available in three closely related chemical forms (Table 24-4): (1) valproic acid itself, (2) the sodium salt of valproic acid, known as *valproate,* and (3) *divalproex sodium,* a combination of valproic acid plus its sodium salt. All three forms have identical antiseizure actions. In this chapter, the term *valproic acid* is used in reference to all three forms.

Chemical Form	Trade Name	Product Description	Comments
Valproic acid	Depakene	Capsules (250 mg)	Immediate release; GI upset is common.
	Stavzor	Capsule, delayed-release, enteric-coated (125, 250, 500 mg)	Capsule is smaller than Depakote and Depakote ER tablets, and hence easier to swallow. Enteric coating may reduce GI upset, but there are no clinical data to show that Stavzor is better tolerated than Depakene.
Valproate sodium	Depakene	Syrup (250 mg/5 mL)	Immediate release; GI upset is common.
Divalproex sodium	Depakote	Tablets, delayed-release, enteric-coated (125, 250, 500 mg)	Released over 8–12 hr, and hence *not* for once-daily administration. *Not interchangeable with Depakote ER* (extended-release tablets) because rate of drug release is different. Less GI upset than Depakene.
	Depakote ER	Tablets, extended-release, enteric-coated (250 and 500 mg)	Released over 18–24 hr, and hence *can* be administered once daily. *Not interchangeable with regular Depakote* (delayed-release tablets) because rate of drug release is different. Not approved for epilepsy (but is used anyway). Less GI upset than Depakene.
	Depakote	"Sprinkle" capsules containing enteric-coated granules (125 mg)	Immediate release. Less GI upset than Depakene. May swallow capsule whole or open and sprinkle granules on a small

TABLE 24-4 Oral Preparations of Valproic Acid and Its Derivatives

Mechanism of Action

Valproic acid appears to act by three mechanisms. First, it shares the same mechanism as phenytoin and carbamazepine: suppression of high-frequency neuronal firing through blockade of sodium channels. Second, it suppresses calcium influx through T-type calcium channels. Third, it may augment the inhibitory influence of GABA.

Pharmacokinetics

Valproic acid is readily absorbed from the GI tract and is widely distributed throughout the body. The drug undergoes extensive hepatic metabolism followed by renal excretion.

Therapeutic responses are often seen at plasma levels of 40 to 100 mcg/mL. However, the correlation between plasma levels and therapeutic effects is not very tight.

Therapeutic Uses

Seizure Disorders.

Valproic acid is considered a first-line drug for all partial and generalized seizures.

Bipolar Disorder.

Like carbamazepine, valproic acid can provide symptomatic control in patients with bipolar disorder (manic-depressive illness). This application is discussed in Chapter 33.

Migraine.

Valproic acid is approved for prophylaxis of migraine (see Chapter 30).

Adverse Effects

Valproic acid is generally well tolerated and causes minimal sedation and cognitive impairment. Gastrointestinal effects are most common. Hepatotoxicity and pancreatitis are rare but serious.

Gastrointestinal Effects.

Nausea, vomiting, and indigestion are common but transient. These effects are most intense with formulations that are not enteric coated. Gastrointestinal reactions can be minimized by administering valproic acid with food and by using an enteric-coated product (see Table 24-4).

Hepatotoxicity.

Rarely, valproic acid has been associated with fatal liver failure. Most deaths have occurred within the first few months of therapy. The overall incidence of fatal hepatotoxicity is about 1 in 40,000. However, in high-risk patients—children under the age of 2 years receiving multidrug therapy—the incidence is much higher: 1 in 500. To minimize the risk of fatal liver injury, the following guidelines have been established:

- Don't use valproic acid in conjunction with other drugs in children under 2 years old.
- Don't use valproic acid in patients with pre-existing liver dysfunction.
- Evaluate liver function at baseline and periodically thereafter. (Unfortunately, monitoring liver function may fail to provide advance warning of severe hepatotoxicity: Fatal liver failure can develop so rapidly that it is not preceded by an abnormal test result.)
- Inform patients about signs and symptoms of liver injury (reduced appetite, malaise, nausea, abdominal pain, jaundice) and instruct them to notify the prescriber if these develop.
- Use valproic acid in the lowest effective dosage.

Pancreatitis.

Life-threatening pancreatitis has developed in children and adults. Some cases have been hemorrhagic, progressing rapidly from initial symptoms to death. Pancreatitis can develop soon after starting therapy or after years of drug use.

Patients should be informed about signs of pancreatitis (abdominal pain, nausea, vomiting, anorexia) and instructed to obtain immediate evaluation if these develop. If pancreatitis is diagnosed, valproic acid should be withdrawn, and alternative medication should be substituted as indicated.

Teratogenic Effects.

Like most other AEDs, valproic acid can harm the developing fetus. Neural tube defects (eg, spina bifida) are the greatest concern, with an incidence of 1% to 2%. Women of child-bearing age should use an effective form of contraception, and should take folic acid supplements (5 mg/day), which can help protect against neural tube damage in case pregnancy occurs. Valproic acid is classified in FDA Pregnancy Risk Category D: There is evidence of human fetal risk, but the drug may be used during pregnancy if the potential benefits are considered to outweigh the risks to the fetus.

Hyperammonemia.

Combining valproic acid with topiramate poses a risk of hyperammonemia (excessive ammonia in the blood), which may occur with or without encephalopathy. Symptoms include vomiting, lethargy, altered level of consciousness, and altered cognitive function. If these symptoms develop, hyperammonemic encephalopathy should be suspected, and blood ammonia should be measured. As a rule, symptoms abate following removal of either drug.

Other Adverse Effects.

Valproic acid may cause *rash, weight gain, hair loss, tremor,* and *blood dyscrasias* (leukopenia, thrombocytopenia, red blood cell aplasia). Significant CNS effects are uncommon.

Drug Interactions

Phenobarbital.

Valproic acid decreases the rate at which phenobarbital is metabolized. Blood levels of phenobarbital may rise by 40%, resulting in significant CNS depression. When the combination is used, levels of phenobarbital should be monitored and, if they rise too high, phenobarbital dosage should be reduced.

Phenytoin.

Valproic acid can displace phenytoin from binding sites on plasma proteins. The resultant increase in free phenytoin may lead to toxicity. Phenytoin levels and clinical status should be monitored.

Topiramate.

See discussion of *Hyperammonemia* above.

Preparations, Dosage, and Administration

Preparations.

Valproic acid is available in several oral formulations (see Table 24-4) and in a 100-mg/mL solution [Depacon] for IV use.

Oral Dosage and Administration.

Daily doses are small initially and then gradually increased. For *adults and older children,* the initial dosage is 5 to 15 mg/kg/day, usually administered in two divided doses. The usual maintenance dosage is 0.75 to 3 gm/day. For *children ages 1 to 12 years,* the initial dosage is 10 to 30 mg/kg/day, usually administered in divided doses. The usual maintenance dosage is 15 to 45 mg/kg/day. For both adults and children, the dosage should be increased if phenobarbital or another inducer of hepatic drug metabolism is taken concurrently.

Patients should be instructed to swallow the tablets and capsules intact, without chewing or crushing. Gastric discomfort can be decreased by administering valproic acid with meals and by using an enteric-coated formulation.

Ethosuximide

Therapeutic Use.

Ethosuximide [Zarontin] is a drug of choice for absence seizures, the only indication the drug has. Absence seizures are abolished in 60% of patients, and, in newly diagnosed patients, practical control is achieved in 80% to 90%. Ethosuximide is inactive against tonic-clonic, simple partial, and complex partial seizures.

Mechanism of Action.

Ethosuximide suppresses neurons in the thalamus that are responsible for generating absence seizures. The specific mechanism is inhibition of low-threshold calcium currents, known as T currents. Ethosuximide does not block sodium channels and does not enhance GABA-mediated neuronal inhibition.

Pharmacokinetics.

Ethosuximide is well absorbed following oral administration. Therapeutic plasma levels range between 40 and 100 mcg/mL. The drug is eliminated by a combination of hepatic metabolism and renal excretion. Its half-life is 60 hours in adults and 30 hours in children. Ethosuximide does not induce drug-metabolizing enzymes.

Adverse Effects and Drug Interactions.

Ethosuximide is generally devoid of significant adverse effects and interactions. During initial treatment, it may cause *drowsiness, dizziness,* and *lethargy*. These diminish with continued use. *Nausea* and *vomiting* may occur and can be reduced by administering the drug with food. Rare but serious reactions include *systemic lupus erythematosus, leukopenia, aplastic anemia,* and *Stevens-Johnson syndrome*.

Preparations, Dosage, and Administration.

Ethosuximide [Zarontin] is available in capsules (250 mg) and in a syrup (250 mg/5 mL). For *children ages 3 to 6 years,* the initial dosage is 250 mg/day. For *older children and adults,* the initial dosage is 500 mg/day. Dosage should be gradually increased until control of seizures is obtained. The usual maintenance dosage is 750 mg/day for adults, and between 15 and 40 mg/kg/day for children. Because ethosuximide has a long half-life, dosing can be done just once a day. However, dosing twice a day is better tolerated.

Since absence seizures occur many times each day, monitoring the clinical response rather than plasma drug levels is the preferred method for dosage determination. Dosage should be increased until seizures have been controlled or until adverse effects become too great.

When withdrawing ethosuximide, dosage should be reduced gradually.

Phenobarbital

Phenobarbital is one of our oldest AEDs. The drug is effective, is inexpensive, and can be administered just once a day. Unfortunately, certain side effects—lethargy, depression, learning impairment—can be significant. Hence, although phenobarbital was used widely in the past, it has largely been replaced by newer drugs that are equally effective but better tolerated.

Phenobarbital belongs to the barbiturate family. However, in contrast to most barbiturates, which produce generalized depression of the CNS, phenobarbital is able to suppress seizures at doses that produce only moderate disruption of CNS function. Because it can reduce seizures without causing sedation, phenobarbital is classified as an *anticonvulsant barbiturate* (to distinguish it from most other barbiturates, which are employed as daytime sedatives or "sleeping pills").

The basic pharmacology of the barbiturates is discussed in Chapter 34. Discussion here is limited to the use of phenobarbital for seizures.

Mechanism of Antiseizure Action

Phenobarbital suppresses seizures by potentiating the effects of GABA. Specifically, the drug binds to GABA receptors, causing the receptor to respond more intensely to GABA itself.

Pharmacokinetics

Phenobarbital is administered orally, and absorption is complete. Elimination occurs through hepatic metabolism and renal excretion. Phenobarbital has a *long half-life*—about 4 days. As a result, once-daily dosing is adequate for most patients. In addition to permitting once-daily dosing, the long half-life has another consequence: 2 to 3 weeks are required for plasma levels to reach plateau. (Recall that, in the absence of a loading dose, an interval equivalent to four half-lives is required to reach plateau.)

Therapeutic Uses

Epilepsy.

Phenobarbital is effective against partial seizures and generalized tonic-clonic seizures but not absence seizures. In the past, phenobarbital was a drug of choice for tonic-clonic seizures and partial seizures in older children and adults. However, most clinicians now prefer to treat these epilepsies with carbamazepine, phenytoin, or valproic acid—drugs that cause fewer neuropsychologic effects than phenobarbital. Intravenous phenobarbital can be used for generalized convulsive SE, but lorazepam and phenytoin are preferred.

Sedation and Induction of Sleep.

Like other barbiturates, phenobarbital can be used for daytime sedation and to promote sleep at night. These applications are discussed in Chapter 34.

Adverse Effects

Neuropsychologic Effects.

Drowsiness is the most common CNS effect. During the initial phase of therapy, sedation develops in practically all patients. With continued treatment, tolerance to sedation develops. Some children experience paradoxical responses: Instead of becoming sedated, they may become irritable and hyperactive. Depression may occur in adults. Elderly patients may experience agitation and confusion.

Physical Dependence.

Like all other barbiturates, phenobarbital can cause physical dependence. However, at the doses employed to treat epilepsy, significant dependence is unlikely.

Exacerbation of Intermittent Porphyria.

Phenobarbital and other barbiturates can increase the risk of acute intermittent porphyria. Accordingly, barbiturates are absolutely contraindicated for patients with a history of this disorder. The relationship of barbiturates to intermittent porphyria is discussed further in Chapter 34.

Use in Pregnancy.

Use of phenobarbital during pregnancy poses a significant risk of major fetal malformations. Women who take phenobarbital during pregnancy or become pregnant while taking the drug should be informed of the potential risk to the fetus.

Like phenytoin, phenobarbital can decrease synthesis of vitamin K–dependent clotting factors, and can thereby cause *bleeding tendencies in newborns*. The risk of neonatal bleeding can be decreased by administering vitamin K to the mother for 1 month prior to delivery and during delivery, and to the infant immediately after delivery.

Other Adverse Effects.

Like phenytoin, phenobarbital can interfere with the metabolism of vitamins D and K. Disruption of vitamin D metabolism can cause *rickets* and *osteomalacia*.

Toxicity

When taken in moderately excessive doses, phenobarbital causes nystagmus and ataxia. Severe overdose produces generalized CNS depression; death results from depression of respiration. Barbiturate toxicity and its treatment are discussed at length in Chapter 34.

Drug Interactions

Induction of Drug-Metabolizing Enzymes.

Phenobarbital induces hepatic drug-metabolizing enzymes, and can thereby accelerate the metabolism of other drugs, causing a loss of therapeutic effects. This is of particular concern with oral contraceptives and warfarin.

CNS Depressants.

Being a CNS depressant itself, phenobarbital can intensify CNS depression caused by other drugs (eg, alcohol, benzodiazepines, opioids). Severe respiratory depression and coma could result. Patients should be warned against combining phenobarbital with other drugs that have CNS-depressant actions.

Valproic Acid.

Valproic acid is an AED that has been used in combination with phenobarbital. By competing with phenobarbital for drug-metabolizing enzymes, valproic acid can increase plasma levels of phenobarbital by approximately 40%. Hence, when this combination is used, the dosage of phenobarbital must be reduced.

Drug Withdrawal

When phenobarbital is withdrawn, *dosage should be reduced gradually,* since abrupt withdrawal can precipitate SE. Patients should be warned of this danger and instructed not to discontinue phenobarbital too quickly.

Preparations, Dosage, and Administration

Preparations.

Phenobarbital is available in three oral formulations—tablets, capsules, and elixir—and in solution (as Luminal) for IM and IV administration.

Dosage.

Adult maintenance dosages range from 60 to 120 mg/day administered as a single dose or two divided doses. *Pediatric* maintenance dosages range from 3 to 6 mg/kg/day. When dosage is being established, plasma drug levels may be used as a guide; target levels are 15 to 45 mcg/mL.

Loading doses may be needed. Because phenobarbital has a long half-life, several weeks are required for drug levels to reach plateau. If plateau must be reached sooner, a loading schedule can be employed. For example, doses that are twice normal can be given for 4 days. Unfortunately, these large doses are likely to produce substantial CNS depression.

Administration.

Phenobarbital may be administered orally, IV, or IM. Oral administration is employed for routine therapy. Intravenous administration is needed for SE. Intramuscular administration is used only when oral dosing is not feasible.

Intravenous injection must be done slowly. If done too fast, excessive CNS depression may result. Phenobarbital is highly alkaline and may cause local tissue injury if extravasation occurs.

Primidone

Primidone [Mysoline] is active against all major seizure disorders except absence seizures. The drug is nearly identical in structure to phenobarbital. As a result, the pharmacology of both agents is very similar.

Pharmacokinetics.

Primidone is readily absorbed following oral administration. In the liver, much of the drug undergoes conversion to two active metabolites: phenobarbital and phenylethylmalonamide. Seizure control is produced by primidone itself and by its metabolites. Therapeutic plasma levels range from 5 to 15 mcg/mL.

Therapeutic Uses.

Primidone is effective against tonic-clonic, simple partial, and complex partial seizures. The drug is not active against absence seizures.

As a rule, primidone is employed in combination with another AED, usually phenytoin or carbamazepine. Primidone is never taken together with phenobarbital. Why? Because phenobarbital is an active metabolite of primidone, and hence concurrent use would be irrational.

Adverse Effects.

Sedation, ataxia, and dizziness are common during initial treatment but diminish with continued drug use. Like phenobarbital, primidone can cause confusion in the elderly and paradoxical hyperexcitability in children. A sense of acute intoxication can occur shortly after administration. As with phenobarbital, primidone is absolutely contraindicated for patients with acute intermittent porphyria. Serious adverse reactions (acute psychosis, leukopenia, thrombocytopenia, systemic lupus erythematosus) can occur but are rare.

Drug Interactions.

Drug interactions for primidone are similar to those for phenobarbital. Primidone can induce hepatic drug-metabolizing enzymes and can thereby reduce the effects of oral contraceptives, warfarin, and other drugs. In addition, primidone can intensify responses to other CNS depressants.

Preparations, Dosage, and Administration.

Primidone [Mysoline] is available in 50- and 250-mg tablets. Therapy in *adults* is initiated with 100 to 125 mg at bedtime. Dosage is gradually increased over the next 10 days to a maintenance level of 250 mg 2 or 3 times a day. The maximum dosage is 500 mg 4 times a day.

NEWER ANTIEPILEPTIC DRUGS

The group of newer AEDs has seven principal members: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide. The oldest of these—gabapentin—was introduced in 1993, and the most recent—zonisamide—was introduced in 2000. Although most newer AEDs have not been compared directly with the traditional AEDs (or with each other, for that matter), all of these drugs appear equally effective. However, because clinical experience with the newer drugs is still limited, they are prescribed less often than the traditional AEDs. Oxcarbazepine and lamotrigine are the primary exceptions to this rule.

Do the newer AEDs have properties that make them appealing? Certainly. As a group, they are better tolerated than the traditional AEDs, and may pose a smaller risk to the developing fetus. Furthermore, only one—oxcarbazepine—induces drug-metabolizing enzymes, and hence interactions with other drugs, including other AEDs, are relatively minor.

The subject of approved indications for the newer AEDs requires comment. When these drugs were introduced, FDA-approved indications were limited to *adjunctive* therapy of certain seizure disorders. None of these drugs was approved for *monotherapy*. Why? Because clinical trials were limited to patients who were refractory to traditional AEDs. When the trials were conducted, rather than switching patients from a traditional AED to the experimental AED, the experimental AED was *added* to the existing regimen. Hence, when the trials were completed, all we knew for sure was that the new AED was ef-

fective when used together with an older AED. We had no data on use of the newer AED alone. As a result, the FDA had no option but to approve the new drug for adjunctive therapy. Since being released, several of the newer AEDs have received FDA approval for monotherapy.

To help prescribers be more comfortable with the newer AEDs, two organizations—the American Academy of Neurology (AAN) and American Epilepsy Society (AES)—convened a panel to evaluate the efficacy and tolerability of these drugs. For some of the newer AEDs, the AAN/AES panel recommended uses not yet approved by the FDA. These recommendations, along with FDA-approved indications, are discussed below.

Oxcarbazepine

Actions and Uses.

Oxcarbazepine [Trileptal], a derivative of carbamazepine, is indicated for monotherapy and adjunctive therapy of partial seizures in adults and children. The drug is as effective as carbamazepine and better tolerated. However, it's also more expensive. Antiseizure effects result from blockade of voltage-sensitive sodium channels in neuronal membranes, an action that stabilizes hyperexcitable neurons and thereby suppresses seizure spread. The drug does not affect neuronal GABA receptors.

Pharmacokinetics.

Oxcarbazepine is well absorbed both in the presence and absence of food. In the liver, the drug undergoes rapid conversion to a 10-monohydroxy metabolite (MHD), its active form. MHD has a half-life of 9 hours and undergoes excretion in the urine.

Adverse Effects.

The most common adverse effects are dizziness (22% to 49%), drowsiness (19% to 36%), double vision (14% to 40%), nystagmus (7% to 26%), headache (13% to 32%), nausea (15% to 29%), vomiting (7% to 36%), and ataxia (5% to 31%). Patients should avoid driving and other hazardous activities, unless the degree of drowsiness is low.

Clinically significant *hyponatremia* (sodium concentration less than 125 mmol/L) develops in 2.5% of patients. Signs include nausea, drowsiness, headache, and confusion. If oxcarbazepine is combined with other drugs that can decrease sodium levels (especially diuretics), monitoring of sodium levels may be needed.

Like carbamazepine, oxcarbazepine can cause *serious skin reactions,* including Stevens-Johnson syndrome and toxic epidermal necrolysis. There is 30% cross sensitivity among patients with hypersensitivity to carbamazepine. Accordingly, patients with a history of severe reactions to either drug should probably not use the other.

Oxcarbazepine has not caused the severe hematologic abnormalities seen with carbamazepine. Accordingly, routine monitoring of blood counts is not required.

Oxcarbazepine has been associated with serious *multiorgan hypersensitivity reactions*. Although manifestations are varied, patients typically present with fever and rash, associated with one or more of the following: lymphadenopathy, hematologic abnormalities, pruritus, hepatitis, nephritis, hepatorenal syndrome, oliguria, arthralgia, or asthenia. If this reaction is suspected, oxcarbazepine should be discontinued.

Use in Pregnancy and Breast-Feeding.

Like carbamazepine (FDA Pregnancy Risk Category D), oxcarbazepine (FDA Pregnancy Risk Category C) may pose a risk of birth defects. Accordingly, women of child-bearing age should use effective contraception. Clearly, the drug should be avoided by women who are already pregnant. In addition, since both oxcarbazepine and its metabolite are excreted in breast milk, the drug should be avoided by women who are breast-feeding.

Drug Interactions.

Oxcarbazepine induces some drug-metabolizing enzymes and inhibits others. It does not induce enzymes that metabolize other AEDs. However, it does induce enzymes that metabolize *oral contraceptives,* and can thereby render them less effective. Accordingly, women should employ an alternative birth control method.

Oxcarbazepine inhibits the enzymes that metabolize phenytoin, and can thereby raise phenytoin levels. Toxicity can result. Phenytoin levels should be monitored and dosage adjusted accordingly.

Drugs that induce drug-metabolizing enzymes (eg, phenytoin, phenobarbital, carbamazepine) can reduce levels of MHD, the active form of oxcarbazepine. Accordingly, dosage of oxcarbazepine may need to be increased.

Alcohol can intensify CNS depression caused by oxcarbazepine, and hence should be avoided.

As noted, oxcarbazepine should be used with caution in patients taking *diuretics* and other drugs that can lower sodium levels.

Preparations, Dosage, and Administration.

Oxcarbazepine [Trileptal] is available in film-coated tablets (150, 300, and 600 mg) and an oral suspension (60 mg/mL).

For *monotherapy in adults,* the initial dosage is 300 mg twice daily. The maximum dosage is 1200 mg twice daily.

For *adjunctive therapy in adults,* the initial dosage is 300 mg twice daily. The maximum dosage is 600 mg twice daily.

For *monotherapy in children* (ages 4 to 16), the initial dosage is 8 to 10 mg/kg/day in two divided doses. Maintenance dosages are related to body weight (see manufacturer's recommendations).

For *adjunctive therapy in children* (ages 2 to 16), the initial dosage is 8 to 10 mg/kg/day in two divided doses. Maintenance dosages are related to body weight: For children weighing 20 to 29 kg, the dosage is 900 mg/day; for children weighing 29.1 to 30 kg, the dosage is 1200 mg/day; and for children weighing above 39 kg, the dosage is 1800 mg/day.

Lamotrigine

Therapeutic Uses.

Lamotrigine [Lamictal], introduced in 1994, has a broad spectrum of antiseizure activity. The drug is FDA approved for (1) adjunctive therapy of partial seizures in adults and children over 2 years old, (2) adjunctive therapy of gen-

eralized seizures associated with Lennox-Gastaut syndrome in adults and children over 2 years old, (3) adjunctive therapy of primary generalized tonic-clonic seizures in adults and children over 2 years old, and (4) monotherapy of partial seizures in patients at least 16 years old who are converting from another AED. In addition, the AAN/AES guidelines recommend using lamotrigine for absence seizures. Lamotrigine is also FDA approved for long-term maintenance therapy of bipolar disorder (see Chapter 33). Investigational uses include myoclonic, absence, and temporal lobe seizures.

Mechanism of Action.

Benefits derive mainly from blockade of sodium channels and partly from blockade of calcium channels. Both actions decrease release of glutamate, an excitatory neurotransmitter.

Pharmacokinetics.

Administration is oral, and absorption is nearly complete both in the presence and absence of food. Blood levels peak in 1.5 to 5 hours and decline with a half-life of 24 hours. The drug undergoes hepatic metabolism followed by renal excretion.

Drug Interactions.

The half-life is dramatically affected by drugs that induce or inhibit hepatic drug-metabolizing enzymes. Enzyme inducers (eg, carbamazepine, phenytoin, phenobarbital) decrease the half-life of lamotrigine to 10 hours, whereas valproate (an enzyme inhibitor) increases the half-life to about 60 hours. Lamotrigine itself is not an inducer or inhibitor of drug-metabolizing enzymes.

Adverse Effects.

Lamotrigine can cause *life-threatening rashes,* including Stevens-Johnson syndrome and toxic epidermal necrolysis. Deaths have occurred. The incidence of severe rash is about 0.8% in patients under 16 years old and 0.3% in adults. Concurrent use of valproic acid increases risk. If a rash develops, lamotrigine should be withdrawn immediately.

In addition to severe rash, lamotrigine commonly causes dizziness, diplopia (double vision), blurred vision, nausea, vomiting, and headache. When used

during pregnancy, lamotrigine may pose a small risk of cleft lip and cleft palate. Whether the drug poses other risks in pregnancy or in breast-feeding has not been determined.

Preparations, Dosage, and Administration.

Lamotrigine [Lamictal] is available in standard tablets (25, 100, 150, and 200 mg) and chewable dispersible tablets (2, 5, and 25 mg). The dosage depends on which other AEDs are being taken. For patients taking an *inducer* of drug metabolism (eg, carbamazepine, phenytoin, phenobarbital), dosing is begun at 50 mg/day, and then gradually increased to between 150 and 500 mg twice a day for maintenance. For patients taking *valproate* (an enzyme inhibitor), dosing is begun at 25 mg every other day, and then gradually increased to between 50 and 75 mg twice daily for maintenance.

Gabapentin

Therapeutic Uses.

Gabapentin [Neurontin], introduced in 1993, has a broad spectrum of antiseizure activity. However, its only FDA-approved use in epilepsy is adjunctive therapy of partial seizures (with or without secondary generalization). The AAN/AES guidelines also recommend the drug for monotherapy of partial seizures. In 2002, gabapentin was approved for treating postherpetic neuralgia. Interestingly, more than 80% of prescriptions are written for off-label uses, including relief of neuropathic pain (other than postherpetic neuralgia), prophylaxis of migraine, and relief of postmenopausal hot flushes. The drug does not appear effective in bipolar disorder.

Mechanism of Action.

Gabapentin's precise mechanism of action is unknown. The drug is an analog of GABA, but does not directly affect GABA receptors. Rather, it may enhance GABA release, thereby increasing GABA-mediated inhibition of neuronal firing.

Pharmacokinetics.

Gabapentin is rapidly absorbed following oral administration and reaches peak plasma levels in 2 to 3 hours. Absorption is not affected by food. However, as the dosage gets larger, the percentage absorbed gets smaller. Why? Because at high doses, the intestinal transport system for uptake of the drug becomes saturated. Gabapentin is not metabolized and is excreted intact in the urine. Its half-life is 5 to 7 hours.

Drug Interactions.

Unlike most AEDs, gabapentin is devoid of significant interactions. It doesn't induce or inhibit drug-metabolizing enzymes, and doesn't affect the metabolism of other drugs. As a result, gabapentin is well suited for combined use with other AEDs.

Adverse Reactions.

Gabapentin is very well tolerated. The most common side effects are somnolence, dizziness, ataxia, fatigue, nystagmus, and peripheral edema. These are usually mild to moderate and often diminish with continued drug use. Patients should avoid driving and other hazardous activities until they are confident they are not impaired. Safety in pregnancy and breast-feeding has not been established.

Preparations, Dosage, and Administration.

Gabapentin [Neurontin] is available in capsules (100, 300, and 400 mg), tablets (600 and 800 mg), and an oral solution (50 mg/mL). Dosing for adults begins with a 300-mg dose at bedtime, followed the next day by 600 mg (in two divided doses), and the next day by 900 mg (in three divided doses). Thereafter, the dosage can be raised rapidly to maintenance levels, typically 1200 to 3600 mg/day in three divided doses. Dosage should be reduced in patients with renal impairment.

Pregabalin

Pregabalin [Lyrica], an analog of GABA, is much like gabapentin. Like gabapentin, pregabalin is used for seizures and neuropathic pain. In addition, pregabalin is approved for fibromyalgia. Pregabalin has very few interactions with other drugs, but adverse effects are common, especially dizziness and

sleepiness. Unlike most other antiseizure agents, pregabalin is regulated under the Controlled Substances Act. The drug was introduced in 2005.

Therapeutic Uses.

Pregabalin has four approved indications: neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia, adjunctive therapy of partial seizures, and fibromyalgia. Of the four indications, fibromyalgia deserves special comment. The disorder is a chronic condition characterized by generalized muscle pain, fatigue, and disturbed sleep. In 2007, pregabalin became the first drug approved for treatment. Unfortunately, benefits are modest. In clinical trials, pregabalin produced a 50% reduction in pain in 28% of patients, compared with 13% of patients taking placebo. Also, for many patients with fibromyalgia, benefits fade within weeks or months.

Mechanism of Action.

Although the precise mechanism of action has not been established, we do know that pregabalin can bind with calcium channels on nerve terminals, and can thereby inhibit calcium influx, which in turn can inhibit release of several neurotransmitters, including glutamate, norepinephrine, and substance P. Reduced transmitter release may underlie seizure control and relief of neuropathic pain. Although pregabalin is an analog of GABA, the drug does not bind with GABA receptors or benzodiazepine receptors, and hence does not work by mimicking or enhancing the inhibitory actions of GABA.

Pharmacokinetics.

Pregabalin is well absorbed after oral administration. Plasma levels peak 1.5 hours after dosing. Food reduces the rate of absorption but not the extent. Oral bioavailability is 90% or greater. Pregabalin does not bind with plasma proteins, but does cross the blood-brain and placental barriers. Elimination is renal, 98% as unchanged drug. Metabolism is negligible. The half-life is 6.3 hours.

Adverse Effects.

Pregabalin can cause a variety of adverse effects. The most common are dizziness (29%) and somnolence (22%), which often persist as long as the drug is

being taken. Blurred vision (6%) develops early, but resolves with continued drug use. About 8% of patients experience significant weight gain (7% or more of body weight in just a few months). Other adverse effects include difficulty thinking (6%), headache (5%), peripheral edema (6%), and dry mouth (4%).

In clinical trials, three patients developed rhabdomyolysis (muscle breakdown). However, it is not clear that pregabalin was the cause. Nonetheless, patients should be instructed to report signs of muscle injury (pain, tenderness, weakness). If rhabdomyolysis is diagnosed, or even suspected, pregabalin should be withdrawn.

Abuse Potential and Physical Dependence.

In clinical trials, 4% to 12% of patients reported euphoria as an adverse effect. When given to recreational users of sedative-hypnotic drugs, pregabalin produced subjective effects perceived as similar to those of diazepam [Valium]. On the basis of these data, the Drug Enforcement Agency has classified pregabalin under Schedule V of the Controlled Substances Act.

Abrupt discontinuation can cause insomnia, nausea, headache, diarrhea, and other symptoms that suggest physical dependence. To avoid withdrawal symptoms, pregabalin should be discontinued slowly, over 1 week or more.

Reproductive Toxicity.

Pregabalin has adverse effects on reproduction and development when taken by females or males.

When given to pregnant female rats and rabbits, pregabalin caused fetal growth retardation, fetal death, structural abnormalities (eg, skeletal and visceral malformation), and impaired function of the nervous and reproductive systems. Data on human reproduction are lacking. At this time, pregabalin is classified in FDA Pregnancy Risk Category C: Animal studies show a risk of fetal harm, but no controlled studies in women have been done.

When given to male rats prior to and during mating with untreated females, pregabalin decreased sperm counts and motility, decreased fertility, reduced fetal weight, and caused fetal abnormalities. Men using the drug should be informed about the possibility of decreased fertility and male-mediated teratogenicity.

Drug Interactions.

Alcohol, opioids, benzodiazepines, and other CNS depressants may intensify the depressant effects of pregabalin. Accordingly, such combinations should be avoided.

Extensive studies have failed to show pharmacokinetic interactions with any other drugs. Pregabalin does not inhibit cytochrome P450 isozymes; whether it can induce these isozymes is unknown. Pregabalin does not interact with oral contraceptives, and does not alter the kinetics of any antiseizure drugs studied (carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid, and tiagabine).

Preparations, Dosage, and Administration.

Pregabalin [Lyrica] is available in capsules (25, 50, 75, 100, 150, 200, 225, and 300 mg) for administration with or without food. Dosage depends on the indication. For patients with renal impairment, dosage should be reduced. When pregabalin is discontinued, dosage should be gradually tapered, over 1 week or longer.

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy.

Dosing is begun at 150 mg/day (50 mg 3 times a day) and may be increased in a week as needed and tolerated to a maintenance level of 300 mg/day (100 mg 3 times a day). Dosages above 300 mg/day are unlikely to increase benefits but will increase the risk of adverse effects.

Postherpetic Neuralgia.

Dosing should begin at 150 mg/day (75 mg twice daily or 50 mg 3 times a day) and may be increased as needed and tolerated to the usual maintenance level of 300 mg/day (150 mg twice daily or 100 mg 3 times a day). For patients with significant pain after 2 to 4 weeks at 300 mg/day, dosage may be increased to a maximum of 600 mg/day (300 mg twice daily or 200 mg 3 times a day).

Epilepsy.

Dosing is the same as for postherpetic neuralgia, with a maximum dosage of 600 mg/day.

Fibromyalgia.

Dosing begins at 75 mg twice daily, and may increase to 225 mg twice daily, if tolerated. Doses above this level increase the risk of side effects, but offer no increase in benefits.

Levetiracetam

Levetiracetam [Keppra], introduced in 1999, is a unique agent that is chemically and pharmacologically different from all other AEDs. How levetiracetam acts is unknown. All we do know is that it does not bind to receptors for GABA or any other known neurotransmitter. The drug is approved for adjunctive therapy of (1) myoclonic seizures in adults and adolescents age 12 and older, (2) partial-onset seizures in adults and children age 4 and older, and (3) primary generalized tonic-clonic seizures in adults and children age 6 years and older. Unlabeled uses include migraine, bipolar disorder, and new-onset pediatric epilepsy.

Following oral administration, levetiracetam undergoes rapid and complete absorption both in the presence and absence of food. Metabolism is minimal and not mediated by hepatic P450 enzymes. Levetiracetam is excreted in the urine, largely (66%) unchanged.

Adverse effects are generally mild to moderate. The most common are drowsiness (14.8%) and asthenia (14.7%). Neuropsychiatric symptoms (agitation, anxiety, depression, psychosis, hallucinations, depersonalization) occur in less than 1% of patients. In contrast to other AEDs, levetiracetam does not impair speech, concentration, or other cognitive functions. Safety for use during pregnancy or breast-feeding has not been determined.

Unlike most other AEDs, levetiracetam does not interact with other drugs. It does not alter plasma concentrations of oral contraceptives, warfarin, digoxin, or other AEDs. Given that levetiracetam is not metabolized by P450 enzymes, its lack of interactions is no surprise.

Levetiracetam is available in tablets (250, 500, 750, and 1000 mg), an oral solution (100 mg/mL), and a solution for IV injection (100 mg/mL). The initial

adult dosage is 500 mg twice daily. The maximum dosage is 3000 mg/day. Because levetiracetam is eliminated by the kidneys, dosage should be reduced in patients with significant renal impairment.

Topiramate

Actions and Uses.

Topiramate [Topamax], introduced in 1996, is another broad-spectrum antiseizure agent. The drug is FDA-approved for (1) *adjunctive* treatment of adults and children 2 years and older with partial seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome; (2) *monotherapy* of adults and children 10 years and older with partial seizures or primary generalized tonic-clonic seizures; and (3) prophylaxis of migraine in adults (see Chapter 30). Seizure reduction occurs by four mechanisms: (1) potentiation of GABA-mediated inhibition, (2) blockade of voltage-dependent sodium channels, (3) blockade of calcium channels, and (4) blockade of receptors for glutamate, an excitatory neurotransmitter. Unlabeled uses include bipolar disorder, cluster headaches, neuropathic pain, infantile spasms, alcohol and cocaine dependence, binge-eating disorder, bulimia nervosa, and weight loss.

Pharmacokinetics.

Topiramate is rapidly absorbed following oral administration. Bioavailability is not affected by food. Plasma levels peak 2 hours after dosing. Most of the drug is eliminated unchanged in the urine.

Adverse Effects.

Although topiramate is generally well tolerated, it can cause multiple adverse effects. Common effects include somnolence (30%), dizziness (28%), ataxia (21%), nervousness (20%), diplopia (15%), nausea (13%), anorexia (12%), and weight loss (12%). Cognitive effects (confusion, memory difficulties, altered thinking, reduced concentration, difficulty finding words) can occur, but the incidence is low at recommended dosages. Kidney stones and paresthesias occur rarely.

Topiramate can cause *metabolic acidosis*. The drug inhibits carbonic anhydrase, and thereby increases renal excretion of bicarbonate, which causes plasma pH to fall. Mild to moderate metabolic acidosis develops in 30% of adult patients, but severe acidosis is rare. Serum bicarbonate should be measured at baseline and periodically thereafter. If metabolic acidosis develops, topiramate should be given in reduced dosage or discontinued.

Topiramate can cause *hypohidrosis* (reduced sweating), thereby posing a risk of hyperthermia. Significant hyperthermia is usually associated with vigorous activity and an elevated environmental temperature.

There have been case reports of *angle-closure glaucoma*. Left untreated, this rapidly leads to blindness. Patients should be informed about symptoms of glaucoma (ocular pain, unusual redness, sudden worsening or blurring of vision) and instructed to seek immediate attention if these develop. Fortunately, topiramate-induced glaucoma is rare.

Drug Interactions.

Phenytoin and carbamazepine can decrease levels of topiramate by about 45%. Topiramate may increase levels of phenytoin.

Preparations, Dosage, and Administration.

Topiramate [Topamax] is available in tablets (25, 50, 100, and 200 mg) and "sprinkle" capsules (15 and 25 mg). *Adult* dosing is begun at 50 mg/day and then gradually increased to 200 mg twice daily for maintenance. *Pediatric* dosing is begun at 25 mg (or less) per day and gradually increased to 3 to 9 mg/kg/day administered in two divided doses. Advise patients not to break the tablets because of bitter taste. The capsules can be swallowed whole or opened and sprinkled onto a small amount (1 tsp) of soft food.

Tiagabine

Actions and Uses.

Tiagabine [Gabitril Filmtabs], introduced in 1997, is FDA-approved only for adjunctive therapy of partial seizures in patients at least 12 years old. The drug blocks reuptake of GABA by neurons and glia. As a result, the inhibitory in-

fluence of GABA is intensified, and seizures are suppressed. Off-label uses include migraine prophylaxis, bipolar disorder, and insomnia. However, owing to a risk of seizures (see below), such off-label use is discouraged.

Pharmacokinetics.

Tiagabine has uncomplicated kinetics. Administration is oral. Absorption is rapid and nearly complete. Food reduces the rate of absorption but not the extent. Plasma levels peak about 45 minutes after dosing. In the blood, tiagabine is highly (96%) bound to plasma proteins. Elimination is by hepatic metabolism followed by excretion in the bile and, to a lesser extent, the urine. The serum half-life is 7 to 9 hours.

Adverse Effects.

Tiagabine is generally well tolerated. Common adverse effects are dizziness (27%), somnolence (18%), asthenia (20%), nausea (11%), nervousness (10%), and tremor (9%). Like most other AEDs, tiagabine can cause dose-related cognitive effects (eg, confusion, abnormal thinking, trouble concentrating).

Tiagabine has *caused* seizures in some patients—but only in those using the drug off-label (ie, those using the drug for a condition other than epilepsy). A few patients have developed SE, which can be life threatening. In most cases, seizures occurred soon after starting tiagabine or increasing the dosage. Because of seizure risk, off-label use of tiagabine should be avoided. Why are people without epilepsy at risk? Possibly because they are not taking AEDs. Remember, tiagabine is approved only for adjunctive use with other AEDs. It may be that these drugs protect against tiagabine-induced seizures. Since people without epilepsy take tiagabine by itself, they are not protected from seizure development.

Drug Interactions.

Tiagabine does not alter the metabolism or serum concentrations of other AEDs. However, levels of tiagabine can be decreased by phenytoin, phenobarbital, and carbamazepine—all of which induce drug-metabolizing enzymes.

Preparations, Dosage, and Administration.

Tiagabine [Gabitril Filmtabs] is available in tablets (2, 4, 12, 16, and 20 mg) for oral administration. Dosing should be done with food. The initial dosage for adults and children is 4 mg once a day. Dosage can be increased by 4 to 8 mg/day at weekly intervals. The maximum daily dose, administered in two to four divided doses, is 56 mg for adults and 32 mg for children under age 18 years. Dosage should be increased in patients taking drugs that can accelerate tiagabine metabolism.

Zonisamide

Actions and Uses.

Zonisamide [Zonegran], introduced in 2000, is approved only for adjunctive therapy of partial seizures in adults. The drug belongs to the same chemical family as the sulfonamide antibiotics, but lacks antimicrobial activity. In animal models, zonisamide suppresses focal seizure activity and spread. The underlying mechanism appears to be blockade of neuronal sodium channels and calcium channels.

Pharmacokinetics.

Zonisamide undergoes rapid absorption from the GI tract. Bioavailability is nearly 100%, both in the presence and absence of food. In the blood, zonisamide is extensively bound to erythrocytes. As a result, its concentration in erythrocytes is 8 times higher than in plasma. Zonisamide is metabolized in the liver by the 3A4 isozyme of cytochrome P450 (CYP3A4). Excretion occurs in the urine, in the form of zonisamide itself (30%) and metabolites. The plasma half-life is 63 hours.

Adverse Effects.

The most common adverse effects are drowsiness (17%), dizziness (13%), anorexia (13%), headache (10%), and nausea (9%). Like most other AEDs, zonisamide can impair speech, concentration, and other cognitive processes. Because the drug can reduce alertness and impair cognition, patients should avoid driving and other hazardous activities until they know how the drug affects them.

Zonisamide can have severe *psychiatric effects*. During clinical trials, 2.2% of patients either discontinued treatment or were hospitalized because of severe depression; 1.1% attempted suicide. Psychosis caused another 2.2% to discontinue treatment.

Like all other sulfonamides, zonisamide can trigger *hypersensitivity reactions,* including some that are potentially fatal (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis). Accordingly, zonisamide is contraindicated for patients with a history of sulfonamide hypersensitivity. Patients who develop a rash should be followed closely, because rash can evolve into a more serious event. If severe hypersensitivity develops, zonisamide should be withdrawn immediately. Fortunately, serious reactions and fatalities are rare.

Zonisamide has adverse effects on the kidneys. In clinical trials, about 4% of patients developed *nephrolithiasis* (kidney stones). The risk can be reduced by drinking 6 to 8 glasses of water a day (to maintain hydration and urine flow). Patients should be informed about signs of kidney stones (sudden back pain, abdominal pain, painful urination, bloody or dark urine) and instructed to report them immediately. In addition to nephrolithiasis, zonisamide can *impair glomerular filtration*. Because of its effects on the kidney, zonisamide should be used with caution in patients with kidney disease.

Rarely, zonisamide causes *hypohidrosis* (decreased sweating) and *hyperthermia* (elevation of body temperature). Pediatric patients may be at special risk. In warm weather, hypohidrosis may lead to heat stroke and subsequent hospitalization. Patients should be monitored closely for reduced sweating and increased body temperature.

Use in Pregnancy and Breast-Feeding.

Zonisamide is teratogenic and embryolethal in laboratory animals. Cardiovascular abnormalities are common. Women of child-bearing age should use effective contraception. Zonisamide is classified in FDA Pregnancy Risk Category C, and hence should be avoided during pregnancy unless the benefits to the mother are deemed to outweigh the potential risks to the fetus. We do not know if zonisamide enters breast milk. Until more is known, prudence dictates that women who are breast-feeding should not take the drug.

Drug and Food Interactions.

Levels of zonisamide can be affected by agents that induce or inhibit CYP3A4. Inducers of CYP3A4—including St. John's wort (an herbal supplement used for depression) and several AEDs (eg, phenytoin, phenobarbital, carbamazepine)—can accelerate the metabolism of zonisamide, and thereby reduce the drug's half-life to as little as 27 hours. Conversely, inhibitors of CYP3A4—including grapefruit juice, azole antifungal agents (eg, ketoconazole), and several protease inhibitors (eg, ritonavir)—can slow the metabolism of zonisamide, and thereby prolong and intensify its effects.

Preparations, Dosage, and Administration.

Zonisamide is available in capsules (25, 50, and 100 mg). The initial dosage is 100 mg once daily. The maximum dosage is 600 mg/day in one or two divided doses.

Felbamate

Felbamate [Felbatol], introduced in 1993, is an effective AED with a broad spectrum of antiseizure activity. Unfortunately, the drug has potentially fatal adverse effects: aplastic anemia and liver failure. Accordingly, use is restricted to patients with severe epilepsy refractory to all other therapy.

Mechanism of Action.

Felbamate increases seizure threshold and suppresses seizure spread. The underlying mechanism is unknown. Unlike some AEDs (eg, phenobarbital, benzodiazepines), felbamate does not interact with GABA receptors and does not enhance the inhibitory actions of GABA.

Pharmacokinetics.

Felbamate is well absorbed following oral administration, in the presence or absence of food. Plasma levels peak in 1 to 4 hours. The drug readily penetrates to the CNS. Although therapeutic plasma levels have not been established, levels of 20 to 120 mcg/mL have been measured during clinical trials. Felbamate is eliminated in the urine, primarily unchanged. Its half-life is 14 to 23 hours.

Therapeutic Uses.

Felbamate is approved for (1) adjunctive or monotherapy in adults with partial seizures (with or without generalization), and (2) adjunctive therapy in children with Lennox-Gastaut syndrome. However, because of toxicity, use of the drug is very limited.

Adverse Effects.

Felbamate can cause *aplastic anemia* and *liver damage*. Aplastic anemia has occurred in at least 21 patients, 3 of whom died. Acute liver failure occurred in eight patients, four of whom died. Because of the risk of liver failure, felbamate should not be used by patients with pre-existing liver dysfunction. In addition, patients taking the drug should be monitored for indications of liver injury.

The most common adverse effects are GI disturbances (anorexia, nausea, vomiting) and CNS effects (insomnia, somnolence, dizziness, headache, diplopia). These occur more frequently when felbamate is combined with other drugs.

Drug Interactions.

Felbamate can alter plasma levels of other AEDs and vice versa. Felbamate increases levels of phenytoin and valproic acid. Levels of felbamate are increased by valproic acid and reduced by phenytoin and carbamazepine. Increased levels of phenytoin and valproic acid (and possibly felbamate) could lead to toxicity; reduced levels of felbamate could lead to therapeutic failure. Therefore, to keep levels of these drugs within the therapeutic range, their levels should be monitored and dosages adjusted accordingly.

Preparations, Dosage, and Administration.

Felbamate [Felbatol] is available in tablets (400 and 600 mg) and an oral suspension (120 mg/mL). For *older children* (over 14 years old) and *adults,* the initial dosage is 1200 mg/day in three divided doses; the maximum dosage is 3600 mg/day in three divided doses. For *younger children* (2 to 14 years old), the initial dosage is 15 mg/kg/day in three divided doses; the maximum dosage is 45

mg/kg/day or 3600 mg/day, whichever is less, administered in three divided doses.

Vigabatrin

Vigabatrin [Sabril] can suppress partial and secondarily generalized seizures, but may exacerbate absence and myoclonic seizures. The drug acts by inhibiting GABA transaminase, the enzyme that degrades GABA. By preventing GABA degradation, vigabatrin increases GABA availability in the CNS, and thereby enhances GABA-mediated inhibition of neuronal activity. Adverse effects include nausea, sedation, depression, psychosis, weight gain, and visual field constriction. The maintenance dosage is 2 to 4 gm once a day. Vigabatrin is available in Europe but not the United States.

MANAGEMENT OF EPILEPSY DURING PREGNANCY

Managing epilepsy during pregnancy is a challenge. Why? Because AEDs can harm the fetus, but so can uncontrolled seizures. There is solid evidence that all of the conventional AEDs increase the risk of minor malformations, major malformations, and growth retardation. At this time, the teratogenic potential of the newer AEDs is less clear. The most common malformations associated with AEDs are oral-facial clefts and midline heart defects. Valproic acid poses an especially high risk of spina bifida and other neural tube defects. The risk of malformation is proportional to AED dosage and to the number of AEDs used. As with other teratogens, the risk of birth defects is greatest from exposure during the first trimester. How do AEDs cause birth defects? One likely mechanism is conversion to reactive epoxide metabolites. In addition to causing birth defects, certain AEDs can cause neonatal hemorrhage.

Uncontrolled seizures carry their own risks—although they don't cause fetal malformation. Generalized tonic-clonic seizures can induce labor and, very rarely, miscarriage. Major seizures during the last month of pregnancy can injure the baby. Seizures of all types can delay development and promote epilepsy in the child. Of course, seizures also pose a risk of falls and injury to the mother.

Given that seizures and AEDs both carry risks, what should we do? Should the drugs be withdrawn, thereby increasing the risk of injury from seizures? Or

should the drugs be continued, thereby posing a risk of drug-induced injury? Most authorities agree that the risk to the fetus from uncontrolled seizures is greater than the risk from AEDs. Hence, as a general rule, women with major seizure disorders should continue to take AEDs throughout pregnancy. To minimize fetal risk, the lowest effective dosage should be determined and maintained. In addition, since the risk of malformation is proportional to the number of drugs taken, just one drug should be used whenever possible.

As discussed in Chapter 9, drug disposition changes during pregnancy. In particular, renal excretion of drugs increases, as do hepatic metabolism and protein binding. As a result, the level of free (active) drug falls, posing a risk of breakthrough seizures. Accordingly, dosage should be increased. To determine dosing requirements, drug levels should be measured at least once a month.

To reduce the risk of neural tube defects, women should take supplemental folic acid prior to conception and throughout pregnancy. A dose of 2 mg/day has been recommended. (This is 5 times the dosage recommended for women not taking AEDs.) Although supplemental folic acid can prevent neural tube defects in the absence of AEDs, it may not prevent AED-induced defects.

Four drugs—*phenobarbital, phenytoin, carbamazepine,* and *primidone*—reduce levels of vitamin K–dependent clotting factors (by inducing hepatic enzymes). As a result, these drugs increase the risk of bleeding. To reduce this risk, women should be given 10 mg of vitamin K daily during the last few weeks of pregnancy, and the baby should be given a 1-mg IM injection of vitamin K at birth.

In addition to their influence on clotting, inducers of hepatic metabolism can decrease blood levels of oral contraceptives, thereby rendering them ineffective. All women of child-bearing age should be informed of this drug interaction, and dosages of oral contraceptives should be increased as required.

MANAGEMENT OF GENERALIZED CONVULSIVE STATUS EPILEPTICUS

Convulsive SE is defined as a continuous series of tonic-clonic seizures that lasts for at least 20 to 30 minutes. Consciousness is lost during the entire attack. Tachycardia, elevation of blood pressure, and hyperthermia are typical.

Metabolic sequelae include hypoglycemia and acidosis. If SE persists for more than 20 minutes, it can cause permanent neurologic injury (cognitive impairment, memory loss, worsening of the underlying seizure disorder) and even death. About 125,000 Americans suffer SE each year. About 20% of them die.

Generalized convulsive SE is a medical emergency that requires immediate treatment. Ideally, treatment should commence within 5 minutes of seizure onset. Experience has shown that, as time passes, SE becomes more and more resistant to therapy.

The goal of treatment is to maintain ventilation, correct hypoglycemia, and terminate the seizure. An IV line is established to draw blood for analysis of glucose levels, electrolyte levels, and drug levels. The line is also used to administer glucose and AEDs.

An IV benzodiazepine—either *lorazepam* [Ativan] or *diazepam* [Valium]—is used initially. Both drugs can terminate seizures quickly. Diazepam has a short duration of action, and hence must be administered repeatedly. In contrast, effects of lorazepam last up to 72 hours. Because of its prolonged effects, lorazepam is generally preferred. The dosage for lorazepam is 0.1 mg/kg administered at a rate of 2 mg/min. The initial dose for diazepam is 0.2 mg/kg administered at a rate of 5 mg/min.

Once seizures have been stopped with a benzodiazepine, either *phenytoin* [Dilantin] or *fosphenytoin* [Cerebyx]* may be given for long-term suppression. Because the effects of diazepam are short lived, follow-up treatment with a long-acting drug is essential when diazepam is used for initial control. However, when lorazepam is used for initial control, follow-up therapy may be unnecessary.

KEY POINTS

- Seizures are initiated by discharge from a group of hyperexcitable neurons, called a focus.
- In partial seizures, excitation undergoes limited spread from the focus to adjacent cortical areas.

- In generalized seizures, excitation spreads widely throughout both hemispheres of the brain.
- AEDs act through four basic mechanisms: blockade of sodium channels, blockade of calcium channels, blockade of receptors for glutamate (an excitatory neurotransmitter), and potentiation of GABA (an inhibitory neurotransmitter).
- The goal in treating epilepsy is to reduce seizures to an extent that enables the patient to live a normal or near-normal life. Complete elimination of seizures may not be possible without causing intolerable side effects.
- AEDs can be divided into two main groups: traditional AEDs and newer AEDs, which were introduced in 1993 or later.
- Many AEDs are selective for particular seizures, and hence successful treatment depends on choosing the correct drug.
- Monitoring plasma drug levels can be valuable for adjusting dosage, monitoring adherence, determining the cause of lost seizure control, and identifying the cause of toxicity, especially in patients taking more than one drug.
- Nonadherence accounts for nearly half of all treatment failures. Hence, promoting adherence is a priority.
- Withdrawal of AEDs must be done very gradually, because abrupt withdrawal can trigger SE.
- All AEDs may pose a risk of suicidal thoughts and behavior.
- Most AEDs cause CNS depression, which can be deepened by concurrent use of other CNS depressants (eg, alcohol, antihistamines, opioids, other AEDs).
- Phenytoin is active against partial seizures and tonic-clonic seizures but not absence seizures.

•The capacity of the liver to metabolize phenytoin is limited. As a result, doses only slightly greater than those needed for therapeutic effects can push phenytoin levels into the toxic range.

- The therapeutic range for phenytoin is 10 to 20 mcg/mL.
- When phenytoin levels rise above 20 mcg/mL, CNS toxicity develops. Signs include nystagmus, sedation, ataxia, diplopia, and cognitive impairment.

•Phenytoin causes gingival hyperplasia in 20% of patients.

- Like phenytoin, carbamazepine is active against partial seizures and tonic-clonic seizures.
- Because carbamazepine is better tolerated than phenytoin, it is often preferred.
- Carbamazepine can cause leukopenia, anemia, and thrombocytopenia—and, very rarely, fatal aplastic anemia. To reduce the risk of serious hematologic toxicity, complete blood counts should be obtained at baseline and periodically thereafter.
- Valproic acid is a very-broad-spectrum AED, having activity against partial seizures and most generalized seizures, including tonic-clonic, absence, atonic, and myoclonic seizures.
- Valproic acid can cause potentially fatal liver injury, especially in children under 2 years old who are taking other AEDs.
- Valproic acid can cause potentially fatal pancreatitis.
- In contrast to other barbiturates, phenobarbital is able to suppress seizures without causing generalized CNS depression.
- Phenytoin, carbamazepine, and phenobarbital induce the synthesis of hepatic drug-metabolizing enzymes, and can thereby accelerate inactivation of other drugs. Inactivation of oral contraceptives and warfarin is of particular concern.
- AEDs can interact with one another in complex ways, causing their blood levels to change. Dosages must be adjusted to compensate for these interactions.
- All traditional AEDs (and some newer AEDs) can harm the developing fetus, especially during the first trimester. However, the fetus and mother are at greater risk from uncontrolled seizures than from AEDs. Accordingly, women with major seizure disorders should continue taking AEDs throughout pregnancy.
- Fetal risk can be minimized by using just one AED (if possible) and in the lowest effective dosage.

- Initial control of generalized convulsive SE is accomplished with an IV benzodiazepine—either diazepam or lorazepam. When diazepam is used, follow-up treatment with phenytoin or fosphenytoin is essential for prolonged seizure suppression.

Summary of Major Nursing Implications*

NURSING IMPLICATIONS THAT APPLY TO ALL ANTIEPILEPTIC DRUGS

Preadministration Assessment

Therapeutic Goal

The goal of treatment is to minimize or eliminate seizure events, thereby allowing the patient to live a normal or near-normal life.

* Fosphenytoin is a prodrug form of phenytoin indicated only for convulsive SE. The drug is given IV and undergoes immediate conversion to phenytoin. Compared with solutions of phenytoin, solutions of fosphenytoin are less irritating to veins and can be infused faster without risk of cardiovascular collapse.

Baseline Data

Before initiating treatment, it is essential to know the type of seizure involved (eg, absence, generalized tonic-clonic) and how often seizure events occur.

Implementation: Administration

Dosage Determination

Dosages are often highly individualized and difficult to establish. Clinical evaluation of therapeutic and adverse effects is essential to establish a dosage that is both safe and effective. For several AEDs (especially those used to treat tonic-clonic seizures), knowledge of plasma AED levels can facilitate dosage adjustment.

Promoting Adherence

Seizure control requires rigid adherence to the prescribed regimen; nonadherence is a major cause of therapeutic failure. **To promote adherence, educate patients about the importance of taking AEDs exactly as prescribed.** Monitoring plasma AED levels can motivate adherence and facilitate assessment of nonadherence.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Teach the patient (or a family member) to maintain a seizure frequency chart, indicating the date, time, and nature of all seizure events. The prescriber can use this record to evaluate treatment, make dosage adjustments, and alter drug selections.

Minimizing Danger from Uncontrolled Seizures

Advise patients to avoid potentially hazardous activities (eg, driving, operating dangerous machinery) until seizure control has been achieved. Also, because seizures may recur after they are largely under control, advise patients to carry some form of identification (eg, Medic Alert bracelet) to aid in diagnosis and treatment if a seizure occurs.

Minimizing Adverse Effects

CNS Depression.

Most AEDs depress the CNS. Signs of CNS depression (sedation, drowsiness, lethargy) are most prominent during the initial phase of treatment and decline with continued drug use. **Forewarn patients about CNS depression, and advise them to avoid driving and other hazardous activities if CNS depression is significant.**

Withdrawal Seizures.

Abrupt discontinuation of AEDs can lead to status epilepticus (SE). Consequently, medication withdrawal should be done slowly (over 6 weeks to several months). **Inform patients about the dangers of abrupt drug withdrawal, and instruct them never to discontinue drug use without consulting the**

prescriber. Advise patients who are planning a trip to carry extra medication to ensure an uninterrupted supply in the event they become stranded where medication is unavailable.

Usage in Pregnancy.

In most cases, the risk from uncontrolled seizures exceeds the risk from fmedication, hence women with major seizure disorders should continue to take AEDs during pregnancy. However, the lowest effective dosage should be employed and, if possible, only one drug should be used. To reduce the risk of neural tube defects, **advise women to take folic acid supplements prior to and throughout pregnancy.**

Suicidal Thoughts and Behavior.

The AEDs pose small risk of suicidal thoughts and behavior, beginning as soon as 1 week after starting treatment. **Patients, families, and caregivers should be informed about signs that may precede suicidal behavior (eg, increased anxiety, agitation, mania, or hostility) and advised to report these immediately.**

Minimizing Adverse Interactions

CNS Depressants.

Drugs with CNS-depressant actions (eg, alcohol, antihistamines, barbiturates, opioids) will intensify the depressant effects of AEDs, thereby posing a serious risk. **Warn patients against using alcohol and other CNS depressants.**

PHENYTOIN

Nursing implications for phenytoin include those presented below as well as those presented above under *Nursing Implications That Apply to All Antiepileptic Drugs*.

Preadministration Assessment

Therapeutic Goal

Oral phenytoin is used to treat partial seizures (simple and complex) and tonic-clonic seizures. Intravenous phenytoin is used to treat convulsive SE.

Identifying High-Risk Patients

Intravenous phenytoin is *contraindicated* for patients with sinus bradycardia, sinoatrial block, second- or third-degree atrioventricular block, or Stokes-Adams syndrome.

Implementation: Administration

Routes

Oral, IV, and (rarely) IM.

Administration

Oral.

Instruct patients to take phenytoin exactly as prescribed. Inform them that, once a safe and effective dosage has been established, small deviations in dosage can lead to toxicity or to loss of seizure control.

Advise patients to take phenytoin with meals to reduce gastric discomfort.

Instruct patients to shake the phenytoin oral suspension before dispensing in order to provide consistent dosing.

Intravenous.

To minimize the risk of severe reactions (eg, cardiovascular collapse), infuse phenytoin slowly (no faster than 50 mg/min).

Do not mix phenytoin solutions with other drugs.

To minimize venous inflammation at the injection site, flush the needle or catheter with saline immediately after completing the phenytoin infusion.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

CNS Effects.

Inform patients that excessive doses can produce sedation, ataxia, diplopia, and interference with cognitive function. Instruct them to notify the prescriber if these occur.

Gingival Hyperplasia.

Inform patients that phenytoin often promotes overgrowth of gum tissue. To minimize harm and discomfort, teach them proper techniques of brushing, flossing, and gum massage.

Use in Pregnancy.

Phenytoin can cause fetal hydantoin syndrome and bleeding tendencies in the neonate. Decrease bleeding risk by giving the mother vitamin K for 1 month prior to delivery and during delivery and to the infant immediately after delivery. Decrease the risk of fetal hydantoin syndrome by using the lowest effective phenytoin dosage.

Skin Rash.

Inform patients that phenytoin can cause a morbilliform (measles-like) rash that may progress to a more serious reaction. Instruct them to notify the prescriber immediately if a rash develops. Use of phenytoin should stop.

Withdrawal Seizures.

Abrupt discontinuation of phenytoin can trigger convulsive SE. **Warn patients against abrupt cessation of treatment.**

Minimizing Adverse Interactions

Phenytoin is subject to a large number of significant interactions with other drugs; a few are noted below. **Warn patients against use of any drugs not specifically approved by the prescriber.**

CNS Depressants.

Warn patients against use of alcohol and all other drugs with CNS-depressant properties, including opioids, barbiturates, and antihistamines.

Warfarin and Oral Contraceptives.

Phenytoin can decrease the effects of these agents (as well as other drugs) by inducing hepatic drug-metabolizing enzymes. Dosages of warfarin and oral contraceptives may need to be increased.

CARBAMAZEPINE

Nursing implications for carbamazepine include those presented below as well as those presented above under *Nursing Implications That Apply to All Antiepileptic Drugs*.

Preadministration Assessment

Therapeutic Goal

Carbamazepine is used to treat partial seizures (simple and complex) and tonic-clonic seizures.

Baseline Data

Obtain complete blood counts prior to treatment.

Identifying High-Risk Patients

Carbamazepine is *contraindicated* for patients with a history of bone marrow depression or adverse hematologic reactions to other drugs.

Implementation: Administration

Route

Oral.

Administration

Advise patients to administer carbamazepine with meals to decrease gastric upset.

To minimize adverse CNS effects, use low initial doses and give the largest portion of the daily dose at bedtime.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

CNS Effects.

Carbamazepine can cause headache, visual disturbances (nystagmus, blurred vision, diplopia), ataxia, vertigo, and unsteadiness. To minimize these effects, initiate therapy with low doses and have the patient take the largest part of the daily dose at bedtime.

Hematologic Effects.

Carbamazepine can cause leukopenia, anemia, thrombocytopenia, and, very rarely, fatal aplastic anemia. To reduce the risk of serious hematologic effects, (1) obtain complete blood counts at baseline and periodically thereafter, (2) avoid carbamazepine in patients with pre-existing hematologic abnormalities, and (3) **inform patients about manifestations of hematologic abnormalities (fever, sore throat, pallor, weakness, infection, easy bruising, petechiae), and instruct them to notify the prescriber if these occur.**

Birth Defects.

Carbamazepine can cause neural tube defects. Use in pregnancy only if the benefits of seizure suppression outweigh the risks to the fetus.

Severe Skin Reactions.

Carbamazepine can cause Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), especially among patients of Asian descent. To reduce risk, the FDA recommends that patients of Asian descent be tested for HLA-B*1502, a genetic variant that predisposes to these reactions. If SJS or TEN develops, carbamazepine should be discontinued.

Minimizing Adverse Interactions

Interactions Due to Induction of Drug Metabolism.

Carbamazepine can decrease responses to other drugs by inducing hepatic drug-metabolizing enzymes. Effects on oral contraceptives and warfarin are of particular concern. Patients using these drugs will require increased dosages to maintain therapeutic responses.

Phenytoin and Phenobarbital.

These drugs can decrease responses to carbamazepine by inducing drug-metabolizing enzymes (beyond the degree of induction caused by carbamazepine itself). Dosage of carbamazepine may need to be increased.

Grapefruit Juice.

Grapefruit juice can increase levels of carbamazepine. **Instruct patients not to drink grapefruit juice.**

VALPROIC ACID

Nursing implications for valproic acid include those presented below as well as those presented above under *Nursing Implications That Apply to All Antiepileptic Drugs*.

Preadministration Assessment

Therapeutic Goal

Valproic acid is used to treat all major seizure disorders: tonic-clonic, absence, myoclonic, atonic, and partial (simple, complex, and secondarily generalized).

Baseline Data

Obtain baseline tests of liver function.

Identifying High-Risk Patients

Valproic acid is *contraindicated* for patients with significant hepatic dysfunction and for children under the age of 3 years who are taking other AEDs.

Implementation: Administration

Routes

Oral, IV.

Administration

Advise patients to take valproic acid with meals, and instruct them to ingest tablets and capsules intact, without crushing or chewing.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Gastrointestinal Effects.

Nausea, vomiting, and indigestion are common. These can be reduced by using an enteric-coated formulation (see Table 24-4) and by taking valproic acid with meals.

Hepatotoxicity.

Rarely, valproic acid has caused fatal liver injury. To minimize risk, (1) don't use valproic acid in conjunction with other drugs in children under the age of 3 years; (2) don't use valproic acid in patients with preexisting liver dysfunction; (3) evaluate liver function at baseline and periodically thereafter; (4) **inform patients about signs and symptoms of liver injury (reduced appetite, malaise, nausea, abdominal pain, jaundice), and instruct them to notify the prescriber if these develop;** and (5) use valproic acid in the lowest effective dosage.

Pancreatitis.

Valproic acid can cause life-threatening pancreatitis. **Inform patients about signs of pancreatitis (abdominal pain, nausea, vomiting, anorexia) and instruct them to get immediate evaluation if these develop.** If pancreatitis is diagnosed, valproic acid should be withdrawn.

Teratogenesis.

Valproic acid may cause neural tube defects and other birth defects. **Advise women of childbearing age to use an effective form of birth control and**

to take 5 mg of folic acid daily (to reduce the risk of neural tube defects if pregnancy should occur.)

Hyperammonemia.

Combining valproic acid with topiramate poses a risk of hyperammonemia. If symptoms develop (vomiting, lethargy, altered level of consciousness and/or cognitive function), blood ammonia should be measured. If the level is excessive, either valproic acid or topiramate should be withdrawn.

Minimizing Adverse Interactions

Antiepileptic Drugs.

Valproic acid can elevate plasma levels of phenytoin and phenobarbital. Levels of phenobarbital and phenytoin should be monitored and their dosages adjusted accordingly.

Topiramate.

See *Hyperammonemia* above.

PHENOBARBITAL

Nursing implications that apply to the antiseizure applications of phenobarbital include those presented below and those presented above under *Nursing Implications That Apply to All Antiepileptic Drugs*. Nursing implications that apply to the barbiturates as a group are summarized in Chapter 34.

Preadministration Assessment

Therapeutic Goal

Oral phenobarbital is used for partial seizures (simple and complex) and tonic-clonic seizures. Intravenous therapy is used for convulsive SE.

Identifying High-Risk Patients

Phenobarbital is *contraindicated* for patients with a history of acute intermittent porphyria.

Use with *caution* during pregnancy.

Implementation: Administration

Routes

Oral and IV.

Administration

Oral.

A loading schedule may be employed to initiate treatment. Monitor for excessive CNS depression when these large doses are used.

Intravenous.

Rapid IV infusion can cause severe adverse effects. Perform infusions slowly.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Neuropsychologic Effects.

Warn patients that sedation may occur during the initial phase of treatment. Advise them to avoid hazardous activities if sedation is significant.

Inform parents that children may become irritable and hyperactive, and instruct them to notify the prescriber if these behaviors occur.

Exacerbation of Intermittent Porphyria.

Phenobarbital can exacerbate acute intermittent porphyria, and hence is absolutely contraindicated for patients with a history of this disorder.

Use in Pregnancy.

Warn women of child-bearing age that barbiturates may cause birth defects.

Withdrawal Seizures.

Abrupt withdrawal of phenobarbital can trigger seizures. **Warn patients against abrupt cessation of treatment.**

Minimizing Adverse Interactions

Interactions Caused by Induction of Drug Metabolism.

Phenobarbital induces hepatic drug-metabolizing enzymes, and can thereby decrease responses to other drugs. Effects on *oral contraceptives* and *warfarin* are a particular concern; their dosages should be increased.

CNS Depressants.

Warn patients against use of alcohol and all other drugs with CNS-depressant properties (eg, opioids, benzodiazepines).

Valproic Acid.

Valproic acid increases blood levels of phenobarbital. To avoid toxicity, reduce phenobarbital dosage.

25 Drugs for Muscle Spasm and Spasticity

In this chapter we consider two groups of drugs that cause skeletal muscle relaxation. One group is used for localized muscle spasm. The other is used for spasticity. With only one exception (dantrolene), these drugs produce their effects through actions in the central nervous system (CNS). As a rule, the drugs used to treat spasticity do not relieve acute muscle spasm and vice versa. Hence, the two groups are not interchangeable.

DRUG THERAPY OF MUSCLE SPASM: CENTRALLY ACTING MUSCLE RELAXANTS

Muscle spasm is defined as involuntary contraction of a muscle or muscle group. Muscle spasm is often painful and decreases the patient's level of functioning. Spasm can result from a variety of causes, including epilepsy, hypocalcemia, acute and chronic pain syndromes, and trauma (localized skeletal muscle injury). Discussion here is limited to spasm resulting from muscle injury.

Treatment of spasm involves physical measures as well as drug therapy. Physical measures include immobilization of the affected muscle, application of cold compresses, whirlpool baths, and physical therapy. For drug therapy, two groups of medicines are used: (1) analgesic anti-inflammatory agents (eg, aspirin), and (2) centrally acting muscle relaxants. The analgesic anti-inflammatory agents are discussed in Chapter 70. The centrally acting muscle relaxants are discussed below.

The family of centrally acting muscle relaxants consists of 9 drugs (Table 25-1). All have similar pharmacologic properties. Hence, we will consider them as a group.

Generic Name	Trade Names	Usual Adult Oral Maintenance Dosage
Baclofen	Lioresal	15–20 mg 3 or 4 times/day
Carisoprodol	Soma	350 mg 3 or 4 times/day
Chlorzoxazone	Paraflex, Parafon Forte, Remular-S	250 mg 3 or 4 times/day
Cyclobenzaprine	Flexeril, Fexmid	5-10 mg 3 times/day
Cyclobenzaprine ER*	Amrix	15 or 30 mg once daily
Diazepam	Valium	2–10 mg 3 or 4 times/day
Metaxalone	Skelaxin	800 mg 3 or 4 times/day
Methocarbamol	Robaxin	1000 mg 4 times/day
Orphenadrine	Norflex	100 mg morning and evening
Tizanidine	Zanaflex	4-8 mg 3 or 4 times/day

TABLE 25-1 Drugs for Muscle Spasm: Centrally Acting Muscle Relaxants

Mechanism of Action

For most centrally acting muscle relaxants, the mechanism of spasm relief is unclear. In laboratory animals, high doses can depress spinal motor reflexes. However, these doses are much higher than those used in humans. Hence, many investigators believe that relaxation of spasm results primarily from the *sedative properties* of these drugs, and not from specific actions exerted on CNS pathways that control muscle tone.

Two drugs—diazepam and tizanidine—are thought to relieve spasm by enhancing presynaptic inhibition of motor neurons in the CNS. Diazepam promotes presynaptic inhibition by enhancing the effects of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. Tizanidine promotes inhibition by acting as an agonist at presynaptic alpha*2* receptors.

Therapeutic Use

The centrally acting muscle relaxants are used to relieve localized spasm resulting from muscle injury. These agents can decrease local pain and tenderness and can increase range of motion. Treatment is almost always associated with sedation. The ability of central muscle relaxants to relieve discomfort of muscle spasm appears about equal to that of aspirin and the other analgesic anti-inflammatory drugs. Since there are no studies to indicate the superiority of one centrally acting muscle relaxant over another, drug selection is based largely on prescriber preference and patient response. With the exception of diazepam, the central muscle relaxants are not useful for treating spasticity or other muscle disorders resulting from CNS pathology.

Adverse Effects

CNS Depression.

All of the centrally acting muscle relaxants can produce generalized depression of the CNS. *Drowsiness, dizziness,* and *lightheadedness* are common. Patients should be warned not to participate in hazardous activities (eg, driving) if CNS depression is significant. In addition, they should be advised to avoid alcohol and all other CNS depressants.

Hepatic Toxicity.

Tizanidine [Zanaflex] and *metaxalone* [Skelaxin] can cause liver damage. Liver function should be assessed before starting treatment and periodically thereafter. If liver injury develops, these drugs should be discontinued. If the patient has pre-existing liver disease, these drugs should be avoided.

Chlorzoxazone [Paraflex, others] can cause hepatitis and potentially fatal hepatic necrosis. Because of this potential for harm, and because the benefits of chlorzoxazone are questionable, the drug should not be used.

Physical Dependence.

Chronic, high-dose therapy can cause physical dependence, manifesting as a potentially life-threatening abstinence syndrome if these drugs are abruptly withdrawn. Accordingly, withdrawal should be done slowly.

Other Adverse Effects.

Cyclobenzaprine and orphenadrine have significant anticholinergic (atropine-like) properties, and hence may cause dry mouth, blurred vision, photophobia, urinary retention, and constipation. *Methocarbamol* may turn urine brown, black, or dark green; patients should be forewarned of this harmless effect. *Tizanidine* can cause dry mouth, hypotension, hallucinations, and psychotic symptoms. *Carisoprodol* can be hazardous to patients predisposed to intermittent porphyria, and hence is contraindicated for this group.

Dosage and Administration

All centrally acting skeletal muscle relaxants can be administered orally. In addition, two agents—methocarbamol and diazepam—can be administered by injection (IM and IV). Average oral maintenance dosages for adults are listed in Table 25-1.

DRUGS FOR SPASTICITY

The term *spasticity* refers to a group of movement disorders of CNS origin. These disorders are characterized by heightened muscle tone, spasm, and loss of dexterity. The most common causes are multiple sclerosis and cerebral palsy. Other causes include traumatic spinal cord lesions and stroke. Spasticity is managed with a combination of drugs and physical therapy.

Three drugs—baclofen, diazepam, and dantrolene—can relieve spasticity. Two of these—baclofen and diazepam—act in the CNS. In contrast, dantrolene acts directly on skeletal muscle. With the exception of diazepam, the drugs employed to treat muscle spasm (ie, the centrally acting muscle relaxants) are not effective against spasticity.

Baclofen

Mechanism of Action

Baclofen [Lioresal] acts within the spinal cord to suppress hyperactive reflexes involved in regulation of muscle movement. The precise mechanism of reflex attenuation is unknown. Since baclofen is a structural analog of the inhibitory

neurotransmitter GABA (Fig. 25-1), it may act by mimicking the actions of GABA on spinal neurons. Baclofen has no direct effects on skeletal muscle.

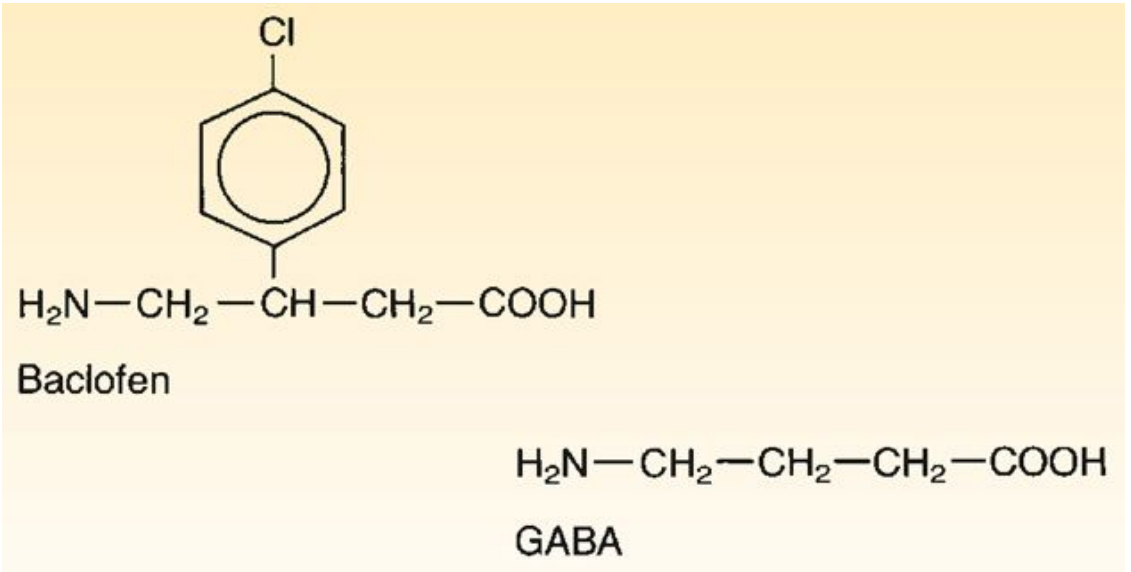


Figure 25-1 Structural similarity between baclofen and gamma-aminobutyric acid (GABA).

Therapeutic Use

Baclofen can reduce spasticity associated with multiple sclerosis, spinal cord injury, and cerebral palsy—but not with stroke. The drug decreases flexor and extensor spasms and suppresses resistance to passive movement. These actions reduce the discomfort of spasticity and allow increased performance. Because baclofen has no direct muscle relaxant action, and hence does not decrease muscle strength, baclofen is preferred to dantrolene in patients whose spasticity is associated with significant muscle weakness. Baclofen does not relieve the spasticity of Parkinson's disease or Huntington's chorea.

Adverse Effects

The most common side effects involve the CNS and GI tract. Serious adverse effects are rare.

CNS Effects.

Baclofen is a CNS depressant and hence frequently causes *drowsiness, dizziness, weakness,* and *fatigue*. These responses are most intense during the early phase of therapy and diminish with continued drug use. CNS depression can be minimized with doses that are small initially and then gradually increased. Patients should be cautioned to avoid alcohol and other CNS depressants, because baclofen will potentiate the depressant actions of these drugs.

Overdose can produce *coma* and *respiratory depression*. Since there is no antidote to baclofen poisoning, treatment is supportive.

Withdrawal.

Although baclofen does not appear to cause physical dependence, abrupt discontinuation has been associated with adverse reactions. Abrupt stoppage of *oral* baclofen can cause visual hallucinations, paranoid ideation, and seizures. Accordingly, withdrawal should be done slowly (over 1 to 2 weeks). Abrupt stoppage of *intrathecal* baclofen can be more dangerous. Potential reactions include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity that, in rare cases, has advanced to rhabdomyolysis (muscle breakdown), multiple organ system failure, and death. To avoid disaster, the infusion system must be programmed properly and carefully monitored.

Other Adverse Effects.

Baclofen frequently causes *nausea, constipation,* and *urinary retention*. Patients should be warned about these possible reactions.

Preparations, Dosage, and Administration

Oral.

Baclofen [Lioresal] is available in tablets (10 and 20 mg) for oral use. Dosages are low initially (eg, 5 mg 3 times a day) and then gradually increased. Maintenance dosages range from 15 to 20 mg administered 3 to 4 times a day.

Intrathecal.

Baclofen can be administered by intrathecal infusion using an implantable pump. The average maintenance dosage is 300 to 800 mcg/day. Intrathecal ad-

ministration is reserved for patients who are unresponsive to or intolerant of oral baclofen.

Diazepam

Diazepam [Valium] is a member of the benzodiazepine family. Although diazepam is the only benzodiazepine labeled for treating spasticity, other benzodiazepines would probably be effective. The basic pharmacology of the benzodiazepines is discussed in Chapter 34.

Actions.

Like baclofen, diazepam acts in the CNS to suppress spasticity. Beneficial effects appear to result from mimicking the actions of GABA at receptors in the spinal cord and brain. Diazepam does not affect skeletal muscle directly. Since diazepam has no direct effects on muscle strength, the drug is preferred to dantrolene in patients whose strength is marginal.

Adverse Effects.

Sedation is common when treating spasticity. To minimize sedation, initial doses should be low. Other adverse effects are discussed in Chapter 34.

Preparations, Dosage, and Administration.

For oral use, diazepam [Valium] is available in tablets (2, 5, and 10 mg), sustained-release capsules (15 mg), and solution (1 and 5 mg/mL). The drug is also available in solution (5 mg/mL) for IM and IV administration. The usual oral dosage for adults is 2 to 10 mg 3 or 4 times a day.

Dantrolene

Mechanism of Action

Unlike baclofen and diazepam, which act within the CNS, dantrolene [Dantrium] acts directly on skeletal muscle. The drug relieves spasm by suppressing release of calcium from the sarcoplasmic reticulum (SR), and hence the muscle is less able to contract. Fortunately, therapeutic doses have only minimal effects on contraction of smooth muscle and cardiac muscle.

Therapeutic Uses

Spasticity.

Dantrolene can relieve spasticity associated with multiple sclerosis, cerebral palsy, and spinal cord injury. Unfortunately, since dantrolene suppresses spasticity by causing a generalized reduction in the ability of skeletal muscle to contract, treatment may be associated with a significant reduction in strength. As a result, for some patients, overall function may be reduced rather than improved. Accordingly, care must be taken to ensure that the benefits of therapy (reduced spasticity) outweigh the harm (reduced strength).

Malignant Hyperthermia.

Malignant hyperthermia is a rare, life-threatening syndrome that can be triggered by any general anesthetic (except nitrous oxide) and by succinylcholine, a neuromuscular blocking agent. Onset of symptoms is most abrupt with succinylcholine (when used alone or in combination with an anesthetic). Prominent symptoms are muscle rigidity and profound elevation of temperature. The heat of malignant hyperthermia is generated by muscle contraction occurring secondary to massive release of calcium from the SR. Dantrolene relieves symptoms by acting on the SR to block calcium release. Malignant hyperthermia is discussed further in Chapter 16.

Adverse Effects

Hepatic Toxicity.

Dose-related liver damage is dantrolene's most serious adverse effect. The incidence is 1 in 1000. Death has occurred. Hepatotoxicity is most common in women over age 35 years. By contrast, liver injury is rare in children under 10 years. To reduce the risk of liver damage, liver function tests (LFTs) should be performed at baseline and periodically thereafter. If LFTs indicate liver injury, dantrolene should be withdrawn. Because of the potential for liver damage, dantrolene should be administered in the lowest effective dosage and for the shortest time necessary.

Other Adverse Effects.

Muscle weakness, drowsiness, and *diarrhea* are the most common side effects. Muscle weakness is a direct extension of dantrolene's pharmacologic action. Other disturbing reactions include *anorexia, nausea, vomiting,* and *acne-like rash*.

Preparations, Dosage, and Administration

Preparations.

Dantrolene sodium [Dantrium] is available in capsules (25, 50, and 100 mg) for oral use and as a powder to be reconstituted for IV injection.

Use in Spasticity.

For treatment of spasticity, administration is oral. The initial adult dosage is 25 mg once daily. The usual maintenance dosage is 100 mg 2 to 4 times a day. If beneficial effects do not develop within 45 days, dantrolene should be stopped.

Use in Malignant Hyperthermia

Preoperative Prophylaxis.

Patients with a history of malignant hyperthermia can be given dantrolene for prophylaxis prior to elective surgery. The dosage is 4 to 8 mg/kg/day in four divided doses for 1 to 2 days preceding surgery.

Treatment of an Ongoing Crisis.

For treatment of malignant hyperthermia, dantrolene is administered by IV push. The initial dose is 2 mg/kg. Administration is repeated until symptoms are controlled or until a total dose of 10 mg/kg has been given. Other management measures are discussed in Chapter 16.

KEY POINTS

- Localized muscle spasm is treated with centrally acting muscle relaxants and aspirin-like drugs.
- Spasticity is treated with three drugs: baclofen, diazepam, and dantrolene.

- All centrally acting muscle relaxants produce generalized CNS depression.
- Chlorzoxazone, a central muscle relaxant, is marginally effective and can cause fatal hepatic necrosis. Accordingly, the drug should be avoided.
- Baclofen and diazepam relieve spasticity by mimicking the inhibitory actions of GABA in the CNS.
- Like the centrally acting muscle relaxants, baclofen and diazepam cause generalized CNS depression.
- In contrast to all other drugs discussed in this chapter, dantrolene acts directly on muscle to promote relaxation.
- Abrupt discontinuation of *intrathecal* baclofen can lead to rhabdomyolysis, multiple organ system failure, and death.
- With prolonged use, dantrolene can cause potentially fatal liver damage. Monitor liver function and minimize dosage and duration of treatment.
- In addition to relief of spasticity, dantrolene is used to treat malignant hyperthermia, a potentially fatal condition caused by succinylcholine and general anesthetics.

Summary of Major Nursing Implications*

DRUGS USED TO TREAT MUSCLE SPASM: CENTRALLY ACTING SKELETAL MUSCLE RELAXANTS

Baclofen

Carisoprodol

Chlorzoxazone

Cyclobenzaprine

Diazepam

Metaxalone

Methocarbamol

Orphenadrine

Tizanidine

Except where noted, the nursing implications summarized below apply to all centrally acting muscle relaxants used to treat muscle spasm.

Preadministration Assessment

Therapeutic Goal

Relief of signs and symptoms of muscle spasm.

Baseline Data

For patients taking metaxalone and tizanidine, obtain baseline LFTs.

Identifying High-Risk Patients

Avoid *chlorzoxazone, metaxalone,* and *tizanidine* in patients with liver disease.

Implementation: Administration

Routes

Oral.

All central skeletal muscle relaxants.

Parenteral.

Methocarbamol and diazepam may be given IM and IV as well as PO.

Dosage

See Table 25-1.

Implementation: Measures to Enhance Therapeutic Effects

The treatment plan should include appropriate physical measures (eg, immobilization of the affected muscle, application of cold compresses, whirlpool baths, and physical therapy).

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

CNS Depression.

All central muscle relaxants cause CNS depression. **Inform patients about possible effects (drowsiness, dizziness, lightheadedness, fatigue) and advise them to avoid driving and other hazardous activities if significant impairment occurs.**

Hepatic Toxicity.

Metaxalone and tizanidine can cause liver damage. Obtain LFTs before treatment and periodically thereafter. If liver damage develops, discontinue treatment. Avoid these drugs in patients with pre-existing liver disease.

Chlorzoxazone can cause hepatitis and potentially fatal hepatic necrosis. The drug should not be used.

Minimizing Adverse Interactions

CNS Depressants.

Caution patients to avoid CNS depressants (eg, alcohol, benzodiazepines, opioids, antihistamines) because these drugs will intensify the depressant effects of muscle relaxants.

Avoiding Withdrawal Reactions

Central muscle relaxants can cause physical dependence. To avoid an abstinence syndrome, withdraw gradually. **Warn the patient against abrupt discontinuation of treatment.**

BACLOFEN

Preadministration Assessment

Therapeutic Goal

Relief of signs and symptoms of spasticity.

Baseline Data

Assess for spasm, rigidity, pain, range of motion, and dexterity. Obtain baseline LFTs.

Implementation: Administration

Routes

Oral, intrathecal.

Administration

Patients with muscle spasm may be unable to self-medicate. Provide assistance if needed.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor for reductions in rigidity, muscle spasm, and pain and for improvements in dexterity and range of motion.

Minimizing Adverse Effects

CNS Depression.

Baclofen is a CNS depressant. **Inform patients about possible depressant effects (drowsiness, dizziness, lightheadedness, fatigue) and advise them to avoid driving and other hazardous activities if significant impairment occurs.**

Minimizing Adverse Interactions

CNS Depressants.

Caution patients to avoid CNS depressants (eg, alcohol, benzodiazepines, opioids, antihistamines) because these drugs will intensify the depressant effects of baclofen.

Avoiding Withdrawal Reactions

Oral Baclofen.

Abrupt withdrawal can cause visual hallucinations, paranoid ideation, and seizures. **Caution the patient against abrupt discontinuation of treatment.**

Intrathecal Baclofen.

Abrupt discontinuation can cause multiple adverse effects, including rhabdomyolysis, multiple organ system failure, and death. Make sure the infusion system is programmed properly and monitored with care.

DANTROLENE

The nursing implications summarized here apply only to the use of dantrolene for spasticity.

Preadministration Assessment

Therapeutic Goal

Relief of signs and symptoms of spasticity.

Baseline Data

Assess for spasm, rigidity, pain, range of motion, and dexterity. Obtain baseline LFTs.

Identifying High-Risk Patients

Dantrolene is *contraindicated* for patients with active liver disease (eg, cirrhosis, hepatitis).

Implementation: Administration

Route

Oral.

Administration

Patients with muscle spasm may be unable to self-medicate. Provide assistance if needed.

Ongoing Evaluation and Interventions

Summary of Monitoring

Therapeutic Effects.

Monitor for reductions in rigidity, spasm, and pain and for improvements in dexterity and range of motion.

Adverse Effects.

Monitor LFTs and assess for reduced muscle strength.

Minimizing Adverse Effects

CNS Depression.

Dantrolene is a CNS depressant. **Inform patients about possible depressant effects (drowsiness, dizziness, lightheadedness, fatigue) and advise them to avoid driving and other hazardous activities if significant impairment occurs.**

Hepatic Toxicity.

Dantrolene is hepatotoxic. Assess liver function at baseline and periodically thereafter. If signs of liver dysfunction develop, withdraw dantrolene. **Inform patients about signs of liver dysfunction (eg, jaundice, abdominal pain, malaise) and instruct them to seek medical attention if these develop.**

Muscle Weakness.

Dantrolene can decrease muscle strength. Evaluate muscle function to ensure that benefits of therapy (decreased spasticity) are not outweighed by reductions in strength.

Minimizing Adverse Interactions

CNS Depressants.

Warn patients to avoid CNS depressants (eg, alcohol, benzodiazepines, opioids, antihistamines), because these drugs will intensify depressant effects of dantrolene.

DIAZEPAM

Nursing implications for diazepam and the other benzodiazepines are summarized in Chapter 34 (Sedative-Hypnotic Drugs).

Drugs for Pain

26 Local Anesthetics

Local anesthetics are drugs that suppress pain by blocking impulse conduction along axons. Conduction is blocked only in neurons located near the site of anesthetic administration. The great advantage of local anesthesia, compared with inhalation anesthesia, is that pain can be suppressed without causing generalized depression of the entire nervous system. Hence, local anesthetics carry much less risk than that associated with general anesthetics.

We begin the chapter by considering the pharmacology of the local anesthetics as a group. After that, we discuss three prototypic agents: procaine, lidocaine, and cocaine. We conclude by discussing specific routes of anesthetic administration.

BASIC PHARMACOLOGY OF THE LOCAL ANESTHETICS

Classification

There are two major groups of local anesthetics: *esters* and *amides*. As shown in Figure 26-1, the ester-type anesthetics, represented by *procaine* [Novocain], contain an ester linkage in their structure. In contrast, the amide-type agents, represented by *lidocaine* [Xylocaine], contain an amide linkage. The ester-type agents and amide-type agents differ in two important ways: method of inactivation and promotion of allergic responses. Contrasts between the esters and amides are summarized in Table 26-1.

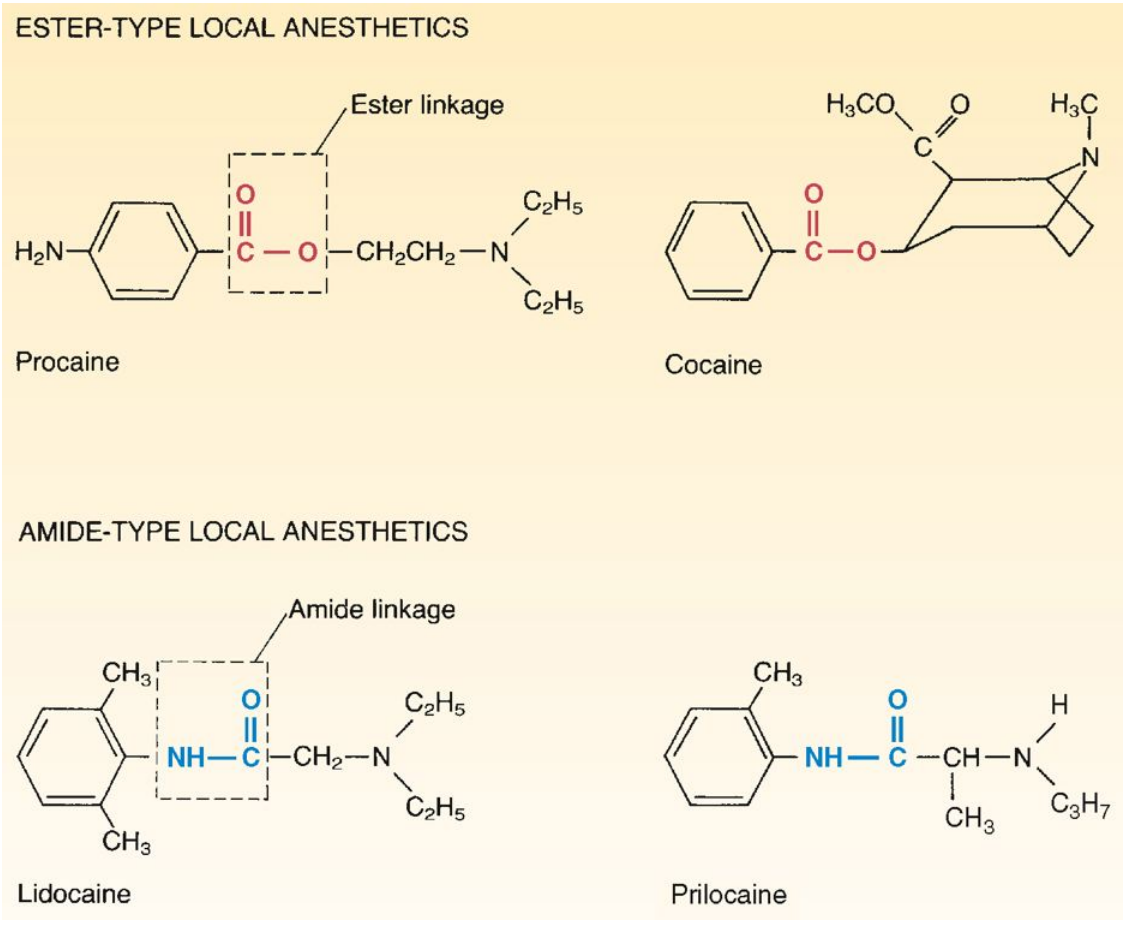


Figure 26-1 Structural formulas of representative local anesthetics.

	Ester-type Anesthetics	Amide-type Anesthetics
Characteristic Chemistry	Ester bond	Amide bond
Representative Agents	Procaine	Lidocaine
Incidence of Allergic Reactions	Low	Very low
Method of Metabolism	Plasma esterases	Hepatic enzymes

TABLE 26-1 Contrasts Between Ester and Amide Local Anesthetics

Mechanism of Action

Local anesthetics stop axonal conduction by *blocking sodium channels* in the axonal membrane. Recall that propagation of an action potential requires movement of sodium ions from outside the axon to the inside. This influx takes place through specialized sodium channels. By blocking axonal sodium channels, local anesthetics prevent sodium entry, and thereby bring conduction to a halt.

Selectivity of Anesthetic Effects

Local anesthetics are nonselective modifiers of neuronal function. That is, they will block action potentials in all neurons to which they have access. The only way we can achieve selectivity is by delivering the anesthetic to a limited area.

Although local anesthetics can block traffic in all neurons, blockade develops more rapidly in some neurons than others. Specifically, small, nonmyelinated neurons are blocked more rapidly than large, myelinated neurons. Because of this differential sensitivity, some sensations are blocked sooner than others. Specifically, perception of pain is lost first, followed in order by perception of cold, warmth, touch, and deep pressure.

It should be noted that the effects of local anesthetics are not limited to sensory neurons; these drugs also block conduction in motor neurons (which is why your face looks funny when you leave the dentist).

Time Course of Local Anesthesia

Ideally, local anesthesia would begin promptly and would persist no longer (or shorter) than needed. Unfortunately, although onset of anesthesia is usually rapid (see Tables 26-2 and 26-3 below), duration of anesthesia is often less than ideal. In some cases, anesthesia persists longer than needed. In others, repeated administration is required to maintain anesthesia of sufficient duration.

Chemical Class	Generic Name	Trade Name	Indications		Time Course of Action*	
			Skin	Mucous Membranes	Peak Effect (min)	Duration (min)
Amides	Dibucaine	Nupercainal	✓		Less than 5	15–45
	Lidocaine†	Xylocaine, Lidoderm, others	✓	✓	2–5	15–45
Esters	Benzocaine	Many names	✓	✓	Less than 5	15–45
	Cocaine	Generic only	✓	✓	1–5	30–60
	Tetracaine†	Generic only	✓	✓	3–8	30–60
Others	Dyclonine	Sucrets (spray)		✓	Less than 10	Less than 60
	Pramoxine	Tronothane, others	✓		3–5	—

TABLE 26-2 Topical Local Anesthetics: Trade Names, Indications, and Time Course of Action

* Based primarily on application to mucous membranes.

† Also administered by injection.

	Generic Name	Trade Name	Time Course of Action* Onset (min)	Duration (hr)
Amides	Lidocaine†	Xylocaine, Octocaine	Less than 2	0.5–1
	Articaine	Septocaine	1–6‡	1‡
	Bupivacaine	Marcaine, Sensorcaine	5	2–4
	Levobupivacaine	Chirocaine	10§	8§
	Mepivacaine	Carbocaine, Polocaine	3–5	0.75–1.5
	Prilocaine	Citanest	Less than 2	1 or more
	Ropivacaine	Naropin	10–30§	0.5–6§
Esters¶	Procaine	Novocain	2–5	0.25–1
	Chloroprocaine	Nesacaine	6–12	0.5
	Tetracaine†	Pontocaine	15 or less	2–3

TABLE 26-3 Injectable Local Anesthetics: Trade Names and Time Course of Action

Onset of local anesthesia is determined largely by the molecular properties of the anesthetic. Before anesthesia can occur, the anesthetic must diffuse from its site of administration to its sites of action within the axon membrane. Anesthesia is delayed until this movement has occurred. The ability of an anesthetic to penetrate the axon membrane is determined by three properties: *molecular size, lipid solubility,* and *degree of ionization at tissue pH*. Anesthetics of small size, high lipid solubility, and low ionization cross the axon membrane rapidly. In contrast, anesthetics of large size, low lipid solubility, and high ionization cross slowly. Obviously, anesthetics that penetrate the axon most rapidly have the fastest onset.

Termination of local anesthesia occurs as molecules of anesthetic diffuse out of neurons and are carried away in the blood. The same factors that determine onset of anesthesia (molecular size, lipid solubility, degree of ionization) also help determine duration. In addition, *regional blood flow* is an important determinant of how long anesthesia will last. In areas where blood flow is high, anesthetic is carried away quickly, and hence effects terminate with relative haste. In regions where blood flow is low, anesthesia is more prolonged.

Use with Vasoconstrictors

Local anesthetics are frequently administered in combination with a vasoconstrictor—usually *epinephrine*. The vasoconstrictor decreases local blood flow and thereby delays systemic absorption of the anesthetic. Delaying absorption has two benefits: It *prolongs anesthesia* and *reduces the risk of toxicity*. Why is toxicity reduced? First, because absorption is slowed, we can use less anesthetic. Second, by slowing absorption, we can establish a more favorable balance between the rate of entry of anesthetic into circulation and the rate of its conversion into inactive metabolites.

It should be noted that absorption of the vasoconstrictor itself can result in systemic toxicity (eg, palpitations, tachycardia, nervousness, hypertension). If adrenergic stimulation from absorption of epinephrine is excessive, symptoms can be controlled with alpha- and beta-adrenergic antagonists.

Fate in the Body

Absorption and Distribution.

Although administered for local effects, local anesthetics do get absorbed into the blood and become distributed to all parts of the body. The rate of absorption is determined largely by blood flow to the site of administration.

Metabolism.

The process by which a local anesthetic is metabolized depends on the class—ester or amide—to which it belongs. *Ester-type* local anesthetics are metabolized in the blood by enzymes known as *esterases*. In contrast, *amide-type* anesthetics are metabolized by enzymes in the *liver*. For both types of anesthetic, metabolism results in inactivation.

The balance between rate of absorption and rate of metabolism is clinically significant. If a local anesthetic is absorbed more slowly than it is metabolized, its level in blood will remain low, and hence systemic reactions will be minimal. Conversely, if absorption outpaces metabolism, plasma drug levels will rise, and the risk of systemic toxicity will increase.

Adverse Effects

Adverse effects can occur locally or distant from the site of administration. Local effects are less common.

Central Nervous System.

When absorbed in sufficient amounts, local anesthetics cause central nervous system (CNS) excitation followed by depression. During the excitation phase, *convulsions* may occur. If needed, excessive excitation can be managed with an IV benzodiazepine (diazepam or midazolam) or with IV thiopental (a rapid-acting barbiturate). Depressant effects range from *drowsiness* to *unconsciousness*. Death can occur secondary to *depression of respiration*. If respiratory depression is prominent, mechanical ventilation with oxygen is indicated.

Cardiovascular System.

When absorbed in sufficient amounts, local anesthetics can affect the heart and blood vessels. In the heart, these drugs suppress excitability in the myocardium and conducting system, and thereby can cause *bradycardia, heart block, reduced contractile force,* and *even cardiac arrest*. In blood vessels, anesthetics relax vascular smooth muscle; the resultant vasodilation can cause *hypotension*. As discussed in Chapter 48 (Antidysrhythmic Drugs), the cardiosuppressant actions of one local anesthetic—lidocaine—are exploited to treat dysrhythmias.

Allergic Reactions.

An array of hypersensitivity reactions, ranging from *allergic dermatitis* to *anaphylaxis,* can be triggered by local anesthetics. These reactions, which are relatively uncommon, are much more likely with the *ester-type* anesthetics (eg, procaine) than with the amides. Patients allergic to one ester-type anesthetic are likely to be allergic to all other ester-type agents. Fortunately, cross-hy-

persensitivity between the esters and amides has not been observed. Hence, the amides can be used when allergies contraindicate use of ester-type anesthetics. Because they are unlikely to cause hypersensitivity reactions, the amide-type anesthetics have largely replaced the ester-type agents when administration by injection is required.

Use in Labor and Delivery.

Local anesthetics can depress uterine contractility and maternal expulsion effort. Both actions can *prolong labor*. Also, local anesthetics can cross the placenta, causing *bradycardia and CNS depression in the neonate*.

PROPERTIES OF INDIVIDUAL LOCAL ANESTHETICS

Procaine

Procaine [Novocain] was synthesized in 1905 and is the prototype of the ester-type local anesthetics. The drug is not effective topically, and hence must be given by injection. Administration in combination with epinephrine delays absorption. Although procaine is readily absorbed, systemic toxicity is rare. Why? Because plasma esterases rapidly convert the drug to inactive, nontoxic products. Being an ester-type anesthetic, procaine poses a greater risk of allergic reactions than the amide-type anesthetics. Individuals allergic to procaine should be considered allergic to all other ester-type anesthetics, but not to the amides.

For many years, procaine was the local anesthetic most preferred for use by injection. However, with the development of newer agents, use of procaine has sharply declined. Once popular in dentistry, procaine is rarely employed in that setting today.

Preparations.

Procaine hydrochloride [Novocain] is available in solution (1%, 2%, and 10%) for administration by injection. Dilution is required for use by some routes. Epinephrine (at a final concentration of 1:100,000 or 1:200,000) may be combined with procaine to delay absorption.

Lidocaine

Lidocaine, introduced in 1948, is the prototype of the amide-type agents. One of today's most widely used local anesthetics, lidocaine can be administered topically and by injection. Anesthesia from lidocaine is more rapid, more intense, and more prolonged than with an equal dose of procaine. Effects can be extended by coadministration of epinephrine. Allergic reactions are rare, and individuals allergic to ester-type anesthetics are not cross-allergic to lidocaine. If plasma levels of lidocaine climb too high, CNS and cardiovascular toxicity can result. Inactivation is by hepatic metabolism.

In addition to its use in local anesthesia, lidocaine is employed to treat dysrhythmias (see Chapter 48). Control of dysrhythmias results from suppression of cardiac excitability secondary to blockade of cardiac sodium channels.

Preparations.

Lidocaine hydrochloride [Xylocaine, others] is available in several formulations (cream, ointment, jelly, solution, aerosol, patch) for topical administration. Lidocaine for injection is available in concentrations ranging from 0.5% to 2%. Some injectable preparations contain epinephrine (1:50,000, 1:100,000, or 1:200,000).

Cocaine

Cocaine was our first local anesthetic. Clinical use was initiated in 1884 by Sigmund Freud and Karl Koller. Freud described the physiologic effects of cocaine while Koller focused on the drug's anesthetic actions. As you can see from its structure (see Fig. 26-1), cocaine is an ester-type anesthetic. In addition to causing local anesthesia, cocaine has pronounced effects on the sympathetic and central nervous systems. Sympathetic and CNS effects are due in large part to the drug's ability to block uptake of norepinephrine by adrenergic neurons.

Anesthetic Use.

Cocaine is an excellent local anesthetic. Administration is topical. The drug is employed for anesthesia of the ear, nose, and throat. Anesthesia develops rapidly and persists for about an hour. Unlike other local anesthetics, cocaine causes intense vasoconstriction (by blocking norepinephrine uptake at sympathetic nerve terminals on blood vessels). Accordingly, the drug should not

be given in combination with epinephrine or any other vasoconstrictor. Despite its ability to constrict blood vessels, cocaine is readily absorbed following application to mucous membranes. Significant effects on the brain and heart can result. The drug is inactivated by plasma esterases and liver enzymes.

CNS Effects.

Cocaine produces generalized CNS stimulation. Moderate doses cause euphoria, loquaciousness, reduced fatigue, and increased sociability and alertness. Excessive doses can cause seizures. Excitation is followed by CNS depression. Respiratory arrest and death can result.

Although cocaine does not seem to cause substantial physical dependence, psychologic dependence can be profound. The drug is subject to widespread abuse and is classified under Schedule II of the Controlled Substances Act. Cocaine abuse is discussed in Chapter 39.

Cardiovascular Effects.

Cocaine stimulates the heart and causes vasoconstriction. These effects result from (1) central stimulation of the sympathetic nervous system and (2) blockade of norepinephrine uptake in the periphery. Stimulation of the heart can produce *tachycardia* and potentially fatal *dysrhythmias*. Vasoconstriction can cause *hypertension*. Cocaine presents an especially serious risk to individuals with cardiovascular disease (eg, hypertension, dysrhythmias, angina pectoris).

When used for local anesthesia, cocaine should not be combined with epinephrine. Why? Because the combination would increase the risk of cardiovascular toxicity. Furthermore, since a vasoconstrictor would not significantly retard cocaine absorption, the combination would be irrational as well as dangerous.

Preparations and Administration.

Cocaine hydrochloride is available as a powder (5 and 25 gm) and in solution (4% and 10%). Administration is topical. For application to the ear, nose, or throat, a 4% solution is usually employed. The drug must be dispensed in accord with the Controlled Substances Act.

Other Local Anesthetics

In addition to the drugs discussed above, several other local anesthetics are available. These agents differ with respect to indications, route of administration, mode of elimination, duration of action, and toxicity.

The local anesthetics can be grouped according to route of administration: topical versus injection. (Very few agents are administered by both routes. Why? Primarily because the drugs that are suitable for topical application are usually too toxic for parenteral use.) Table 26-2 lists the topically administered local anesthetics along with trade names and time course of action. Table 26-3 presents equivalent information for the injectable agents.

CLINICAL USE OF LOCAL ANESTHETICS

Local anesthetics may be administered *topically* (for surface anesthesia) and *by injection* (for infiltration anesthesia, nerve block anesthesia, intravenous regional anesthesia, epidural anesthesia, and spinal anesthesia). The uses and hazards of these anesthesia techniques are discussed below.

Topical Administration

Surface anesthesia is accomplished by applying the anesthetic directly to the skin or a mucous membrane. The agents employed most commonly are *lidocaine, tetracaine,* and *cocaine*.

Therapeutic Uses.

Local anesthetics are applied to the *skin* to relieve pain, itching, and soreness of various causes, including infection, thermal burns, sunburn, diaper rash, wounds, bruises, abrasions, plant poisoning, and insect bites. Application may be made to *mucous membranes* of the nose, mouth, pharynx, larynx, trachea, bronchi, vagina, and urethra. In addition, local anesthetics may be used to relieve discomfort associated with hemorrhoids, anal fissures, and pruritus ani.

Systemic Toxicity.

Topical anesthetics can be absorbed in amounts sufficient to produce systemic toxicity. Cardiovascular reactions and CNS reactions are the principal concerns. Because the extent of absorption is proportional to the surface area

covered, the risk of toxicity is greatest when the surface area is large. Also, because absorption occurs more readily through mucous membranes than through the skin, application to mucous membranes poses the greater risk. If the skin is abraded or otherwise injured, absorption will be increased, thereby increasing risk.

Administration by Injection

Injection of local anesthetics carries significant risk and requires special skills. Accordingly, injections are usually performed by an anesthesiologist. Because severe systemic reactions may occur, equipment for resuscitation should be immediately available. Also, an IV line should be in place to permit rapid treatment of toxicity. Inadvertent injection into an artery or vein can cause severe toxicity. To ensure the needle is not in a blood vessel, it should be aspirated prior to injection. Following administration, the patient should be monitored for cardiovascular status, respiratory function, and state of consciousness. To reduce the risk of toxicity, local anesthetics should be administered in the lowest effective dose.

Infiltration Anesthesia

Infiltration anesthesia is achieved by injecting a local anesthetic directly into the immediate area of surgery or manipulation. Anesthesia can be prolonged by combining the anesthetic with epinephrine. However, epinephrine should not be used in areas supplied by end arteries (toes, fingers, nose, ears, penis), because restriction of blood flow at these sites may result in gangrene. The agents employed most frequently for infiltration anesthesia are *lidocaine* and *bupivacaine*.

Nerve Block Anesthesia

Nerve block anesthesia is achieved by injecting a local anesthetic into or near nerves that supply the surgical field, but at a site distant from the field itself. This technique has the advantage of producing anesthesia with doses that are smaller than those needed for infiltration anesthesia. Drug selection is based on required duration of anesthesia. For shorter procedures, *lidocaine* or *mepivacaine* might be used. For longer procedures, *bupivacaine* would be appropriate.

Intravenous Regional Anesthesia

Intravenous regional anesthesia is employed to anesthetize the extremities—hands, feet, arms, and lower legs, but not the entire leg (because too much anesthetic would be needed). Anesthesia is produced by injection into a distal vein of an arm or leg. Prior to giving the anesthetic, blood is removed from the limb (by gravity or by application of an Esmarch bandage), and a tourniquet is applied to the limb (proximal to the site of anesthetic injection) to prevent anesthetic from entering the systemic circulation. To ensure complete blockade of arterial flow throughout the procedure, a double tourniquet is used. Following injection, the anesthetic diffuses out of the vasculature and becomes evenly distributed to all areas of the occluded limb. When the tourniquet is loosened at the end of surgery, about 15% to 30% of administered anesthetic is released into the systemic circulation. *Lidocaine—without epinephrine*—is the preferred agent for this type of anesthesia.

Epidural Anesthesia

Epidural anesthesia is achieved by injecting a local anesthetic into the epidural space (ie, within the spinal column but outside the dura mater). A catheter placed in the epidural space allows administration by bolus or by continuous infusion. Following administration, diffusion of anesthetic across the dura into the subarachnoid space blocks conduction in nerve roots and in the spinal cord itself. Diffusion through intervertebral foramina blocks nerves located in the paravertebral region. With epidural administration, anesthetic can reach the systemic circulation in significant amounts. As a result, when the technique is used during delivery, neonatal depression may result. *Lidocaine* and *bupivacaine* are popular drugs for epidural anesthesia. Because of the risk of death from cardiac arrest, the concentrated (0.75%) solution of bupivacaine must not be used in obstetric patients.

Spinal (Subarachnoid) Anesthesia

Technique.

Spinal anesthesia is produced by injecting local anesthetic into the subarachnoid space. Injection is made in the lumbar region below the termination of the cord. Spread of anesthetic within the subarachnoid space determines the

level of anesthesia achieved. Movement of anesthetic within the subarachnoid space is determined by two factors: (1) the density of the anesthetic solution and (2) the position of the patient. Anesthetics employed most commonly are *bupivacaine, lidocaine,* and *tetracaine*. All must be free of preservatives.

Adverse Effects.

The most significant adverse effect of spinal anesthesia is hypotension. Blood pressure is reduced by venous dilation secondary to blockade of sympathetic nerves. (Loss of venous tone decreases the return of blood to the heart, causing a reduction in cardiac output and a corresponding fall in blood pressure.) Loss of venous tone can be compensated for by placing the patient in a 10- to 15-degree head-down position, which promotes venous return to the heart. If blood pressure cannot be restored through head-down positioning, drugs may be indicated; ephedrine and phenylephrine have been employed to promote vasoconstriction and enhance cardiac performance.

Autonomic blockade may disrupt function of the intestinal and urinary tracts, causing fecal incontinence and either urinary incontinence or urinary retention. The prescriber should be notified if the patient fails to void within 8 hours of the end of surgery.

Spinal anesthesia frequently causes headache. These "spinal" headaches are posture dependent and can be relieved by having the patient assume a supine position.

KEY POINTS

- Local anesthetics stop nerve conduction by blocking sodium channels in the axon membrane.
- Small, nonmyelinated neurons are blocked more rapidly than large, myelinated neurons.
- There are two classes of local anesthetics: ester-type anesthetics and amide-type anesthetics.
- Ester-type anesthetics (eg, procaine) occasionally cause allergic reactions and are inactivated by esterases in the blood.

- Amide-type anesthetics (eg, lidocaine) rarely cause allergic reactions and are inactivated by enzymes in the liver.
- Onset of anesthesia occurs most rapidly with anesthetics that are small, lipid soluble, and nonionized at physiologic pH.
- Termination of local anesthesia is determined in large part by regional blood flow. Hence, coadministration of epinephrine, a vasoconstrictor, will prolong anesthesia.
- Local anesthetics can be absorbed in amounts sufficient to cause systemic toxicity. Principal concerns are cardiac depression, vasodilation, and CNS excitation followed by depression.
- Because of the risk of systemic toxicity, an IV line should be in place prior to anesthetic administration (to permit administration of required emergency drugs), and facilities for resuscitation should be immediately available.

Summary of Major Nursing Implications*

TOPICAL LOCAL ANESTHETICS

Benzocaine

Cocaine

Dibucaine

Dyclonine

Lidocaine

Pramoxine

Tetracaine

Preadministration Assessment

Therapeutic Goal

Reduction of discomfort associated with local disorders of the skin and mucous membranes.

Identifying High-Risk Patients

Ester-type local anesthetics are *contraindicated* for patients with a history of serious allergic reactions to these drugs.

Implementation: Administration

Routes

Topical application to skin and mucous membranes.

Administration

Apply in the lowest effective dosage to the smallest area required. If possible, avoid application to skin that is abraded or otherwise injured. Wear gloves when applying the anesthetic.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Systemic Toxicity.

Absorption into the general circulation can cause systemic toxicity. Effects on the heart (bradycardia, atrioventricular [AV] heart block, cardiac arrest) and CNS (excitation, possibly including convulsions, followed by depression) are of greatest concern. Monitor blood pressure, pulse rate, respiratory rate, and state of consciousness. Have facilities for cardiopulmonary resuscitation available.

The risk of systemic toxicity is determined by the extent of absorption. To minimize absorption, apply topical anesthetics to the smallest surface area needed and, when possible, avoid application to injured skin.

Allergic Reactions.

Severe allergic reactions are rare but can occur. Allergic reactions are most likely with ester-type anesthetics. Avoid ester-type agents in patients with a history of allergy to these drugs.

INJECTED LOCAL ANESTHETICS

Articaine

Bupivacaine

Chloroprocaine

Levobupivacaine

Lidocaine

Mepivacaine

Prilocaine

Procaine

Ropivacaine

Tetracaine

Preadministration Assessment

Therapeutic Goal

Production of local anesthesia for surgical, dental, and obstetric procedures.

Identifying High-Risk Patients

Ester-type local anesthetics are *contraindicated* for patients with a history of serious allergic reactions to these drugs.

Implementation: Administration

Preparation of the Patient

The nurse may be responsible for preparing the patient to receive an injectable local anesthetic. Preparation includes cleansing the injection site, shaving the site when indicated, and placing the patient in a position appropriate to receive the injection. Children, elderly patients, and uncooperative patients may require restraint prior to injection by some routes.

Administration

Injection of local anesthetics is performed by clinicians with special training in their use (physicians, dentists, nurse anesthetists).

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Systemic Reactions.

Absorption into the general circulation can cause systemic toxicity. Effects on the CNS and heart are of greatest concern. CNS toxicity manifests as a brief period of excitement, possibly including convulsions, followed by CNS depression, which can result in respiratory depression. Cardiotoxicity can manifest as bradycardia, AV heart block, and cardiac arrest. Monitor blood pressure, pulse rate, respiratory rate, and state of consciousness. Have facilities for cardiopulmonary resuscitation available. Manage CNS excitation with IV diazepam or IV thiopental.

Allergic Reactions.

Severe allergic reactions are rare but can occur. These are most likely with ester-type anesthetics. Avoid ester-type agents in patients with a history of allergy to these drugs.

Labor and Delivery.

Use of local anesthetics during delivery can cause bradycardia and CNS depression in the newborn. Monitor cardiac status. Avoid concentrated (0.75%) bupivacaine.

Self-Inflicted Injury.

Since anesthetics eliminate pain, and since pain warns us about injury, patients recovering from anesthesia must be protected from inadvertent harm until the anesthetic wears off. **Caution the patient against activities that might result in unintentional harm.**

Spinal Headache and Urinary Retention.

Patients recovering from spinal anesthesia may experience headache and urinary retention. Headache is posture dependent and can be minimized by having the patient remain supine for about 12 hours. Notify the prescriber if the patient fails to void within 8 hours.

27 General Anesthetics

General anesthetics are drugs that produce unconsciousness and a lack of responsiveness to all painful stimuli. In contrast, *local anesthetics* do not reduce consciousness and they blunt sensation only in a limited area (see Chapter 26).

General anesthetics can be divided into two groups: (1) inhalation anesthetics and (2) intravenous anesthetics. The inhalation anesthetics are the main focus of this chapter.

When considering the anesthetics, we need to distinguish between the terms *analgesia* and *anesthesia*. Analgesia refers specifically to loss of sensibility to pain. In contrast, anesthesia refers not only to loss of pain but to loss of all other sensations as well (eg, touch, temperature, taste). Hence, while analgesics (eg, aspirin, morphine) can selectively reduce pain without affecting other sensory modalities and without reducing consciousness, the general anesthetics have no such selectivity: During general anesthesia, all sensation is lost, and consciousness is lost as well.

The development of general anesthetics has had an incalculable impact on the surgeon's art. The first general anesthetic—ether—was introduced by Dr. William T. Morton in 1846. Prior to this, surgery was a brutal and exquisitely painful ordeal, undertaken only in the most desperate circumstances. Immobilization of the surgical field was accomplished with the aid of strong men and straps. Survival of the patient was determined by the surgeon's speed—not his finesse. With the advent of general anesthesia, all of this changed. General anesthesia produced a patient who slept through surgery and experienced no pain. These changes allowed surgeons to develop the lengthy and intricate procedures that are routine today. Such procedures were unthinkable before general anesthetics became available.

In addition to their use in surgery, general anesthetics are used to facilitate many other procedures, including endoscopy, urologic procedures, radiation therapy, electroconvulsive therapy, transbronchial biopsy, and various cardiologic procedures.

BASIC PHARMACOLOGY OF THE INHALATION ANESTHETICS

In this section, we consider the inhalation anesthetics as a group. Our focus is on properties of an ideal anesthetic, pharmacokinetics of inhalation anesthetics, adverse effects of the inhalation anesthetics, and drugs employed as adjuncts to anesthesia.

Properties of an Ideal Inhalation Anesthetic

An ideal inhalation anesthetic would produce unconsciousness, analgesia, muscle relaxation, and amnesia. Furthermore, induction of anesthesia would be brief and pleasant, as would the process of emergence. Depth of anesthesia could be raised or lowered with ease. Adverse effects would be minimal, and the margin of safety would be large. As you might guess, the ideal inhalation anesthetic does not exist: No single agent has all of these qualities.

Balanced Anesthesia

The term *balanced anesthesia* refers to the use of a combination of drugs to accomplish what we cannot achieve with an inhalation anesthetic alone. Put another way, balanced anesthesia is a technique employed to compensate for the lack of an ideal anesthetic. Drugs are combined in balanced anesthesia to ensure that induction is smooth and rapid, and that analgesia and muscle relaxation are adequate. The agents used most commonly to achieve these goals are (1) short-acting barbiturates (for induction of anesthesia), (2) neuromuscular blocking agents (for muscle relaxation), and (3) opioids and nitrous oxide (for analgesia). The primary benefit of combining drugs to achieve surgical anesthesia is that doing so permits full general anesthesia at doses of the inhalation anesthetic that are lower (safer) than those that would be required if surgical anesthesia were attempted using an inhalation anesthetic alone.

Molecular Mechanism of Action

Our understanding of how inhalation anesthetics act has changed dramatically in the past decade. Attention has shifted from nonspecific effects on neuronal membranes to selective alteration of synaptic transmission. However, despite recent advances, we still don't know with certainty just how these drugs work.

More than 100 years ago, scientists postulated that inhalation anesthetics produced their effects through nonspecific interactions with lipid components of

the neuronal cell membrane. This long-standing theory was based on the observation that there was a direct correlation between the potency of an anesthetic and its lipid solubility. That is, the more readily an anesthetic could dissolve in the lipid matrix of the neuronal membrane, the more readily that agent could produce anesthesia. Hence the theory that anesthetics dissolve into neuronal membranes, disrupt their structure, and thereby suppress axonal conduction and possibly synaptic transmission. However, this theory was called into question by an important observation: enantiomers of the same anesthetic have different actions. Recall that enantiomers are simply mirror-image molecules that have identical atomic components, and hence have identical physical properties, including lipid solubility. Therefore, since enantiomers have the same ability to penetrate the axonal membrane, but do not have the same ability to produce anesthesia, a property other than lipid solubility must underlie anesthetic actions.

Current data indicate that inhalation anesthetics work by *enhancing transmission at inhibitory synapses* and by *depressing transmission at excitatory synapses*. Except for nitrous oxide, all of the agents used today enhance activation of receptors for gamma-aminobutyric acid (GABA), the principal inhibitory transmitter in the central nervous system (CNS). As a result, these drugs promote generalized inhibition of CNS function. It should be noted that anesthetics do not activate GABA receptors directly. Rather, by binding with the GABA receptor, they increase receptor sensitivity to activation by GABA itself. How does nitrous oxide work? Probably by blocking the actions of *N*-methyl-D-aspartate (NMDA), an excitatory neurotransmitter. Nitrous oxide appears to bind with the NMDA receptor and thereby prevent receptor activation by NMDA itself.

Minimum Alveolar Concentration

The minimum alveolar concentration (MAC), also known as the median alveolar concentration, is an index of inhalation anesthetic potency. The MAC is defined as *the minimum concentration of drug in the alveolar air that will produce immobility in 50% of patients exposed to a painful stimulus*. Note that, by this definition, a *low* MAC indicates *high* anesthetic potency.

From a clinical perspective, knowledge of the MAC of an anesthetic is of great practical value: The MAC tells us approximately how much anesthetic the in-

spired air must contain to produce anesthesia. A low MAC indicates that the inspired air need contain only low concentrations of the anesthetic to produce surgical anesthesia. The opposite is true for drugs with a high MAC. Fortunately, most inhalation anesthetics have low MACs (Table 27-1). However, one important agent—nitrous oxide—has a very high MAC. The MAC is so high, in fact, that surgical anesthesia cannot be achieved using nitrous oxide alone.

Please note that, to produce general anesthesia in *all* patients, the inspired anesthetic concentration should be 1.2 to 1.5 times the MAC. Why? Because if the concentration were simply equal to the MAC, 50% of patients would be receiving less than they need.

Drug	MAC* (%)	Analgesic Effect	Effect on Blood Pressure	Effect on Respiration	Muscle Relaxant Effect	Extent of Metabolism	Compatible with Epinephrine
Nitrous oxide	105	+ + + +	→	→	0	0	Yes
Halothane	0.75	+ +	↓	↓ ↓	+	20%	No
Desflurane	4.58	+ +	↓	↓ ↓	+ +	0.02%	Yes
Enflurane	1.68	+ +	↓	↓ ↓	+ +	2.4%	Yes†
Isoflurane	1.15	+ +	↓	↓ ↓	+ +	0.2%	Yes
Sevoflurane	1.71	+ +	↓	↓ ↓	+ +	3%	Yes

TABLE 27-1 Properties of the Major Inhalation Anesthetics

* Minimal alveolar concentration.

† Enflurane sensitizes the myocardium to catecholamines, but less so than halothane.

Pharmacokinetics

Uptake and Distribution

To produce therapeutic effects, an inhalation anesthetic must reach a CNS concentration sufficient to suppress neuronal excitability. The principal determinants of anesthetic concentration are (1) uptake from the lungs and (2) distribution to the CNS and other tissues. The kinetics of anesthetic uptake and distribution are complex, and we will not try to cover them in depth.

Uptake.

A major determinant of anesthetic uptake is the concentration of anesthetic in the inspired air: The greater the anesthetic concentration, the more rapid uptake will be. Other factors that influence uptake are pulmonary ventilation, solubility of the anesthetic in blood, and blood flow through the lungs. An increase in any of these will increase uptake rate.

Distribution.

Distribution to specific tissues is determined largely by regional blood flow. Anesthetic levels rise rapidly in the brain, kidney, heart, and liver—tissues that receive the largest fraction of the cardiac output. Anesthetic levels in these tissues equilibrate with those in blood 5 to 15 minutes after the onset of administration. In skin and skeletal muscle—tissues with an intermediate blood flow—equilibration occurs more slowly. The most poorly perfused tissues—fat, bone, ligaments, and cartilage—are the last to equilibrate with anesthetic levels in the blood.

Elimination

Export in the Expired Breath.

Inhalation anesthetics are eliminated almost entirely via the lungs; hepatic metabolism is minimal. The same factors that determine anesthetic uptake (pulmonary ventilation, blood flow to the lungs, anesthetic solubility in blood and tissues) also determine the rate of elimination. Since blood flow to the brain is high, anesthetic levels in the brain drop rapidly when administration is stopped. Anesthetic levels in tissues that have a lower blood flow decline more slowly. Because anesthetic levels in the CNS decline more rapidly than levels in other tissues, patients can awaken from anesthesia long before all anesthetic has left the body.

Metabolism.

Most inhalation anesthetics undergo very little metabolism. Hence, metabolism does not influence the time course of anesthesia. However, since some metabolites can be toxic, metabolism is nonetheless clinically significant.

Adverse Effects

The adverse effects discussed here apply to the inhalation anesthetics as a group. Not all of these effects are seen with every anesthetic.

Respiratory and Cardiac Depression.

Depression of respiratory and cardiac function is a concern with virtually all inhalation anesthetics. Doses only 2 to 4 times greater than needed for surgical anesthesia are sufficient to cause potentially lethal depression of pulmonary and cardiac function. To compensate for respiratory depression, and to maintain a steady rate of administration, almost all patients require mechanical support of ventilation.

Sensitization of the Heart to Catecholamines.

Some anesthetics—most notably *halothane*—can increase the sensitivity of the heart to stimulation by catecholamines (eg, norepinephrine, epinephrine). While in this sensitized state, the heart may develop dysrhythmias in response to catecholamines. Exposure to catecholamines may result from two causes: (1) release of endogenous catecholamines (in response to pain or other stimuli of the sympathetic nervous system), and (2) topical application of catecholamines to control bleeding in the surgical field.

Malignant Hyperthermia.

Malignant hyperthermia is a rare but potentially fatal reaction that can be triggered by all inhalation anesthetics (except nitrous oxide). Predisposition to the reaction is genetic. Malignant hyperthermia is characterized by muscle rigidity and a profound elevation of temperature—sometimes to as high as 43°C (109°F). Left untreated, the reaction can rapidly prove fatal. The risk of malignant hyperthermia is greatest when an inhalation anesthetic is combined with *succinylcholine,* a neuromuscular blocker that also can trigger the reaction. Diagnosis and management of malignant hyperthermia are discussed in Chapter 16.

Aspiration of Gastric Contents.

During the state of anesthesia, reflexes that normally prevent aspiration of gastric contents into the lungs are abolished. Aspiration of gastric fluids can

cause bronchospasm and pneumonia. Use of an endotracheal tube isolates the trachea and can thereby help prevent these complications.

Hepatotoxicity.

Rarely, patients receiving inhalation anesthesia develop serious liver dysfunction. The risk is about equal with all anesthetics.

Toxicity to Operating Room Personnel.

Chronic exposure to low levels of anesthetics may harm operating room personnel. Suspected reactions include headache, reduced alertness, and spontaneous abortion. Risk can be reduced by venting anesthetic gases from the operating room.

Drug Interactions

Several classes of drugs—analgesics, CNS depressants, CNS stimulants—can influence the amount of anesthetic required to produce anesthesia. Opioid analgesics allow a reduction in anesthetic dosage. Why? Because, when opioids are present, analgesia needn't be produced by the anesthetic alone. Similarly, because CNS depressants (barbiturates, benzodiazepines, alcohol) add to the depressant effects of anesthetics, concurrent use of CNS depressants lowers the required dose of anesthetic. Conversely, concurrent use of CNS stimulants (amphetamines, cocaine) increases the required dose of anesthetic.

Adjuncts to Inhalation Anesthesia

Adjunctive drugs are employed to complement the beneficial effects of inhalation anesthetics and to counteract their adverse effects. Some adjunctive agents are administered before surgery, some during, and some after.

Preanesthetic Medications

Preanesthetic medications are administered for three main purposes: (1) reducing anxiety, (2) producing perioperative amnesia, and (3) relieving preoperative and postoperative pain. In addition, preanesthetic medications may be used to suppress certain adverse responses: excessive salivation, excessive bronchial secretion, coughing, bradycardia, and vomiting.

Benzodiazepines.

Benzodiazepines are given preoperatively to reduce anxiety and promote amnesia. When administered properly, these drugs produce sedation with little or no respiratory depression. Intravenous midazolam [Versed] is used most often.

Opioids.

Opioids (eg, morphine, fentanyl) are administered to relieve preoperative and postoperative pain. These drugs may also help by suppressing cough.

Opioids can have adverse effects. Because they depress the CNS, opioids can delay awakening after surgery. Effects on the bowel and urinary tract may result in postoperative constipation and urinary retention. Stimulation of the chemoreceptor trigger zone promotes vomiting. Opioid-induced respiratory depression adds with anesthetic-induced respiratory depression, thereby increasing the risk of postoperative respiratory distress.

Alpha*2*-Adrenergic Agonists.

Two alpha*2* agonists—clonidine and dexmedetomidine—are employed as adjuncts to anesthesia. Both produce their effects through actions in the CNS.

Clonidine is used for hypertension and pain reduction. When administered prior to surgery, the drug reduces anxiety and causes sedation. In addition, it permits a reduction in anesthetic and analgesic dosages. Analgesic properties of clonidine are discussed further in Chapter 28; antihypertensive properties are discussed in Chapters 19 and 46. The formulation used for analgesia is marketed under the trade name *Duraclon;* the formulation for hypertension is marketed as *Catapres*.

Dexmedetomidine [Precedex] is a highly selective alpha*2*-adrenergic agonist currently approved only for short-term sedation in critically ill patients. However, the drug is also used for other purposes, including enhancement of sedation and analgesia in patients undergoing anesthesia. The pharmacology of dexmedetomidine is discussed further in Chapter 28.

Anticholinergic Drugs.

Anticholinergic drugs (eg, atropine) may be given to decrease the risk of bradycardia during surgery. Surgical manipulations can trigger parasympathetic reflexes, which in turn can produce profound vagal slowing of the heart. Pretreatment with a cholinergic antagonist prevents bradycardia from this cause.

At one time, anticholinergic drugs were needed to prevent excessive bronchial secretions associated with anesthesia. Older anesthetic agents (eg, ether) irritate the respiratory tract, and thereby cause profuse bronchial secretions. Cholinergic blockers were given to suppress this response. Since the inhalation anesthetics used today are much less irritating, bronchial secretions are minimal. Consequently, although anticholinergic agents are still employed as adjuncts to anesthesia, their purpose is no longer to suppress bronchial secretions (although they may still help by suppressing salivation).

Neuromuscular Blocking Agents

Most surgical procedures require skeletal muscle relaxation, a state achieved with neuromuscular blockers (eg, succinylcholine, pancuronium). By using these drugs, we can reduce the dose of general anesthetic. Why? Because we don't need the very high doses of anesthetic that would be required if we tried to produce muscle relaxation with the anesthetic by itself.

Muscle relaxants can have adverse effects. Neuromuscular blocking agents prevent contraction of all skeletal muscles, including the diaphragm and other muscles of respiration. Accordingly, patients require mechanical support of ventilation during surgery. Patients recovering from anesthesia may have reduced respiratory capacity owing to residual neuromuscular blockade. Accordingly, respiration must be monitored until recovery is complete.

It is important to appreciate that neuromuscular blockers produce a state of total flaccid paralysis. In this condition, a patient could be fully awake while seeming asleep. Incidents in which paralyzed patients have been awake during surgery, but unable to communicate their agony, are all too common: Every year in the United States, of the 21 million people who undergo anesthesia, an estimated 2000 to 4000 wake up during the procedure. Because neuromuscular blockade can obscure depth of anesthesia, and because failure to maintain adequate anesthesia can result in true horror, the clinician administering an-

esthesia must be especially watchful to ensure that the anesthetic dosage is adequate.

Postanesthetic Medications

Analgesics.

Analgesics are needed to control postoperative pain. If pain is severe, opioids are indicated. For mild pain, aspirin-like drugs may suffice.

Antiemetics.

Patients recovering from anesthesia often experience nausea and vomiting. This can be suppressed with antiemetics. Among the most effective is *ondansetron* [Zofran], a drug developed to suppress nausea and vomiting in patients undergoing cancer chemotherapy. Other commonly used antiemetics are *promethazine* and *droperidol*.

Muscarinic Agonists.

Abdominal distention (from atony of the bowel) and urinary retention are potential postoperative complications. Both conditions can be relieved through activation of muscarinic receptors. The muscarinic agonist employed most often is *bethanechol*.

Dosage and Administration

Administration of inhalation anesthetics is performed only by anesthesiologists (physicians) and anesthetists (nurses). Clinicians who lack the training of these specialists have no authority to administer anesthesia. Since knowledge of anesthetic dosage and administration is the responsibility of specialists, and since this text is designed for beginning students, details on dosage and administration are not presented. If you need this information, consult a textbook of anesthesiology.

Classification of Inhalation Anesthetics

Inhalation anesthetics fall into two basic categories: *gases* and *volatile liquids*. The gases, as their name implies, exist in a gaseous state at atmospheric pressure. The volatile liquids exist in a liquid state at atmospheric pressure, but

can be easily volatilized (converted to a vapor) for administration by inhalation. The inhalation anesthetics in current use are listed in Table 27-2. The volatile liquids—halothane, enflurane, isoflurane, desflurane, and sevoflurane—are similar to one another in structure and function. The only gas in current use is nitrous oxide.

	Anesthetic	
Class	**Generic Name**	**Trade Name**
Volatile Liquids	Halothane	Fluothane
	Enflurane	Ethrane
	Isoflurane	Forane
	Desflurane	Suprane
	Sevoflurane	Ultane
Gases	Nitrous oxide	

TABLE 27-2 Classification of the Inhalation Anesthetics

PROPERTIES OF INDIVIDUAL INHALATION ANESTHETICS

Halothane

Halothane [Fluothane] is the prototype of the volatile inhalation anesthetics. The drug was introduced in 1956 and remains the standard against which the newer volatile liquids are compared. Halothane is commonly used in children.

However, because of concerns about liver failure (see below), use in adults has sharply declined.

Anesthetic Properties

Halothane is an effective anesthetic. For some procedures, anesthesia may be produced with halothane alone. Other procedures require adjunctive drugs.

Potency.

Halothane is a high-potency anesthetic, and hence has a low MAC (0.75%), indicating that unconsciousness can be produced when the drug's concentration in alveolar air is only 0.75%.

Time Course.

Induction of anesthesia is smooth and relatively rapid. However, although halothane can act quickly, in actual practice, induction is usually produced with thiopental, a rapid-acting barbiturate. Once the patient is unconscious, depth of anesthesia can be raised or lowered with ease. Patients awaken about 1 hour after ceasing halothane inhalation.

Analgesia.

Halothane is a weak analgesic. Consequently, when the drug is used for surgical anesthesia, coadministration of a strong analgesic is usually required. The analgesics most commonly employed are opioids (eg, morphine) and nitrous oxide.

Muscle Relaxation.

Although halothane has muscle relaxant actions, the degree of relaxation is generally inadequate for surgery. Accordingly, concurrent use of a neuromuscular blocking agent (eg, pancuronium) is usually required. Although relaxation of skeletal muscle is only moderate, halothane does promote significant relaxation of uterine smooth muscle. Consequently, when used in obstetrics, halothane may inhibit uterine contractions, thereby delaying delivery and possibly increasing postpartum bleeding.

Adverse Effects

Hypotension.

Halothane causes a dose-dependent reduction in blood pressure. Doses only twice those needed for surgical anesthesia can produce complete circulatory failure and death. Halothane promotes hypotension by two mechanisms. First, the drug depresses myocardial contractility, and can thereby reduce cardiac output by 20% to 50%. Second, halothane increases vagal tone, which slows heart rate and thereby reduces cardiac output even further.

Respiratory Depression.

Halothane produces significant depression of respiration. To ensure adequate oxygenation, two measures are implemented: (1) mechanical or manual ventilatory support and (2) enrichment of the inspired gas mixture with oxygen.

Promotion of Dysrhythmias.

Halothane promotes dysrhythmias in two ways. First, the drug sensitizes the myocardium to catecholamines. Second, it prolongs the QT interval (see discussion of QT interval drugs in Chapter 7). To reduce the risk of dysrhythmias, epinephrine and other catecholamines should be used with caution. Also, caution is required in patients with existing QT prolongation and in those taking other drugs known to prolong the QT interval.

Malignant Hyperthermia.

Genetically predisposed patients may experience malignant hyperthermia. Accordingly, patients with a personal or familial history of malignant hyperthermia should not receive halothane, unless there is no other option. If halothane *is* employed, it must not be combined with succinylcholine, which would further increase the risk of malignant hyperthermia.

Hepatotoxicity.

Rarely, halothane produces hepatitis, sometimes progressing to massive hepatic necrosis and death. The incidence of fulminant hepatic failure is 1 in 30,000. Hepatotoxicity is thought to result from an autoimmune process triggered by metabolites of halothane that have formed complexes with liver proteins. Halothane-induced liver failure has occurred in adults only—never

in children. Because of concerns about liver damage, halothane is rarely given to adults. However, the drug still enjoys widespread use in children.

Other Adverse Effects.

Postoperative *nausea* and *vomiting* may occur, but these reactions are less common with halothane than with older anesthetics (eg, ether). By decreasing blood flow to the kidney, halothane can cause a substantial *decrease in urine output*.

Elimination

The majority (60% to 80%) of an administered dose is eliminated intact in the exhaled breath. Hepatic metabolism accounts for about 20% of elimination.

Isoflurane

Isoflurane [Forane] is widely used. The drug is potent (MAC =1.15%) and has properties much like those of halothane. Induction of anesthesia is smooth and rapid, depth of anesthesia can be adjusted with speed and ease, and patients emerge from anesthesia rapidly. Like other volatile liquids, isoflurane causes respiratory depression and hypotension. With isoflurane, hypotension results from vasodilation rather than from reduced cardiac output. Isoflurane is a better muscle relaxant than halothane, but nonetheless is usually employed with a neuromuscular blocker. Like halothane, isoflurane suppresses uterine contraction. In contrast to halothane, isoflurane is not associated with renal or hepatic toxicity. Isoflurane is eliminated almost entirely in the expired breath; only 0.2% undergoes metabolism.

The cardiac actions of isoflurane differ significantly from those of halothane. Unlike halothane, isoflurane does not cause myocardial depression. Hence, cardiac output is not decreased. Furthermore, isoflurane does not sensitize the myocardium to catecholamines. Hence, patients can be given epinephrine and other catecholamines with little fear of precipitating a dysrhythmia. Finally, isoflurane is not associated with QT prolongation.

Enflurane

Enflurane [Ethrane] has pharmacologic properties very similar to those of halothane. Enflurane was introduced in 1973 and became quite popular.

However, with the introduction of newer agents with preferable kinetics and fewer risks, use of the drug has declined.

Comparison of enflurane with halothane reveals important similarities and a few significant differences. Both anesthetics are very potent: the MAC of enflurane is 1.68%, compared with 0.75% for halothane. As with halothane, induction of anesthesia is smooth and rapid, and depth of anesthesia can be changed quickly and easily. Like halothane, enflurane produces substantial depression of respiration. Accordingly, patients are likely to need ventilatory support; the concentration of inspired oxygen should be at least 35%. Muscle relaxation induced by enflurane is greater than with halothane. However, despite this action, a neuromuscular blocker is usually employed (to permit a reduction of enflurane dosage). Like halothane, enflurane can suppress uterine contractions, thereby impeding labor. Significantly, sensitization of the myocardium to catecholamines is less than with halothane. As a result, patients can be given catecholamines with relative safety. High doses of enflurane can induce seizures, a response not seen with halothane. Obviously, enflurane should be avoided in patients with a history of seizure disorders. Like halothane, enflurane is eliminated primarily in the exhaled breath as the intact parent compound. About 2% is eliminated by hepatic metabolism.

Desflurane

Desflurane [Suprane] is nearly identical in structure to isoflurane. Induction occurs more rapidly than with any other volatile anesthetic; depth of anesthesia can be changed quickly; and recovery occurs only minutes after ceasing administration. Desflurane is indicated for *maintenance* of anesthesia in adults and children and for *induction* of anesthesia in adults. The drug is not approved for induction in children and infants because of a high incidence of respiratory difficulties (laryngospasm, apnea, increased secretions), which are caused by the drug's pungency. Like isoflurane, desflurane can cause respiratory depression and hypotension secondary to vasodilation. During induction, or in response to an abrupt increase in desflurane blood levels, heart rate and blood pressure may increase, causing tachycardia and hypertension. Postoperative nausea and vomiting are possible. Malignant hypertension has occurred in experimental animals. Desflurane undergoes even less metabolism than isoflurane. Hence, the risk of postoperative organ injury is probably low.

Sevoflurane

Sevoflurane [Ultane] is similar to desflurane. The drug is approved for induction and maintenance of anesthesia in adults and children. As with desflurane, induction is rapid, depth of anesthesia can be adjusted easily, and recovery occurs minutes after ceasing inhalation. Because onset and recovery occur quickly, sevoflurane is widely used for outpatient procedures. In contrast to desflurane, sevoflurane has a pleasant odor and is not a respiratory irritant. Accordingly, the drug is suitable for mask induction in children. Sevoflurane has a MAC of 1.71% and is eliminated primarily in the exhaled breath; about 3% gets metabolized. Adverse effects are minimal. The most common problem is postoperative nausea and vomiting. In contrast to desflurane, sevoflurane does not cause tachycardia or hypertension. Occasionally, sevoflurane produces extreme heat and even fire in the administration apparatus, usually when the CO_2 adsorbent in the apparatus has become desiccated.

Nitrous Oxide

Nitrous oxide (aka "laughing gas") differs from the volatile liquid anesthetics with respect to pharmacologic properties and uses. Pharmacologically, nitrous oxide is unique in two ways: (1) it has very low *anesthetic* potency, whereas the anesthetic potency of the other inhalation agents is high, and (2) it has very high *analgesic* potency, whereas the analgesic potency of other inhalation agents is low. Because of these properties, nitrous oxide has a unique pattern of use: owing to its low anesthetic potency, nitrous oxide is never employed as a primary anesthetic. However, owing to its high analgesic potency, nitrous oxide is frequently combined with other inhalation agents to enhance analgesia.

Because nitrous oxide has such low anesthetic potency, *it is virtually impossible to produce surgical anesthesia employing nitrous oxide alone*. The MAC of nitrous oxide is very high—greater than 100%. This tells us that, even if it were possible to administer 100% nitrous oxide (ie, inspired gas that contains only nitrous oxide and no oxygen), this would still be insufficient to produce surgical anesthesia. Because practical considerations (ie, the need to administer at least 30% oxygen) limit the maximum usable concentration of nitrous oxide to 70%, and because much higher concentrations are needed to produce surgical

anesthesia, it is clear that full anesthesia cannot be achieved with nitrous oxide alone.

Despite its low anesthetic potency, nitrous oxide is one of our most widely used inhalation agents: *Many patients undergoing general anesthesia receive nitrous oxide to supplement the analgesic effects of the primary anesthetic*. As indicated in Table 27-1, the analgesic effects of nitrous oxide are substantially greater than those of the other inhalation agents. In fact, nitrous oxide is such a potent analgesic that inhaling 20% nitrous oxide can produce pain relief equivalent to that of morphine. The advantage of providing analgesia with nitrous oxide, rather than relying entirely on the primary anesthetic, is that the dosage of the primary anesthetic can be significantly decreased—usually by 50% or more. As a result, respiratory and cardiac depression are reduced, and emergence from anesthesia is accelerated. When employed in combination with other inhalation anesthetics, nitrous oxide is administered at a concentration of 70%.

At therapeutic concentrations, nitrous oxide has no serious adverse effects. The drug is not toxic to the CNS, and does not cause cardiovascular or respiratory depression. Furthermore, the drug is not likely to precipitate malignant hyperthermia. The major concern with nitrous oxide is postoperative *nausea* and *vomiting,* which occur more often with this agent than with any other inhalation anesthetic.

In certain settings, nitrous oxide can be used alone—but only for *analgesia,* not anesthesia. Nitrous oxide alone is used for analgesia in dentistry and during delivery.

Obsolete Inhalation Anesthetics

Several once-popular anesthetics are now obsolete. Five of these agents—*ethylene, cyclopropane, diethyl ether (ether), vinyl ether,* and *ethyl chloride*—are gases. They were abandoned because they are explosive and because they offer no advantages over newer, less hazardous anesthetics. Only one volatile liquid—*methoxyflurane*—has become obsolete. The reason is concern about kidney damage.

INTRAVENOUS ANESTHETICS

Intravenous anesthetics may be used alone or to supplement the effects of inhalation agents. When combined with an inhalation anesthetic, IV agents offer two potential benefits: (1) they permit dosage of the inhalation agent to be reduced and (2) they produce effects that cannot be achieved with an inhalation agent alone. Three of the drug families discussed in this section—opioids, barbiturates, and benzodiazepines—are considered at length in other chapters. Discussion here is limited to their use in anesthesia.

Short-Acting Barbiturates (Thiobarbiturates)

Short-acting barbiturates, administered intravenously, are employed for *induction of anesthesia*. Two agents are available: *thiopental sodium* [Pentothal] and *methohexital sodium* [Brevital]. Almost every time an inhalation anesthetic is used, a short-acting barbiturate is administered first for induction.

Thiopental.

Thiopental [Pentothal] was the first short-acting barbiturate and is the prototype for the group. This drug acts rapidly to produce unconsciousness. Analgesic and muscle-relaxant effects are weak.

Thiopental has a rapid onset and short duration. Unconsciousness occurs 10 to 20 seconds after IV injection. If thiopental is not followed by inhalation anesthesia, the patient will wake up in about 10 minutes.

The time course of anesthesia is determined by thiopental's pattern of distribution. Thiopental is highly lipid soluble, and therefore enters the brain rapidly to begin its effects. Anesthesia is terminated as thiopental undergoes redistribution from the brain and blood to other tissues. Practically no metabolism of the drug takes place between the time of administration and the time of awakening.

Like most of the inhalation anesthetics, thiopental causes cardiovascular and respiratory depression. If administered too rapidly, the drug may cause apnea.

Benzodiazepines

When administered in large doses, benzodiazepines produce unconsciousness and amnesia. Because of this ability, IV benzodiazepines are occasionally given to induce anesthesia. However, short-acting barbiturates are generally pre-

ferred. Three benzodiazepines—diazepam, lorazepam, and midazolam—are administered IV for induction. Diazepam is the prototype for the group. The basic pharmacology of the benzodiazepines is discussed in Chapter 34.

Diazepam.

Induction with IV diazepam [Valium] is slower than with barbiturates. Unconsciousness develops in about 1 minute. Diazepam causes very little muscle relaxation and no analgesia. Cardiovascular and respiratory depression are usually only moderate. However, on occasion respiratory depression is severe. Therefore, whenever diazepam is administered IV, facilities for respiratory support must be immediately available.

Midazolam.

Intravenous midazolam [Versed] may be used for *induction of anesthesia* and to produce *conscious sedation*. When used for induction, midazolam is usually combined with a short-acting barbiturate. Unconsciousness develops in 80 seconds.

Conscious sedation can be produced by combining midazolam with an opioid analgesic (eg, morphine, fentanyl). The state is characterized by sedation, analgesia, amnesia, and lack of anxiety. The patient is unperturbed and passive, but responsive to commands, such as "open your eyes." Conscious sedation persists for an hour or so and is suitable for minor surgeries and endoscopic procedures.

Midazolam can cause dangerous cardiorespiratory effects, including respiratory depression and respiratory and cardiac arrest. Accordingly, the drug should be used only in a setting that permits constant monitoring of cardiac and respiratory status. Facilities for resuscitation must be immediately available. The risk of adverse effects can be minimized by injecting midazolam slowly (over 2 or more minutes) and by waiting another 2 or more minutes for full effects to develop before dosing again.

Propofol

Actions and Uses.

Propofol [Diprivan] is an IV sedative-hypnotic used for induction and maintenance of anesthesia. In addition, propofol can be used to sedate patients undergoing mechanical ventilation and certain noninvasive procedures (eg, radiation therapy, endoscopy, magnetic resonance imaging). Like thiopental, propofol has a rapid onset and short duration of action. Unconsciousness develops within 60 seconds and lasts for 3 to 5 minutes following a single injection. As with thiopental, redistribution from the brain to other tissues explains the speed of awakening. For extended effects, a continuous, low-dose infusion is used.

Adverse Effects.

Propofol can cause profound *respiratory depression* (including apnea) and *hypotension*. Accordingly, the drug should be used with caution in elderly patients, hypovolemic patients, and patients with compromised cardiac function. With all patients, facilities for respiratory support should be immediately available.

Propofol poses a high risk of *bacterial infection*. Why? Because the drug is supplied in a mixture of soybean oil, glycerol, and egg lecithin—an excellent medium for bacterial growth. In surgical patients, use of preparations that have become contaminated after opening has caused sepsis and death. To minimize the risk of infection, propofol solutions and opened vials should be discarded within 6 hours. Unopened vials should be stored at 22°C (72°F).

Propofol can cause transient pain at the site of IV injection. This can be minimized by using a large vein and by injecting IV lidocaine (a local anesthetic) at the site just prior to injecting propofol.

Etomidate

Etomidate [Amidate] is a potent hypnotic agent used for induction of surgical anesthesia. Unconsciousness develops rapidly and lasts about 5 minutes. The drug has no analgesic actions. Adverse effects associated with single injections include transient apnea, venous pain at the injection site, and suppression of plasma cortisol levels for 6 to 8 hours. Repeated administration can cause hypotension, oliguria, electrolyte disturbances, and a high incidence (50%) of postoperative nausea and vomiting. Cardiovascular effects are less than with

barbiturates, and hence the drug is preferred for patients with cardiovascular disorders.

Ketamine

Anesthetic Effects.

Ketamine [Ketalar] produces a state known as *dissociative anesthesia* in which the patient feels dissociated from his or her environment. In addition, the drug causes sedation, immobility, analgesia, and amnesia; responsiveness to pain is lost. Induction is rapid and emergence begins within 10 to 15 minutes. Full recovery, however, may take several hours.

Adverse Psychologic Reactions.

During recovery from ketamine, unpleasant psychologic reactions may occur, including hallucinations, disturbing dreams, and delirium. In some cases, these reactions recur days or even weeks after ketamine was used. To minimize these effects, the patient should be kept in a soothing, stimulus-free environment until recovery is complete. Premedication with diazepam or midazolam reduces the risk of an adverse reaction. Psychologic reactions are least likely in children under the age of 15 years and in adults over the age of 65. Despite its adverse psychologic effects, ketamine has become a popular drug of abuse (see Chapter 39).

Therapeutic Uses.

Ketamine is especially valuable for anesthesia in young children undergoing minor surgical and diagnostic procedures. The drug is frequently used to facilitate changing of burn dressings. Because of its potential for adverse psychologic effects, ketamine should generally be avoided in patients with a history of psychiatric illness, although the drug has produced short-term relief in patients with intractable depression.

Neuroleptic-Opioid Combination: Droperidol Plus Fentanyl

A unique state, known as *neurolept analgesia,* can be produced with a combination of fentanyl, a potent opioid, plus droperidol, a neuroleptic (antipsychot-

ic) agent. In the past, the combination was available premixed under the trade name *Innovar*.

Neurolept analgesia is characterized by quiescence, indifference to surroundings, and insensitivity to pain. The patient appears to be asleep but is not (ie, complete loss of consciousness does not occur). In large part, neurolept analgesia is similar to the dissociative anesthesia produced by ketamine. Neurolept analgesia is employed for diagnostic and minor surgical procedures (eg, bronchoscopy, repeated changing of burn dressings).

Droperidol prolongs the QT interval on the electrocardiogram, indicating that it can cause potentially fatal dysrhythmias. Accordingly, droperidol should be used only when safer drugs are ineffective or intolerable. Droperidol is contraindicated for patients with existing QT prolongation, and should be used with great caution in those at risk of developing QT prolongation. The issue of drug-induced QT prolongation is discussed at length in Chapter 7 (Adverse Drug Reactions and Medication Errors).

Other adverse effects include hypotension and respiratory depression. Respiratory depression can be severe and may persist for hours. Respiratory assistance is usually required. Like other neuroleptics, droperidol blocks receptors for dopamine, and hence should not be given to patients with Parkinson's disease.

For some procedures, the combination of fentanyl plus droperidol is supplemented with nitrous oxide. The state produced by this three-drug regimen is called *neurolept anesthesia*. Neurolept anesthesia produces more analgesia and a greater reduction of consciousness than does *neurolept analgesia*. Neurolept anesthesia can be used for major surgical procedures.

KEY POINTS

- General anesthetics produce unconsciousness and insensitivity to painful stimuli. In contrast, analgesics reduce sensitivity to pain but need not reduce consciousness.

- The term *balanced anesthesia* refers to the use of several drugs to ensure that induction of anesthesia is smooth and rapid and that analgesia and muscle relaxation are adequate.
- The minimum alveolar concentration (MAC) of an inhalation anesthetic is defined as the minimum concentration of drug in alveolar air that will produce immobility in 50% of patients exposed to a painful stimulus. A *low* MAC indicates *high* anesthetic potency!
- Inhalation agents work by enhancing transmission at inhibitory synapses and by inhibiting transmission at excitatory synapses.
- Inhalation anesthetics are eliminated almost entirely in the expired air. As a rule, they undergo minimal hepatic metabolism.
- The principal adverse effects of general anesthetics are depression of respiration and cardiac performance.
- Malignant hyperthermia is a rare, genetically determined, life-threatening reaction to general anesthetics. Coadministration of succinylcholine, a neuromuscular blocker, increases the risk of the reaction.
- By enhancing analgesia, opioids reduce the required dosage of general anesthetic.
- By enhancing muscle relaxation, neuromuscular blockers reduce the required dosage of general anesthetic.
- Nitrous oxide differs from other general anesthetics in two important ways: (1) it has a very high MAC, and therefore cannot be used alone to produce general anesthesia; and (2) it has high analgesic potency, and therefore is frequently combined with other general anesthetics to supplement their analgesic effects.
- Induction of anesthesia is usually accomplished with a short-acting barbiturate, such as thiopental.
- Ketamine is an IV anesthetic that produces a state known as dissociative anesthesia. Patients recovering from ketamine may experience adverse psychologic reactions.

Summary of Major Nursing Implications

ALL GENERAL ANESTHETICS

Desflurane

Enflurane

Halothane

Isoflurane

Nitrous oxide

Sevoflurane

Nursing management of the patient receiving general anesthesia is almost exclusively preoperative and postoperative; intraoperative management is the responsibility of anesthesiologists and anesthetists. Accordingly, our summary of anesthesia-related nursing implications is divided into two sections: (1) implications that pertain to the preoperative patient and (2) implications that pertain to the postoperative patient. Intraoperative implications are not considered.

The nursing implications summarized here are limited to ones that are directly related to anesthesia. Nursing implications regarding the overall management of the surgical patient (ie, implications unrelated to anesthesia) are not presented. (Overall nursing management of the surgical patient is discussed fully—and appropriately—in medical-surgical texts.)

Nursing implications for drugs employed as adjuncts to anesthesia (barbiturates, benzodiazepines, anticholinergic agents, opioids, neuromuscular blocking agents) are summarized in other chapters. Only those implications that apply specifically to their adjunctive use are addressed here.

Preoperative Patients: Counseling, Assessment, and Medicating

Counseling

Anxiety is common among patients anticipating surgery: the patient may fear the surgery itself, or may be concerned about the possibility of waking up or experiencing pain during the procedure. Since excessive anxiety can disrupt

the smoothness of the surgical course (in addition to being distressing to the patient), you should attempt to dispel preoperative fears. To some extent, fear can be allayed by reassuring the patient that anesthesia will keep him or her asleep for the entire procedure, will prevent pain, and will create amnesia about the experience.

Assessment

Medication History.

The patient may be taking drugs that can affect responses to anesthetics. Drugs that act on the respiratory and cardiovascular systems are of particular concern. To decrease the risk of adverse interactions, obtain a thorough history of drug use. *All* drugs—prescription medications, over-the-counter preparations, and illicit agents—should be considered. With illicit drugs (eg, heroin, barbiturates) and with alcohol, it is important to determine both the duration of use and the amount used per day.

Respiratory and Cardiovascular Function.

Most general anesthetics produce cardiovascular and respiratory depression. In order to evaluate the effects of anesthesia, baseline values for blood pressure, heart rate, and respiration are required. Also, any disease of the cardiovascular and respiratory systems should be noted.

Preoperative Medication

Preoperative medications (eg, benzodiazepines, opioids, anticholinergic agents) are employed to (1) calm the patient, (2) provide analgesia, and (3) counteract adverse effects of general anesthetics. As a rule, the nurse is responsible for administering these drugs. Since preoperative medication can have a significant impact on the overall response to anesthesia, it is important that these drugs be given at an appropriate time—typically 30 to 60 minutes before surgery. Because preoperative medication may produce drowsiness or hypotension, the patient should remain in bed. A calm environment will complement the effect of sedatives.

Postoperative Patients: Ongoing Evaluation and Interventions

When receiving a patient for postoperative care, you should know all of the drugs the patient has received in the hospital (anesthetics and adjunctive medications). In addition, you should know what medications the patient was taking at home, especially drugs for hypertension. With this information, you will be able to anticipate the time course of emergence from anesthesia as well as potential drug-related postoperative complications.

Evaluations and Interventions That Pertain to Specific Organ Systems

Cardiovascular and Respiratory Systems.

Anesthetics depress cardiovascular and respiratory function. Monitor vital signs until they return to baseline. Determine blood pressure, pulse rate, and respiration immediately upon receipt of the patient, and repeat monitoring at brief intervals until recovery is complete. During the recovery period, observe the patient for respiratory and cardiovascular distress. Be alert for (1) reductions in blood pressure; (2) altered cardiac rhythm; and (3) shallow, slow, or noisy breathing. Ensure that the airway remains patent. Have facilities for respiratory support available.

Central Nervous System.

Return of CNS function is gradual, and precautions are needed until recovery is complete. When appropriate, employ side rails or straps to avoid accidental falls. Assist ambulation until the patient is able to stand steadily. During the early stage of emergence, the patient may be able to hear, even though he or she may appear unconscious. Accordingly, exercise discretion in conversation.

Gastrointestinal Tract.

Bowel function may be compromised by the surgery itself or by the drugs employed as adjuncts to anesthesia (eg, opioids, anticholinergics). Constipation or atony of the bowel may occur. Monitor bowel function. A muscarinic agonist (eg, bethanechol) may be needed to restore peristalsis. Determine bowel sounds before giving oral medications.

Nausea and vomiting are potential postanesthetic reactions. To reduce the risk of aspiration, position the patient with his or her head to the side. Have equipment for suctioning available. Antiemetic medication may be needed.

Urinary Tract.

Anesthetics and their adjuncts can disrupt urinary tract function. Anesthetics can decrease urine production by reducing renal blood flow. Opioids and anticholinergic drugs can cause urinary retention. Monitor urine output. If the patient fails to void, follow hospital protocol. Catheterization or medication (eg, bethanechol) may be needed.

Management of Postoperative Pain

As anesthesia wears off, the patient may experience postoperative pain. An opioid may be required. Since respiratory depression from opioids will add to residual respiratory depression from anesthesia, use opioids with caution; balance the need to relieve pain against the need to maintain ventilation.

Implications for Ketamine

Adverse psychologic reactions can develop as the patient emerges from ketamine-induced anesthesia. To minimize these reactions, provide a calm and stimulus-free environment until recovery is complete.

28 Opioid (Narcotic) Analgesics, Opioid Antagonists, and Nonopioid Centrally Acting Analgesics

Analgesics are drugs that relieve pain without causing loss of consciousness. In this chapter, we focus mainly on the opioid analgesics—the most effective pain relievers available. The opioid family, whose name derives from *opium,* includes such widely used agents as morphine, fentanyl, codeine, oxycodone [Oxy-Contin], and propoxyphene [Darvon].

INTRODUCTION TO THE OPIOIDS

Terminology

Opioid is a general term defined as any drug, natural or synthetic, that has actions similar to those of morphine. The term *opiate* is more specific and applies only to compounds present in opium (eg, morphine, codeine).

The term *narcotic* has had so many definitions that it cannot be used with precision. *Narcotic* has been used to mean an analgesic, a central nervous system (CNS) depressant, and any drug capable of causing physical dependence. *Narcotic* has also been employed in a legal context to designate not only the opioids but also such diverse drugs as cocaine, marijuana, and lysergic acid diethylamide (LSD). Because of its more precise definition, *opioid* is clearly preferable to *narcotic* as a label for a discrete family of pharmacologic agents.

Endogenous Opioid Peptides

The body has three families of peptides—*enkephalins, endorphins,* and *dynorphins*—that have opioid-like properties. Although we know that endogenous opioid peptides serve as neurotransmitters, neurohormones, and neuromodulators, their precise physiologic role is not fully understood. Endogenous opioid peptides are found in the CNS and in peripheral tissues.

Opioid Receptors

There are three main classes of opioid receptors, designated *mu, kappa,* and *delta*. From a pharmacologic perspective, mu receptors are the most important.

Why? Because opioid analgesics act primarily by activating mu receptors, although they also produce weak activation of kappa receptors. As a rule, opioid analgesics do not interact with delta receptors. In contrast to opioid analgesics, endogenous opioid peptides act through all three types of opioid receptors, including delta receptors. Important responses to activation of mu and kappa receptors are summarized in Table 28-1.

	Receptor Type	
Response	**Mu**	**Kappa**
Analgesia	✓	✓
Respiratory depression	✓	
Sedation	✓	✓
Euphoria	✓	
Physical dependence	✓	
Decreased GI motility	✓	✓

TABLE 28-1 Important Responses to Activation of Mu and Kappa Receptors

Mu Receptors.

Responses to activation of mu receptors include analgesia, respiratory depression, euphoria, and sedation. In addition, mu activation is related to physical dependence.

A study in genetically engineered mice underscores the importance of mu receptors in drug action. In this study, researchers studied mice that lacked the gene for mu receptors. When these mice were given morphine, the drug had no effect. It did not produce analgesia, it did not produce physical dependence, and it did not reinforce social behaviors that are thought to indicate subjective effects. Hence, at least in mice, mu receptors appear both necessary and sufficient to mediate the major actions of opioid drugs.

Kappa Receptors.

As with mu receptors, activation of kappa receptors can produce analgesia and sedation. In addition, kappa activation may underlie psychotomimetic effects seen with certain opioids.

Classification of Drugs That Act at Opioid Receptors

Drugs that act at opioid receptors are classified on the basis of how they affect receptor function. At each type of receptor, a drug can act in one of three ways: as an *agonist, partial agonist,* or *antagonist*. (Recall from Chapter 5 that a partial agonist is a drug that produces low to moderate receptor activation when administered alone, but will block the actions of a full agonist if the two are given together.) Based on these actions, drugs that bind opioid receptors fall into three major groups: (1) pure opioid agonists, (2) agonist-antagonist opioids, and (3) pure opioid antagonists. The actions of drugs in these groups at mu and kappa receptors are summarized in Table 28-2.

	Receptor Type	
Drugs	**Mu**	**Kappa**
Pure Opioid Agonists		
Morphine, codeine, meperidine, and other morphine-like drugs	Agonist	Agonist
Agonist-Antagonist Opioids		
Pentazocine, nalbuphine, butorphanol	Antagonist	Agonist
Buprenorphine	Partial agonist	Antagonist
Pure Opioid Antagonists		
Naloxone, naltrexone, nalmefene	Antagonist	Antagonist

TABLE 28-2 Drug Actions At Mu and Kappa Receptors

Pure Opioid Agonists.

The pure opioid agonists activate mu receptors and kappa receptors. By doing so, the pure agonists can produce analgesia, euphoria, sedation, respiratory depression, physical dependence, constipation, and other effects. As indicated in Table 28-3, the pure agonists can be subdivided into two groups: *strong opioid agonists* and *moderate to strong opioid agonists*. Morphine is the prototype of the strong agonists. Codeine is the prototype of the moderate to strong agonists.

Drug and Category	CSA* Schedule	Abuse Liability	Maximal Pain Relief
Strong Opioid Agonists			
Alfentanil	II	High	High
Fentanyl	II	High	High
Hydromorphone	II	High	High
Levorphanol	II	High	High
Meperidine	II	High	High
Methadone	II	High	High
Morphine	II	High	High
Oxymorphone	II	High	High
Remifentanil	II	—	High
Sufentanil	II	High	High
Moderate to Strong Opioid Agonists			
Codeine	II	Moderate	Low
Hydrocodone	III†	Moderate	Moderate
Oxycodone	II	Moderate	Moderate
Propoxyphene	IV	Low	Low
Agonist-Antagonist Opioids			
Buprenorphine	V	Low	Moderate to high
Butorphanol	IV	Low	Moderate to high
Nalbuphine	NR‡	Low	Moderate to high
Pentazocine	IV	Low	Moderate

TABLE 28-3 Opioid Analgesics: Abuse Liability and Maximal Pain Relief

Agonist-Antagonist Opioids.

Four agonist-antagonist opioids are available: pentazocine, nalbuphine, butorphanol, and buprenorphine. The actions of these drugs at mu and kappa receptors are summarized in Table 28-2. When administered alone, the agonist-antagonist opioids produce analgesia. However, if given to a patient who is taking a pure opioid agonist, these drugs can *antagonize* analgesia caused by the pure agonist. Pentazocine [Talwin] is the prototype of the agonist-antagonists.

Pure Opioid Antagonists.

The pure opioid antagonists act as antagonists at mu and kappa receptors. These drugs do not produce analgesia or any of the other effects caused by opioid agonists. Their principal use is reversal of respiratory and CNS depression caused by overdose with opioid agonists. In addition, one of these drugs—methylnaltrexone—is used to treat opioid-induced constipation. Naloxone [Narcan] is the prototype of the pure opioid antagonists.

BASIC PHARMACOLOGY OF THE OPIOIDS

Morphine

Morphine is the prototype of the strong opioid analgesics and remains the standard by which newer opioids are measured. Morphine has multiple pharmacologic effects, including analgesia, sedation, euphoria, respiratory depression, cough suppression, and suppression of bowel motility. The drug is named after Morpheus, the Greek god of dreams.

Source

Morphine is found in the seedpod of the poppy plant, *Papaver somniferum*. The drug is prepared by extraction from opium (the dried juice of the poppy seedpod). In addition to morphine, opium contains two other medicinal compounds: codeine (an analgesic) and papaverine (a smooth muscle relaxant).

Overview of Pharmacologic Actions

Morphine has multiple pharmacologic actions. In addition to relieving pain, the drug causes drowsiness, mental clouding, anxiety reduction, and a sense of well-being. Through actions in the CNS and periphery, morphine can cause respiratory depression, constipation, urinary retention, orthostatic hypotension, emesis, miosis, cough suppression, and biliary colic. With prolonged use, the drug produces tolerance and physical dependence.

Individual effects of morphine may be beneficial, detrimental, or both. For example, analgesia is clearly beneficial, whereas respiratory depression and urinary retention are clearly detrimental. Certain other effects, such as sedation and reduced bowel motility, may be beneficial or detrimental, depending on the circumstances of drug use.

Therapeutic Use: Relief of Pain

The principal indication for morphine is relief of moderate to severe pain. The drug can relieve postoperative pain, chronic pain of cancer, and pain associated with labor and delivery. In addition, morphine can be used to relieve pain of myocardial infarction and dyspnea associated with left ventricular failure and pulmonary edema—although it is no longer the drug of choice for these disorders. Morphine may also be administered preoperatively for sedation and anxiety reduction.

Morphine relieves pain without affecting other senses (eg, sight, touch, smell, hearing) and without causing loss of consciousness. The drug is more effective against constant, dull pain than against sharp, intermittent pain. However, even sharp pain can be relieved by large doses. The ability of morphine to cause mental clouding, sedation, euphoria, and anxiety reduction can contribute to relief of pain.

The use of morphine and other opioids to relieve pain is discussed further in Chapter 29 and under *Clinical Use of Opioids* in this chapter.

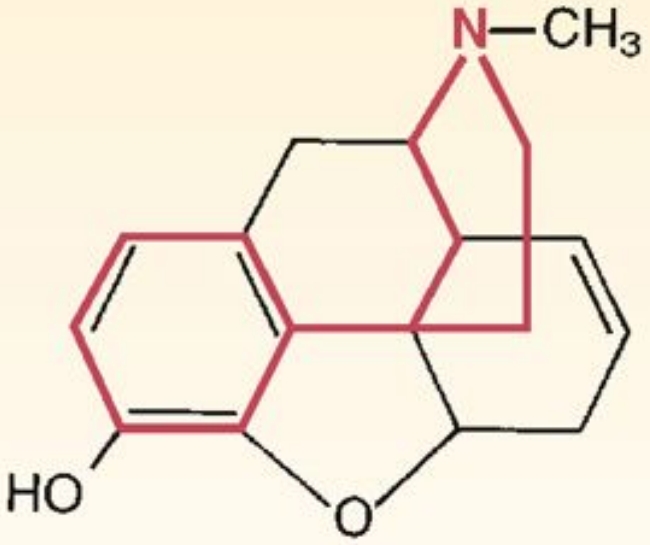
Mechanism of Analgesic Action.

Morphine and other opioid agonists are thought to relieve pain by mimicking the actions of endogenous opioid peptides, primarily at mu receptors. This hypothesis is based on the following observations:

- Opioid peptides and morphine-like drugs both produce analgesia when administered to experimental subjects.
- Opioid peptides and morphine-like drugs share structural similarities (Fig. 28-1).
- Opioid peptides and morphine-like drugs bind to the same receptors in the CNS.
- The receptors to which opioid peptides and morphine-like drugs bind are located in regions of the brain and spinal cord associated with perception of pain.
- Subjects rendered tolerant to analgesia from morphine-like drugs show cross-tolerance to analgesia from opioid peptides.
- The analgesic effects of opioid peptides and morphine-like drugs can both be blocked by the same antagonist: naloxone.

From these data we can postulate that (1) opioid peptides serve a physiologic role as modulators of pain perception, and (2) morphine-like drugs produce analgesia by mimicking the actions of endogenous opioid peptides.

Met-enkephalin



Morphine

Figure 28-1 Structural similarity between morphine and met-enkephalin. In the morphine structural formula, highlighting indicates the part of the molecule thought responsible for interaction with opioid receptors. In the met-enkephalin structural formula, highlighting indicates the region of structural similarity with morphine.

Adverse Effects

Respiratory Depression.

Respiratory depression is the most serious adverse effect of the opioids. At equianalgesic doses, all of the pure opioid agonists depress respiration to the same extent. Death following overdose is almost always from respiratory arrest. Opioids depress respiration primarily through activation of mu receptors, although activation of kappa receptors also contributes.

The time course of respiratory depression varies with route of administration. Depressant effects begin about 7 minutes after IV injection, 30 minutes after IM injection, and up to 90 minutes after subQ injection. With all three routes, significant depression may persist for 4 to 5 hours. When morphine is administered by spinal injection, onset of respiratory depression may be delayed for hours; be alert to this possibility.

With prolonged use of opioids, tolerance develops to respiratory depression. Huge doses that would be lethal to nontolerant individuals have been taken by opioid addicts without noticeable effect. Similarly, tolerance to respiratory depression develops during long-term clinical use of opioids (eg, in patients with cancer).

When administered at usual therapeutic doses, opioids rarely cause significant respiratory depression. However, although uncommon, substantial respiratory depression can occur. Accordingly, respiratory rate should be determined prior to opioid administration. If the rate is 12 breaths per minute or less, the opioid should be withheld and the prescriber notified. Certain patients, including the very young, the elderly, and those with respiratory disease (eg, asthma, emphysema) are especially sensitive to respiratory depression and must be mon-

itored closely. Outpatients should be informed about the risk of respiratory depression and instructed to notify the prescriber if respiratory distress occurs.

Respiratory depression is increased by concurrent use of other drugs that have CNS-depressant actions (eg, alcohol, barbiturates, benzodiazepines). Accordingly, these drugs should be avoided. Outpatients should be warned against use of alcohol and all other CNS depressants.

Constipation.

Opioids promote constipation through actions in the CNS and GI tract. Specifically, these drugs can suppress propulsive intestinal contractions, intensify nonpropulsive contractions, increase the tone of the anal sphincter, and inhibit secretion of fluids into the intestinal lumen. As a result, constipation can develop after a few days of opioid use.

The risk of opioid-induced constipation can be reduced with a combination of pharmacologic and nonpharmacologic measures. The goal is to produce a soft, formed stool every 1 to 2 days. Principal nondrug measures are physical activity and increased intake of fiber and fluids. Most patients also require prophylactic drugs. A stimulant laxative, such as senna, is given to counteract reduced bowel motility. A stool softener, such as docusate [Colace, others], provides additional benefit. As discussed later in the chapter, a new drug—*methylnaltrexone* [Relistor]—helps by blocking opioid receptors in the intestine. The drug can't cross the blood-brain barrier, and hence does not reduce analgesia. Severe constipation can be managed with an osmotic laxative, such as sodium phosphate.

Because of their effects on the intestine, opioids are highly effective for treating diarrhea. In fact, antidiarrheal use of these drugs preceded analgesic use by centuries. The effect of opioids on intestinal function is an interesting example of how an effect can be detrimental (constipation) or beneficial (relief of diarrhea) depending on who is taking the medication. Opioids employed specifically to treat diarrhea are discussed in Chapter 78.

Orthostatic Hypotension.

Morphine-like drugs lower blood pressure by blunting the baroreceptor reflex and by dilating peripheral arterioles and veins. Peripheral vasodilation results primarily from morphine-induced release of histamine. Hypotension is mild in the recumbent patient but can be substantial when the patient stands up. Patients should be informed about symptoms of hypotension (lightheadedness, dizziness) and instructed to sit or lie down if they occur. Also, patients should be informed that hypotension can be minimized by moving slowly when changing from a supine or seated position to an upright position. Patients should be warned against walking if hypotension is significant. Hospitalized patients may require ambulatory assistance. Hypotensive drugs can exacerbate opioid-induced hypotension.

Urinary Retention.

Morphine can cause urinary hesitancy and urinary retention by increasing tone in the bladder sphincter. Also, by increasing tone in the detrusor muscle, the drug can elevate pressure within the bladder, causing urinary urgency. In addition to its direct effects on the urinary tract, morphine may interfere with voiding by suppressing awareness of bladder stimuli. Accordingly, patients should be encouraged to void every 4 hours. Urinary hesitancy or retention is especially likely in patients with prostatic hypertrophy. Drugs with anticholinergic properties (eg, tricyclic antidepressants, antihistamines) can exacerbate the problem.

Urinary retention should be assessed by monitoring intake and output and by palpating the lower abdomen every 4 to 6 hours for bladder distention. If a change in intake/output ratio develops, or if bladder distention is detected, or if the patient reports difficulty voiding, the prescriber should be notified. Catheterization may be required.

In addition to causing urinary retention, morphine may decrease urine production. How? Largely by decreasing renal blood flow, and partly by promoting release of antidiuretic hormone.

Cough Suppression.

Morphine-like drugs act at opioid receptors in the medulla to suppress cough. Suppression of spontaneous cough may lead to accumulation of secretions in

the airway. Accordingly, patients should be instructed to actively cough at regular intervals. Lung status should be assessed by auscultation for rales. The ability of opioids to suppress cough is put to clinical use in the form of codeine- and hydrocodone-based cough remedies.

Biliary Colic.

Morphine can induce spasm of the common bile duct, causing pressure within the biliary tract to rise dramatically. Symptoms range from epigastric distress to biliary colic. In patients with pre-existing biliary colic, morphine may intensify pain rather than relieve pain. Certain opioids (eg, meperidine) cause less smooth muscle spasm than morphine, and hence are less likely to exacerbate biliary colic.

Emesis.

Morphine promotes nausea and vomiting through direct stimulation of the chemoreceptor trigger zone of the medulla. Emetic reactions are greatest with the initial dose and diminish with subsequent doses. Nausea and vomiting are uncommon in recumbent patients, but occur in 15% to 40% of ambulatory patients, suggesting a vestibular component. Nausea and vomiting can be reduced by pretreatment with an antiemetic (eg, prochlorperazine) and by having the patient remain still.

Elevation of Intracranial Pressure.

Morphine can elevate intracranial pressure (ICP). The mechanism is indirect: By suppressing respiration, morphine increases the CO_2 content of blood, which dilates the cerebral vasculature, causing ICP to rise. Accordingly, if respiration is maintained at a normal rate, ICP will remain normal too.

Euphoria/Dysphoria.

Euphoria is defined as an exaggerated sense of well-being. Morphine often produces euphoria when given to patients in pain. Although euphoria can enhance pain relief, it also contributes to the drug's potential for abuse. Euphoria is caused by activation of mu receptors.

In some individuals, morphine causes *dysphoria* (a sense of anxiety and unease). Dysphoria is uncommon among patients in pain, but may occur when morphine is taken in the absence of pain.

Sedation.

When administered to relieve pain, morphine is likely to cause drowsiness and some mental clouding. Although these effects can complement analgesic actions, they can also be detrimental. Outpatients should be warned about CNS depression and advised to avoid hazardous activities (eg, driving) if sedation is significant. Sedation can be minimized by (1) taking smaller doses more often, (2) using opioids that have short half-lives, and (3) giving small doses of a CNS stimulant (methylphenidate or dextroamphetamine) in the morning and early afternoon.

Miosis.

Morphine and other opioids cause pupillary constriction (miosis). In response to toxic doses, the pupils may constrict to "pinpoint" size. Since miosis can impair vision in dim light, room light should be kept bright during waking hours.

Neurotoxicity.

Opioid-induced neurotoxicity can cause delirium, agitation, myoclonus, hyperalgesia, and other symptoms. Primary risk factors are renal impairment, pre-existing cognitive impairment, and prolonged, high-dose opioid use. Management consists of hydration and dose reduction. For patients who must take opioids long term, opioid rotation (periodically switching from one opioid to another) may reduce neurotoxicity development.

Adverse Effects from Prolonged Use.

Clinical and preclinical studies indicate that prolonged use of opioids can cause hormonal changes and can alter immune function. Hormonal changes include a progressive decline in cortisol levels, an increase in prolactin levels, and a decrease in levels of luteinizing hormone, follicle-stimulating hormone, testosterone, and estrogen. With prolonged opioid exposure, immune function is suppressed. We do not yet know the extent to which these changes are clinically relevant.

Pharmacokinetics

Morphine is administered by several routes: oral, IM, IV, subQ, epidural, and intrathecal. Onset of effects is slower with oral administration than with parenteral administration. With three routes—IM, IV, and subQ—analgesia lasts 4 to 5 hours. With two routes—epidural and intrathecal—analgesia may persist up to 24 hours. With oral therapy, duration depends on the formulation. For example, with immediate-release tablets, effects last 4 to 5 hours, whereas with extended-release capsules, effects last 24 hours.

In order to relieve pain, morphine must cross the blood-brain barrier and enter the CNS. Because the drug is not very lipid soluble, it does not cross the barrier easily. Consequently, only a small fraction of each dose reaches sites of analgesic action. Since the blood-brain barrier is not well developed in infants, these patients generally require lower doses than do older children and adults.

Morphine is inactivated by hepatic metabolism. When taken by mouth, the drug must pass through the liver on its way to the systemic circulation. Much of an oral dose is inactivated during this first pass through the liver. Consequently, oral doses need to be substantially larger than parenteral doses to produce equivalent analgesic effects. In patients with liver disease, analgesia and other effects may be intensified and prolonged. Accordingly, it may be necessary to reduce the dosage or lengthen the dosing interval.

Tolerance and Physical Dependence

With continuous use, morphine can cause tolerance and physical dependence. These phenomena, which are generally inseparable, reflect cellular adaptations that occur in response to prolonged opioid exposure.

Tolerance.

Tolerance can be defined as a state in which a larger dose is required to produce the same response that could formerly be elicited by a smaller dose. Alternatively, tolerance can be defined as a condition in which a particular dose now produces a smaller response than it did when treatment began. Because of tolerance, dosage must be increased to maintain analgesic effects.

Tolerance develops to many—but not all—of morphine's actions. With prolonged treatment, tolerance develops to *analgesia, euphoria,* and *sedation*. As a result, with long-term therapy, an increase in dosage may be required to maintain these desirable effects. Fortunately, as tolerance develops to these therapeutic effects, tolerance also develops to *respiratory depression*. As a result, the high doses needed to control pain in the tolerant individual are not associated with increased respiratory depression.

Very little tolerance develops to *constipation* and *miosis*. Even in highly tolerant addicts, constipation remains a chronic problem, and constricted pupils are characteristic.

Cross-tolerance exists among the opioid agonists (eg, oxycodone, methadone, fentanyl, codeine, heroin). Accordingly, individuals tolerant to one of these agents will be tolerant to the others. No cross-tolerance exists between opioids and general CNS depressants (eg, barbiturates, ethanol, benzodiazepines, general anesthetics).

Physical Dependence.

Physical dependence is defined as a state in which an abstinence syndrome will occur if drug use is abruptly stopped. Opioid dependence results from adaptive cellular changes that occur in response to the continuous presence of these drugs. Although the exact nature of these changes is unknown, it is clear that, once these compensatory changes have taken place, the body requires the continued presence of opioids to function normally. If opioids are withdrawn, an abstinence syndrome will follow.

The intensity and duration of the opioid abstinence syndrome depends on two factors: the half-life of the drug being used and the degree of physical dependence. With opioids that have relatively short half-lives (eg, morphine), symptoms of abstinence are intense but brief. In contrast, with opioids that have long half-lives (eg, methadone), symptoms are less intense but more prolonged. With any opioid, the intensity of withdrawal symptoms parallels the degree of physical dependence.

For individuals who are highly dependent, the abstinence syndrome can be extremely unpleasant. Initial reactions include yawning, rhinorrhea, and sweating. Onset occurs about 10 hours after the last dose. These early responses are

followed by anorexia, irritability, tremor, and "gooseflesh"—hence the term *cold turkey*. At its peak, the syndrome manifests as violent sneezing, weakness, nausea, vomiting, diarrhea, abdominal cramps, bone and muscle pain, muscle spasm, and kicking movements—hence, "kicking the habit." Giving an opioid at any time during withdrawal rapidly reverses all signs and symptoms. Left untreated, the morphine withdrawal syndrome runs its course in 7 to 10 days. It should be emphasized that, although withdrawal from opioids is unpleasant, the syndrome is rarely dangerous. In contrast, withdrawal from general CNS depressants (eg, barbiturates, alcohol) can be lethal (see Chapter 34).

To minimize the abstinence syndrome, opioids should be withdrawn gradually. When the degree of dependence is moderate, symptoms can be avoided by administering progressively smaller doses over 3 days. When the patient is highly dependent, dosage should be tapered more slowly—over 7 to 10 days. With a proper withdrawal procedure, withdrawal symptoms will resemble those of a mild case of flu—even when the degree of dependence is high.

It is important to note that physical dependence is rarely a complication when opioids are taken *acutely* to treat pain. Hospitalized patients receiving morphine 2 to 3 times a day for up to 2 weeks show no significant signs of dependence. If morphine is withheld from these patients, no significant signs of withdrawal can be detected. The issue of physical dependence as a clinical concern is discussed further later in the chapter.

Infants exposed to opioids *in utero* may be born drug dependent. If the infant is not provided with opioids, an abstinence syndrome will ensue. Signs of withdrawal include excessive crying, sneezing, tremor, hyperreflexia, fever, and diarrhea. The infant can be weaned from drug dependence by administering dilute paregoric in progressively smaller doses.

Cross-dependence exists among pure opioid agonists. As a result, any pure agonist will prevent withdrawal in a patient who is physically dependent on any other pure agonist.

Abuse Liability

Morphine and the other opioids are subject to abuse, largely because of their ability to cause pleasurable experiences (eg, euphoria, sedation, a sensation in the lower abdomen resembling orgasm). Physical dependence contributes to

abuse: Once dependence exists, the ability of opioids to ward off withdrawal serves to reinforce their desirability in the mind of the abuser.

The abuse liability of the opioids is reflected in their classification under the Controlled Substances Act. (The provisions of this act are discussed in Chapter 37.) As shown in Table 28-3, morphine and all other strong opioid agonists are classified under Schedule II. This classification reflects a moderate to high abuse liability. The agonist-antagonist opioids have a lower abuse liability and hence are classified under Schedule IV (butorphanol, pentazocine) or Schedule V (buprenorphine), or have no classification at all (nalbuphine). Healthcare personnel who prescribe, dispense, and administer opioids must adhere to the procedures set forth in the Controlled Substances Act.

Fortunately, abuse is rare when opioids are employed to treat pain. The issue of abuse as a clinical concern is addressed in depth later in the chapter.

Precautions

Some patients are more likely than others to experience adverse effects. Common sense dictates that opioids be used with special caution in these people. Conditions that can predispose patients to adverse reactions are discussed immediately below.

Decreased Respiratory Reserve.

Because morphine depresses respiration, it can further compromise respiration in patients with impaired pulmonary function. Accordingly, the drug should be used with caution in patients with asthma, emphysema, kyphoscoliosis, chronic cor pulmonale, and extreme obesity. Caution is also needed in patients taking other drugs that can depress respiration (eg, barbiturates, benzodiazepines, general anesthetics).

Pregnancy.

Morphine does not cause birth defects in humans. However, regular use of opioids during pregnancy *can* cause physical dependence in the fetus. Accordingly, prolonged use by pregnant women should be avoided if possible.

Labor and Delivery.

Use of morphine during delivery can suppress uterine contractions and cause respiratory depression in the neonate. Following delivery, respiration in the neonate should be monitored closely. Respiratory depression can be reversed with naloxone. The use of opioids in obstetrics is discussed further later in the chapter.

Head Injury.

Morphine and other opioids must be used with caution in patients with head injury. Head injury can cause respiratory depression accompanied by elevation of ICP. Morphine can exacerbate these symptoms. In addition, since miosis, mental clouding, and vomiting can be valuable diagnostic signs following head injury, and since morphine can cause these same effects, use of opioids can confound diagnosis.

Other Precautions.

Infants and *elderly patients* are especially sensitive to morphine-induced respiratory depression. In patients with *inflammatory bowel disease,* morphine may cause toxic megacolon or paralytic ileus. Since morphine and all other opioids are inactivated by liver enzymes, effects may be intensified and prolonged in patients with *liver impairment*. Severe hypotension may occur in patients with preexisting *hypotension* or *reduced blood volume*. In patients with *prostatic hypertrophy,* opioids may cause acute urinary retention; repeated catheterization may be required.

Drug Interactions

The major interactions between morphine and other drugs are summarized in Table 28-4. Some interactions are adverse, and some are beneficial.

Interacting Drugs	Outcome of the Interaction
Adverse Interactions	
CNS depressants	Increased respiratory depression and sedation
Barbiturates	
Benzodiazepines	
Alcohol	
General anesthetics	
Antihistamines	
Phenothiazines	
Agonist-antagonist opioids	Precipitation of a withdrawal reaction
Anticholinergic drugs	Increased constipation and urinary retention
Atropine-like drugs	
Antihistamines	
Phenothiazines	
Tricyclic antidepressants	
Hypotensive agents	Increased hypotension
Monoamine oxidase inhibitors	Hyperpyrexic coma
Beneficial Interactions	
Amphetamines	Increased analgesia and decreased sedation
Antiemetics	Suppression of nausea and vomiting
Naloxone	Suppression of symptoms of opioid overdose
Dextromethorphan	Increased analgesia; possible reduction in tolerance

TABLE 28-4 Interactions of Morphine-like Drugs with Other Drugs

CNS Depressants.

All drugs with CNS-depressant actions (eg, barbiturates, benzodiazepines, alcohol) can intensify sedation and respiratory depression caused by morphine and other opioids. Outpatients should be warned against use of alcohol and all other CNS depressants.

Anticholinergic Drugs.

These agents (eg, antihistamines, tricyclic antidepressants, atropine-like drugs) can exacerbate morphine-induced constipation and urinary retention.

Hypotensive Drugs.

Antihypertensive drugs and other drugs that lower blood pressure can exacerbate morphine-induced hypotension.

Monoamine Oxidase Inhibitors.

The combination of meperidine (a morphine-like drug) with a monoamine oxidase (MAO) inhibitor has produced a syndrome characterized by excitation, delirium, hyperpyrexia, convulsions, and severe respiratory depression. Deaths have occurred. Although this reaction has not been reported with combined use of an MAO inhibitor and morphine, prudence suggests that the combination nonetheless be avoided.

Agonist-Antagonist Opioids.

These drugs (eg, pentazocine, buprenorphine) can precipitate a withdrawal syndrome if given to an individual physically dependent on a pure opioid agonist. The basis of this reaction is considered later in the chapter. Patients taking pure opioid agonists should be weaned from these drugs before beginning treatment with an agonist-antagonist.

Opioid Antagonists.

Opioid antagonists (eg, naloxone) can counteract most actions of morphine and other pure opioid agonists. Opioid antagonists are employed primarily to treat

opioid overdose. The actions and uses of the opioid antagonists are discussed in detail later in the chapter.

Other Interactions.

Antiemetics of the phenothiazine type (eg, promethazine [Phenergan]) may be combined with opioids to reduce nausea and vomiting. *Amphetamines, clonidine,* and *dextromethorphan* can enhance opioid-induced analgesia. *Amphetamines* can also offset sedation.

Toxicity

Clinical Manifestations.

Opioid overdose produces a classic triad of signs: *coma, respiratory depression,* and *pinpoint pupils*. Coma is profound, and the patient cannot be aroused. Respiratory rate may be as low as 2 to 4 breaths per minute. Although the pupils are constricted initially, they may dilate as hypoxia sets in (secondary to respiratory depression). Hypoxia may cause blood pressure to fall. Prolonged hypoxia may result in shock. When death occurs, respiratory arrest is almost always the immediate cause.

Treatment.

Treatment consists primarily of *ventilatory support* and giving an *opioid antagonist*. Traditionally, naloxone [Narcan] has been the antagonist of choice. However, nalmefene [Revex], a newer and longer acting antagonist, may be preferred for many patients. The pharmacology of the opioid antagonists is discussed later.

Preparations, Dosage, and Administration

General Guidelines on Dosage and Administration.

Dosage must be individualized. High doses are required for patients with a low tolerance to pain or with extremely painful disorders. Patients with sharp, stabbing pain need higher doses than patients with dull pain. Elderly adults generally require lower doses than younger adults. Neonates require relatively low doses because their blood-brain barrier is not fully developed. For

all patients, dosage should be reduced as pain subsides. Outpatients should be warned not to increase dosage without consulting the physician.

Before an opioid is administered, respiratory rate, blood pressure, and pulse rate should be determined. The drug should be withheld and the prescriber notified if respiratory rate is at or below 12 breaths per minute, if blood pressure is significantly below the pretreatment value, or if pulse rate is significantly above or below the pretreatment value.

As a rule, *opioids should be administered on a fixed schedule—not PRN*. With a fixed schedule, medication is given before intense pain returns. As a result, the patient is spared needless discomfort. Furthermore, anxiety about recurrence of pain is reduced. If breakthrough pain occurs, supplemental doses of a short-acting preparation should be given.

Morphine and practically all other opioid agonists are classified under Schedule II of the Controlled Substances Act and must be dispensed accordingly.

Preparations.

Morphine sulfate is available in 11 formulations: *immediate-release tablets* (15 and 30 mg); *controlled-release tablets* [MS Contin] (15, 30, 60, 100, and 200 mg) and [Oramorph SR] (15, 30, 60, and 100 mg); *extended-release tablets* (15, 30, 60, 100, and 200 mg); *sustained-release capsules* [Kadian] (10, 20, 30, 50, 60, 80, 100, and 200 mg); *extended-release capsules* [Avinza] (30, 60, 90, and 120 mg); *standard oral solution* [MSIR] (2 and 4 mg/mL); *concentrated oral solution* [MSIR, Roxanol] (20 mg/mL); *rectal suppositories* [RMS] (5, 10, 20, and 30 mg); *soluble tablets for injection* (10, 15, and 30 mg); *standard solution for injection* [Astramorph PF, Duramorph, Infumorph] (0.5, 1, 2, 4, 5, 8, 10, 15, 25, and 50 mg/mL); and *extended-release liposomal solution for injection* [DepoDur] (10 mg/mL).

Dosage and Routes of Administration. Oral.

Oral administration is generally reserved for patients with chronic, severe pain, such as that associated with cancer. Because oral morphine undergoes extensive metabolism on its first pass through the liver, oral doses are usually higher than parenteral doses. A typical dosage is 10 to 30 mg repeated every 4 hours as needed. However, oral dosing is highly individualized, and hence some patients may require 75 mg or more. Controlled-release formulations

may be administered every 8 to 12 hours, and the extended-release formulation [Avinza] is given every 24 hours. Patients should be instructed to swallow these products intact, without crushing or chewing. Also, *warn patients using Avinza not to drink alcohol,* which can accelerate release of morphine from this formulation.

Intramuscular and Subcutaneous.

Both routes are painful and unreliable, and hence should generally be avoided. For adults, dosing is initiated at 5 to 10 mg every 4 hours, and then adjusted up or down as needed. The usual dosage for children is 0.1 to 0.2 mg/kg repeated every 4 hours as needed.

Intravenous.

Intravenous morphine should be injected slowly (over 4 to 5 minutes). Rapid IV injection can cause severe adverse effects (profound hypotension, cardiac arrest, respiratory arrest) and should be avoided. When IV injections are made, an opioid antagonist (eg, naloxone) and facilities for respiratory support should be available. Injections should be given with the patient lying down to minimize hypotension. The usual dose for adults is 4 to 10 mg (diluted in 4 to 5 mL of sterile water for injection). The usual pediatric dose is 0.05 to 0.1 mg/kg.

Epidural and Intrathecal.

When morphine is employed for spinal analgesia, epidural injection is preferred to intrathecal. With either route, onset of analgesia is rapid and the duration prolonged (up to 24 hours). The most troubling side effects are delayed respiratory depression and delayed cardiac depression. Be alert for possible late reactions. The usual adult epidural dose is 5 mg. Intrathecal doses are much smaller—about one-tenth the epidural dose.

The extended-release liposomal formulation [DepoDur] is intended for *epidural use only*. Inadvertent intrathecal and subarachnoid administration has been associated with profound and prolonged respiratory depression, which can be managed with a naloxone infusion.

Other Strong Opioid Agonists

In an effort to produce a strong analgesic with a low potential for respiratory depression and abuse, pharmaceutical scientists have created many new opioid analgesics. However, none of the newer pure opioid agonists can be considered truly superior to morphine: These drugs are essentially equal to morphine with respect to analgesic action, abuse liability, and the ability to cause respiratory depression. Also, to varying degrees, they all cause sedation, euphoria, constipation, urinary retention, cough suppression, hypotension, and miosis. However, despite their similarities to morphine, the newer drugs do have unique qualities. Hence one agent may be more desirable than another in a particular clinical situation. With all of the newer pure opioid agonists, toxicity can be reversed with an opioid antagonist (eg, naloxone). Important differences between morphine and the newer strong opioid analgesics are discussed below. Table 28-5 summarizes dosages, routes, and time courses for morphine and the newer agents.

Drug and Route[a]	Equianalgesic Dose (mg)[b]	Time Course of Analgesic Effects		
		Onset (min)	Peak (min)	Duration (hr)
Codeine				
PO	200	30–45	60–120	4–6
IM	130	10–30	30–60	4–6
SubQ	130	10–30	30–60	4–6
Fentanyl				
IM	0.1	7–8	—	1–2
IV	0.1	—	—	0.5–1
Transdermal[c]	—	Delayed	24–72	72
Hydrocodone				
PO	30	10–30	30–60	4–6
Hydromorphone				
PO	7.5	30	90–120	4
IM	1.5	15	30–60	4–5
IV	1.5	10–15	15–30	2–3
SubQ	1.5	15	30–90	4
Levorphanol				
PO	4	10–60	90–120	6–8
IM	2	—	60	6–8
IV	2	—	Within 20	6–8
SubQ	2	—	60–90	6–8
Meperidine				
PO	300	15	60–90	2–4
IM	75	10–15	30–50	2–4
IV	75	1	5–7	2–4
SubQ	75	10–15	30–50	2–4
Methadone				
PO	20	30–60	90–120	4–6[d]
IM	10	10–20	60–120	4–5[d]
IV	10	—	15–30	3–4[d]
Morphine				
PO	30	—	60–120	4–5[§]
IM	10	10–30	30–60	4–5
IV	10	—	20	4–5
SubQ	10	10–30	50–90	4–5
Epidural	—	15–60	—	Up to 24
Intrathecal	—	15–60	—	Up to 24
Oxycodone				
PO	20	15–30	60	3–4[e]
Oxymorphone				
IM	1	10–15	30–90	3–6
IV	1	5–10	15–30	3–4
SubQ	1	10–20	—	3–6
Rectal	10	15–30	120	3–6
Propoxyphene				
PO	—[f]	15–60	120	4–6
Remifentanil				
IV	0.1	—	—	0.1–0.2[g]

TABLE 28-5 Clinical Pharmacology of Pure Opioid Agonists

a IM administration should be avoided whenever possible.

b Dose in milligrams that produces a degree of analgesia equivalent to that produced by a 10-mg IM dose of morphine.

c Data are for the transdermal patch, not the transdermal iontophoretic system.

d With repeated doses, methadone's duration of action may increase up to 48 hours.

e Effects of extended-release formulations may persist for 8 to 12 hours.

f A dose of propoxyphene equivalent to 10 mg of morphine would be too toxic to administer.

g Analgesia stops 5 to 10 minutes after stopping the infusion.

Fentanyl

Fentanyl [Sublimaze, Duragesic, Fentora, Actiq, Ionsys] is a strong opioid analgesic with a high milligram potency (about 100 times that of morphine). Like other strong opioids, fentanyl overdose poses a risk of fatal respiratory depression. Fentanyl is metabolized by CYP3A4 (the 3A4 isozyme of cytochrome P450), and hence fentanyl levels can be increased by CYP3A4 inhibitors (eg, ritonavir, ketoconazole). Patients taking these inhibitors should be closely monitored for severe respiratory depression and other signs of toxicity. Fentanyl is available in five formulations for administration by three routes: parenteral, transdermal, and transmucosal. All preparations are regulated under Schedule II of the Controlled Substances Act.

Parenteral.

Parenteral fentanyl [Sublimaze], administered IM or IV, is employed primarily for induction and maintenance of surgical anesthesia. The drug is well suited for these applications because it has a rapid onset and short duration. Most effects are like those of morphine. In addition, fentanyl can cause muscle rigidity, which can interfere with induction of anesthesia. As discussed in Chapter 27 (General Anesthetics), the combination of fentanyl plus droperidol is used to produce a state known as “neurolept analgesia.”

Transdermal.

Fentanyl for transdermal administration is available in two formulations: (1) a patch [Duragesic] that releases fentanyl slowly over an extended time and (2) an iontophoretic system [Ionsys] that releases a small dose each time the sys-

tem is activated. The iontophoretic system is indicated only for *postoperative pain* in hospitalized patients. In contrast, the patch is indicated for *persistent pain* in patients who are already opioid tolerant, and is specifically *contraindicated* for postoperative pain.

Standard Transdermal System (Patch)

The standard fentanyl transdermal system [Duragesic] consists of a fentanyl-containing patch that is applied to the skin of the upper torso. The drug is slowly released from the patch and absorbed through the skin, reaching effective levels in 24 hours. Levels remain steady for another 48 hours, after which the patch should be replaced. If a new patch is not applied, effects will nonetheless persist for several hours, owing to continued absorption of residual fentanyl remaining in the skin.

Transdermal fentanyl is indicated only for persistent severe pain in patients who are already opioid tolerant. Use in nontolerant patients can cause fatal respiratory depression. The patch should not be used in children under 2 years old, or in anyone under 18 who weighs less than 110 pounds. Also, the patch should not be used for postoperative pain, intermittent pain, or pain that responds to a less powerful analgesic.

Transdermal fentanyl has the same adverse effects as other opioids: respiratory depression, sedation, constipation, urinary retention, nausea, and so forth. Of these, respiratory depression is the greatest concern. Adverse effects may persist for hours following patch removal owing to continued absorption from the skin. Signs of toxicity can be reversed with an opioid antagonist (eg, naloxone). Used or damaged patches should be flushed down the toilet. Unused patches should be stored out of reach of children.

Heat can accelerate fentanyl release from the patch, thereby increasing the risk of toxicity. Accordingly, patients should be advised to avoid exposing the patch to external heat sources, including heating pads, electric blankets, heat lamps, saunas, hot tubs, and heated water beds. Sunbathing and hot baths should be avoided as well. Patients with fever should be monitored for signs of increased drug levels and, if toxicity develops, fentanyl dosage should be reduced.

Fentanyl patches are available in five sizes, which deliver fentanyl to the systemic circulation at rates of 12.5, 25, 50, 75, and 100 mcg/hr. The smallest effective patch should be used. If a dosage greater than 100 mcg/hr is required, a combination of patches can be applied. When the patch is in place, it must not be exposed to direct heat (eg, heating pads, hot baths, electric blankets), because doing so can accelerate fentanyl release, as can fever, sunbathing, and strenuous exercise. Because full analgesic effects can take up to 24 hours to develop, PRN therapy with a short-acting opioid may be required until the patch takes effect. As with other long-acting opioids, if breakthrough pain occurs, supplemental dosing with a short-acting opioid is indicated. For the majority of patients, patches can be replaced every 72 hours, although some may require a new patch in 48 hours.

Transdermal Iontophoretic System.

The transdermal iontophoretic system [Ionsys]—a self-contained credit card–sized device—is the first *needle-free* patient-activated system for on-demand delivery of analgesia. The device, which is applied to the skin, delivers fentanyl by iontophoresis, a process in which a low-intensity electrical field (generally imperceptible to the patient) drives the drug across the skin and into the systemic circulation. Ionsys is approved only for acute management of postoperative pain in hospitalized adult patients, and should be removed prior to discharge. Pain control is equivalent to that achieved with an IV patient-controlled analgesia pump. The most common adverse effect is nausea (38%).

Ionsys consists of a plastic case that houses a 3-volt battery, control electronics, and a reservoir containing 10.8 mg of fentanyl hydrochloride. The upper surface of the device has a recessed dosing button and a red light; the lower surface has adhesive to hold the device to the skin. When pain relief is needed, the patient presses the dosing button twice (within 3 seconds), causing delivery of a 40-mcg dose over a 10-minute interval. An audible beep indicates the process has begun and the red light remains on while delivery takes place. One Ionsys device can be used for 24 hours or delivery of 80 doses, whichever comes first. Ionsys should be applied to intact, nonirritated, nonirradiated skin of the chest or outer upper arm. Excessive hair should be removed by clipping, not shaving. All patients should be titrated to comfort with an appropriate analgesic before Ionsys is employed.

Transmucosal.

Fentanyl for transmucosal administration is available in two formulations: lozenges on a stick [Actiq] and buccal tablets [Fentora]. Both products are approved only for breakthrough cancer pain in patients who are already taking opioids and who have developed some degree of tolerance, defined as needing more than 60 mg of morphine/day, at least 25 mcg of fentanyl/hr, or an equianalgesic dose of another opioid for a week or more. These products must not be used for acute pain, postoperative pain, headache, or athletic injuries. It is essential to appreciate that the dose of fentanyl in either formulation is sufficient to kill nontolerant individuals—especially children. Accordingly, these products must be stored in a secure, child-resistant location.

Lozenge on a Stick.

The fentanyl lozenge on a stick [Actiq]—also known as OTFC (oral transmucosal fentanyl citrate)—consists of a raspberry-flavored lozenge on a plastic handle, and looks much like a lollypop. Six strengths are available: 200, 400, 600, 800, 1200, and 1600 mcg. As noted, the Actiq system is approved only for *breakthrough cancer pain* in patients who are already opioid tolerant.

To administer the unit, patients place it between the cheek and the lower gum and actively suck it. Periodically, the unit should be moved from one side of the mouth to the other. Consumption of the entire lozenge should take 15 minutes. As the patient sucks, some of the drug is absorbed directly and rapidly through the oral mucosa, and some is swallowed and absorbed slowly from the GI tract. Analgesia begins in 10 to 15 minutes, peaks in 20 minutes, and persists 1 to 2 hours.

Dosing should begin with a 200-mcg unit. If breakthrough pain persists, the patient can take another 200-mcg unit 15 minutes after finishing the first one (ie, 30 minutes after starting the first). Unit size should be gradually increased until an effective dose is determined. If the patient needs more than 4 units/day, it may be time to give a higher dose of his or her long-acting opioid.

Adverse effects of the Actiq system are like those of other opioids. The most common are dizziness, anxiety, confusion, nausea, vomiting, constipation, dyspnea, weakness, and headache. The biggest concerns are respiratory de-

pression and shock. If dizziness, nausea, or signs of overdose develop, the unit should be removed from the patient's mouth and disposed of immediately.

To promote safe and effective use of the Actiq system, the manufacturer provides an Actiq Welcome Kit with the initial drug supply. The kit contains educational materials and safe storage containers for unused, partially used, and completely used units.

Buccal Tablets

Like the Actiq lozenges, fentanyl buccal tablets [Fentora] are indicated only for breakthrough cancer pain in patients who are already taking opioids and have developed some degree of tolerance. Administration to nontolerant patients could result in severe respiratory depression.

The buccal tablets are much like the lozenges, but with one very important difference: *absorption from the tablets is more complete than from the lozenges,* and hence the two formulations are not directly interchangeable. For example, a 100-mcg buccal tablet produces about the same fentanyl blood level as a 200-mcg lozenge. Hence, when patients are switched from the lozenge to the tablet, the dosage must be reduced (see below). Failure to do so could prove fatal.

Fentanyl buccal tablets are available in five strengths, identifiable by color: 100 mcg (blue), 200 mcg (orange), 400 mcg (green), 600 mcg (pink), and 800 mcg (yellow). Patients should be instructed to place the tablet above a rear molar between the cheek and the gum and let it dissolve in place, usually in 15 to 30 minutes. Remaining fragments should be swallowed with a glass of water. Whole tablets should never be split, chewed, sucked, or swallowed.

Dosage is based on current opioid use. For patients switching from Actiq, the initial Fentora tablet should be 100 mcg (for patients using 200 mcg or 400 mcg of Actiq), 200 mcg (for patients using 600 mcg or 800 mcg of Actiq), or 400 mcg (for patients using 1200 mcg or 1600 mcg of Actiq). For patients not using Actiq, the initial dose of Fentora should be 100 mcg. The dosage may then be titrated using up to four 100-mcg Fentora tablets per dose. If a higher dosage is needed, larger Fentora tablets should be used.

Alfentanil and Sufentanil

Alfentanil [Alfenta] and sufentanil [Sufenta] are intravenous opioids related to fentanyl. Both drugs are used for induction of anesthesia, for maintenance of anesthesia (in combination with other agents), and as sole anesthetic agents. Pharmacologic effects are like those of morphine. Sufentanil has an especially high milligram potency (about 1000 times that of morphine); alfentanil is about 10 times more potent than morphine. Both drugs have a rapid onset, and both are Schedule II agents.

Remifentanil

Remifentanil [Ultiva] is an intravenous opioid with a rapid onset and brief duration. The brief duration results from rapid metabolism by plasma and tissue esterases, and not from hepatic metabolism or renal excretion. Like fentanyl, remifentanil is about 100 times more potent than morphine. Remifentanil is approved for analgesia during surgery and during the immediate postoperative period. Administration is by continuous IV infusion. Effects begin in minutes, and terminate 5 to 10 minutes after the infusion is stopped. For surgical analgesia, the infusion rate is 0.05 to 2 mcg/kg/min. For postoperative analgesia, the infusion rate is 0.025 to 0.2 mcg/kg/min. Adverse effects during the infusion include respiratory depression, hypotension, bradycardia, and muscle rigidity sufficient to compromise breathing. Postinfusion effects include nausea (44%), vomiting (22%), and headache (18%). Remifentanil is regulated as a Schedule II substance.

Meperidine

Meperidine [Demerol] shares the major pharmacologic properties of morphine. With parenteral and oral administration, analgesia is strong. In the past, meperidine was considered a first-line drug for relief of moderate to severe pain. Now, however, use of meperidine is in decline. Why? First, the drug has a short half-life, and hence dosing must be repeated at short intervals. Second, meperidine interacts adversely with a number of drugs. Third, with continuous use, there is a risk of harm owing to accumulation of a toxic metabolite. Accordingly, routine use of the drug should be avoided. However, meperidine may still be appropriate for patients who can't take other opioids, and for patients with drug-induced rigors or postanesthesia shivering.

Meperidine can interact with MAO inhibitors to cause excitation, delirium, hyperpyrexia, and convulsions. Coma and death can follow. The underlying mechanism appears to be excessive activation of serotonin receptors owing to meperidine-induced blockade of serotonin reuptake. Clearly, the combination of meperidine with an MAO inhibitor should be avoided. Other drugs that increase serotonin availability (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors) may also pose a risk.

Repeated dosing results in accumulation of normeperidine, a toxic metabolite that can cause dysphoria, irritability, tremors, and seizures. To avoid toxicity, *treatment should not exceed 48 hours, and the dosage should not exceed 600 mg/24 hr*.

Meperidine is available in tablets (50 and 100 mg) and a syrup (10 mg/mL) for oral use, and in solution (25, 50, 75, and 100 mg/mL) for injection (IV, IM, or subQ). The usual adult dosage is 50 to 150 mg (IM, subQ, or PO) repeated every 3 to 4 hours as needed—up to a maximum of 600 mg/day. The usual dosage for children is 1 to 1.8 mg/kg (IM, subQ, or PO) repeated every 3 to 4 hours as needed. As noted, prolonged use must be avoided.

Methadone

Methadone [Diskets, Dolophine, Methadose] has pharmacologic properties very similar to those of morphine. The drug is effective orally and has a long duration of action. Repeated dosing can result in accumulation. Methadone is used to relieve pain and to treat opioid addicts. The use of methadone in drug-abuse treatment programs is discussed in Chapter 39.

Methadone prolongs the QT interval, and hence may pose a risk of potentially fatal dysrhythmias. Torsades de pointes has developed in patients taking 65 to 400 mg/day. To reduce risk, methadone should be used with great caution—if at all—in patients with existing QT prolongation and in those taking other QT-prolonging drugs (eg, amiodarone, quinidine, erythromycin, tricyclic antidepressants).

In recent years, there have been increasing reports of deaths and life-threatening side effects (especially dysrhythmias and respiratory depression) among patients taking methadone to relieve pain. The presumed cause of toxicity is high drug levels, owing largely to excessive dosage. To reduce risk, patients should be warned against taking more methadone than was prescribed,

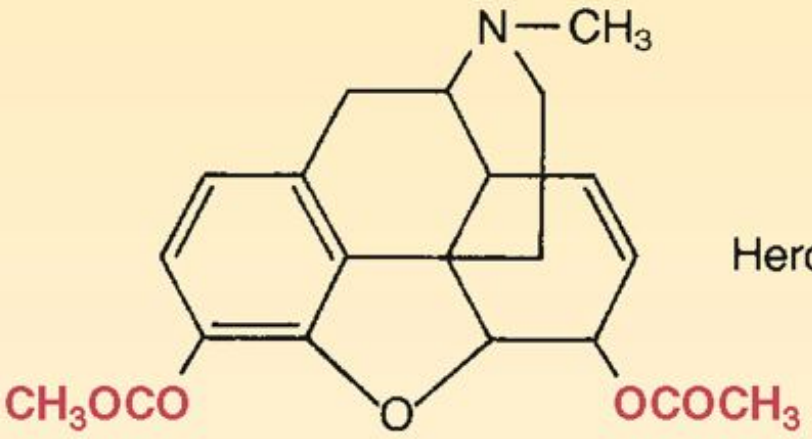
and should be cautioned to avoid other CNS depressants, including benzodiazepines, alcohol, and other opioids. Drugs that inhibit CYP3A4 (the enzyme that metabolizes methadone) can raise methadone levels, and hence should be used with care. Among these inhibitors are clarithromycin, fluvoxamine, fluconazole, and nelfinavir.

Methadone is supplied in standard tablets (5 and 10 mg) and solution (1, 2, and 10 mg/mL) for oral use, and in solution (10 mg/mL) for IM and subQ injection. In addition, the drug is available in dispersible 40-mg tablets for detoxification and maintenance of opioid addicts. Usual oral analgesic doses for adults range from 2.5 to 20 mg repeated every 3 to 4 hours as needed.

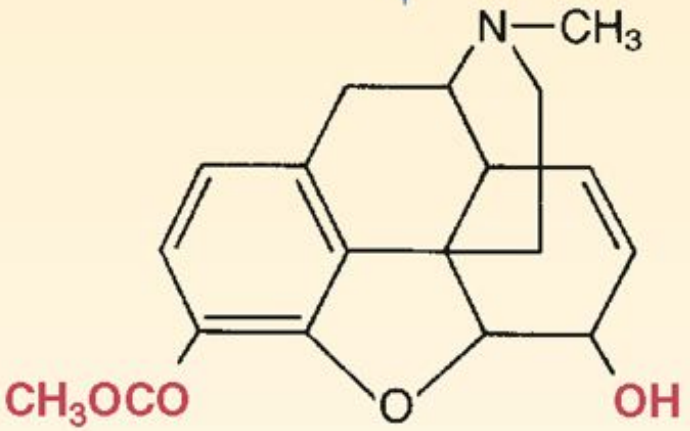
Heroin

Heroin is a strong opioid agonist very similar to morphine in structure and actions. The drug is an effective analgesic and is employed legally in Europe to relieve pain. In the United States, federal legislation prohibits the medical use of this drug. Why? Because heroin has a high abuse liability and is no better than other opioids at relieving pain.

What makes heroin so attractive as a drug of abuse? Pharmacokinetics: Heroin has greater lipid solubility than morphine, and therefore crosses the blood-brain barrier more readily. As a result, when heroin is injected IV, it accumulates in the brain more rapidly and to a higher level than would an equivalent dose of morphine. Once in the brain, heroin (diacetylmorphine) is rapidly converted into active metabolites: monoacetylmorphine and morphine (Fig. 28-2). It is these metabolites, and not heroin itself, that produce the subjective effects that follow heroin injection. In this regard, heroin can be viewed as a vehicle for facilitating transport of morphine into the brain.



Heroin



Monoacetylmorphine

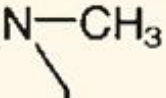


Figure 28-2 Biotransformation of heroin into morphine. Heroin, as such, is biologically inactive. After crossing the blood-brain barrier, heroin is converted to monoacetylmorphine (MAM) and then into morphine itself. MAM and morphine are responsible for the effects elicited by injection of heroin.

Hydromorphone, Oxymorphone, and Levorphanol

Basic Pharmacology.

All three drugs are strong opioid agonists with pharmacologic actions like those of morphine, and all three are indicated for moderate to severe pain. Dosages and time courses are summarized in Table 28-5. Adverse effects include respiratory depression, sedation, cough suppression, constipation, urinary retention, nausea, and vomiting. Toxicity can be reversed with an opioid antagonist (eg, naloxone). All three drugs are Schedule II agents.

Preparations, Dosage, and Administration

Hydromorphone.

Hydromorphone [Dilaudid] is available in five formulations: (1) oral tablets (2, 4, and 8 mg); (2) oral liquid (1 mg/mL); (3) rectal suppositories (3 mg); (4) solutions (1, 2, 4, and 10 mg/mL) for IM and subQ injection; and (5) a powder (250 mg), to be reconstituted to a 10-mg/mL solution for IM and subQ injection. With the tablets, the usual adult dosage is 2 mg every 4 to 6 hours. With the oral liquid, the usual adult dosage is 2.5 to 10 mg every 3 to 6 hours. With the rectal suppositories, the usual dosage is 3 mg every 6 to 8 hours. With subQ and IM injection, dosages range from 1 to 4 mg every 4 to 6 hours.

Oxymorphone.

Oxymorphone is available in three formulations: (1) immediate-release tablets (5 and 10 mg) sold as *Opana;* (2) extended-release tablets (5, 7.5, 10, 15, 20, 30, and 40 mg) sold as *Opana ER;* and (3) solution for IM, IV, or subQ injection (1 mg/mL) sold as *Opana*. All oxymorphone tablets should be taken on an empty stomach, because dosing with food can produce excessive peak levels. Also, alcohol should be avoided, since it can increase blood levels of oral oxymorphone. For

IV therapy, the initial dose is 0.5 mg. Usual subQ and IM dosages are 1 to 1.5 mg every 4 to 6 hours as needed.

Levorphanol.

Levorphanol [Levo-Dromoran] is available in 2-mg oral tablets and in solution (2 mg/mL) for IM, IV, or subQ injection. The usual adult oral dosage is 2 mg, repeated in 6 to 8 hours as needed. For IV therapy, the usual dosage is 1 mg, repeated in 3 to 6 hours as needed, up to a maximum of 4 to 8 mg/24 hr. For IM or subQ therapy, the usual dosage is 1 to 2 mg, repeated in 6 to 8 hours as needed, up to a maximum of 3 to 8 mg/24 hr.

Moderate to Strong Opioid Agonists

The moderate to strong opioid agonists are similar to morphine in most respects. Like morphine, these drugs produce analgesia, sedation, and euphoria. In addition, they can cause respiratory depression, constipation, urinary retention, cough suppression, and miosis. Differences between the moderate to strong opioids and morphine are primarily quantitative: The moderate to strong opioids produce less analgesia and respiratory depression than morphine and have a somewhat lower potential for abuse. As with morphine, toxicity from the moderate to strong agonists can be reversed with naloxone.

Codeine

Codeine is indicated for relief of mild to moderate pain. The drug is usually administered by mouth. Side effects are dose limiting. As a result, although taking codeine can produce significant pain relief, the degree of pain relief that can be achieved *safely* is quite low—much lower than with morphine. When taken in its usual analgesic dose (30 mg), codeine produces about as much pain relief as 325 mg of aspirin or 325 mg of acetaminophen.

In the liver, about 10% of each codeine dose undergoes conversion to *morphine,* the active form of codeine. The enzyme responsible is CYP2D6 (the 2D6 isomer of cytochrome P450). Among people who lack an effective gene for CYP2D6, codeine cannot be converted to morphine, and hence codeine cannot produce analgesia. Conversely, among ultrarapid metabolizers, who carry multiple copies of the CYP2D6 gene, codeine is unusually effective. Ultrarapid metabolism occurs in 7% of whites, 3% of blacks, and 1% of Hispanics and Asians.

Very rarely, severe toxicity develops in breast-fed infants whose mothers are taking codeine. The cause is high levels of morphine in breast milk, owing to ultrarapid codeine metabolism. Nursing mothers who are taking codeine should be alert for signs of infant intoxication—excessive sleepiness, breathing difficulties, lethargy, poor feeding—and should seek medical attention if these develop.

For analgesic use, codeine is formulated alone and in combination with nonopioid analgesics (either aspirin or acetaminophen). Since codeine and nonopioid analgesics relieve pain by different mechanisms, the combinations can produce greater pain relief than either agent alone. Codeine alone is classified under Schedule II of the Controlled Substances Act. The combination preparations are classified under Schedule III. Although codeine is classified along with morphine in Schedule II, the abuse liability of codeine appears to be significantly lower.

Codeine is an extremely effective cough suppressant and is widely used for this action. The antitussive dose (10 mg) is lower than analgesic doses. Codeine is formulated in combination with various agents to suppress cough. These mixtures are classified under Schedule V.

Preparations, Dosage, and Administration.

Codeine is administered orally and parenterally (IV, IM, and subQ). For oral therapy, the drug is available in tablets (15, 30, and 60 mg) and in solution (3 mg/mL). For parenteral therapy, the drug is available in solution (15 and 30 mg/mL).

The usual analgesic dosage for adults is 15 to 60 mg (PO, IV, IM, or subQ) every 3 to 6 hours (to a maximum of 120 mg/24 hr). The usual analgesic dosage for children 1 year and older is 0.5 mg/kg (PO, IM, or subQ) every 4 to 6 hours (to a maximum of 60 mg/24 hr).

Oxycodone

Oxycodone [OxyContin, Roxicodone, Combunox, Percodan, Percocet, others] has analgesic actions equivalent to those of codeine. Administration is oral. Oxycodone is available by itself in immediate-release tablets (5, 10, 15, 20, and 30 mg), immediate-release capsules (5 mg), controlled-release tablets (10, 15,

20, 30, 40, 60, and 80 mg), and oral solution (1 and 20 mg/mL). In addition, the drug is available in combination with aspirin (as Percodan), acetaminophen (as Percocet, Roxicet, others), and ibuprofen (as Combunox). All formulations are classified under Schedule II.

Controlled-release oxycodone [OxyContin] is a long-acting analgesic designed to relieve moderate to severe pain around-the-clock for an extended time. Dosing is done every 12 hours—not PRN. If breakthrough pain occurs, supplemental dosing with a short-acting analgesic is indicated.

Owing to increasing reports of OxyContin abuse, safety warnings have been strengthened. When prescribed and used properly, controlled-release oxycodone tablets are safe and effective. However, abusers do not take them properly. Rather, they crush the tablets and then "snort" the resulting powder, or dissolve the powder in water and inject it IV. Both practices allow *immediate* absorption of the entire dose, and thereby produce drug blood levels that are much higher than those produced when the tablets are ingested whole and absorbed gradually. The result can be an intense "high" coupled with a risk of fatal respiratory depression. At least 39 deaths have been reported. To prevent the immediate release of a potentially fatal dose, the controlled-release tablets must be swallowed whole, without breaking, crushing, or chewing. Furthermore, the 80-mg formulation must be reserved for patients who are already opioid tolerant. OxyContin tablets should never be dissolved and injected. Why? Because the tablets contain insoluble particulate matter (especially talc) that can cause local tissue necrosis, pulmonary granulomas, endocarditis, and valvular heart injury. As with all other opioids, concerns about abuse and addiction should not interfere with using OxyContin to manage pain. Rather, the drug must simply be prescribed appropriately and then used as prescribed.

Hydrocodone

Hydrocodone is the most widely prescribed drug in the United States. In 2007, more than 108 million prescriptions were written—far more than the 65 million for atorvastatin (a cholesterol-lowering drug) or the 34 million for amoxicillin (an antibiotic). Hydrocodone has analgesic actions equivalent to those of codeine. The drug is taken orally to relieve pain and to suppress cough. The usual dosage is 5 mg. Hydrocodone is available only in combination with other drugs. For analgesic use, hydrocodone is combined with aspirin, acet-

aminophen, or ibuprofen. For cough suppression, the drug is combined with antihistamines and nasal decongestants. All of these combination products are currently classified under Schedule III. However, owing to widespread abuse of hydrocodone-containing products, the Drug Enforcement Agency (DEA) would like the classification changed to Schedule II. Trade names for combination products containing hydrocodone include *Vicodin, Vicoprofen*, and *Lortab*.

Propoxyphene

Propoxyphene [Darvon] has analgesic effects about equal to those of aspirin. The drug is frequently prescribed in combination with a nonopioid analgesic, either aspirin or acetaminophen. These combinations can produce greater pain relief than either propoxyphene or the nonopioid alone. Propoxyphene has a low potential for abuse, primarily because large doses cause toxic psychosis. Furthermore, excessive doses often prove fatal. Accordingly, the drug should not be prescribed for patients with suicidal tendencies. Physical dependence is minimal. Propoxyphene—alone or in combination with a nonopioid analgesic—is classified under Schedule IV.

Propoxyphene is available as two salts: propoxyphene hydrochloride and propoxyphene napsylate. Both are administered orally. Propoxyphene hydrochloride is available in 65-mg capsules (as *Darvon Pulvules*); the usual adult dosage is 65 mg repeated every 4 hours as needed. Propoxyphene napsylate is available in 100-mg tablets (as *Darvon-N*); the usual adult dosage is 100 mg repeated every 4 hours as needed. In addition to these single-ingredient products, propoxyphene napsylate is available in combinations with acetaminophen, sold as *Darvocet* and *Propacet*.

Agonist-Antagonist Opioids

Four agonist-antagonist opioids are available: pentazocine, nalbuphine, butorphanol, and buprenorphine. With the exception of buprenorphine, these drugs act as antagonists at mu receptors and agonists at kappa receptors (see Table 28-2). Compared with pure opioid agonists, the agonist-antagonists have a low potential for abuse, produce less respiratory depression, and generally have less powerful analgesic effects. If given to a patient who is physically dependent on a pure opioid agonist, these drugs can precipitate withdrawal. The clinical pharmacology of the agonist-antagonists is summarized in Table 28-6.

Drug and Route*	Equianalgesic Dose (mg)†	Time Course of Analgesic Effects		
		Onset (min)	Peak (min)	Duration (hr)
Buprenorphine				
IM	0.3	15	60	Up to 6
IV	0.3	Under 15	Under 60	Up to 6
Butorphanol				
IM	2–3	10	30–60	3–4
IV	2–3	2–3	30–60	3–4
Intranasal	2–3	Within 15	60–120	4–5
Nalbuphine				
IM	10	Within 15	60	3–6
IV	10	2–3	30	3–6
SubQ	10	Within 15	60	3–6
Pentazocine				
PO	—	15–30	60–90	3‡
IM	30	15–20	30–60	4–6‡
IV	30	2–3	15–30	4–6‡
SubQ	30	15–20	30–60	4–6‡

TABLE 28-6 Clinical Pharmacology of Opioid Agonists-Antagonists

* IM administration should be avoided whenever possible.

† Dose in milligrams that produces a degree of analgesia equivalent to that produced by a 10-mg IM dose of morphine.

‡ Duration may increase greatly in patients with liver disease.

Pentazocine

Actions and Uses.

Pentazocine [Talwin] was the first agonist-antagonist opioid available and can be considered the prototype for the group. The drug is indicated for mild to moderate pain. Pentazocine is much less effective than morphine against severe pain.

Pentazocine acts as an *agonist* at kappa receptors and as an *antagonist* at mu receptors. By activating kappa receptors, the drug produces analgesia, sedation, and respiratory depression. However, unlike the respiratory depression caused by morphine, *respiratory depression caused by pentazocine is limited:* Beyond a certain dose, no further depression occurs. Because it lacks agonist actions at mu receptors, pentazocine produces little or no euphoria. In fact, at supratherapeutic doses, pentazocine produces unpleasant reactions (anxiety, strange thoughts, nightmares, hallucinations). These psychotomimetic effects may result from activation of kappa receptors. Because of its subjective effects, pentazocine has a low potential for abuse and is classified under Schedule IV.

Adverse effects are generally like those of morphine. However, in contrast to the pure opioid agonists, pentazocine increases cardiac work. Accordingly, a pure agonist (eg, morphine) is preferred to pentazocine for relieving pain in patients with myocardial infarction.

If administered to a patient who is physically dependent on a pure opioid agonist, pentazocine can precipitate withdrawal. Recall that mu receptors mediate physical dependence on pure opioid agonists and that pentazocine acts as an antagonist at these receptors. By blocking access of the pure agonist to mu receptors, pentazocine will prevent receptor activation, thereby triggering withdrawal. Accordingly, *pentazocine and other drugs that block mu receptors should never be administered to a person who is physically dependent on a pure opioid agonist*. If a pentazocine-like agent is to be used, the pure opioid agonist must first be withdrawn.

Physical dependence can occur with pentazocine, but symptoms of withdrawal are generally mild (eg, cramps, fever, anxiety, restlessness). Treatment is rarely required. As with pure opioid agonists, toxicity from pentazocine can be reversed with naloxone.

Preparations, Dosage, and Administration.

Pentazocine is administered orally. A formulation for parenteral use has been withdrawn. Pentazocine [Talwin NX] is formulated in 50-mg tablets that also contain 0.5 mg of naloxone (to prevent abuse). The usual adult dosage is 50 mg every 3 to 4 hours as needed. The drug is also available in combination with aspirin [Talwin Compound] and with acetaminophen [Talacen].

Nalbuphine

Nalbuphine [Nubain] has pharmacologic actions similar to those of pentazocine. The drug is an agonist at kappa receptors and an antagonist at mu receptors. At low doses, nalbuphine has analgesic actions equal to those of morphine. However, as dosage increases, a ceiling to analgesia is reached. As a result, the maximal pain relief that can be produced with nalbuphine is much lower than with morphine. As with pain relief, there is also a ceiling to respiratory depression. Like pentazocine, nalbuphine can cause psychotomimetic reactions. With prolonged treatment, physical dependence can develop. Symptoms of abstinence are less intense than with morphine but more intense than with pentazocine. When used during labor and delivery, nalbuphine has caused serious adverse effects, including bradycardia in the fetus and apnea, cyanosis, and hypotonia in the neonate. Accordingly, use during labor and delivery should be avoided, if possible. Nalbuphine has a low abuse potential and is not regulated under the Controlled Substances Act. As with the pure opioid agonists, toxicity can be reversed with naloxone. Like pentazocine, nalbuphine will precipitate a withdrawal reaction if administered to an individual physically dependent on a pure opioid agonist. Nalbuphine is supplied in solution (10 and 20 mg/mL) for IV, IM, and subQ injection. The usual adult dosage is 10 mg repeated every 3 to 6 hours as needed.

Butorphanol

Butorphanol [Stadol] has actions similar to those of pentazocine. The drug is an agonist at kappa receptors and an antagonist at mu receptors. Analgesic effects are less than those of morphine. As with pentazocine, there is a "ceiling" to respiratory depression. The drug can cause psychotomimetic reactions, but these are rare. Butorphanol increases cardiac work and should not be given to patients with myocardial infarction. Physical dependence can occur, but symptoms of withdrawal are relatively mild. The drug may induce a withdrawal reaction in patients physically dependent on a pure opioid agonist. Butorphanol has a low potential for abuse and is regulated under Schedule IV of the Controlled Substances Act. Toxicity can be reversed with naloxone.

Butorphanol is administered parenterally (IM and IV) and by nasal spray (primarily to treat migraine). The usual adult IV dosage is 1 mg every 3 to 4 hours as needed. The usual IM dosage is 2 mg every 3 to 4 hours as needed. The usual intranasal dosage is 1 mg (1 spray from the metered-dose spray device) repeated in 60 to 90 minutes if needed. The two-dose sequence may then be repeated every 3 to 4 hours as needed.

Buprenorphine

Buprenorphine [Buprenex, Subutex, Suboxone] differs significantly from other opioid agonist-antagonists. The drug is a partial agonist at mu receptors and an antagonist at kappa receptors. Analgesic effects are like those of morphine, but significant tolerance has not been observed. Although buprenorphine can depress respiration, severe respiratory depression has not been reported. Like pentazocine, buprenorphine can precipitate a withdrawal reaction in persons physically dependent on a pure opioid agonist. Psychotomimetic reactions can occur but are rare. Physical dependence develops but symptoms of abstinence are delayed; peak responses may not occur until 2 weeks after the last dose was taken. Prolonged use may pose a risk of liver damage. Buprenorphine is currently classified as a Schedule III substance. In addition to its use for analgesia, buprenorphine is used to treat opioid addiction (see Chapter 39).

Although pretreatment with naloxone can prevent toxicity from buprenorphine, naloxone cannot readily reverse toxicity that has already developed. It appears that buprenorphine binds very tightly to its receptors, and hence cannot be readily displaced by naloxone.

To manage *pain,* buprenorphine [Buprenex] is supplied in solution (0.3 mg/mL) for administration by IM or slow IV injection. The usual dosage for patients age 13 years and older is 0.3 mg repeated every 6 hours as needed.

To manage *opioid addiction,* buprenorphine is available in two sublingual formulations. One [Subutex] contains buprenorphine alone, and the other [Suboxone] contains buprenorphine plus naloxone (see Chapter 39).

CLINICAL USE OF OPIOIDS

Dosing Guidelines

Pain Assessment

Assessment is an essential component of pain management. Pain status should be evaluated prior to opioid administration and about 1 hour after. Unfortunately, because pain is a subjective experience, affected by multiple factors (eg, cultural influences, patient expectations, associated disease), there is no reliable objective method for determining just how much discomfort the patient is feeling. That is, we cannot measure pain with instruments equivalent to those employed to monitor blood pressure, cardiac performance, and other physiologic parameters. As a result, assessment must ultimately be based on the patient's description of his or her experience. Accordingly, you should ask the patient where the pain is located, what type of pain is present (eg, dull, sharp, stabbing), how the pain changes with time, what makes the pain better, and what makes it worse. In addition, you should assess for psychologic factors that can reduce pain threshold (anxiety, depression, fear, anger).

When attempting to assess pain, keep in mind that, on occasion, what the patient says may not accurately reflect his or her experience. For example, a few patients who are pain free may claim to feel pain so as to receive medication for its euphoriant effects. Conversely, some patients may claim to feel fine even though they are experiencing considerable discomfort. Reasons for under-reporting pain include fear of addiction, fear of needles, and a need to be stoic and bear the pain. Patients suspected of under-reporting pain must be listened to with care if their true pain status is to be evaluated.

Pain assessment is discussed at length in Chapter 29 (Pain Management in Patients with Cancer).

Dosage Determination

Dosage of opioid analgesics must be adjusted to accommodate individual variation. "Standard" doses cannot be relied upon as appropriate for all patients. For example, if a "standard" 10-mg dose of morphine were employed for all adults, only 70% would receive adequate relief; the other 30% would be undertreated. Not all patients have the same tolerance for pain, and hence some need larger doses than others for the same disorder. Some conditions hurt more than others. For example, patients recovering from open chest surgery are likely to experience greater pain and need larger doses than patients recovering from an appendectomy. Elderly patients metabolize opioids slowly, and therefore require lower doses than younger adults. Because the blood-brain barrier of newborns is poorly developed, these patients are especially sensitive to opioids; therefore, they generally require smaller doses (on a milligram-per-kilogram basis) than older infants and young children.

Dosing Schedule

As a rule, *opioids should be administered on a fixed schedule* (eg, every 4 hours) rather than PRN. With a fixed schedule, each dose is given before pain returns, thereby sparing the patient needless discomfort. In contrast, when PRN dosing is employed, there can be a long delay between onset of pain and production of relief: Each time pain returns, the patient must call the nurse, wait for the nurse to respond, wait for the nurse to evaluate the pain, wait for the nurse to sign out medication, wait for the nurse to prepare and administer the injection, and then wait for the drug to undergo absorption and finally produce analgesia. This delay causes unnecessary discomfort and creates anxiety about pain recurrence. Use of a fixed dosing schedule reduces these problems. As discussed below, allowing the patient to self-administer opioids with a patient-controlled analgesia (PCA) device can provide even greater protection against pain recurrence than can be achieved by having you administer opioids on a fixed schedule. The differences between PRN dosing, fixed-schedule dosing, and use of a PCA device are shown graphically in Figure 28-3.

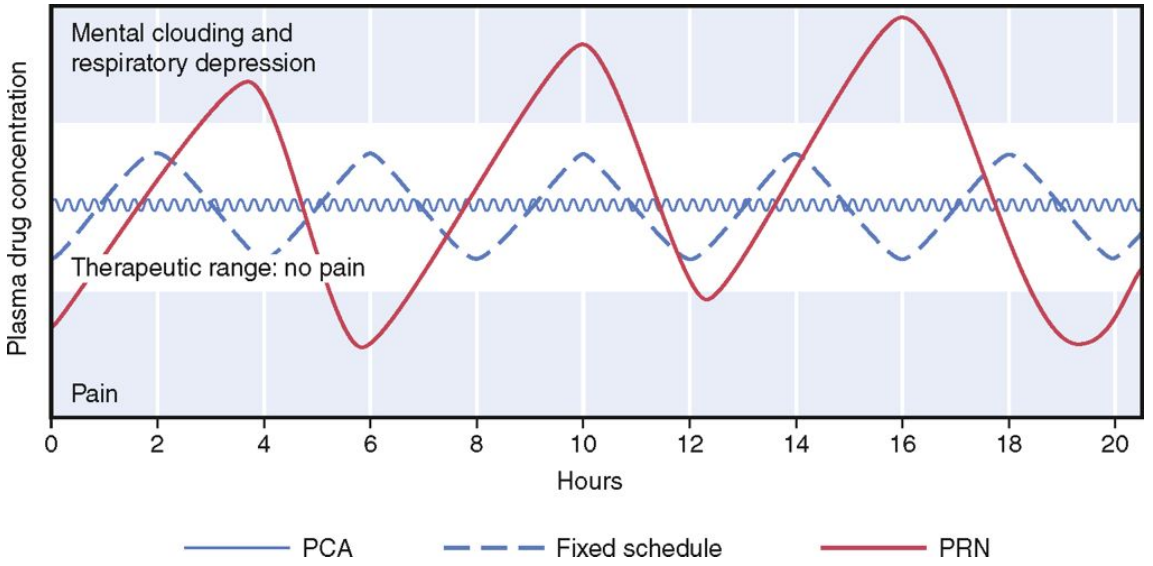


Figure 28-3 Fluctuation in opioid blood levels seen with three dosing procedures. Note that with PRN dosing, opioid levels can fluctuate widely, going from subtherapeutic to excessive and back again. In contrast, when opioids are administered with a PCA device or on a fixed schedule, levels stay within the therapeutic range, allowing continuous pain relief with minimal adverse effects.

Avoiding a Withdrawal Reaction

When opioids are administered in high doses for 20 days or more, clinically significant physical dependence may develop. Under these conditions, abrupt withdrawal will precipitate an abstinence syndrome. To minimize symptoms of abstinence, opioids should be withdrawn slowly, tapering the dosage over 3 days. If the degree of dependence is especially high, as can occur in opioid addicts, dosage should be tapered over 7 to 10 days.

Physical Dependence, Abuse, and Addiction as Clinical Concerns

Most people in our society, including many health professionals, harbor strong fears about the ability of "narcotics" to cause "addiction." In a clinical setting, such excessive concern is both unwarranted and counterproductive.

Because of inappropriate fears, physicians frequently prescribe less pain medication than patients need, and nurses frequently administer less than was prescribed. The result, according to one estimate, is that only 25% of patients receive doses of opioids that are sufficient to relieve suffering. One pain specialist described this unacceptable situation as follows: "The excessive and unrealistic concern about the dangers of addiction in the hospitalized medical patient is a significant and potent force for the undertreatment with narcotics [opioids]."

When treating a patient for pain, you may have to decide how much opioid to give and when to give it. If you are excessively concerned about the ability of opioids to cause physical dependence and addiction, you will be unable to make a rational decision. Furthermore, in your role as patient advocate, it is your responsibility to intervene and request an increase in dosage if the prescribed dosage has proved inadequate. If you fear that dosage escalation may cause "addiction," you are less likely to make the request.

The object of the following discussion is to dispel excessive concerns about dependence, abuse, and addiction in the medical patient so these concerns do not result in undermedication and needless suffering.

Definitions

Before we can discuss the clinical implications of physical dependence, abuse, and addiction, we need to define these terms.

Physical Dependence.

As noted, physical dependence is a state in which an abstinence syndrome will occur if the dependence-producing drug is abruptly withdrawn. *Physical dependence should NOT be equated with addiction*.

Abuse.

Abuse can be broadly defined as *drug use that is inconsistent with medical or social norms*. By this definition, abuse is determined primarily by the reason for drug use and by the setting in which that use occurs—and not by the pharmacologic properties of the drug itself. For example, whereas it is *not* considered abuse to administer 20 mg of morphine in a hospital to relieve pain, it *is* considered

abuse to administer the same dose of the same drug on the street to produce euphoria. The concept of abuse is discussed at length in Chapter 37.

Addiction.

Addiction can be defined as *a behavior pattern characterized by continued use of a psychoactive substance despite physical, psychologic, or social harm*. Note that nowhere in this definition is addiction equated with physical dependence. In fact, physical dependence is not even part of the definition. The concept of addiction is discussed further in Chapter 37.

Although physical dependence is not required for addiction to occur, physical dependence *can* contribute to addictive behavior. If an individual has already established a pattern of compulsive drug use, physical dependence can reinforce that pattern. For the individual with a marginal resolve to discontinue opioid use, the desire to avoid symptoms of withdrawal may be sufficient to promote continued drug use. However, in the presence of a strong desire to become drug free, physical dependence, by itself, is insufficient to motivate continued addictive behavior.

Minimizing Fears About Physical Dependence

For two important reasons, there is little to fear regarding physical dependence on opioids in the hospitalized patient:

- Development of significant physical dependence is extremely rare when opioids are given acutely to relieve pain. For most patients, the doses employed and the duration of treatment are insufficient to cause significant dependence.
- Even when physical dependence *does* occur, patients rarely develop addictive behavior and continue opioid administration after their pain has subsided. The vast majority of patients who become physically dependent in a clinical setting simply go through gradual withdrawal and never take opioids again. This observation emphasizes the point that physical dependence per se is insufficient to cause addiction.

From the preceding, we can see there is little to fear regarding physical dependence during the therapeutic use of opioids. We can conclude, therefore,

that there is no justification for withholding opioids from patients in pain on the basis of concerns about physical dependence.

Minimizing Fears About Addiction

The principal reason for abandoning fears about opioid addiction in patients is simple: *Development of addiction to opioids as a result of clinical exposure to these drugs is extremely rare*. Results of the Boston Collaborative Drug Study showed that, of 12,000 hospitalized patients taking opioids, only 4 became drug abusers. Furthermore, as discussed below, if abuse or addiction *does* occur, it is probable that these behaviors reflect tendencies that existed before the patient entered the hospital, and hence are not the result of inappropriate medical use of opioids during the hospital stay.

For the purpose of this discussion, the population can be divided into two groups: individuals who are prone to drug abuse and individuals who are not. One source estimates that about 8% of the population is prone to drug abuse, whereas the other 92% is not. Individuals who are prone to drug abuse have a tendency to abuse drugs inside the hospital and out. Nonabusers, on the other hand, will not abuse drugs in a clinical setting or anywhere else. Withholding analgesics from abuse-prone individuals is not going to reverse their tendency to abuse drugs. Conversely, administering opioids to non–abuse-prone persons will not convert them into "drug fiends."

If a patient who did not formerly abuse opioids does abuse these drugs following therapeutic exposure, you should not feel responsible for having created an addict. That is, if a patient tries to continue opioid use after leaving the hospital, it is probable that the patient was abuse prone before you met him or her. Therefore, the pattern of abuse that emerged during clinical exposure to opioids was the result of factors that existed before the patient ever entered the hospital—and not the consequence of therapy. The only action that might have prevented opioid abuse by such a patient would have been to withhold opioids entirely—an action that would not have been feasible.

Balancing the Need to Provide Pain Relief with the Desire to Minimize Abuse

Although concerns about opioid abuse in the clinical setting are small, they cannot be dismissed entirely. You are still obliged to administer opioids with discretion in an effort to minimize abuse. Some reasonable attempt must be made to determine who is likely to abuse drugs and who is not. As a rule, distinguishing abusers from nonabusers can be done with some confidence. When nonabusers say they need more pain relief, believe them and provide it. In contrast, when an obvious abuser requests more analgesic, some healthy skepticism is in order. When there is doubt as to whether a patient is abuse prone or not, logic dictates giving the patient the benefit of the doubt and providing the medication. If the patient is an abuser, little harm will result from giving unneeded medication. However, if the patient is a nonabuser, failure to provide medication would intensify suffering for no justifiable reason.

In order to minimize physical dependence and abuse, opioid analgesics should be administered in the lowest effective dosages for the shortest time needed. Be aware, however, that larger doses are needed for patients who have more intense pain and for those who have developed tolerance. As pain diminishes, opioid dosage should be reduced. As soon as possible, the patient should be switched to a nonopioid analgesic, such as aspirin or acetaminophen.

In summary, when working with opioids, as with any other drugs, you must balance the risks of therapy against the benefits. The risk of addiction from therapeutic use of opioids is real but very small. Consequently, concerns about addiction should play a real but secondary role in making decisions about giving these drugs. Dosages should be sufficient to relieve pain. Suffering because of insufficient dosage is unacceptable. However, it is also unacceptable to promote possible abuse through failure to exercise good judgment.

Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) is a method of drug delivery that permits the patient to self-administer parenteral (transdermal, IV, subQ, epidural) opioids on an “as-needed” basis. PCA has been employed primarily for relief of pain in postoperative patients. Other candidates include patients experiencing pain caused by cancer, trauma, myocardial infarction, vaso-occlusive sickle cell crisis, and labor. As discussed below, PCA offers several advantages over opioids administered by the nurse.

PCA Devices.

PCA was made possible by the development of reliable PCA devices. Two kinds are available: traditional PCA pumps and the fentanyl iontophoretic system [Ionsys]. The PCA pumps consist of an electronically controlled infusion pump that can be activated by the patient to deliver a preset bolus dose of an opioid, which is delivered through an indwelling catheter. In addition to providing bolus doses on demand, some PCA pumps can deliver a basal infusion of opioid. As discussed above, the Ionsys device uses iontophoresis, not a pump, to deliver a transdermal dose of opioid (fentanyl).

An essential feature of all PCA pumps is a timing control. This control limits the total dose that can be administered each hour, thereby minimizing the risk of overdose. In addition, the timing control regulates the minimum interval (eg, 10 minutes) between doses. This interval, referred to as the "lock-out" or "delay" interval, prevents the patient from administering a second dose before the first has had time to produce its full effect.

Drug Selection and Dosage Regulation.

The opioid used most extensively for PCA is morphine. Other pure opioid agonists (eg, methadone, hydromorphone, fentanyl) have also been employed, as have agonist-antagonist opioids (eg, nalbuphine, buprenorphine).

Prior to starting PCA, the postoperative patient should be given an opioid loading dose (eg, 2 to 10 mg of morphine). Once effective opioid levels have been established with the loading dose, PCA can be initiated, provided the patient has recovered sufficiently from anesthesia. For PCA with morphine, initial bolus doses of 1 mg are typical. The size of the bolus should be increased if analgesia is inadequate, and decreased if excessive sedation occurs. The size of the bolus dose is usually increased during sleeping hours, thereby promoting rest by prolonging the interval between doses.

Comparison of PCA with Traditional IM Therapy.

The objective of therapy with analgesics is to provide comfort while minimizing sedation and other side effects, especially respiratory depression. This objective is best achieved by maintaining plasma levels of opioids that have

minimal fluctuations. In this manner, side effects from excessively high levels can be avoided, as can the return of severe pain when levels dip too low.

In the traditional management of postoperative pain, patients are given an IM injection of an opioid every 3 to 4 hours. With this dosing schedule, plasma drug levels can vary widely. Shortly after the injection, plasma levels may rise very high, causing excessive sedation and possibly respiratory depression. Late in the dosing interval, pain may return as plasma levels drop to their lowest point.

In contrast to traditional therapy, PCA is ideally suited to maintain steady levels of opioids. Why? Because PCA relies on small doses given frequently (eg, 1 mg of morphine every 10 minutes) rather than on large doses given infrequently (eg, 20 mg of morphine every 3 hours). Maintenance of steady drug levels can be facilitated further if the PCA device is capable of delivering a basal infusion. Because plasma drug levels remain relatively steady, PCA can provide continuous control of pain while avoiding the adverse effects associated with excessive drug levels.

An additional advantage of PCA is rapid relief of pain. Because the patient can self-administer a parenteral dose of opioid as soon as pain begins to return, there is minimal delay between detection of pain and restoration of an adequate drug level. With traditional therapy, the patient must wait for the nurse to respond to a request for more drug; this delay allows pain to grow more intense.

Studies indicate that PCA is associated with accelerated recovery. When compared with patients receiving traditional IM analgesia, postoperative patients receiving PCA show improved early mobilization, greater cooperation during physical therapy, and a shorter hospital stay.

Patient Education.

Patient education is essential for successful PCA. Surgical patients should be educated preoperatively. Education should include an explanation of what PCA is, along with instruction on how to activate the PCA device.

Patients should be told not to fear overdose; the PCA device will not permit self-administration of excessive doses. Patients should be informed that there is a time lag (about 10 minutes) between activation of the device and produc-

tion of maximal analgesia. To reduce discomfort associated with physical therapy, changing of dressings, ambulation, and other potentially painful activities, patients should be taught to activate the pump prophylactically (eg, 10 minutes prior to the anticipated activity). Patients should be informed that, at night, the PCA device will be adjusted to deliver larger doses than during waking hours. This will prolong the interval between doses and thereby facilitate sleep.

Using Opioids for Specific Kinds of Pain

Postoperative Pain.

Opioid analgesics offer several benefits to the postoperative patient. The most obvious is increased comfort through reduction of pain. In addition, by reducing painful sensation, opioids can facilitate early movement and intentional cough. In patients who have undergone thoracic surgery, opioids permit chest movement that would otherwise be too uncomfortable to allow adequate ventilation. By promoting ventilation, opioids can reduce the risk of hypoxia and pneumonitis.

Opioids are not without drawbacks for the postoperative patient. These agents can cause constipation and urinary retention. Suppression of reflex cough can result in respiratory tract complications. In addition, analgesia may delay diagnosis of postoperative complications—because pain will not be present to signal their development.

Obstetric Analgesia.

When administered to relieve pain during delivery, opioids may depress fetal respiration and uterine contractions. Since these effects are less likely with meperidine than with other strong opioids, *meperidine* is often the preferred opioid for obstetric use. Dosage should be high enough to reduce maternal discomfort to a tolerable level, but not so high as to cause pronounced respiratory depression in the neonate. Because opioids cross the blood-brain barrier of the infant more readily than that of the mother, doses that have little effect on maternal respiration may nonetheless cause profound respiratory depression in the infant. For meperidine, the usual dosage is 50 to 100 mg every 2 to 3 hours. Administration should be parenteral (IV or IM). Timing of ad-

ministration is important: if the drug is given too early, it can inhibit or delay the progress of uterine contractions; if given too late, it can cause excessive neonatal sedation and respiratory depression. Following delivery, respiration in the neonate should be monitored closely. Naloxone can reverse respiratory depression and should be on hand.

Myocardial Infarction.

Morphine is the opioid of choice for decreasing pain of myocardial infarction. With careful control of dosage, morphine can reduce discomfort without causing excessive respiratory depression and adverse cardiovascular effects. In addition, by lowering blood pressure, morphine can decrease cardiac work. If excessive hypotension or respiratory depression occurs, it can be reversed with naloxone. Because *pentazocine* and *butorphanol* increase cardiac work and oxygen demand, these agonist-antagonist opioids should generally be avoided.

Head Injury.

Opioids must be employed with caution in patients with head injury. Head injury can cause respiratory depression accompanied by elevation of ICP; opioids can exacerbate these symptoms. In addition, since miosis, mental clouding, and vomiting can be valuable diagnostic signs following head injury, and since opioids can cause these same effects, use of opioids can complicate diagnosis.

Cancer-Related Pain.

Treating chronic pain of cancer differs substantially from treating acute pain of other disorders. When treating cancer pain, the objective is to maximize comfort. Psychologic and physical dependence are minimal concerns. Patients should be given as much medication as needed to relieve pain. In the words of one pain specialist, “No patient should wish for death because of the physician's reluctance to use adequate amounts of opioids.” With proper therapy, cancer pain can be effectively managed in about 90% of patients. Cancer pain is discussed fully in Chapter 29.

Chronic Noncancer Pain.

In many patients with chronic pain of nonmalignant origin, opioids can reduce discomfort, improve mood, and enhance function. Accordingly, pain experts generally recommend that opioids not be withheld from these people. Nonetheless, because of concerns about addiction, tolerance, adverse effects, diversion to street use, and regulatory action, physicians and nurse practitioners are often reluctant to prescribe these drugs. To some degree, all of these concerns are legitimate. However, patients still have a right to effective treatment. Hence there is a need to balance patient's rights with prescribers' concerns. To help achieve that balance, the American Academy of Pain Medicine and the American Pain Society issued guidelines for using opioids in patients with chronic noncancer pain. Provisions include

- Using opioids only after nonopioid analgesics have failed
- Discussing the benefits and risks of long-term opioids with the patient
- When possible, using only one prescriber and one pharmacy
- Ensuring comprehensive follow-up to assess efficacy and side effects of treatment, and to monitor for signs of opioid abuse
- Stopping opioids if they don't work
- Fully documenting the entire process

OPIOID ANTAGONISTS

Opioid antagonists are drugs that block the effects of opioid agonists. Principal uses are treatment of opioid overdose, relief of opioid-induced constipation, reversal of postoperative opioid effects (eg, respiratory depression, ileus), and management of opioid addiction. Five pure antagonists are available: naloxone [Narcan], methylnaltrexone [Relistor], alvimopan [Entereg], nalmefene [Revex], and naltrexone [ReVia, Depade].

Naloxone

Mechanism of Action

Naloxone [Narcan] is a structural analog of morphine that acts as a competitive antagonist at opioid receptors, thereby blocking opioid actions. Naloxone

can reverse most effects of the opioid agonists, including respiratory depression, coma, and analgesia.

Pharmacologic Effects

When administered in the absence of opioids, naloxone has no significant effects. If administered prior to giving an opioid, naloxone will block opioid actions. If administered to a patient who is already receiving opioids, naloxone will reverse analgesia, sedation, euphoria, and respiratory depression. If administered to an individual who is physically dependent on opioids, naloxone will precipitate an immediate withdrawal reaction.

Pharmacokinetics

Naloxone may be administered IV, IM, or subQ. Following IV injection, effects begin almost immediately and persist about 1 hour. Following IM or subQ injection, effects begin within 2 to 5 minutes and persist several hours. Elimination is by hepatic metabolism. The half-life is approximately 2 hours. Naloxone cannot be used orally because of rapid first-pass inactivation.

Therapeutic Uses

Reversal of Opioid Overdose.

Naloxone is the drug of choice for treating overdose with pure opioid agonists. The drug reverses respiratory depression, coma, and other signs of opioid toxicity. Naloxone can also reverse toxicity from agonist-antagonist opioids (eg, pentazocine, nalbuphine). However, the doses required may be higher than those needed to reverse poisoning by pure agonists.

Dosage must be carefully titrated when treating toxicity in opioid addicts. Because the degree of physical dependence in these individuals is usually high, if dosage is excessive, naloxone can transport the patient from a state of poisoning to one of acute withdrawal. Accordingly, treatment should be initiated with a series of small doses rather than one large dose. Because the half-life of naloxone is shorter than that of most opioids, repeated dosing is required until the crisis has passed.

In some cases of accidental poisoning, there may be uncertainty as to whether unconsciousness is due to opioid overdose or to overdose with a general CNS depressant (eg, barbiturate, alcohol, benzodiazepine). When uncertainty exists, naloxone is nonetheless indicated. If the cause of poisoning is a barbiturate or another general CNS depressant, naloxone will be of no benefit—but neither will it cause any harm. If a cumulative dose of 10 mg fails to elicit a response, it is unlikely that opioids are involved, and hence other intoxicants should be suspected.

Reversal of Postoperative Opioid Effects.

Following surgery, naloxone may be employed to reverse excessive respiratory and CNS depression caused by opioids given preoperatively or intraoperatively. Dosage should be titrated with care; the objective is to achieve adequate ventilation and alertness without reversing opioid actions to the point of unmasking pain.

Reversal of Neonatal Respiratory Depression.

When opioids are given for analgesia during labor and delivery, respiratory depression may occur in the neonate. If respiratory depression is substantial, naloxone should be administered to restore ventilation.

Preparations, Dosage, and Administration

Preparations and Routes.

Naloxone [Narcan] is available in solution (0.4 mg/mL) for IV, IM, and subQ injection.

Opioid Overdose.

The initial dose is 0.4 mg for adults and 10 mcg/kg for children. The preferred route is IV. However, if IV administration is not possible, then IM or subQ injection may be employed. Dosing is repeated at 2- to 3-minute intervals until a satisfactory response has been achieved. Additional doses may be needed at 1- to 2-hour intervals for up to 72 hours, depending on the duration of action of the offending opioid.

Postoperative Opioid Effects.

Initial therapy for adults consists of 0.1 to 0.2 mg IV repeated every 2 to 3 minutes until an adequate response has been achieved. Additional doses may be required at 1- to 2-hour intervals.

Neonatal Respiratory Depression.

The initial dose is 10 mcg/kg (IV, IM, or subQ). This dose is repeated every 2 to 3 minutes until respiration is satisfactory.

Other Opioid Antagonists

Methylnaltrexone

Actions and Therapeutic Use.

Methylnaltrexone [Relistor], approved in 2008, is a selective mu opioid antagonist indicated for opioid-induced constipation in patients with late-stage disease who are taking opioids continuously to relieve pain, and who have not responded to standard laxative therapy. Benefits derive from blocking mu opioid receptors in the GI tract. In clinical trials, the drug worked in about half of those treated: within 4 hours of receiving subQ methylnaltrexone, defecation occurred in 48% of patients, compared with only 15% of those receiving placebo. In about 30% of methylnaltrexone recipients, defecation occurred rapidly—within 30 minutes. Because it contains a methyl group, methylnaltrexone cannot readily cross membranes, including those of the blood-brain barrier, and hence does not block opioid receptors in the CNS. Accordingly, the drug does not decrease analgesia and cannot precipitate opioid withdrawal.

Pharmacokinetics.

Methylnaltrexone is rapidly absorbed following subQ injection, reaching peak plasma levels within 30 minutes. Because membrane passage is restricted, distribution of the drug is limited. Methylnaltrexone undergoes minimal metabolism and is excreted in the urine (50%) and feces (50%), primarily as unchanged drug. The terminal half-life is 8 hours.

Adverse Effects, Precautions, and Drug Interactions.

Methylnaltrexone is generally well tolerated. The most common adverse effects are *abdominal pain* (28.5%), *flatulence* (13.3%), *nausea* (11.5%), *dizziness* (4.3%), and *diarrhea* (5.5%). In the event of severe or persistent diarrhea, the drug should be discontinued. In patients with known or suspected mechanical GI obstruction, methylnaltrexone should be avoided. No significant drug interactions have been reported.

Preparations, Dosage, and Administration.

Methylnaltrexone [Relistor] is available in solution (12 mg/0.6 mL) for subQ injection into the upper arm, abdomen, or thigh. Because defecation can occur rapidly, a bathroom should be immediately available. Dosing is usually done once every 48 hours, and should not exceed once every 24 hours. Dosage is based on weight as follows: 8 mg for patients from 38 kg to under 62 kg (84 lb to under 136 lb); 12 mg for patients 62 to 114 kg (136 to 251 lb); and 0.15 mg/kg for patients under 38 kg or over 114 kg. In patients with severe renal impairment, defined as creatinine clearance below 30 mL/min, dosage should be reduced by 50%. Methylnaltrexone should be stored at room temperature and protected from light.

Alvimopan

Like methylnaltrexone, alvimopan [Entereg] is a selective, peripherally acting mu opioid antagonist developed to counteract the adverse effects of opioids on bowel function. At therapeutic doses, alvimopan does not reduce opioid-mediated analgesia, in part because of limited ability to cross the blood-brain barrier. In contrast to methylnaltrexone, which is approved for long-term therapy of constipation in patients taking opioids for chronic pain, alvimopan is approved only for short-term therapy of opioid-induced ileus following partial small or large bowel resection with primary anastomosis. The goal of treatment is to accelerate time to recovery of upper and lower bowel function, which can be impaired by opioids used for analgesia during and after surgery. Alvimopan was approved in 2008.

When used short term in postoperative patients, alvimopan is very well tolerated. However, when used long term in patients taking opioids for chronic

pain, the drug has been associated with an increased incidence of myocardial infarction, although a causal relationship has not been established. Because myocardial infarction may be a risk with prolonged dosing, the drug is approved only for short-term (7-day) use, and only for hospitalized patients. Furthermore, hospitals that dispense the drug must enroll in the Entereg Access Support and Education program, designed to minimize risk of myocardial infarction.

Alvimopan is available in 12-mg capsules for oral dosing. The regimen consists of 12 mg given 0.5 to 5 hours before surgery, followed by 12 mg twice daily (beginning the day after surgery) for a total of 15 or fewer doses.

Naltrexone

Naltrexone [ReVia, Vivitrol] is a pure opioid antagonist approved for opioid and alcohol abuse. In opioid abuse, the objective is to prevent euphoria if the abuser should take an opioid. Since naltrexone can precipitate a withdrawal reaction in persons who are physically dependent on opioids, candidates for treatment must be rendered opioid-free before naltrexone is given. Although naltrexone can block opioid-induced euphoria, the drug does not prevent craving for opioids. As a result, many addicts fail to comply with treatment. Therapy with naltrexone has been considerably less successful than with methadone, a drug that eliminates craving for opioids while blocking euphoria. Use of naltrexone in alcoholism and opioid addiction is discussed further in Chapters 38 and 39, respectively.

When dosage is excessive, naltrexone can cause hepatocellular injury. Accordingly, the drug is contraindicated for patients with acute hepatitis or liver failure. Warn patients about the possibility of liver injury, and advise them to discontinue the drug if signs of hepatitis develop.

Naltrexone is available in two formulations: (1) 50-mg tablets, marketed as *ReVia,* for oral dosing; and (2) an extended-release suspension (380 mg/vial), marketed as *Vivitrol,* for IM dosing. For oral therapy, a typical dosing schedule consists of 100 mg on Monday and Wednesday and 150 mg on Friday. Alternatively, the drug can be administered daily in 50-mg doses. For IM dosing, the usual regimen is 380 mg once a month.

Nalmefene

Uses.

Nalmefene [Revex] is a *long-acting* analog of naltrexone. The drug is approved for reversing postoperative opioid effects and treating opioid overdose. Nalmefene must be used with caution when treating overdose in patients suspected of being opioid dependent, because too much nalmefene could precipitate prolonged withdrawal.

Pharmacokinetics.

Effects begin 2 minutes after IV injection (the usual route) and peak within 5 minutes. Duration of action depends on dosage: Effects may fade within 30 to 60 minutes after a small dose, and may last many hours after a large dose. Most importantly, when nalmefene dosage is adequate, effects persist longer than those of most opioids. Nalmefene undergoes complete but slow hepatic metabolism, followed by renal excretion. The half-life is 11 hours—considerably longer than that of naloxone.

Preparations, Dosage, and Administration.

Nalmefene [Revex] is available in two concentrations. The low concentration (100 mcg/mL), supplied in blue-labeled ampules, is used to reverse postoperative opioid effects. The high concentration (1 mg/mL), supplied in green-labeled ampules, is used for opioid overdose.

The usual route is IV. However, if IV access is impossible, nalmefene may be given IM or subQ. Dosages are the same for all routes. However, with IM or subQ administration, onset is delayed.

For *postoperative* use, the initial dose is 0.25 mcg/kg. This dose is repeated at 2- to 5-minute intervals (for a maximum of four total doses) until the desired degree of opioid reversal has been achieved.

Treatment of *opioid overdose* depends on whether the patient is opioid dependent. If the patient is not dependent, treatment consists of two doses: 0.5 mg/70 kg initially, followed by 1 mg/70 kg 2 to 5 minutes later. If opioid dependency is suspected, a small challenge dose (0.1 mg/70 kg) is given. If the chal-

lenge dose does not precipitate withdrawal, then treatment continues as for patients who are not dependent.

NONOPIOID CENTRALLY ACTING ANALGESICS

Four centrally acting analgesics—tramadol [Ultram], clonidine [Duraclon], ziconotide [Prialt], and dexmedetomidine [Precedex]—relieve pain by mechanisms largely or completely unrelated to opioid receptors. These drugs do not cause respiratory depression, physical dependence, or abuse, and are not regulated under the Controlled Substances Act.

Tramadol

Tramadol [Ultram, Ultram ER] is a moderately strong analgesic with minimal potential for dependence, abuse, or respiratory depression. The drug relieves pain through a combination of opioid and nonopioid mechanisms.

Mechanism of Action.

Tramadol is an analog of codeine that relieves pain in part through weak agonist activity at mu opioid receptors. However, it seems to work primarily by blocking uptake of norepinephrine and serotonin, thereby activating monoaminergic spinal inhibition of pain. Naloxone, an opioid antagonist, only partially blocks tramadol's effects.

Therapeutic Use.

Tramadol is approved for moderate to moderately severe pain. The drug is less effective than morphine and no more effective than codeine combined with aspirin or acetaminophen. Analgesia begins 1 hour after oral dosing, is maximal at 2 hours, and continues for 6 hours.

Pharmacokinetics.

Tramadol is administered by mouth and reaches peak plasma levels in 2 hours. Elimination is by hepatic metabolism and renal excretion. The half-life is 5 to 6 hours.

Adverse Effects.

Tramadol has been used by millions of patients, and serious adverse effects have been rare. The most common side effects are *sedation, dizziness, headache, dry mouth,* and *constipation*. Respiratory depression is minimal. *Seizures* have been reported in over 280 patients, and hence the drug should be avoided in patients with epilepsy and other neurologic disorders. Severe allergic reactions occur rarely.

Drug Interactions.

Tramadol can intensify responses to *CNS depressants* (eg, alcohol, benzodiazepines), and therefore should not be combined with these drugs.

By inhibiting uptake of norepinephrine, tramadol can precipitate a hypertensive crisis if combined with an *MAO inhibitor*. Accordingly, the combination is absolutely contraindicated.

By inhibiting uptake of serotonin, tramadol can cause *serotonin syndrome* in patients taking *drugs that enhance serotonergic transmission*. Among these are selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, MAO inhibitors, and triptans. If these drugs must be combined with tramadol, the patient should be monitored carefully, especially during initial therapy and times of dosage escalation.

Abuse Liability.

Abuse liability is very low, and hence tramadol is not regulated under the Controlled Substances Act. Nonetheless, there have been a few reports of abuse, dependence, withdrawal, and intentional overdose, presumably for subjective effects. Consequently, tramadol should not be given to patients with a history of drug abuse, and the recommended dosage should not be exceeded.

Preparations, Dosage, and Administration.

Tramadol is available alone (as Ultram and Ultram ER) and in combination with acetaminophen (as Ultracet).

Tramadol *alone* is available in two formulations: (1) 50-mg immediate-release (IR) tablets, sold as Ultram; and (2) extended-release tablets (100, 200, and 300 mg), sold as Ultram ER. Dosages are as follows:

- *Immediate-release tablets [Ultram]*—The recommended adult dosage is 50 to 100 mg every 4 to 6 hours as needed, up to a maximum of 400 mg/day. In patients with significant renal or hepatic impairment, the dosing interval should be increased to 12 hours, and the total daily dose should not exceed 200 mg (with renal impairment) or 100 mg (with hepatic impairment).
- *Extended-release tablets [Ultram ER]*—For patients who are not currently taking IR tramadol, the dosage is 100 mg once a day initially, and then titrated every 5 days in 100-mg increments to a maximum of 300 mg once a day. For patients currently taking IR tramadol, the initial once-daily dosage should equal the total daily dosage of IR tramadol (rounded *down* to the nearest 100 mg). Dosage can then be titrated up or down as needed. Extended-release tramadol should not be used by patients with severe hepatic or renal impairment.

Tramadol *combined with acetaminophen* [Ultracet] is indicated for short-term therapy of acute pain. Each tablet contains 37.5 mg tramadol and 325 mg acetaminophen. The recommended dosage is 2 tablets every 4 to 6 hours (but should not exceed 8 tablets/day). Treatment duration should not exceed 5 days.

Clonidine

Clonidine [Duraclon] has two approved applications: treatment of hypertension and relief of severe pain. To relieve pain, clonidine is administered by continuous epidural infusion. To treat hypertension, the drug is given by mouth or as a transdermal patch. Because the antihypertensive pharmacology of clonidine differs dramatically from its analgesic pharmacology, antihypertensive pharmacology is discussed separately (in Chapters 19 and 46. To avoid errors, you should know that the trade name employed for clonidine depends on the application: When used for pain relief, clonidine is marketed as *Duraclon;* when used for hypertension, the drug is marketed as *Catapres*. Clonidine has no abuse potential and is not regulated under the Controlled Substances Act.

Mechanism of Pain Relief.

As discussed in Chapter 19, clonidine is an alpha2-adrenergic agonist. The drug appears to relieve pain by binding to presynaptic and postsynaptic alpha2 receptors in the spinal cord. The result is blockade of nerve traffic in pathways that transmit pain signals from the periphery to the brain. Pain relief is not blocked by opioid antagonists.

Analgesic Use.

Clonidine, in combination with an opioid analgesic, is approved for treating severe cancer pain that cannot be relieved by an opioid alone. Administration is by continuous infusion through an implanted epidural catheter. The drug is more effective against neuropathic pain (electrical, burning, or shooting in nature) than diffuse (unlocalized) visceral pain. Pain relief occurs only in regions innervated by sensory nerves that come from the part of the spinal cord where clonidine is present in high concentration.

Pharmacokinetics.

Clonidine is highly lipid soluble, and hence readily moves from the spinal cord to the blood. About half of each dose undergoes hepatic metabolism. The rest is excreted unchanged in the urine. Because urinary excretion is substantial, dosage should be reduced in patients with significant renal impairment.

Adverse Effects. Hypotension.

The greatest concern is severe hypotension secondary to massive vasodilation. The cause of vasodilation is activation of alpha2 receptors in the CNS. Hypotension is most likely during the first 4 days of treatment—and is most intense following infusion into the upper thoracic region of the spinal cord. Because of the risk of hypotension, vital signs should be monitored closely, especially during the first few days of treatment. Hypotension can be managed by infusing IV fluids. If necessary, IV ephedrine can be used to promote vasoconstriction.

Bradycardia.

Clonidine can slow heart rate. The underlying mechanism is activation of alpha2 receptors in the CNS. Severe bradycardia can be managed with atropine.

Rebound Hypertension.

As discussed in Chapter 19, abrupt discontinuation of clonidine can cause rebound hypertension. Accordingly, when the drug is withdrawn, dosage should be tapered over 2 to 4 days. Rebound hypertension can be managed with IV clonidine or phentolamine.

Catheter-Related Infection.

Infection is common with implanted epidural catheters. If the patient develops a fever of unknown origin, infection should be suspected.

Other Adverse Effects.

As with oral clonidine, epidural clonidine can cause *dry mouth, dizziness, sedation, anxiety,* and *depression*.

Contraindications.

Because of the risk of severe hypotension and bradycardia, epidural clonidine is contraindicated for patients who are hemodynamically unstable, and for obstetric, postpartum, or surgical patients. Additional contraindications are infection at the site of infusion, administration above the C4 dermatome, and use by patients receiving anticoagulants.

Preparations, Dosage, and Administration.

Clonidine [Duraclon] is available in 10-mL vials containing 100 or 500 mcg/mL. The drug is administered through an implanted epidural catheter using a continuous infusion device. The initial infusion rate is 30 mcg/hr.

Ziconotide

Ziconotide [Prialt], approved in 2004, is a centrally acting analgesic with a novel structure and mechanism. Administration is intrathecal (IT). The drug is indicated only for severe, chronic pain in patients for whom IT therapy is warranted, and who are intolerant of or refractory to other treatments, including systemic and IT morphine. In clinical trials, analgesic responses were modest (at least in opioid-resistant patients), and adverse effects (eg, hallucin-

ations, confusion, muscle injury) were common. Accordingly, ziconotide cannot be considered a first-choice drug.

Mechanism of Action.

Ziconotide is a small synthetic peptide equivalent to a peptide found naturally in *Conus magus,* a marine snail. The drug is a selective antagonist at N-type voltage-sensitive calcium channels on neurons. Benefits derive from blocking calcium channels on primary nociceptive afferent neurons in the dorsal horn of the spinal cord, an action that prevents transmission of pain signals from the periphery to the brain. To maximize analgesia and minimize effects on peripheral nerves, ziconotide must be administered by IT infusion. The drug does not interact with opioid receptors, and does not cause tolerance, physical dependence, or respiratory depression. Abrupt discontinuation does not cause a withdrawal syndrome.

Clinical Trials.

Ziconotide was evaluated in three randomized, placebo-controlled trials involving patients with severe, intractable pain. In all three trials, pain relief was modest. In one trial, for example, patients had severe pain that was unresponsive to IT morphine, IT clonidine, and/or IT bupivacaine. At baseline, mean pain scores were 81, as measured with a Visual Analog Scale of Pain Intensity (where 100 mm equals the worst pain possible and 0 mm equals no pain). Patients were randomized to receive IT ziconotide or IT placebo. The result? At the end of 3 weeks, the mean improvement in pain scores was only 12% in the ziconotide group, compared with 5% in the placebo group. Only 16% of ziconotide recipients improved by 30% or more, and nearly 50% did not respond at all. Keep in mind, however, that none of these patients responded to IT morphine either. Hence, before concluding that ziconotide is not very effective, it would be nice to see if the drug works well in patients who *do* respond to morphine.

Pharmacokinetics.

Following IT infusion, ziconotide distributes throughout the cerebrospinal fluid (CSF) and spinal cord, and then undergoes transport to the systemic circulation, followed by uptake into most tissues of the body, where it undergoes

cleavage by peptidases at multiple sites on the molecule. The resulting fragments have not been identified, nor has their biologic activity been assessed. Little or no proteolytic cleavage takes place in the CSF or blood. The drug's half-life in CSF is 4.6 hours.

Adverse Effects.

Adverse CNS effects—mainly cognitive impairment and psychiatric symptoms—are common. In clinical trials, patients reported the following cognitive effects: *confusion* (33%), *memory impairment* (22%), *speech impairment* (14%), *aphasia* (12%), and *abnormal thinking* (8%). As a rule, these resolved within 2 weeks after stopping treatment. The most common psychiatric effect—*hallucinations*—developed in 12% of patients. Ziconotide can also cause *paranoid reactions* and *depression*. Patients with a history of psychiatric disorders should probably avoid this drug.

Ziconotide can cause *muscle injury*. In clinical trials, 40% of patients had abnormally high serum levels of creatine kinase (CK), a marker for muscle breakdown. However, serious muscle pain, soreness, or weakness was uncommon. Because of the risk of muscle injury, serum CK should be monitored. In patients with high CK levels combined with symptoms of muscle injury, the prescriber should consider reducing ziconotide dosage or discontinuing treatment.

Drug Interactions.

Formal studies on drug interactions have not been conducted. However, given that ziconotide is a peptide that is not metabolized by CYP450 enzymes, the drug is unlikely to affect the disposition of most other drugs, which *are* metabolized by CYP450 enzymes. Combined use with CNS depressants may increase the risk of adverse CNS events, such as dizziness and confusion. Combined use with *systemic* opioids appears safe, but combined use with *intrathecal* opioids is not recommended.

Preparations, Dosage, and Administration.

Ziconotide [Prialt] is available in single-use vials (25 and 100 mcg/mL) for IT infusion using a programmable microinfusion device, either external or implanted. The initial infusion rate is 0.1 mcg/hr (2.4 mcg/day). The rate may be

gradually increased in steps of 0.1 mcg/hr every 2 to 3 days, up to a maximum of 0.8 mcg/hr (19.2 mcg/day) at the end of 3 weeks. Dosage adjustments are based on pain relief and tolerability of side effects.

Dexmedetomidine

Actions and Therapeutic Use.

Dexmedetomidine [Precedex], like clonidine, is a selective alpha*2*-adrenergic agonist. The drug acts in the CNS to cause sedation and analgesia. At this time dexmedetomidine is approved only for short-term sedation in critically ill patients who are initially intubated and undergoing mechanical ventilation. However, in addition to this approved use, the drug has a variety of off-label uses, including enhancement of sedation and analgesia in patients undergoing general anesthesia. In contrast to clonidine, which is administered by epidural infusion, dexmedetomidine is administered by IV infusion.

Pharmacokinetics.

With IV infusion, dexmedetomidine undergoes wide distribution to tissues. In the blood, the drug is 94% protein bound. Dexmedetomidine undergoes rapid and complete hepatic metabolism, followed by excretion in the urine. The elimination half-life is 2 hours.

Adverse Effects.

The most common adverse effects are *hypotension* and *bradycardia*. The mechanism is activation of alpha*2*-adrenergic receptors in the CNS and periphery, which results in decreased release of norepinephrine from sympathetic neurons innervating the heart and blood vessels. If these cardiovascular effects are too intense, they can managed in several ways, including (1) decreasing or stopping the infusion, (2) infusing fluid, (3) and elevating the lower extremities. Giving a muscarinic antagonist (eg, atropine) can increase heart rate.

Additional adverse effects include *nausea, dry mouth,* and *transient hypertension*. Importantly, dexmedetomidine does *not* cause respiratory depression.

Drug Interactions.

Dexmedetomidine can enhance the actions of anesthetics, sedatives, hypnotics, and opioids. Excessive CNS depression can be managed by reducing the dosage of dexmedetomidine or the other agents.

Preparations, Dosage, and Administration.

Dexmedetomidine [Precedex] is supplied in solution (100 mcg/mL), which must be diluted to 4 mcg/mL prior to use. Administration is by IV infusion. Treatment consists of a loading dose (1 mcg/kg infused over 10 minutes) followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr for no more than 24 hours.

KEY POINTS

- Analgesics are drugs that relieve pain without causing loss of consciousness.
- Opioids are the most effective analgesics available.
- There are three major classes of opioid receptors, designated mu, kappa, and delta.
- Morphine and other pure opioid agonists relieve pain by mimicking the actions of endogenous opioid peptides—primarily at mu receptors, and partly at kappa receptors.
- Opioid-induced sedation and euphoria can complement pain relief.
- Because opioids produce euphoria and other desirable subjective effects, they have a high liability for abuse.
- Respiratory depression is the most serious adverse effect of the opioids.
- Other important adverse effects are constipation, urinary retention, orthostatic hypotension, emesis, and elevation of ICP.
- Because of first-pass metabolism, oral doses of morphine must be larger than parenteral doses to produce equivalent analgesic effects.
- Because the blood-brain barrier is poorly developed in infants, these patients need smaller doses of opioids (adjusted for body weight) than do older children and adults.

- With prolonged opioid use, tolerance develops to analgesia, euphoria, sedation, and respiratory depression, but not to constipation and miosis.
- Cross-tolerance exists among the various opioid agonists, but not between opioid agonists and general CNS depressants.
- With prolonged opioid use, physical dependence develops. An abstinence syndrome will occur if the opioid is abruptly withdrawn.
- In contrast to the withdrawal syndrome associated with general CNS depressants, the withdrawal syndrome associated with opioids, although unpleasant, is not dangerous.
- To minimize symptoms of abstinence, opioids should be withdrawn gradually.
- Precautions to opioid use include pregnancy, labor and delivery, head injury, and decreased respiratory reserve.
- Patients taking opioids should avoid alcohol and other CNS depressants—because these drugs can intensify opioid-induced sedation and respiratory depression.
- Patients taking opioids should avoid anticholinergic drugs (eg, antihistamines, tricyclic antidepressants, atropine-like drugs)—because these drugs can exacerbate opioid-induced constipation and urinary retention.
- Opioid overdose produces a classic triad of signs: coma, respiratory depression, and pinpoint pupils.
- All strong opioid agonists are essentially equal to morphine with regard to analgesia, abuse liability, and respiratory depression.
- Use of meperidine [Demerol] should not exceed 48 hours—so as to avoid accumulation of normeperidine, a toxic metabolite.
- Like morphine, codeine and other moderate to strong opioid agonists produce analgesia, sedation, euphoria, respiratory depression, constipation, urinary retention, cough suppression, and miosis. These drugs differ from morphine in that they produce less analgesia and respiratory depression and have a lower potential for abuse.

- The combination of codeine with a nonopioid analgesic (eg, aspirin, acetaminophen) produces greater pain relief than can be achieved with either agent alone.
- Most agonist-antagonist opioids act as agonists at kappa receptors and antagonists at mu receptors.
- Pentazocine and other agonist-antagonist opioids produce less analgesia than morphine and have a lower potential for abuse.
- With agonist-antagonist opioids, there is a ceiling to respiratory depression.
- If given to a patient who is physically dependent on pure opioid agonists, an agonist-antagonist will precipitate withdrawal.
- Pure opioid antagonists act as antagonists at mu receptors and at kappa receptors.
- Naloxone and other pure opioid antagonists can reverse respiratory depression, coma, analgesia, and most other effects of pure opioid agonists. The only exception is methylnaltrexone, which doesn't cross the blood-brain barrier.
- Pure opioid antagonists are used primarily to treat opioid overdose. One agent—methylnaltrexone—is used for opioid-induced constipation, and another—alvimopan—for opioid-induced ileus.
- If administered in excessive dosage to an individual who is physically dependent on opioid agonists, naloxone will precipitate an immediate withdrawal reaction.
- Opioid dosage must be individualized. Patients with a low tolerance to pain or with extremely painful conditions need high doses. Patients with sharp, stabbing pain need higher doses than patients with dull pain. Elderly adults generally require lower doses than younger adults. Neonates require relatively low doses.
- As a rule, opioids should be administered on a fixed schedule (with supplemental doses for breakthrough pain) rather than PRN.
- Most PCA devices are electronically controlled pumps that can be activated by the patient to deliver a preset dose of opioid through an indwelling catheter. Some PCA devices also deliver a basal opioid infusion.

- PCA devices provide steady plasma drug levels, thereby maintaining continuous pain control while avoiding unnecessary sedation and respiratory depression.
- Use of parenteral opioids during delivery can suppress uterine contractions and cause respiratory depression in the neonate.
- Addiction is a behavior pattern characterized by continued use of a psychoactive substance despite physical, psychologic, or social harm. Physical dependence and addiction are not the same.
- Abuse is defined as drug use that is inconsistent with medical or social norms.
- Because of excessive and inappropriate fears about addiction and abuse, physicians frequently prescribe less pain medication than patients need, and nurses frequently administer less medication than was prescribed.
- Please! Dispel your concerns about abuse and addiction and give your patients the medication they need to relieve suffering. That's what opioids are for, after all.

Summary of Major Nursing Implications*

PURE OPIOID AGONISTS

Alfentanil

Codeine

Fentanyl

Hydrocodone

Hydromorphone

Levorphanol

Meperidine

Methadone

Morphine

Oxycodone

Oxymorphone

Propoxyphene

Remifentanil

Sufentanil

Preadministration Assessment

Therapeutic Goal

Relief or prevention of moderate to severe pain while causing minimal respiratory depression, constipation, urinary retention, and other adverse effects.

Baseline Data

Pain Assessment.

Assess pain before administration and 1 hour later. Determine the location, time of onset, and quality of pain (eg, sharp, stabbing, dull). Also, assess for psychologic factors that can lower pain threshold (anxiety, depression, fear, anger). Because pain is subjective and determined by multiple factors (eg, cultural influences, patient expectations, associated disease), there is no reliable objective method for determining how much discomfort the patient is experiencing. Ultimately, you must rely on your ability to interpret what patients have to say about their pain. When listening to patients, be aware that a few may claim discomfort when their pain is under control, and others may claim to feel fine when they actually hurt.

Vital Signs.

Prior to administration, determine respiratory rate, blood pressure, and pulse rate.

Identifying High-Risk Patients

All opioids are *contraindicated* for premature infants (both during and after delivery). *Morphine* is *contraindicated* following biliary tract surgery. *Meperidine* is *contraindicated* for patients taking MAO inhibitors.

Use opioids with *caution* in patients with head injury, profound CNS depression, coma, respiratory depression, pulmonary disease (eg, emphysema, asthma), cardiovascular disease, hypotension, reduced blood volume, prostatic hypertrophy, urethral stricture, and liver impairment. *Caution* is also required when treating infants, elderly or debilitated patients, and patients receiving MAO inhibitors, CNS depressants, anticholinergic drugs, and hypotensive agents.

Implementation: Administration

Routes

Oral, IM, IV, subQ, rectal, epidural, intrathecal, transdermal (fentanyl), and transmucosal (fentanyl). Routes for specific opioids are summarized in Tables 28-5 and 28-6.

Dosage

General Guidelines.

Adjust dosage to meet individual needs. Higher doses are required for patients with low pain tolerance or with especially painful conditions. Patients with sharp, stabbing pain need higher doses than patients with dull, constant pain. Elderly patients generally require lower doses than younger adults. Neonates require relatively low doses because the blood-brain barrier is poorly developed. For all patients, dosage should be reduced as pain subsides.

Oral doses are larger than parenteral doses. Check to ensure that the dose is appropriate for the intended route.

Tolerance may develop with prolonged treatment, necessitating dosage escalation.

Warn outpatients not to increase dosage without consulting the prescriber.

Dosage in Patients with Cancer.

Cancer is the principal disease for which opioids are used chronically. The objective is to maximize comfort. Physical dependence is a minor concern. Cancer patients should receive opioids on a fixed schedule around-the-clock—not PRN. If breakthrough pain occurs, fixed dosing should be supplemented PRN with a short-acting opioid. Because of tolerance to opioids or intensification of pain, dosage escalation may be required. Hence, patients should be re-evaluated on a regular basis to determine if pain control is adequate.

Discontinuing Opioids.

Although significant dependence in hospitalized patients is rare, it can occur. To minimize symptoms of abstinence, withdraw opioids slowly, tapering the dosage over 3 days. **Warn outpatients against abrupt discontinuation of treatment.**

Administration

Prior to administration, determine respiratory rate, blood pressure, and pulse rate. Withhold medication and notify the prescriber if respiratory rate is at or below 12 breaths per minute, if blood pressure is significantly below the pretreatment value, or if pulse rate is significantly above or below the pretreatment value.

As a rule, opioids should be administered on a fixed schedule, with supplemental doses as needed.

Perform IV injections slowly (over 4 to 5 minutes). Rapid injection may produce severe adverse effects (profound hypotension, respiratory arrest, cardiac arrest) and should be avoided. When making an IV injection, have an opioid antagonist (eg, naloxone) and facilities for respiratory support available.

Perform injections (especially IV) with the patient lying down to minimize hypotension.

Warn patients using fentanyl patches to avoid exposing the patch to direct heat (eg, heating pad, hot tub) because doing so can accelerate fentanyl release.

Opioid agonists are regulated under the Controlled Substances Act and must be dispensed accordingly. All of the pure agonists are Schedule II substances, except propoxyphene (Schedule IV) and hydrocodone (Schedule III).

Concern for Opioid Abuse as a Factor in Dosage and Administration

Although opioids have a high potential for abuse, abuse is rare in the clinical setting. Consequently, when balancing the risk of abuse against the need to relieve pain, do not give excessive weight to concerns about abuse. The patient must not be allowed to suffer because of your unwarranted fears about abuse and dependence.

Although abuse is rare in the clinical setting, it can occur. To keep abuse to a minimum: (1) exercise clinical judgment when interpreting requests for opioid doses that seem excessive, (2) use opioids in the lowest effective doses for the shortest time required, (3) reserve opioid analgesics for patients with moderate to severe pain, and (4) switch to a nonopioid analgesic when the intensity of pain no longer justifies an opioid.

Responses to analgesics can be reinforced by nondrug measures, such as positioning the patient comfortably, showing concern and interest, and reassuring the patient that the medication will provide relief. Rest, mood elevation, and diversion can raise pain threshold and should be promoted. Conversely, anxiety, depression, fatigue, fear, and anger can lower pain threshold and should be minimized.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Evaluate for pain control 1 hour after opioid administration. If analgesia is insufficient, consult the physician about an increase in dosage. Patients taking opioids chronically for suppression of cancer pain should be re-evaluated on a regular basis to determine if dosage is adequate.

Minimizing Adverse Effects

Respiratory Depression.

Monitor respiration in all patients. If respiratory rate is 12 breaths per minute or less, withhold medication and notify the prescriber. **Warn outpatients about respiratory depression and instruct them to notify the prescriber if respiratory distress occurs.**

Certain patients, including the very young, the elderly, and those with respiratory disease (eg, asthma, emphysema), are especially sensitive to respiratory depression and must be monitored closely.

Delayed respiratory depression may develop following spinal administration of morphine. Be alert to this possibility.

When employed during labor and delivery, opioids may cause respiratory depression in the neonate. Monitor the infant closely. Have naloxone available to reverse opioid toxicity.

Sedation.

Inform patients that opioids may cause drowsiness. Warn them against doing hazardous activities (eg, driving) if sedation is significant. Sedation can be minimized by (1) using smaller doses given more frequently, (2) using opioids with short half-lives, and (3) giving small doses of a CNS stimulant (methylphenidate or dextroamphetamine) in the morning and early afternoon.

Orthostatic Hypotension.

Monitor blood pressure and pulse rate. **Inform patients about symptoms of hypotension (dizziness, lightheadedness), and advise them to sit or lie down if these occur. Inform patients that hypotension can be minimized by moving slowly when assuming an erect posture. Warn patients against walking if hypotension is significant.** If appropriate, assist hospitalized patients with ambulation.

Constipation.

The risk of constipation can be reduced by maintaining physical activity, increasing intake of fiber and fluids, and prophylactic treatment with a stimulant laxative (eg, bisacodyl) plus a stool softener (eg, docusate). Methylnal-

trexone, an opioid antagonist, may help too. Severe constipation can be managed with an osmotic laxative (eg, sodium phosphate).

Urinary Retention.

To evaluate urinary retention, monitor intake and output, and palpate the lower abdomen for bladder distention every 4 to 6 hours. If there is a change in intake/output ratio, if bladder distention is detected, or if the patient reports difficulty voiding, notify the prescriber. Catheterization may be required. Difficulty with voiding is especially likely in patients with prostatic hypertrophy.

Because opioids may suppress awareness of bladder stimuli, encourage patients to void every 4 hours.

Biliary Colic.

By constricting the common bile duct, morphine can increase pressure within the biliary tract, thereby causing severe pain. Biliary colic may be less pronounced with meperidine.

Emesis.

Initial doses of opioids may cause nausea and vomiting. These reactions can be minimized by pretreatment with an antiemetic (eg, promethazine) and by having the patient remain still. Tolerance to emesis develops quickly.

Cough Suppression.

Cough suppression may result in accumulation of secretions in the airway. **Instruct patients to cough at regular intervals. Auscultate the lungs for rales.**

Miosis.

Miosis can impair vision in dim light. Keep hospital room lighting bright during waking hours.

Neurotoxicity.

Neurotoxicity—delirium, agitation, myoclonus, hyperalgesia—can develop with prolonged high-dose therapy. Symptoms can be reduced with hydration, dose reduction, and opioid rotation.

Opioid Dependence in the Neonate.

The infant whose mother abused opioids during pregnancy may be born drug dependent. Observe the infant for signs of withdrawal (eg, excessive crying, sneezing, tremor, hyperreflexia, fever, diarrhea) and notify the physician if these develop (usually within a few days after birth). The infant can be weaned from drug dependence by administering dilute paregoric in progressively smaller doses.

Minimizing Adverse Interactions

CNS Depressants.

Opioids can intensify responses to other CNS depressants (eg, barbiturates, benzodiazepines, alcohol, antihistamines), thereby presenting a risk of profound sedation and respiratory depression. **Warn patients against use of alcohol and other depressants.**

Agonist-Antagonist Opioids.

These drugs (eg, pentazocine, nalbuphine) can precipitate an abstinence syndrome if administered to a patient who is physically dependent on a pure opioid agonist. Before administering an agonist-antagonist, make certain the patient has been withdrawn from opioid agonists.

Anticholinergic Drugs.

These agents (eg, atropine-like drugs, tricyclic antidepressants, phenothiazines, antihistamines) can exacerbate opioid-induced constipation and urinary retention.

Hypotensive Drugs.

Antihypertensive agents and other drugs that lower blood pressure can exacerbate opioid-induced orthostatic hypotension.

Opioid Antagonists.

Opioid antagonists (eg, naloxone) can precipitate an abstinence syndrome if administered in excessive dosage to a patient who is physically dependent on opioids. To avoid this problem, carefully titrate the dosage of the antagonist.

MAO Inhibitors.

Combining *meperidine* with an MAO inhibitor can cause delirium, hyperthermia, rigidity, convulsion, coma, and death. Obviously, the combination must be avoided.

CYP3A4 Inhibitors.

Inhibitors of CYP3A4 (eg, ritonavir, ketoconazole) can increase levels of *fentanyl,* thereby posing a risk of fatal respiratory depression. Monitor patients using this combination with care.

AGONIST-ANTAGONIST OPIOIDS

Buprenorphine

Butorphanol

Nalbuphine

Pentazocine

Except for the differences presented below, the nursing implications for these drugs are much like those for the pure opioid agonists.

Therapeutic Goal

Relief of moderate to severe pain.

Routes

Oral, IV, IM, subQ, and intranasal *(butorphanol)*. Routes for individual agents are summarized in Table 28-6.

Differences from Pure Opioid Agonists

Maximal pain relief with the agonist-antagonists is generally lower than with pure opioid agonists.

Most agonist-antagonists have a ceiling to respiratory depression, thereby minimizing concerns about insufficient oxygenation.

Agonist-antagonists cause little euphoria. Hence, abuse liability is low.

Agonist-antagonists increase cardiac work and should not be given to patients with acute myocardial infarction.

Because of their antagonist properties, agonist-antagonists can precipitate an abstinence syndrome in patients physically dependent on opioid agonists. Accordingly, patients must be withdrawn from pure opioid agonists before receiving an agonist-antagonist.

NALOXONE

Therapeutic Goal

Reversal of postoperative opioid effects, opioid-induced neonatal respiratory depression, and overdose with pure opioid agonists.

Routes

Intravenous, IM, and subQ. For initial treatment, administer IV. Once opioid-induced CNS depression and respiratory depression have been reversed, IM or subQ administration may be employed.

Dosage

Titrate dosage carefully. In opioid addicts, excessive doses can precipitate withdrawal. In postoperative patients, excessive doses can unmask pain by reversing opioid-mediated analgesia.

29 Pain Management in Patients with Cancer

Our topic for this chapter—cancer pain management—is of note both for its good news and bad news. The good news is that pain can be relieved with simple interventions in 90% of cancer patients. The bad news is that, despite the availability of effective treatments, pain goes unrelieved far too often. Multiple factors contribute to undertreatment (Table 29-1). Important among these are inadequate prescriber training in pain management; unfounded fears of addiction (shared by prescribers, patients, and families); and a healthcare system that focuses more on treating disease than relieving suffering.

Pain has a profound impact on both the patient and family. Pain undermines quality of life for the patient and puts a heavy burden on the family. Unrelieved pain compromises the patient's ability to work, enjoy leisure activities, and fulfill his or her role in the family and in society at large. Furthermore, pain can impede recovery, hasten death from cancer, and possibly even create a risk of suicide.

Every patient has the right to expect that pain management will be an integral part of treatment throughout the course of his or her disease. The goal is to minimize pain and thereby maintain a reasonable quality of life, including the ability to function at work and at play, and within the family and society. In addition, if the cancer is incurable, treatment should permit the patient a relatively painless death when that time comes.

TABLE 29-1 Barriers to Cancer Pain Management

Barriers Related to Healthcare Professionals

Inadequate knowledge of pain management

Poor assessment of pain

Concerns stemming from regulations on controlled substances

Fear of patient addiction

Concern about side effects of analgesics

Concern about tolerance to analgesics

Barriers Related to Patients

Reluctance to report pain

Fear of distracting physicians from treating the cancer

Fear that pain means the cancer is worse

Concern about not being a "good" patient

Reluctance to take pain medication

Fear of addiction or being thought of as an addict

Worries about unmanageable side effects

Concern about becoming tolerant to pain medications

Inability to pay for treatment

Barriers Related to the Healthcare System

Low priority given to cancer pain management

Inadequate reimbursement: The most appropriate treatment may not be reimbursed

Restrictive regulation of controlled substances

Treatment is unavailable or access is limited

PATHOPHYSIOLOGY OF PAIN

What Is Pain?

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Note that, by this definition, pain is not simply a sensory experience resulting from activation of pain receptors. Rather, it also includes the patient's emotional and cognitive responses to both the sensation of pain and the underlying cause (eg, tissue damage caused by cancer). Most importantly, we must appreciate that pain is inherently *personal and subjective*. Hence, when assessing pain, the most reliable method is to have the patient describe his or her experience.

Neurophysiologic Basis of Painful Sensations

The following discussion is a simplified version of how we perceive pain. Nonetheless, it should be adequate as a basis for understanding the interventions used for pain relief.

Sensation of pain is the net result of activity in two opposing neuronal pathways. The first pathway carries pain impulses from their site of origin to the brain, and thereby generates pain sensation. The second pathway, which originates in the brain, suppresses impulse conduction along the first pathway, and thereby diminishes pain sensation.

Pain impulses are initiated by activation of pain receptors, which are simply free nerve endings. These receptors can be activated by three types of stimuli: mechanical (eg, pressure), thermal, and chemical (eg, bradykinin, serotonin, histamine). In addition, *prostaglandins* and *substance P* can enhance the sensitivity of pain receptors to activation, although these compounds do not activate pain receptors directly.

Conduction of pain impulses from the periphery to the brain occurs by way of a multineuron pathway. The first neuron carries impulses from the periphery to a synapse in the spinal cord, where it releases either *glutamate* or *substance P* as a transmitter. The next neuron carries the impulse up the cord to a synapse in the thalamus. And the next neuron carries impulses from the thalamus to the cerebral cortex.

The brain is able to suppress pain conduction using endogenous opioid compounds, especially *enkephalins* and *beta-endorphin*. These compounds are released at synapses in the brain and spinal cord. Release within the spinal cord is controlled by a descending neuronal pathway that originates in the brain. The opioids that we give as drugs (eg, morphine) produce analgesia by activating the same receptors that are activated by this endogenous pain-suppressing system.

Nociceptive Pain Versus Neuropathic Pain

In patients with cancer, pain has two major forms, referred to as *nociceptive* and *neuropathic*. Nociceptive pain results from injury to *tissues,* whereas neuropathic pain results from injury to *peripheral nerves*. These two forms of pain respond differently to analgesic drugs. Accordingly, it is important to differenti-

ate between them. Among cancer patients, nociceptive pain is more common than neuropathic pain.

Nociceptive pain has two forms, known as *somatic* and *visceral*. Somatic pain results from injury to somatic tissues (eg, bones, joints, muscles), whereas visceral pain results from injury to visceral organs (eg, small intestine). Patients generally describe somatic pain as localized and sharp. In contrast, they describe visceral pain as vaguely localized with a diffuse, aching quality. Both forms of nociceptive pain respond well to *opioid analgesics* (eg, morphine). In addition, they may respond to *nonopioids* (eg, ibuprofen).

Neuropathic pain produces different sensations than nociceptive pain and responds to a different group of drugs. Patients describe neuropathic pain with such words as "burning," "shooting," "jabbing," "tearing," "numb," "dead," and "cold." Unlike nociceptive pain, neuropathic pain responds poorly to opioid analgesics. However, it does respond to drugs known collectively as *adjuvant analgesics*. Among these are certain antidepressants (eg, imipramine), anticonvulsants (eg, carbamazepine, gabapentin), and local anesthetics/antidysrhythmics (eg, lidocaine).

Pain in Cancer Patients

Among patients with cancer, pain can be caused by the cancer itself and by therapeutic interventions. Cancer can cause pain through direct invasion of surrounding tissues (eg, nerves, muscles, visceral organs) and through metastatic invasion at distant sites. Metastases to bone are very common, causing pain in up to 50% of patients. Cancer can cause neuropathic pain through infiltration of nerves, and visceral pain through infiltration, obstruction, and compression of visceral structures.

The incidence and intensity of cancer-induced pain is a function of cancer type and the stage of disease progression. Among patients with advanced disease, about 75% experience significant pain. Of these, 40% to 50% report moderate to severe pain, and 25% to 30% report very severe pain.

Therapeutic interventions—especially chemotherapy, radiation, and surgery—cause significant pain in at least 25% of patients, and probably more. Chemotherapy can cause painful mucositis, diffuse neuropathies, and aseptic necrosis of joints. Radiation can cause osteonecrosis, chronic visceral pain,

and peripheral neuropathy (secondary to causing fibrosis of nerves). Surgery can cause a variety of pain syndromes, including phantom limb syndrome and postmastectomy syndrome.

MANAGEMENT STRATEGY

Management of cancer pain is an ongoing process that involves repeating cycles of assessment, intervention, and reassessment. The goal is to create and implement a flexible treatment plan that can meet the changing needs of the individual patient. The flow chart in Figure 29-1 summarizes the steps involved. Management begins with a comprehensive assessment. Once the nature of the pain has been determined, a treatment modality is selected. Analgesic drugs are preferred, and hence are usually tried first. If drugs are ineffective, other modalities can be implemented. Among these are radiation, surgery, and nerve blocks. After each intervention, pain is reassessed. Once relief has been achieved, the effective intervention is continued, accompanied by frequent reassessments. If severe pain returns or new pain develops, a new comprehensive assessment should be performed—followed by appropriate interventions and reassessment. Throughout this process, the healthcare team should make every effort to ensure active involvement of the patient and his or her family. Without their involvement, maximal benefits cannot be achieved. The importance of patient and family involvement is reflected in the clinical approach to pain management recommended by the Agency for Healthcare Research and Quality (AHRQ):

A **Ask** about pain regularly.

Assess pain systematically.

B **Believe** the patient and family in their reports of pain and what relieves it.

C **Choose** pain control options appropriate for the patient, family, and setting.

D **Deliver** interventions in a timely, logical, and coordinated fashion.

E **Empower** patients and their families.

Enable patients to control their treatment to the greatest extent possible.

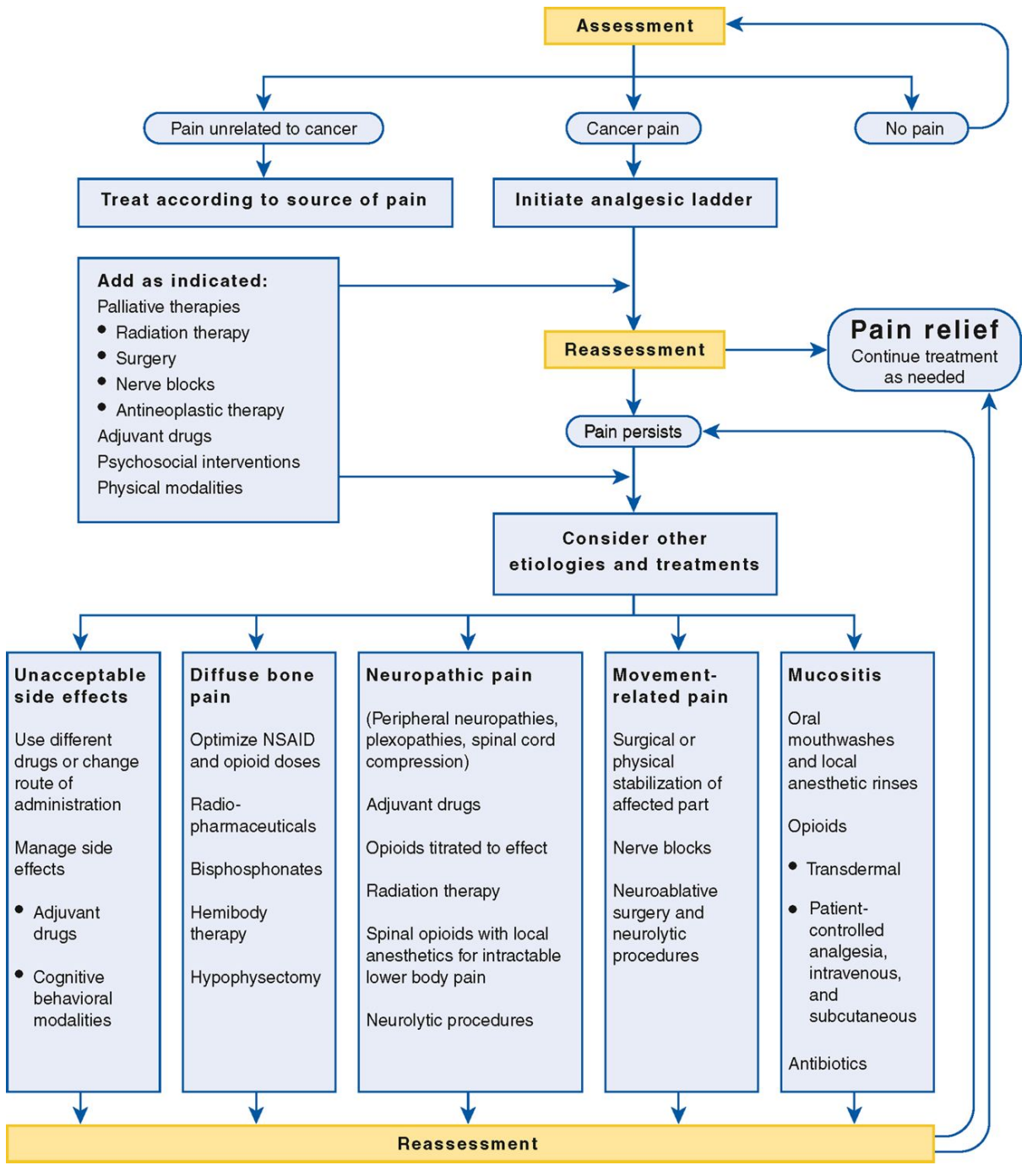

Assessment
Pain unrelated to cancer
Cancer pain
No pain
Treat according to source of pain
Initiate analgesic ladder
Add as indicated:
Palliative therapies
• Radiation therapy
• Surgery
• Nerve blocks
• Antineoplastic therapy
Adjuvant drugs
Psychosocial interventions
Physical modalities
Reassessment
Pain relief
Continue treatment as needed
Pain persists
Consider other etiologies and treatments
Unacceptable side effects
Use different drugs or change route of administration
Manage side effects
• Adjuvant drugs
• Cognitive behavioral modalities
Diffuse bone pain
Optimize NSAID and opioid doses
Radio-pharmaceuticals
Bisphosphonates
Hemibody therapy
Hypophysectomy
Neuropathic pain
(Peripheral neuropathies, plexopathies, spinal cord compression)
Adjuvant drugs
Opioids titrated to effect
Radiation therapy
Spinal opioids with local anesthetics for intractable lower body pain
Neurolytic procedures
Movement-related pain
Surgical or physical stabilization of affected part
Nerve blocks
Neuroablative surgery and neurolytic procedures
Mucositis
Oral mouthwashes and local anesthetic rinses
Opioids
• Transdermal
• Patient-controlled analgesia, intravenous, and subcutaneous
Antibiotics
Reassessment

Figure 29-1 Flow chart for pain management in patients with cancer. NSAID = nonsteroidal anti-inflammatory drug.

ASSESSMENT AND ONGOING EVALUATION

Assessment is the foundation of treatment. In the absence of thorough assessment, effective pain management is impossible. Assessment begins with a comprehensive evaluation and then continues with regular follow-up evaluations. The initial assessment provides the basis for designing the treatment program. Follow-ups let us know how well treatment is working.

Comprehensive Initial Assessment

The initial assessment employs an extensive array of tests. The primary objective is to characterize the pain and identify its cause. This information provides the basis for designing a pain management plan. In addition, by documenting the patient's baseline pain status, the initial assessment provides a basis for evaluating the efficacy of treatment.

Assessment of Pain Intensity and Character: The Patient Self-Report

The patient's description of his or her pain is the cornerstone of pain assessment. No other component of assessment is more important! Remember, pain is a personal experience. Accordingly, if we want to assess pain, we must rely on the patient to tell us about it. Furthermore, we must act on what the patient says—even if we personally believe the patient may not be telling the truth.

The best way to ensure an accurate report is to ask the right questions and listen carefully to the answers. We cannot elicit comprehensive information by asking, "How do you feel?" Rather, we must ask a series of specific questions. The answers should be recorded on a pain inventory form. The following information should be obtained:

- *Onset and temporal pattern*—When did your pain begin? How often does it occur? Has the intensity increased, decreased, or remained constant? Does the intensity vary throughout the day?

- *Location*—Where is your pain? Do you feel pain in more than one place? Ask patients to point to the exact location of the pain, either on themselves, on you, or on a full-body drawing.
- *Quality*—What does your pain feel like? Is it sharp or dull? Does it ache? Is it shooting or stabbing? Burning or tingling? These questions can help distinguish neuropathic pain from nociceptive pain.
- *Intensity*—On a scale of 0 to 10, with 0 being no pain and 10 the most intense pain you can imagine, how would you rank your pain now? How would you rank your pain at its worst? And at its best? A pain intensity scale (see below) can be very helpful for this assessment.
- *Modulating factors*—What makes your pain worse? What makes it better?
- *Previous treatment*—What treatments have you tried to relieve your pain (eg, analgesics, acupuncture, relaxation techniques)? Are they effective now? If not, were they ever effective in the past?
- *Impact*—How does the pain affect your ability to function, both physically and socially? For example, does the pain interfere with your general mobility, work, eating, sleeping, socializing, or sex life?

Physical and Neurologic Examinations

The physical and neurologic examinations help to further characterize the pain, identify its source, and identify any complications related to the underlying pathology. The clinician should examine the site of pain and determine if palpation or manipulation makes it worse. Nonverbal cues (eg, protecting the painful area, limited movement in an arm or leg) that may indicate pain should be noted. Common patterns of referred pain should be assessed. For example, if the patient has hip pain, the assessment should determine if the pain actually originates in the hip or if it is referred pain caused by pathology in the lumbar spine. Potential neurologic complications should be considered. For example, patients with back pain should be evaluated for impaired motor and sensory function in the limbs, and for impaired rectal and urinary sphincter function.

Diagnostic Tests

Diagnostic tests are performed to identify the underlying cause of pain (eg, progression of cancer, tissue injury caused by cancer treatments). The repertoire of diagnostic tests includes imaging studies (eg, computed tomography scan, magnetic resonance imaging), neurophysiologic tests, and tests for tumor markers in blood. To ensure that abnormalities identified in the diagnostic tests really do explain the patient's pain, these findings should be correlated with findings from the physical and neurologic examinations.

Psychosocial Assessment

Psychosocial assessment is directed at both the patient and his or her family. The information is used in making pain management decisions. Some important issues to address include

- The impact of significant pain on the patient in the past
- The patient's usual coping responses to pain and stress
- The patient's preferences regarding pain management methods
- The patient's concerns about using opioids and other controlled substances (anxiolytics, stimulants)
- Changes in the patient's mood (anxiety, depression) brought on by cancer and pain
- The impact of cancer and its treatment on the family
- The level of care the family can provide and the potential need for outside help (eg, hospice)

Pain Intensity Scales

Pain intensity scales are useful tools for assessing pain intensity. Representative scales are shown in Figures 29-2 and 29-3. The *descriptive scale* and *numeric scale* (Fig. 29-2) are used for adults and older children. The *pain affect FACES scale* (Fig. 29-3) is used for young children and for patients with cognitive impairment, who may have difficulty understanding the descriptive and numeric scales.

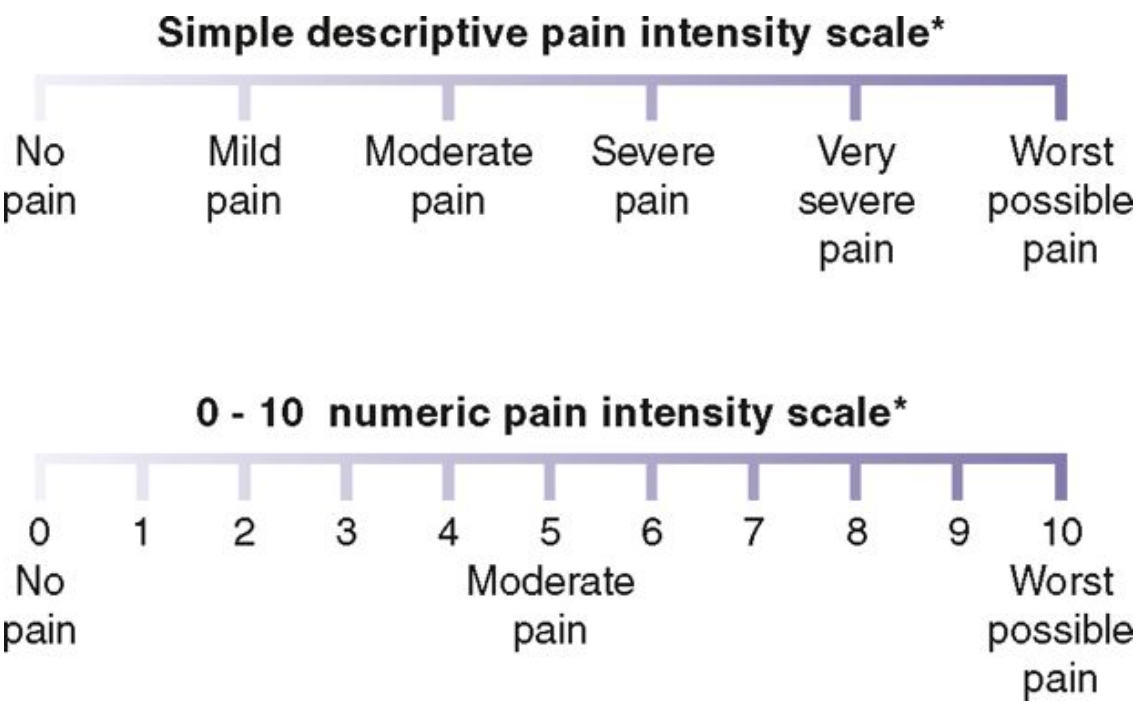


Figure 29-2 Linear pain intensity scales.*If used as a graphic rating scale, a 10-cm baseline is recommended.

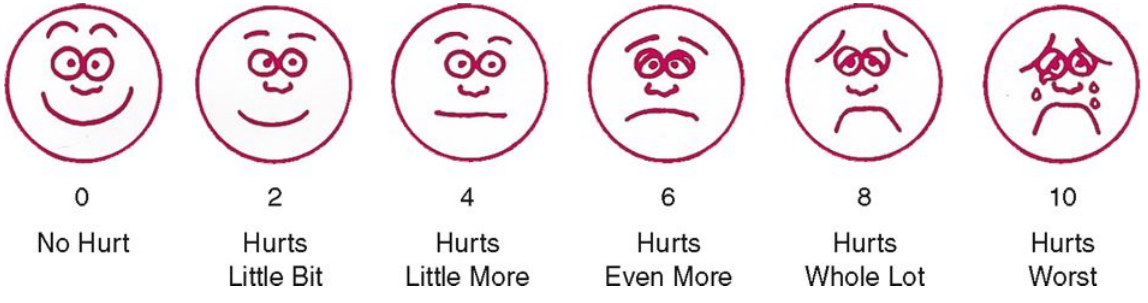


Figure 29-3 Wong-Baker FACES pain rating scale. Explain to the patient that the first face represents a person who feels happy because he or she has no pain, and that the other faces represent people who feel sad because they have pain, ranging from a little to a lot. Explain that face 10 represents a person who hurts as much as you can imagine, but that you don't have to be crying to feel this bad. Ask the patient to choose the face that best reflects how he or she is feeling. The numbers below the faces cor-

respond to the values in the numeric pain scale shown in Figure 29-2.

Pain intensity scales are valuable not only for assessing pain intensity, but also for *setting pain relief goals and evaluating treatment*. When setting goals, the patient and prescriber should agree on a target pain intensity rating that will permit the patient to participate in recovery activities, perform activities of daily living, and enjoy activities that contribute to quality of life. The objective of treatment is to reduce pain to the agreed-upon level—and lower, if possible.

Ongoing Evaluation

Once a treatment plan has been implemented, pain should be reassessed frequently. The objective is to determine the efficacy of treatment and to allow early diagnosis and treatment of new pain. Each time an analgesic drug is administered, pain should be evaluated after sufficient time has elapsed for the drug to take effect. Because most patients are treated at home, patients and caregivers should be taught to conduct and document pain evaluations. The prescriber will use the documented record to make adjustments to the pain management plan.

Prescribers, patients, and caregivers should be alert for new pain. In the majority of cases, new pain results from a new cause (eg, metastasis, infection, fracture). Accordingly, whenever new pain occurs, a rigorous diagnostic workup is indicated.

Barriers to Assessment

As stressed above, pain assessment relies heavily on a report from the patient. Unfortunately, the report is not always accurate: Some patients report more pain than they have, some report less, and some are unable to report at all. With other patients, cultural and language differences impede assessment. In all cases, reliance on behavioral cues and facial expression is a poor substitute for an accurate report by the patient.

Many patients under-report pain, frequently because of misconceptions. Some fear addiction to opioids, and hence want to minimize opioid use. Some believe they are expected to be stoic and "tough it out." Some deny their pain because they fear pain signifies disease progression. When underreporting of

pain is suspected, the patient should be interviewed in an effort to discover the reason. If a misconception is responsible for under-reporting, educating the patient can help fix the problem.

Some patients fear they may be denied sufficient pain medication, and hence, to ensure adequate dosing, report more pain than they actually have. When exaggeration is suspected, the patient should be reassured that adequate pain relief will be provided, and should be taught that inaccurate reporting serves only to make appropriate treatment more difficult.

Language barriers and cultural barriers can impede pain assessment. For patients who do not speak English, a translator should be provided. Obtaining a pain rating scale in the patient's own language would obviously help. *A pain affect FACES scale* can be useful, since facial expressions reflecting discomfort are the same in all cultures. Cultural beliefs may cause some patients to hide overt expression of pain and report less pain than is present. The interviewer should be alert to this possibility.

When assessing pain, we must keep in mind that behavior and facial expression may be poor indicators of pain status. For example, in patients approaching the end of life, behavioral cues of pain (eg, vocalizing, grimacing) are often absent. Other patients may simply have good coping skills, and hence may smile and move around in apparent comfort, even though they are in considerable pain. Because appearances can be deceiving, we must not rely on them to assess pain.

Assessment in young children and other nonverbal patients is a special challenge. By definition, nonverbal patients are unable to self-report pain. Accordingly, we must use less reliable methods of assessment, including observing the patient for cues. Assessment in children is discussed further under *Pain Management in Special Populations*.

DRUG THERAPY

Analgesic drugs are the most powerful weapons we have for conquering cancer pain. With proper use, these agents can relieve pain in 90% of patients. Because analgesics are so effective, drug therapy is the principal modality for pain treatment. Three types of analgesics are employed:

- Nonopioid analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs] and acetaminophen)
- Opioid analgesics (eg, oxycodone, fentanyl, morphine)
- Adjuvant analgesics (eg, amitriptyline, carbamazepine, dextroamphetamine)

These classes differ in their abilities to relieve pain. With the nonopioid and adjuvant analgesics, there is a ceiling to how much relief we can achieve. In contrast, there is no ceiling to relief with the opioids.

Selection among the analgesics is based on pain intensity and pain type. To help guide drug selection, the World Health Organization (WHO) devised a drug selection ladder (Fig. 29-4). The first step of the ladder—for mild to moderate pain—consists of nonopioid analgesics: NSAIDs and acetaminophen. The second step—for more severe pain—*adds* opioid analgesics of moderate strength (eg, oxycodone, hydrocodone). The top step—for severe pain—substitutes powerful opioids (eg, morphine, fentanyl) for the weaker ones. Adjuvant analgesics, which are especially effective against neuropathic pain, can be used on any step of the ladder. Specific drugs to *avoid* are listed in Table 29-2.

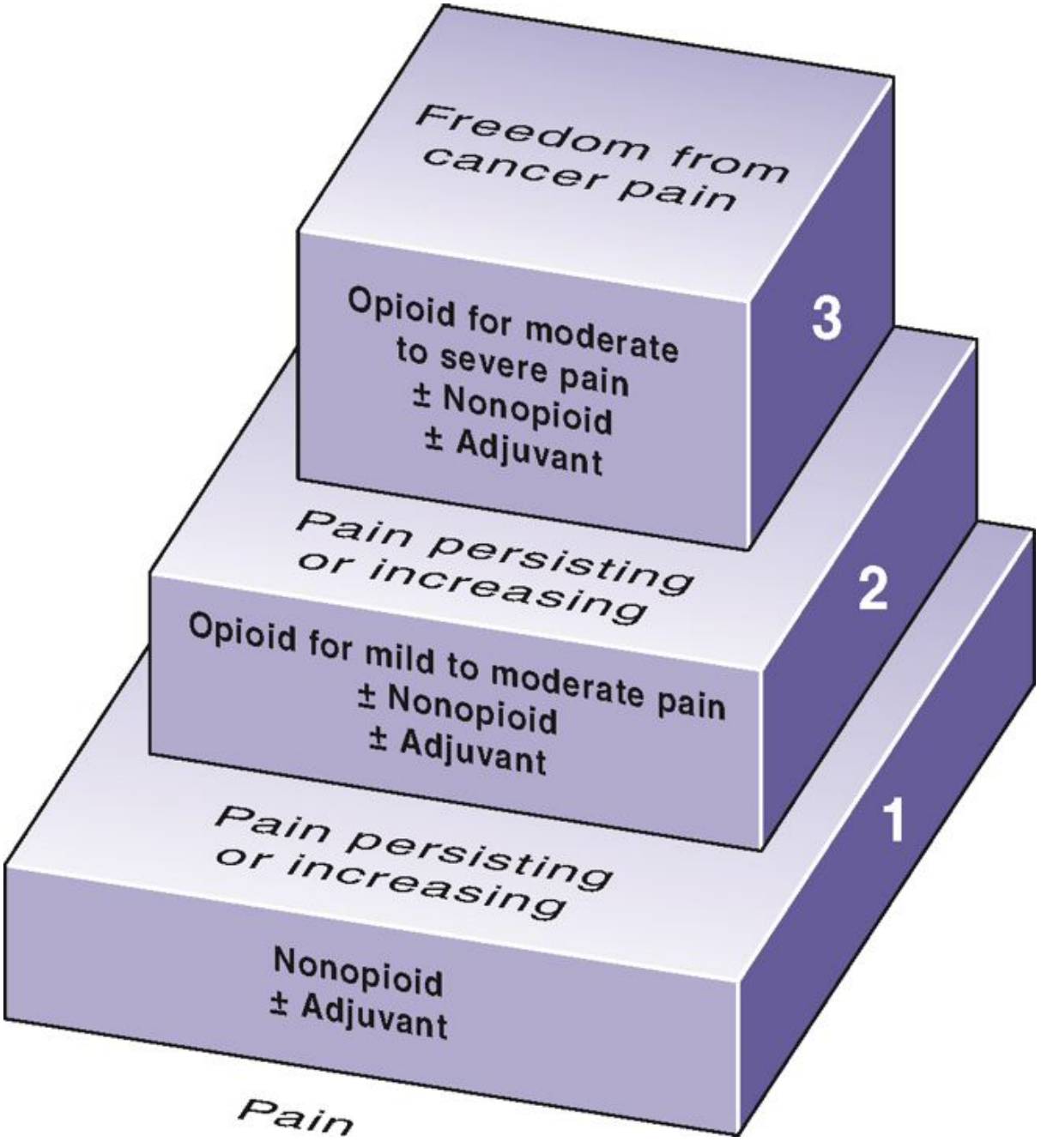

Freedom from cancer pain
Opioid for moderate to severe pain
± Nonopioid
± Adjuvant
3
Pain persisting or increasing
Opioid for mild to moderate pain
± Nonopioid
± Adjuvant
2
Pain persisting or increasing
Nonopioid
± Adjuvant
1
Pain

Figure 29-4 The WHO analgesic ladder for cancer pain management. Note that steps represent pain intensity. Accordingly, if a patient has intense pain at the outset, then treatment can be initiated with an opioid (step 2), rather than trying a nonopioid first (step 1).

Traditionally, patients have been given opioid analgesics only after a trial with nonopioids has failed. Guidelines from the National Comprehensive Cancer Network (NCCN) recommend a different approach, in which initial drug selection is based on pain intensity. Specifically, if the patient reports pain in the 4 to 10 range (as measured on a numeric rating scale), then treatment should start directly with an opioid; an initial trial with a non-opioid is considered unnecessary. If the patient reports pain in the 1 to 3 range, then treatment usually begins with a nonopioid, although starting with an opioid remains an alternative.

It is common practice to combine an opioid with a nonopioid. Why? Because the combination can be more effective than either drug alone. When pain is only moderate, opioids and nonopioids can be given in a fixed-dose combination formulation, thereby simplifying dosing. However, when pain is severe, these drugs must be given separately. Why? Because, with a fixed-dose combination, side effects of the nonopioid would become intolerable as the dosage grew large, and hence would limit how much opioid could be given.

Drug therapy of cancer pain should adhere to the following principles:

- Perform a comprehensive pretreatment assessment to identify pain intensity and the underlying cause.
- Individualize the treatment plan.
- Use the WHO analgesic ladder and NCCN guidelines to guide drug selection.
- Use oral therapy whenever possible.
- Avoid IM injections whenever possible.
- For persistent pain, administer analgesics on a fixed schedule around-the-clock (ATC), and provide additional rescue doses of a short-acting agent if breakthrough pain occurs.
- Evaluate the patient frequently for pain relief and drug side effects.

Drug Class	Drug	Why the Drug Is Not Recommended
Opioids		
Pure Agonists	Meperidine	A toxic metabolite accumulates with prolonged use
	Codeine	Maximal pain relief is limited owing to dose-limiting side effects
Agonist-Antagonists	Buprenorphine	Ceiling to analgesic effects; can precipitate withdrawal in opioid-dependent patients; cause psychotomimetic reactions
	Butorphanol	
	Nalbuphine	
	Pentazocine	
Opioid Antagonists	Naloxone	Can precipitate withdrawal in opioid-dependent patients; limit use to reversing life-threatening respiratory depression caused by opioid overdose
	Naltrexone	
	Nalmefene	
Benzodiazepines	Diazepam	Sedation from benzodiazepines limits opioid dosage; no demonstrated analgesic action
	Lorazepam others	
Barbiturates	Amobarbital	Sedation from barbiturates limits opioid dosage; no demonstrated analgesic action
	Secobarbital others	
Miscellaneous	Cocaine	No analgesic efficacy, either alone or in combination with an opioid
	Marijuana	Side effects (dysphoria, drowsiness, hypotension, bradycardia) preclude routine use as an analgesic
	Brompton's cocktail*	Analgesic efficacy is no better than that of a single opioid

TABLE 29-2 Drugs That Are Not Recommended for Treating Cancer Pain

* Brompton's cocktail consists of heroin (in variable amounts), 10 mg of cocaine, 2.5 mL of 98% ethanol, 5 mL of syrup, and chloroform water.

Nonopioid Analgesics

The nonopioid analgesics—NSAIDs and acetaminophen—constitute the first rung of the WHO analgesic ladder. These agents are the initial drugs of choice for patients with mild pain. There is a ceiling to how much pain relief nonopioid drugs can provide. Hence, there is no benefit to exceeding recommended dosages (Table 29-3). Acetaminophen is about equal to the NSAIDs in *analgesic* efficacy but lacks *antiinflammatory* actions. Because of this difference and others, acetaminophen is considered separately below. The NSAIDs and acetaminophen are discussed at length in Chapter 70. Accordingly, discussion here is brief.

Drug	Usual Adult Dosage*	
	Body Weight 50 kg or More	Body Weight Less Than 50 kg
Acetaminophen	650 mg q 4 h *or* 975 mg q 6 h or 1300 mg q8h	10–15 mg/kg q 4 h *or* 15–20 mg/kg q 4 h (rectal)
NSAIDs: Salicylates		
Aspirin	650 mg q 4 h *or* 975 mg q 6 h	10–15 mg/kg q 4 h *or* 15–20 mg/kg q 4 h (rectal)
Magnesium salicylate [Magan]†	650 mg q 4 h	—
Sodium salicylate†	325–650 mg q 3–4 h	—
NSAIDs: Propionic Acid Derivatives		
Fenoprofen	300–600 mg q 6 h	—
Ibuprofen [Motrin, Advil, others]	400–800 mg q 6 h	10 mg/kg q 6–8 h
Ketoprofen	25–60 mg q 6–8 h	—
Naproxen [Naprosyn]	250–275 mg q 6–8 h	5 mg/kg q 8 h
Naproxen sodium [Anaprox, Aleve, Naprelan, others]	275 mg q 6–8 h	—
NSAIDs: Miscellaneous		
Diflunisal	500 mg q 12 h	—
Etodolac	200–400 mg q 6–8 h	—
Meclofenamate sodium	50–100 mg q 6 h	—
Mefenamic acid [Ponstel]	250 mg q 6 h	—
NSAIDs: Selective COX-2 Inhibitors		
Celecoxib [Celebrex]	200 mg q 12 h	—

TABLE 29-3 Dosages for Nonopioid Analgesics: Acetaminophen and Selected NSAIDs

* All dosages are oral except where indicated.

† Magnesium salicylate and sodium salicylate are nonacetylated, and hence, unlike aspirin, are safe for patients with thrombocytopenia.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs (eg, aspirin, ibuprofen) can produce a variety of effects. Primary beneficial effects are pain relief, suppression of inflammation, and reduction of fever. Primary adverse effects are gastric ulceration, acute renal failure, and bleeding. In addition, all NSAIDs *except aspirin* increase the risk of thrombotic events (eg, myocardial infarction, stroke). In contrast to opioids, NSAIDs do not cause tolerance, physical dependence, or psychologic dependence.

NSAIDs are effective analgesics that can relieve mild to moderate pain. All of the NSAIDs have essentially equal analgesic efficacy, although individual patients may respond better to one NSAID than to another. NSAIDs relieve pain by a mechanism different from that of the opioids. As a result, combined use of an NSAID with an opioid can produce greater pain relief than either agent alone.

NSAIDs produce their effects—both good and bad—by inhibiting cyclooxygenase (COX), an enzyme that has two forms, known as COX-1 and COX-2. Most NSAIDs inhibit both COX-1 and COX-2, although a few are COX-2 selective. The selective COX-2 inhibitors (eg, celecoxib [Celebrex]) cause less GI damage than the nonselective inhibitors. Unfortunately, the selective inhibitors pose a greater risk of thrombotic events, and hence long-term use of these drugs is not recommended.

For patients undergoing chemotherapy, inhibition of platelet aggregation by NSAIDs is a serious concern. Many anticancer drugs suppress bone marrow function, and thereby decrease platelet production. The resultant thrombocytopenia puts patients at risk of bruising and bleeding. Obviously, this risk will be increased by drugs that inhibit platelet function. Among the conventional NSAIDs, only one subclass—the nonacetylated salicylates (eg, magnesium salicylate)—does not inhibit platelet aggregation, and hence is safe for patients with thrombocytopenia. All other conventional NSAIDs should be avoided. *Aspirin* is especially dangerous because it causes *irreversible* inhibition of platelet aggregation. Hence, its effects persist for the life of the platelet (about 8

days). Because COX-2 inhibitors do not affect platelets, these drugs are safe for patients with thrombocytopenia.

Acetaminophen

Acetaminophen [Tylenol, others] is similar to the NSAIDs in some respects and different in others. Like the NSAIDs, acetaminophen is an effective analgesic, and hence can relieve mild to moderate pain. Benefits derive from inhibiting COX in the central nervous system (CNS), but not in the periphery. Combining acetaminophen with an opioid can produce greater analgesia than either drug alone (because acetaminophen and opioids relieve pain by different mechanisms).

Acetaminophen differs from the NSAIDs in several important ways. Because it does not inhibit COX in the periphery, acetaminophen lacks anti-inflammatory actions, does not inhibit platelet aggregation, and does not promote gastric ulceration, renal failure, or thrombotic events. Because acetaminophen does not affect platelets, the drug is safe for patients with thrombocytopenia.

Acetaminophen has important interactions with two other drugs: alcohol and warfarin (an anticoagulant). Combining acetaminophen with alcohol, even in moderate amounts, can result in potentially fatal liver damage. Accordingly, patients taking acetaminophen should minimize alcohol consumption. Acetaminophen also can increase the risk of bleeding in patients taking warfarin. The mechanism appears to be inhibition of warfarin metabolism, which causes warfarin to accumulate to dangerous levels.

Opioid Analgesics

Opioids are the most effective analgesics available, and hence are the primary drugs for treating moderate to severe cancer pain. With proper dosing, opioids can safely relieve pain in about 90% of cancer patients. Unfortunately, many patients are denied adequate doses, owing largely to unfounded fears of addiction. In the past, opioids were known as *narcotics,* a term that is now obsolete.

Opioids produce a variety of pharmacologic effects. In addition to analgesia, they can cause sedation, euphoria, constipation, respiratory depression, urinary retention, and miosis. With continuous use, tolerance develops to most of

these effects, with the notable exception of constipation. Continuous use also results in physical dependence, which must not be equated with addiction.

The opioids are discussed at length in Chapter 28. Discussion here focuses on their use in patients with cancer.

Mechanism of Action and Classification

Opioid analgesics relieve pain by mimicking the actions of endogenous opioid peptides (enkephalins, dynorphins, endorphins), primarily at mu receptors and partly at kappa receptors.

Based on their actions at mu and kappa receptors, the opioids fall into two major groups: (1) *pure (full) agonists* (eg, morphine) and (2) *agonist-antagonists* (eg, butorphanol). The pure agonists can be subdivided into (1) agents for mild to moderate pain and (2) agents for moderate to severe pain. The pure agonists act as agonists at mu receptors *and* at kappa receptors. In contrast, the agonist-antagonists act as agonists only at kappa receptors; at mu receptors, these drugs act as *antagonists*. Because their agonist actions are limited to kappa receptors, the agonist-antagonists have a ceiling to their analgesic effects. Furthermore, because of their antagonist actions, the agonist-antagonists can block access of the pure agonists to mu receptors, and can thereby prevent the pure agonists from relieving pain. Accordingly, agonist-antagonists are not recommended for managing cancer pain.

Tolerance and Physical Dependence

Over time, opioids cause tolerance and physical dependence. These phenomena, which are generally inseparable, reflect neuronal adaptations to prolonged opioid exposure. Some degree of tolerance and physical dependence will develop after 1 to 2 weeks of opioid use.

Tolerance.

Tolerance can be defined as a state in which a specific dose (eg, 10 mg of morphine) produces a smaller effect than it could when treatment began. Put another way, tolerance is a state in which dosage must be increased to maintain the desired response. In patients with cancer, however, a need for larger

doses isn't always a sign of tolerance. In fact, it's usually a sign that pain is getting worse (owing to disease progression).

Tolerance develops to some opioid effects but not to others. Tolerance does develop to analgesia, euphoria, respiratory depression, and sedation. In contrast, little or no tolerance develops to constipation.

There is cross-tolerance among opioids. Accordingly, significant tolerance to one opioid confers a similar degree of tolerance to all others.

Physical Dependence.

Physical dependence is a state in which an abstinence syndrome will occur if a drug is abruptly withdrawn. With opioids, the abstinence syndrome can be very unpleasant—but not dangerous. The intensity and duration of the abstinence syndrome are determined in part by the duration of drug use and in part by the half-life of the drug taken. Because drugs with a short half-life leave the body rapidly, the abstinence syndrome is brief but intense. Conversely, for drugs with long half-lives, the syndrome is prolonged but relatively mild. The abstinence syndrome can be minimized by withdrawing opioids slowly (ie, by giving progressively smaller doses over several days). Please note that *physical dependence is not the same as addiction!*

Addiction

Opioid addiction is an important issue in pain management—not because addiction occurs (it rarely does), but because *inappropriate fears of addiction* are a major cause for undertreatment.

The American Society of Addiction Medicine defines addiction as *a disease process characterized by continued use of a psychoactive substance despite physical, psychologic, or social harm*. According to this definition, addiction is primarily a *behavior pattern*—and is *not* equated with physical dependence. Although it is true that physical dependence can contribute to addictive behavior, other factors—especially *psychologic dependence*—are the primary underlying cause. All cancer patients who take opioids chronically develop substantial physical dependence, but only a few (less than 1%) develop addictive behavior. Most patients, if their cancer were cured, would simply go through gradual with-

drawal, and never think about or use opioids again. Clearly, these patients cannot be considered addicted, despite their physical dependence.

Because of misconceptions about opioid addiction, prescribers often order lower doses than patients need, nurses administer lower doses than were ordered, patients report less pain than they actually have, and family members discourage opioid use. The end result? The majority of cancer patients receive lower doses of opioids than they need. How can we improve this unacceptable situation? We must educate physicians, nurses, patients, and family members. Specifically, we must teach them about the nature of addiction and inform them that development of addiction in the therapeutic setting is very rare. Hopefully, this information will dispel unfounded fears of addiction, and will thereby help ensure delivery of opioids in doses that are sufficient to relieve suffering. After all, that *is* what opioids are for.

Drug Selection

Preferred Opioids.

For all cancer patients, *pure opioid agonists* are preferred to the agonist-antagonists. If pain is not too intense, a moderately strong opioid (eg, oxycodone) is appropriate. If pain is moderate to severe, a strong opioid (eg, morphine) should be used. Since morphine is inexpensive, available in multiple dosage forms, and clinically well understood, this opioid is used more than any other. Preferred opioids are listed in Table 29-4.

Drug	Equianalgesic Dose[a] Parenteral	Oral	Duration (hr)[b]
Agents for Mild to Moderate Pain			
Codeine[c]	130 mg	200 mg	3–4
Hydrocodone[d]	NA	30–200 mg	3–5
Oxycodone[e]	NA	15 mg	3–5
Tramadol[f,g]	NA	50–100 mg	3–7
Agents for Moderate to Severe Pain			
Morphine[h]	10 mg	30 mg	3–4
Fentanyl[i]	100 mcg	NA	1–3
Hydromorphone	1.5 mg	7.5 mg	2–3
Levorphanol[j]	2 mg	4 mg	3–6
Methadone[j]	10 mg	3–20 mg[k]	4–8
Oxymorphone[e]	1 mg	10 mg	3–6

Modified from NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain, Vol. 1. Atlanta: National Comprehensive Cancer Network, Inc., 2008.

NA = not available.

TABLE 29-4 Equianalgesic Doses of Pure Opioid Agonists and Tramadol

a Equianalgesic dose = dose that will produce the same degree of analgesia as 10 mg of parenteral morphine.

b Duration values apply to parenteral administration and to immediate-release oral formulations. Four opioids—morphine, oxycodone, oxymorphone, and tramadol—are available in immediate-release and sustained-release oral formulations.

c Codeine is not generally recommended for chronic therapy because the doses required to produce significant analgesia also produce significant side effects.

d Equivalence data not substantiated. Usually combined with aspirin or acetaminophen.

e Available in a sustained-release formulation administered every 12 hours.

f Tramadol is a weak opioid agonist with some antidepressant activity. Reserve for mild to moderate pain. The recommended dosage is 100 mg 4 times a day. At the maximum dosage of 400 mg/day, tramadol is less effective than morphine and other strong pure opioid agonists.

g Available in a sustained-release formulation administered every 24 hours.

h Available in sustained-release formulations administered every 12 or 24 hours.

i Available in a long-acting transdermal system (applied every 48 to 72 hours), and in short-acting transmucosal and buccal systems for control of breakthrough pain.

j Has a long half-life. May need to be dosed every 4 hours initially, and then every 6 to 8 hours after steady state is achieved (in 1 to 2 weeks).

k For patients converting from morphine to methadone, choosing the proper methadone dosage is complex, and should be done with the advice of a pain specialist familiar with methadone prescribing.

Opioid Rotation.

Opioid rotation—switching from one opioid to another—has become an accepted practice. Because opioids have different side effect profiles, switching among them can help minimize adverse effects while maintaining good analgesia. To make the switch, the current opioid is stopped abruptly and immediately replaced with an equianalgesic dose of an alternative opioid.

Opioids to Use with Special Caution.

Methadone [Dolophine, Methadose] and *levorphanol* [Levo-Dromoran] must be used with caution. Both drugs have prolonged half-lives, which makes dosage titration difficult. If dosing is not done skillfully, these drugs can accumulate to dangerous levels, causing excessive sedation and respiratory depression.

Codeine deserves special comment. Although codeine is capable of producing significant analgesia, side effects limit the dose that can be given. As a result, the degree of pain relief that can be achieved safely is quite low.

Opioids to Avoid.

Meperidine [Demerol], a pure opioid agonist, may be used for a few days, but no longer. When the drug is taken chronically, a toxic metabolite—normeperidine—can accumulate, thereby posing a risk of adverse CNS effects (dysphoria, agitation, seizures).

The *agonist-antagonists*—buprenorphine, butorphanol, nalbuphine, and pentazocine—should be avoided. Why? First, they are much less effective than pure opioid agonists, and hence, there is little reason to choose them. Second, if given to a patient who is physically dependent on a pure opioid agonist, these drugs can prevent the pure agonist from working, and can thereby block analgesia and precipitate withdrawal. Third, the agonist-antagonists can cause adverse psychologic reactions (nightmares, hallucinations, dysphoria).

Dosage

Dosage must be individualized. The objective is to find a dosage that can relieve pain without causing intolerable side effects. For patients with moderate pain and low opioid tolerance, very low doses (eg, 2 mg of parenteral morphine every 4 hours) can be sufficient. In contrast, when pain is severe or tolerance is high, much larger doses (eg, 600 mg of parenteral morphine every few hours) may be required. The upper limit to dosage is determined only by the intensity of side effects. Accordingly, as pain and/or tolerance increase, dosage should be increased until pain is relieved—unless intolerable side effects (eg, excessive respiratory depression) occur first.

The dosing schedule is determined by the temporal pattern of the pain. If pain is intermittent and infrequent, PRN dosing can suffice. However, since most patients have persistent pain, PRN dosing is inappropriate. Instead, dosing should be done *on a fixed schedule* ATC. Why? Because a fixed schedule can prevent opioid levels from becoming subtherapeutic, and can thereby prevent pain recurrence. As a result, the patient is spared needless suffering, both from the pain itself and from anxiety about its return.

What dose should be used when switching from one opioid to another, or from one route of administration to another? To help make this decision, an *equianalgesia table* (see Table 29-4) should be consulted. Equianalgesia tables indicate equivalent analgesic doses for different opioids, and for the same opioid administered by different routes. Let's assume, for example, that our patient has been getting 10 mg of IV morphine every 4 hours, and we want to switch to oral hydromorphone. By consulting Table 29-4, we can see that 7.5 mg of oral hydromorphone is about equivalent to 10 mg of parenteral morphine, with both drugs being given every 4 hours. Hence, we might begin oral hydromorphone at 7.5 mg. However, there is a caveat: Because cross-tolerance among opioids

is incomplete, the listed equianalgesic dose may actually produce a *stronger* effect than advertised. Accordingly, when switching drugs, it is safer to use a dose that is somewhat *lower* than the equianalgesic dose, and then titrate up.

Routes of Administration

Because most patients with cancer pain must take analgesics continuously, the route should be as convenient, affordable, and noninvasive as possible. Oral administration meets these criteria best, and hence is preferred for most patients. If oral medication cannot be used, the preferred alternative routes are rectal and transdermal: Both are relatively convenient, affordable, and noninvasive. If these routes are ineffective or inappropriate, then parenteral administration (IV or subQ) is indicated (IM injections should be avoided). For patients who cannot be managed with IV or subQ therapy, more invasive routes—intraspinal or intraventricular—can be tried.

Oral.

Oral administration is the preferred route for chronic therapy. Why? Because oral dosing is cheap, convenient, and noninvasive. Accordingly, in the absence of contraindications (eg, vomiting, inability to swallow), oral therapy should be considered for all patients. Opioids are available in several formulations (eg, tablets, capsules, solution) for oral use. To reduce the number of daily doses, a long-acting formulation (eg, controlled-release morphine) can be used. Because oral opioids undergo substantial first-pass metabolism, oral doses must be larger than parenteral doses to achieve equivalent analgesic effects.

Rectal.

Rectal administration is a preferred alternative for patients who cannot take drugs by mouth. Three opioids—morphine, hydromorphone, and oxymorphone—are available in rectal formulations (suppositories). When switching from oral to rectal administration, dosing is begun with the same dose that was used orally, and then adjusted as needed. Rectal administration is inappropriate for patients with diarrhea or lesions of the rectum or anus. Also, children frequently object to this route.

Transdermal.

Transdermal administration is a preferred alternative to oral therapy. Only one opioid—fentanyl [Duragesic]—is available for chronic transdermal use. Fentanyl patches provide steady analgesia for 72 hours, and hence are appropriate for patients with pain that is continuous and does not fluctuate much in intensity. Absorption from the patch is very slow. As a result, when the first patch is applied, effective analgesia may take 12 to 24 hours to develop. During this time, PRN therapy with a short-acting opioid may be required. Fentanyl patches are available in five strengths, allowing dosage to be matched with pain intensity. As with other long-acting opioids, rescue doses with a short-acting opioid are needed when breakthrough pain occurs.

Intravenous and Subcutaneous.

Intravenous and subQ administration are acceptable alternatives when less invasive routes (oral, transdermal, rectal) cannot be used. The IV and subQ routes have two advantages: (1) onset of analgesia is quick and (2) these routes permit rapid escalation of dosage. Obvious disadvantages are inconvenience and increased cost. In addition, frequent subQ dosing is uncomfortable. Conditions that might justify IV or subQ administration include

- Persistent nausea and vomiting (which preclude oral dosing)
- Inability to swallow (which precludes oral dosing)
- Delirium or stupor (which precludes oral dosing)
- Pain that requires a large number of pills (which makes oral dosing inconvenient)
- Unstable pain that requires rapid dosage escalation (which precludes oral, rectal, and transdermal administration)

Dosages for IV and subQ administration are the same.

Intramuscular.

Intramuscular administration should be avoided. IM injections are painful, and hence unacceptable for repeated dosing. In addition, absorption from IM sites is inconsistent, hence pain relief is unpredictable.

Intraspinal.

Intraspinal administration is reserved for patients with intractable pain that cannot be controlled with less invasive routes (eg, IV, subQ). In this technique, opioids are delivered to the epidural or subarachnoid space via a percutaneous catheter connected to an infusion pump or injection port. By using this route, we can achieve high opioid concentrations at receptors on pain pathways in the spinal cord. It is important to note, however, that effects will not be limited to the spinal cord: Intraspinal opioids undergo absorption into the blood in amounts sufficient to cause systemic effects. In fact, blood levels may be equivalent to those achieved with conventional routes (eg, subQ). Intraspinal administration is especially useful for patients with severe pain in the lower body: Pain is relieved in up to 90% of appropriate candidates. Patients who are tolerant to opioids delivered by other routes will also be tolerant to opioids given intraspinally; dosage should be adjusted accordingly. Patients should have access to rescue medication in case breakthrough pain occurs, owing either to delivery system malfunction or inadequate dosing. Side effects with intraspinal administration are the same as with other routes. In addition, there is a risk of *delayed* respiratory depression as well as infection associated with the catheter.

Intraventricular.

Like intraspinal administration, intraventricular administration is reserved for patients whose pain cannot be controlled with less invasive routes. In this procedure, morphine is delivered to the cerebral ventricles via a catheter connected to an external infusion pump (for continuous administration) or a subcutaneous reservoir (for intermittent administration). Because morphine is delivered directly to the brain, bypassing the blood-brain barrier, analgesia can be achieved with extremely low doses (eg, 5 mg daily). Pain is relieved in 90% of patients. Intraventricular administration is especially helpful for patients with intractable pain caused by head and neck malignancies or tumors that affect the brachial plexus.

Patient-Controlled Analgesia.

Patient-controlled analgesia (PCA) is a method of drug delivery that permits patients to control the amount of opioid they receive. PCA is accomplished us-

ing a PCA device to deliver opioids through an indwelling IV or subQ catheter. The PCA device is an electronically controlled infusion pump that (1) delivers a continuous basal infusion of opioid and (2) can be activated manually by the patient to deliver additional bolus doses for breakthrough pain. To prevent an overdose, the device (1) limits the total dose of opioid that can be delivered per hour and (2) sets a minimum interval (eg, 10 minutes) between bolus doses, thereby preventing the patient from giving a second dose before the first one can take full effect. PCA devices are safe for use in the hospital and at home, but should not be used by patients who are sedated or confused. PCA administration is discussed at length in Chapter 28.

Managing Breakthrough Pain

Many patients whose pain is well controlled most of the day experience transient episodes of moderate to severe pain, known as breakthrough pain. Breakthrough pain develops quickly, reaches peak intensity in minutes, and may persist from minutes to hours (the median duration is 30 minutes). At least 50% of cancer patients experience these episodes, typically 1 to 4 times a day. Breakthrough pain may occur spontaneously, or it may be precipitated by coughing or other movements. In contrast to end-of-dose pain, which occurs because analgesic levels are lowest at that time, breakthrough pain can occur at any time during the dosing interval.

All patients receiving ATC opioids for persistent pain should have access to a rescue medication to manage breakthrough pain. Because breakthrough pain is both severe and self-limited, the best medication is a strong opioid with a rapid onset and short duration. The rapid onset permits speedy relief, and the short duration facilitates dosage titration. For ease of administration, oral and transmucosal formulations are preferred; examples include immediate-release oral morphine and transmucosal fentanyl [Actiq, Fentora]. The dosage, as recommended by the American Pain Society, should be equivalent to one-sixth of the total daily opioid dose, repeated in 2 hours if needed.

Managing Side Effects

Side effects of the opioids include respiratory depression, constipation, sedation, orthostatic hypotension, nausea, and vomiting. All can be effectively managed. In many patients, side effects can be reduced simply by decreasing

the dosage (typically by 25%). If dosage reduction causes pain to return, adding a nonopioid analgesic may take care of the problem. Over time, tolerance develops to sedation, respiratory depression, nausea, and vomiting—but not to constipation.

Respiratory Depression.

Respiratory depression is the most serious side effect of the opioids; death can result. Fortunately, when dosage and monitoring are appropriate, significant respiratory depression is rare. Pain counteracts the depressant actions of opioids. Hence, as pain decreases, respiratory depression may deepen.

Respiratory depression is greatest at the outset of treatment and then decreases as tolerance develops. As a result, small initial doses of opioids (eg, 5 mg of IV morphine every hour) can pose a greater risk than much larger doses (eg, 1000 mg of IV morphine every hour) later on.

Significant respiratory depression is most likely when dosage is being titrated up. The best way to assess the risk of impending respiratory depression is to monitor opioid-induced sedation. Why? Because an increase in sedation generally precedes an increase in respiratory depression. Hence, if excessive sedation is observed, further dosing should be delayed.

Respiratory depression is increased by other drugs with CNS-depressant actions (eg, alcohol, barbiturates, benzodiazepines). Accordingly, these agents should be avoided.

Severe respiratory depression can be reversed with *naloxone* [Narcan], a pure opioid antagonist. However, caution is required: Excessive dosing will reverse analgesia, thereby putting the patient in great pain. Accordingly, naloxone dosage must be titrated carefully.

When death is near, should opioids be withheld out of fear that respiratory depression may bring death sooner? For several reasons, the answer is “No.” First, significant respiratory depression is rare in the tolerant patient. Hence, concerns about hastening death are largely unfounded. Second, unrelieved pain can itself hasten death. Third, when death is imminent, it is more important to provide comfort than prolong life. Accordingly, adequate opioids should be provided, even if doing so means life ends a bit sooner.

Constipation.

Constipation occurs in most patients. Opioids promote constipation by decreasing propulsive intestinal contractions, increasing nonpropulsive contractions, increasing the tone of the anal sphincter, and reducing fluid secretion into the intestinal lumen. No tolerance to these effects develops. To reduce constipation, all patients should increase dietary fiber and fluid. However, most patients also need pharmacologic help. Options include stool softeners (eg, docusate), stimulant laxatives (eg, senna), osmotic laxatives (eg, sodium phosphate), and methylnaltrexone [Relistor], which blocks opioid receptors in the intestine. For prophylaxis of constipation, current guidelines recommend daily therapy with a combination product, such as Senokot-S, which contains both senna and docusate. Osmotic laxatives are reserved for severe constipation. Methyl-naltrexone [Relistor] is indicated only for constipation in patients with end-stage disease. Drugs with anticholinergic properties (eg, tricyclic antidepressants, antihistamines) can exacerbate opioid-induced constipation (by further depressing bowel function), and hence should be avoided.

Sedation.

Sedation is common early in therapy, but tolerance develops quickly. If sedation persists, it can be reduced by giving smaller doses of the opioid more frequently, while keeping the total daily dose the same. This dosing schedule decreases peak opioid levels, and thereby reduces excessive CNS depression. If necessary, sedation can be opposed with a CNS stimulant (eg, caffeine, methylphenidate, dextroamphetamine, modafinil).

Nausea and Vomiting.

Initial doses of opioids may cause nausea and vomiting. Fortunately, tolerance develops rapidly. Nausea and vomiting can be minimized by pretreatment with an antiemetic (eg, prochlorperazine, metoclopramide). A serotonin antagonist (eg, granisetron, ondansetron) may also be tried, but these drugs may increase constipation.

Other Side Effects.

Opioids promote histamine release, and can thereby cause *itching,* which can be relieved with an antihistamine (eg, diphenhydramine).

Opioids increase the tone in the urinary bladder sphincter, and can thereby cause *urinary retention*. Prostatic hypertrophy and use of anticholinergic drugs will exacerbate the problem. Patients should be monitored for urinary retention and encouraged to void every 4 hours.

Opioids can cause *orthostatic hypotension*. Patients should be informed about symptoms of hypotension (lightheadedness, dizziness) and instructed to sit or lie down if they occur. Orthostatic hypotension can be minimized by moving slowly when changing from a supine or seated position to an upright posture.

Opioid-induced *neurotoxicity* is a recently recognized syndrome. Symptoms include delirium, agitation, myoclonus, and hyperalgesia. Primary risk factors are renal impairment, pre-existing cognitive impairment, and prolonged, high-dose opioid use. Management consists of hydration, dose reduction, and opioid rotation.

Adjuvant Analgesics

Adjuvant analgesics are used to *complement* the effects of opioids. Accordingly, these drugs are employed in *combination* with opioids—not as substitutes. Adjuvant analgesics can (1) enhance analgesia from opioids, (2) help manage concurrent symptoms that exacerbate pain, and (3) treat side effects caused by opioids. Several of the adjuvants are especially useful for *neuropathic pain*. The adjuvant analgesics differ from opioids in that pain relief is limited and less predictable, and often develops slowly.

Adjuvant agents may be employed at any step on the analgesic ladder. The adjuvants are interesting in that, although they can relieve pain, all of them were developed to treat other conditions (eg, depression, seizures, dysrhythmias). Accordingly, it is important to reassure patients that the adjuvant is being used to alleviate pain, and not for its original purpose. Dosages for the adjuvant analgesics are summarized in Table 29-5.

Drug	Usual Adult Dosage	Beneficial Actions
Tricyclic Antidepressants		
Amitriptyline [Elavil]	25–150 mg/day PO	Reduce neuropathic pain
Desipramine [Norpramin]	10–150 mg/day PO	
Doxepin [Sinequan]	25–150 mg/day PO	
Imipramine [Tofranil]	20–100 mg/day PO	
Nortriptyline [Aventyl, Pamelor]	10–150 mg/day PO	
Other Antidepressants		
Bupropion [Wellbutrin]	100–450 mg/day PO	Reduce neuropathic pain
Duloxetine [Cymbalta]	30–60 mg/day PO	
Venlafaxine [Effexor]	37.5–225 mg/day PO	
Antiseizure Drugs		
Carbamazepine [Tegretol]	200–1600 mg/day PO	Reduce neuropathic pain
Gabapentin [Neurontin]	300–3600 mg/day PO	
Lamotrigine [Lamictal]	25–400 mg/day PO	
Phenytoin [Dilantin]	300–500 mg/day PO	
Pregabalin [Lyrica]	100–600 mg/day PO	
Local Anesthetics/Antidysrhythmics		
Lidocaine	5 mg/kg/day IV or subQ	Reduce neuropathic pain
Mexiletine [Mexitil]	450–600 mg/day PO	
CNS Stimulants		
Dextroamphetamine [Dexedrine]	5–10 mg/day PO	Enhance analgesia and reduce sedation from opioids
Methylphenidate [Ritalin]	10–15 mg/day PO	
Antihistamine		
Hydroxyzine [Vistaril]	300–450 mg/day IM or	Reduces anxiety, insomnia

TABLE 29-5 Adjuvant Drugs for Cancer Pain

Antidepressants

Tricyclic Antidepressants.

Amitriptyline [Elavil] and other tricyclic antidepressants (TCAs) can reduce pain of *neuropathic* origin. TCAs have analgesic effects of their own and they enhance the effects of opioids, and may thereby allow a reduction in opioid dosage. As a side benefit, TCAs can elevate mood. Important adverse effects are orthostatic hypotension, sedation, anticholinergic effects (dry mouth, urinary retention, constipation), and weight gain (secondary to improved appetite). Dosing at bedtime takes advantage of sedative effects, and minimizes hypotension during the day. Effects begin in 1 to 2 weeks and reach their maximum in 4 to 6 weeks. The TCAs are discussed at length in Chapter 32.

Other Antidepressants.

In addition to the tricyclic agents, certain other antidepressants (eg, bupropion, duloxetine, venlafaxine) can help with neuropathic pain.

Antiseizure Drugs

Certain antiseizure drugs can help relieve *neuropathic pain*. Lancinating pain (sharp, darting pain) is especially responsive, although other forms of neuropathic pain (cramping pain, aching pain, burning pain) also respond. Analgesia is thought to result from suppressing spontaneous neuronal firing. Of the available anticonvulsants, *carbamazepine* [Tegretol] has been used most widely. Because carbamazepine is myelosuppressive, it must be used with caution in patients receiving anticancer drugs that suppress bone marrow function. As discussed in Chapter 24, caution is also needed in patients of Asian descent, owing to an increased risk of severe dermatologic reactions. Recent experience indicates that *gabapentin* [Neurontin] can be very effective, while causing fewer side effects than carbamazepine. Dosage should be low initially (100 mg once a day) and then gradually increased; dosages as high as 1200 mg 3 times a day have been employed. The anticonvulsants are discussed at length in Chapter 24.

Local Anesthetics/Antidysrhythmics

Lidocaine (a local anesthetic and antidysrhythmic) and *mexiletine* (an antidysrhythmic related to lidocaine) are considered second-line agents for *neuropathic pain*. Intravenous infusion of lidocaine produces analgesia in 10 to 15 minutes. The drug may be most appropriate for rapidly escalating neuropathic pain. Both lidocaine and mexiletine are discussed in Chapter 48 (Antidysrhythmic Drugs). Lidocaine is also discussed in Chapter 26 (Local Anesthetics).

CNS Stimulants

The CNS stimulants, such as *dextroamphetamine* [Dexedrine] and *methylphenidate* [Ritalin], have two beneficial effects: they can enhance opioid-induced analgesia and they can counteract opioid-induced sedation. In addition, they can be used for rapid elevation of mood. Principal adverse effects are weight loss (because of appetite suppression) and insomnia (because of CNS stimulation). To minimize interference with sleep, dosing late in the day should be avoided. The CNS stimulants are discussed in Chapter 36.

Antihistamines

Hydroxyzine [Vistaril], an antihistamine, promotes drowsiness and reduces anxiety. Although widely believed to enhance analgesia, proof is lacking. Drawbacks include worsening of constipation, urinary retention, and cognitive impairment. The antihistamines are discussed in Chapter 69.

Glucocorticoids

Although glucocorticoids lack direct analgesic actions, they can help manage painful cancer-related conditions. Because glucocorticoids can reduce cerebral and spinal edema, they are essential for the emergency management of elevated intracranial pressure and epidural spinal cord compression. Similarly, glucocorticoids are part of the standard therapy for tumor-induced spinal cord compression. In addition to these benefits, glucocorticoids can improve appetite and impart a general sense of well-being; both actions help in managing anorexia (loss of appetite) and cachexia (weakness and emaciation) associated with terminal illness.

Glucocorticoids are very safe when used short term (even in high doses) and very dangerous when used long term (even in low doses). In particular, long-term therapy can cause adrenal insufficiency, osteoporosis, glucose intoler-

ance (hyperglycemia), increased vulnerability to infection, thinning of the skin, and, possibly, peptic ulcer disease (PUD). Therapy with NSAIDs augments the risk of PUD. The risk of osteoporosis can be reduced by giving calcium supplements and vitamin D along with calcitonin or a bisphosphonate (eg, etidronate). The glucocorticoids are discussed in Chapter 71.

Bisphosphonates

Bisphosphonates, such as *etidronate* [Didronel] and *pamidronate* [Aredia], can reduce cancer-related *bone pain* in some patients. Bone pain is common when cancers metastasize to bone. The cause of pain may be tumor-induced bone resorption, which can also cause hypercalcemia, osteoporosis, and related fractures. Bisphosphonates inhibit bone resorption and are approved for treating hypercalcemia of malignancy—but not bone pain. However, when these drugs were given to treat hypercalcemia, many patients reported a reduction in bone pain, although others did not. Hence, although these drugs appear promising, their use for management of bone pain is still considered investigational. The bisphosphonates are discussed in Chapter 74.

NONDRUG THERAPY

Invasive Procedures

Invasive therapies are the last resort for relieving intractable pain. Hence, for most patients, all other options should be exhausted first.

Neurolytic Nerve Block

The goal of this procedure is to destroy neurons that transmit pain from a limited area, thereby providing permanent pain relief. Nerve destruction is accomplished through local injection of a neurolytic (neurotoxic) substance, typically alcohol or phenol. To ensure that the right nerves are destroyed, reversible nerve block is done first, using a local anesthetic. If the local anesthetic relieves the pain, a neurolytic agent is then applied to the same site. Neurolytic nerve block can eliminate pain in up to 80% of patients. However, even if pain relief is only partial, the procedure can still permit some reduction in opioid dosage, and can thereby decrease side effects, such as sedation and constipation. When nerve block is successful and opioids are discontin-

ued, opioid dosage should be tapered gradually to avoid withdrawal. Nerve block is not without risk. Potential complications include hypotension, paresis (slight paralysis), paralysis, and disruption of bowel and bladder function (eg, diarrhea, incontinence). The incidence of complications ranges between 0.5% and 2%.

Neurosurgery

Neurosurgeons can relieve cancer pain in several ways. They can destroy neurons that transmit pain signals; they can implant opioid infusion systems; and, in a procedure known as neuroaugmentation, they can implant electrodes to stimulate neurons that release endogenous opioid peptides (eg, endorphins). Nerve damage incurred during these surgeries can result in neurologic deficits and new pain. Less than 10% of cancer patients undergo neurosurgery for pain relief.

Tumor Surgery

When curative excision of a tumor is not feasible, it may still be appropriate to surgically debulk the tumor with the goal of relieving pain. Unfortunately, palliative debulking only provides temporary relief: Growth of residual cancer cells eventually causes pain to return. Radiation therapy following the surgery may extend pain relief.

Radiation Therapy

Radiation therapy relieves pain by causing tumor regression. Palliative treatment can be directed at primary tumors and at metastases anywhere in the body.

Radiation can be delivered in three forms: *brachytherapy* (implanted radioactive pellets), *teletherapy* (external beam radiation), and *intravenous radiopharmaceuticals*. With brachytherapy, cell kill is limited to the immediate area of the implanted pellets; hence, the technique is suited only for localized tumors. With teletherapy, cell kill can be localized or widespread, depending on the size of the beam employed; hence, the technique can be used for both local tumors and metastases. Intravenous radiopharmaceuticals travel throughout the body, and hence are best suited for widespread metastases.

With radiation therapy, as with chemotherapy, damage to normal tissue is dose limiting. Therefore, the challenge is to deliver a dose of radiation that is large enough to kill cancer cells, but not so large that it causes intolerable damage to healthy tissue.

Some side effects of radiation occur early and some are late. Early effects develop during or immediately after radiation exposure. Late reactions develop months or years later. The most common early effects are skin inflammation and lesions of the GI mucosa. Fortunately, in the regimens employed for palliation, these acute effects are generally mild. The most common late reaction is fibrosis, which occurs mainly in tissues that have a limited ability to regenerate (eg, brain, peripheral neurons, lung). Late reactions are of limited concern, however, because most patients die from their cancer before late reactions can develop.

Physical and Psychosocial Interventions

Physical and psychosocial interventions can help reduce pain, but the degree of relief is limited. Accordingly, these interventions should be used only in conjunction with drug therapy—not as substitutes.

Physical Interventions

Physical interventions (eg, heat, massage, vibration) can help relieve aches and pains associated with cancer.

Heat.

Application of heat can benefit the patient in at least two ways: (1) heat promotes vasodilation, and can thereby increase delivery of oxygen and nutrients to damaged tissue; and (2) heat increases elasticity in muscle, and can thereby reduce stiffness. Heat may be applied in several ways, including use of hot compresses, hot water bottles, and electric heating pads. Heat may be harmful to tissues exposed to radiation, and hence these should be avoided. There is some concern that heat may actually stimulate tumor growth and metastatic spread, although convincing data are lacking.

Cold.

Application of cold can reduce inflammation and muscle spasm. Cold can be applied using ice packs, chemical gel packs, and towels soaked in ice water. Application should last no longer than 15 minutes. Cold should not be applied to areas damaged by radiation. In addition, because cold promotes vasoconstriction, it should be avoided in patients with peripheral vascular disease, Raynaud's phenomenon, and all other disorders that can be exacerbated by vasoconstriction.

Massage.

Massage is primarily a comfort measure that provides relief through distraction and relaxation. In addition, massage may help ease discomfort at specific sites by increasing local circulation.

Exercise.

Exercise can reduce subacute and chronic pain by increasing muscle strength and joint mobility. Additional benefits include improved cardiovascular conditioning and restoration of coordination and balance. Range-of-motion exercises can preserve strength and joint function. When patients cannot perform these exercises on their own, family members should be taught to assist. Although weight-bearing exercise is desirable, it should be avoided in patients who are at risk of fractures because of tumor invasion or osteoporosis.

Acupuncture and Transcutaneous Electrical Nerve Stimulation.

In theory, these techniques reduce pain by stimulating peripheral nerves, which in turn activate central pain-modulating pathways. However, the efficacy of both techniques in cancer patients is uncertain. Acupuncture is performed by inserting solid needles through the skin into the underlying muscle. Transcutaneous electrical nerve stimulation (TENS) is performed using low-voltage cutaneous electrodes. Because the efficacy of these techniques is questionable, pain status must be closely monitored.

Psychosocial Interventions

Psychosocial interventions can help patients cope by (1) increasing the sense of control over pain, (2) reversing negative thoughts and feelings, and (3) of-

fering social support. Interventions that require learning and practice should be introduced early, so that they can be perfected while the patient still has sufficient energy and strength to learn them.

Relaxation and Imagery.

The aim of these techniques is to reduce pain by inducing both mental relaxation (alleviation of anxiety) and physical relaxation (release of tension in skeletal muscles). These techniques are easy to learn and require little or no special equipment. Examples include (1) meditation, (2) slow rhythmic breathing, (3) imagining a peaceful scene (eg, gentle waves breaking on a secluded, sunny beach), and (4) active listening to recorded music (eg, tapping a finger in time to an enjoyable tune).

Cognitive Distraction.

The goal of cognitive distraction is to divert attention away from pain and associated negative emotions. Distractions may be internal or external. Examples of internal distractions include praying, counting or singing in one's head, and repeating positive thoughts, such as "I can cope." External distractions include watching TV, listening to music, and conversing with friends.

Peer Support Groups.

Support groups composed of other cancer patients can help members cope with pain and all other sequelae of their disease. These groups can provide emotional support, cancer-related information, and a sense of social belonging. Talking with other cancer survivors can be especially helpful for the newly diagnosed. Some support groups welcome patients who have any form of cancer; others are dedicated to just one form of the disease (eg, breast cancer). Resources for locating a support group in your community include (1) the National Coalition for Cancer Survivorship, at 1-877-622-7937; (2) the National Cancer Information Service, at 1-800-4-CANCER; and (3) your local chapter of the American Cancer Society, whose number should be in your phone book.

PAIN MANAGEMENT IN SPECIAL POPULATIONS

The Elderly

In elderly patients, two issues are of special concern: (1) undertreatment of pain and (2) increased risk of adverse effects. Paradoxically, a third issue—heightened drug sensitivity—contributes to both problems.

Heightened Drug Sensitivity.

The elderly are more sensitive to drugs than are younger adults, owing largely to a decline in organ function. In particular, rates of hepatic metabolism and renal excretion decline with age. As a result, drugs tend to accumulate in the body, causing responses to be more intense and prolonged.

Undertreatment of Pain.

Undertreatment is common in the elderly. In addition to the usual reasons (fears about tolerance, addiction, adverse effects, and regulatory actions), the elderly are denied adequate medication for two more: difficulties with assessment and erroneous ideas about old age.

Assessment is made difficult by cognitive impairment (eg, delirium, dementia) and by impairment of vision and hearing. As a result, self-reporting of pain may be inaccurate or even impossible. Because of these obstacles, special effort must be made to help ensure that assessment is accurate. However, because accuracy cannot be guaranteed, frequent reassessment is recommended.

Misconceptions about the elderly contribute to undertreatment. Specifically, providers may believe (incorrectly) that dosage should be low because (1) the elderly are relatively insensitive to pain; (2) if pain occurs, the elderly can tolerate it well; and (3) the elderly are highly sensitive to opioid side effects. The first two concepts have no basis in fact, and therefore must not be allowed to influence treatment. Although there is some truth to the third concept, concern about side effects is no excuse for inadequate dosing.

Increased Risk of Side Effects and Adverse Interactions.

For several reasons, elderly patients may experience more side effects than younger adults. As noted, drug elimination in the elderly is impaired, posing a risk that drug levels may rise dangerously high. However, with careful dosing, drug levels can be kept within a range that is both safe and effective. Drugs

with prolonged half-lives (eg, methadone) pose an increased risk of excessive accumulation, and should be avoided.

The risk of gastric ulceration and renal toxicity from NSAIDs is increased in older patients. Gastric erosion can be reduced by concurrent therapy with misoprostol. There is no specific way to prevent renal toxicity. Hence, the best we can do is monitor closely for evolving kidney damage.

Older patients are at increased risk of adverse drug-drug interactions. Why? Because, in addition to the disorder that's causing pain, the elderly are likely to have other disorders, and hence require more drugs than younger adults. The risk of serious injury from drug interactions can be reduced by careful drug selection and by monitoring for potential reactions.

Young Children

Management of cancer pain in children is much like management in adults. The principal difference is that assessment in children is more difficult. In addition, children frequently experience more pain from chemotherapy and other interventions than from the cancer itself.

Assessment

Assessment must be tailored to the child's developmental level and personality. Selecting an appropriate assessment method is especially important for children with developmental delays, learning disabilities, and emotional disturbances. Assessment can be greatly facilitated by open communication about pain between the child, family, and healthcare team.

Assessment methods include self-reporting, behavioral observation, and measurement of physiologic parameters (eg, heart rate, blood pressure, respiratory rate, sweating). As stressed earlier, self-reporting is preferred and should be employed whenever appropriate. Behavioral observation is a distant second choice. Because many factors other than pain can alter physiologic parameters, measuring these is the least reliable way to assess pain.

Verbal Children.

For children who can verbalize and are over the age of 4 years, self-reporting is the most reliable way to assess pain. Since children rarely claim to have

pain that isn't there, there is little risk of error from over-reporting. However, there *is* a significant risk of error from under-reporting. Children may report less pain than they have for several reasons. These include (1) fear that revealing their pain will lead to additional injections and other painful procedures, (2) lack of awareness that we can help their pain go away, (3) a desire to protect their parents from the knowledge that their cancer is getting worse, and (4) a desire to please. Because the self-report may conceal pain, it can be helpful to supplement the self-report with behavioral observation (see below).

Preverbal and Nonverbal Children.

Since preverbal and nonverbal children cannot self-report pain, a less reliable method must be used for assessment. The principal alternative is *behavioral observation*. Behavioral cues suggesting pain include vocalization (crying, whining, groaning), facial expression (grimacing, frowning, reduced affect), muscle tension, inability to be consoled, protection of body areas, and reduced activity. The biggest drawback to behavioral observation is the risk of a false-negative conclusion. That is, a child may be in pain although his or her behavior may lead the observer to conclude otherwise. For example, sleeping, watching TV, or laughing may suggest that a child is comfortable. However, these behaviors can actually represent an attempt to control pain. Similarly, although sitting quietly might indicate comfort, it could also mean that moving and talking are painful. When behavioral observation leaves doubt about whether the child is in pain, a trial with an analgesic can help confirm the assessment.

Treatment

Therapy of cancer pain in children is essentially the same as in adults. As in adults, drugs are the cornerstone of treatment; nondrug therapies are used only as supplements. Drug selection is guided by the WHO analgesic ladder. Because of the risk of Reye's syndrome, children with influenza or chickenpox should not receive NSAIDs; acetaminophen is a safe alternative. As in adults, oral administration is preferred; more invasive routes should be reserved for patients who cannot take drugs by mouth. Children generally object to rectal administration, and may refuse treatment by this route. Administration with a PCA device is an option for children over the age of 7 years.

Neonates and infants are highly sensitive to drugs, and hence must be treated with special caution. Drug sensitivity occurs for two reasons: (1) the blood-brain barrier is incompletely formed, giving drugs ready access to the CNS; and (2) the kidneys and liver are poorly developed, causing drug elimination to be slow. Because of heightened drug sensitivity, neonates and infants are at increased risk of respiratory depression from opioids. Accordingly, when opioids are given to nonventilated infants, the initial dosage should be very low (about one-third the dosage employed for older children). Furthermore, use of opioids should be accompanied by intensive monitoring of respiration.

Opioid Abusers

When treating cancer pain in opioid abusers, we have two primary obligations: we must try to (1) relieve the pain and (2) avoid giving opioids simply because the patient wants to get high. Both obligations are difficult to meet. Because of the challenge, treatment should be directed by a clinician trained in substance abuse as well as pain management.

Concerns about abuse can result in undertreatment of pain. This must be avoided. Remember, abusers feel pain like everyone else, and therefore need opioids like everyone else. Clinicians must take special care not to withhold opioids because they have confused relief-seeking behavior with drug-seeking behavior. In the end, we have little choice but to base treatment on the patient's self-report of pain. Hence, if the patient tells us that pain is persisting, adequate doses of opioids should be provided.

Because of opioid tolerance, initial doses in abusers must be higher than in nonabusers. To estimate how high the initial dosage should be, we must try to estimate the existing degree of tolerance by interviewing the patient about the extent of opioid use.

As with other adults, drug selection can be guided by the WHO analgesic ladder and the NCCN guidelines. If pain is sufficient to justify opioids, then opioids should be used; nonopioids (NSAIDs and acetaminophen) should not be substituted for opioids out of concern for addiction. If the patient is on methadone maintenance, methadone can be used for the pain. However, because regulations limit the dosage of methadone that drug-abuse clinics can dispense, the increased dosage required to manage pain will have to come

from another source. One group of opioids—the agonist-antagonists—will precipitate withdrawal in opioid abusers, and hence must never be prescribed for these patients.

Drug delivery with a PCA device can be helpful. By using a PCA device, we can avoid potential conflicts between the patient and the clinician, who would otherwise have to administer each dose. Excessive dosing can be prevented by setting the PCA device to limit how much opioid the patient can self-administer.

PATIENT EDUCATION

Patient education is an integral part of cancer pain management. When education is successful, it can help reduce anxiety, dispel hopelessness, facilitate assessment, enhance compliance, decrease complications, provide a sense of control, and enable patients to take an active role in their care. All of these will promote pain relief.

General Issues

Common sense tells us that patient education should be accurate, comprehensive, and understandable. To reinforce communication, information should be presented at least twice and in more than one way. Major topics to discuss are (1) the nature and causes of pain, (2) assessment and the importance of honest self-reporting, and (3) plans for drug and nondrug therapy. Patients should be encouraged to express their fears and concerns about cancer, cancer pain, and pain treatment—and they should be reassured that pain can be effectively controlled in most cases. All patients should receive a written pain management plan. To facilitate ongoing education, patients should be invited to contact care providers whenever they feel the need—be it to discuss specific concerns with treatment or simply to acquire new information. Finally, patients should know when and how to contact the prescriber to report treatment failure, serious side effects, or new pain.

Drug Therapy

The goal in teaching patients about analgesic drugs is to maximize pain relief and minimize harm. To help achieve this goal, patients should know the following about each drug they take:

- Drug name and therapeutic category
- Dosage size and dosing schedule
- Route and technique of administration
- Expected therapeutic response and when it should develop
- Duration of treatment
- Method of drug storage
- Symptoms of major adverse effects and measures to minimize discomfort and harm
- Major adverse drug-drug and drug-food interactions
- Whom to contact in the event of therapeutic failure, severe adverse effects, or severe adverse interactions

The dosing schedule should be discussed. Patients should understand that PRN dosing is appropriate only if pain is intermittent. When pain is persistent, as it is for most patients, the objective is to *prevent* pain from returning. Hence, dosing should be done on a fixed schedule ATC, not PRN. However, even with ATC dosing, breakthrough pain can occur. Hence, patients should be taught what dosage to use for rescue treatment.

Fears based on misconceptions about opioids can impair compliance, and can thereby impair pain control. The misconceptions that influence compliance most relate to tolerance, physical dependence, addiction, and side effects. To correct these misconceptions, and thereby dispel fears and improve compliance, the following topics should be discussed:

- *Tolerance*—Some patients fear that, because of tolerance, taking opioids now will decrease their effectiveness later. Hence, to help ensure pain relief in the future, they limit opioid use now, and thus suffer needless pain. These patients should be reassured that, if tolerance does develop, efficacy can be restored by increasing the dosage; tolerance does not mean that efficacy is lost.
- *Physical Dependence and Addiction*—Many patients fear opioid addiction, and hence are reluctant to take these drugs. This fear is based largely on the misconception that physical dependence (which eventually develops in all pa-

tients) equals addiction. Patients should be taught that physical dependence is not the same as addiction, and that physical dependence itself is nothing to fear. In addition, they should be taught that the behavior pattern that constitutes addiction rarely develops in people who take opioids in a therapeutic setting.

- *Fear of Severe Side Effects*—Some patients fear that opioids cannot relieve pain without causing severe side effects. These patients should be reassured that, when used correctly, opioids are both safe and effective. The most dangerous side effect—respiratory depression—is uncommon.

The rationale for using an adjuvant analgesic should be discussed. With all of the adjuvants, the objective is to *complement* the effects of opioid and nonopioid analgesics. Adjuvants are not intended to substitute for these drugs. Furthermore, because the drugs we use as adjuvants were originally developed to treat disorders other than pain, the rationale for prescribing specific adjuvants should be explained. For example, when imipramine is prescribed, the patient should understand that the objective is to relieve neuropathic pain and not depression, the disorder for which this drug was originally developed.

Basic issues related to patient education in drug therapy are discussed at length in Chapter 2.

Nondrug Therapy

Education regarding nondrug therapy focuses on psychosocial interventions. Patients should understand that these interventions are intended as complements to analgesics—not as alternatives. Techniques for imagery, relaxation, and distraction should be introduced early in treatment. Family caregivers should be taught how to apply heat and cold and how to give a therapeutic massage. Patients should be informed about the benefits of peer support groups and given assistance in locating one.

THE JOINT COMMISSION PAIN MANAGEMENT STANDARDS

Thanks to *The Joint Commission* (TJC)—formerly known as the *Joint Commission on Accreditation of Healthcare Organizations* (JCAHO)—undertreatment of pain will no longer be tolerated. For readers who may not know, TJC is the authority that accredits hospitals and other healthcare institutions in the United

States. On January 1, 2001, TJC established a set of standards designed to make assessment and management of pain a priority in the nation's healthcare system. Under the standards, *accountability for pain management is shifted from individual practitioners to the institution as a whole*. Compliance is mandatory: Healthcare organizations that fail to meet the standards will lose accreditation. This is serious. Why? Because loss of accreditation would mean loss of insurance reimbursement, and would disqualify teaching hospitals from offering training programs. Hence, thanks to the enforcement power wielded by TJC, healthcare institutions in the United States now have a very real incentive to correct the persistent problem of pain undertreatment. It should be noted that the standards are *not* a guideline on how to treat specific kinds of pain. Rather, they focus on (1) the rights of patients to receive appropriate assessment and management of pain and (2) ways for institutions to establish a formalized, systematic approach to pain management that involves interdisciplinary teams whose members have clearly identified responsibilities. Specific provisions include the following:

- Institutions must recognize assessment and management of pain as a right of all patients.
- Institutions must assess all patients for pain and, if pain is present, identify its nature and intensity.
- Pain must be regarded as a "fifth vital sign," and pain intensity must be quantified and recorded along with blood pressure, heart rate, respiration, and temperature.
- Institutions must educate patients and their families about pain management, and must provide ready access to educational materials.
- Institutions must educate clinical staff about assessment and management of pain and must document the education provided.
- Institutions must establish a system to monitor pain management, including a system of checks and balances in which individuals who assess and manage pain are monitored for compliance with standards set by the institution.
- Institutions must monitor patient satisfaction with pain management.
- Discharge planning must provide for continuing reassessment and management of pain.

Where can you find the new standards? Unfortunately, they don't exist as a separate document. Rather, TJC has inserted content related to pain management throughout existing manuals, including the *Comprehensive Accreditation Manual for Hospitals: The Official Handbook*. If you don't want to search through the manuals, a summary is available: *Pain Assessment and Management: An Organizational Approach,* published by Joint Commission Resources, Inc.

KEY POINTS

- Cancer pain can be relieved in 90% of patients.
- Despite the availability of effective treatments, cancer pain goes unrelieved in a large number of patients.
- Barriers to pain relief include inadequate prescriber training, fears of addiction, and a healthcare system that, until recently, has put a low priority on pain management.
- Pain is a personal, subjective experience that encompasses not only the sensory perception of pain but also the patient's emotional and cognitive responses to both the painful sensation and the underlying disease.
- Pain has two major forms: nociceptive pain, which results from injury to tissues, and neuropathic pain, which results from injury to peripheral nerves.
- Management of cancer pain is an ongoing process that involves repeated cycles of assessment, intervention, and reassessment. The goal is to create an individualized treatment plan that can meet the changing needs of the patient.
- The patient self-report is the cornerstone of assessment.
- Behavioral observation is a poor substitute for the patient self-report as a method of assessment.
- Analgesic drugs are the principal modality for treating cancer pain.
- Three groups of analgesics are employed: nonopioid analgesics (NSAIDs and acetaminophen), opioid analgesics, and adjuvant analgesics.

- Drug selection is guided by the WHO analgesic ladder: As pain intensity increases, treatment progresses from nonopioid analgesics to opioids of moderate strength (eg, oxycodone), and then to powerful opioids (eg, morphine). Adjuvant analgesics can be used at any time. If pain is already intense, treatment can start with an opioid, rather than trying a nonopioid first.
- Because nonopioids and opioids relieve pain by different mechanisms, combining an opioid with a nonopioid can be more effective than either drug alone.
- NSAIDs produce their effects by inhibiting cyclooxygenase (COX), an enzyme with two basic forms: COX-1 and COX-2.
- Most NSAIDs inhibit both COX-1 and COX-2. A few NSAIDs are COX-2 selective.
- Principal adverse effects of the NSAIDs are GI injury, acute renal failure, and bleeding. In addition, all NSAIDs except aspirin pose a risk of thrombotic events.
- The COX-2 inhibitors cause less GI injury than the nonselective NSAIDs, but they pose a greater risk of thrombotic events. Accordingly, long-term use of COX-2 inhibitors is no longer recommended.
- By inhibiting platelet aggregation, NSAIDs increase the risk of bruising and bleeding in patients with thrombocytopenia, a common side effect of cancer chemotherapy.
- In contrast to opioids, NSAIDs do not cause tolerance, physical dependence, or psychologic dependence.
- Acetaminophen relieves pain but, unlike the NSAIDs, does not suppress inflammation, inhibit platelet aggregation, or promote gastric ulceration or renal failure.
- Because acetaminophen does not affect platelets, the drug is safe for patients with thrombocytopenia.
- Combining acetaminophen with alcohol, even in moderate amounts, can result in potentially fatal liver damage.
- Opioids are the most effective analgesics available, and hence are the primary drugs for treating moderate to severe cancer pain.

- Opioids are especially effective against nociceptive pain; efficacy against neuropathic pain is limited.
- Opioid analgesics relieve pain by mimicking the actions of endogenous opioid peptides (enkephalins, dynorphins, endorphins), primarily at mu receptors in the CNS.
- The opioids fall into two major groups: pure (full) agonists (eg, morphine) and agonist-antagonists (eg, butorphanol).
- There is a ceiling to pain relief with the agonist-antagonists, but not with the pure agonists. Hence, for patients with cancer, pure agonists are generally preferred.
- For most patients, opioids should be given on a fixed schedule ATC, with additional doses provided for breakthrough pain. PRN dosing should be limited to patients with intermittent pain.
- Oral administration is preferred for most patients; transdermal administration is a good alternative.
- Intramuscular opioids are painful and should be avoided.
- PCA is a desirable method of opioid delivery because it gives patients more control over their treatment.
- An equianalgesia table can facilitate dosage selection when switching from one opioid to another or from one route to another.
- Over time, opioids cause tolerance, a state in which a specific dose produces a smaller effect than it could when treatment began.
- Tolerance develops to analgesia, euphoria, respiratory depression, and sedation, but not to constipation.
- Over time, opioids produce physical dependence, a state in which an abstinence syndrome will occur if the drug is abruptly withdrawn. *Note:* Physical dependence is NOT the same as addiction!
- Addiction is a behavior pattern characterized by continued use of a psychoactive substance despite physical, psychologic, or social harm. *Note:* Addiction is NOT the same as physical dependence!
- Addiction to opioids is very rare in people taking these drugs to relieve pain.

- Misconceptions about opioid addiction are a major cause for undertreatment of cancer pain. Accordingly, we must correct these misconceptions by teaching physicians, nurses, patients, and family members that (1) addiction is not the same as physical dependence and (2) addiction is very rare in therapeutic settings.
- Respiratory depression is the most dangerous side effect of the opioids. Fortunately, significant respiratory depression is rare.
- Respiratory depression is increased by other drugs with CNS-depressant actions (eg, alcohol, barbiturates, benzodiazepines). Accordingly, combining these agents with opioids should be avoided.
- Severe respiratory depression can be reversed with naloxone [Narcan], an opioid antagonist. However, because excessive naloxone will reverse opioid analgesia and precipitate withdrawal, dosage must be titrated carefully.
- Opioids cause constipation in most patients. No tolerance develops. Constipation can be minimized by increasing dietary fiber and fluids, and by taking one or more appropriate drugs (stool softener, stimulant laxative, osmotic laxative, peripherally acting opioid antagonist).
- Use of meperidine (a pure opioid agonist) should be limited to a few days because, with longer use, a toxic metabolite can accumulate.
- Agonist-antagonist opioids must not be given to patients taking pure opioid agonists because doing so could reduce analgesia and precipitate withdrawal.
- Adjuvant analgesics can enhance analgesia from opioids, help manage concurrent symptoms that exacerbate pain, and treat side effects caused by opioids. In addition, several adjuvants are effective against neuropathic pain.
- Adjuvant analgesics are given to complement the effects of opioids. Accordingly, these drugs are employed in combination with opioids—not as substitutes.
- Invasive therapies (nerve blocks, neurosurgical procedures, radiation) are the last resort for relieving intractable pain. All other options should be exhausted before these are tried.

- Physical interventions (eg, heat, cold, massage, acupuncture, TENS) and psychosocial interventions (eg, relaxation, imagery, cognitive distraction, peer support groups) can help reduce pain, but the degree of relief is limited. Accordingly, these interventions should be used only in conjunction with drug therapy—not as substitutes.
- Elderly patients are more sensitive to drugs than are younger adults. The principal reason is drug accumulation secondary to a decline in hepatic metabolism and renal excretion.
- Undertreatment of pain is especially common in the elderly. Undertreatment is inexcusable and must not be allowed.
- The elderly are at risk of increased side effects and adverse drug interactions. Careful drug selection and monitoring can minimize risk.
- Management of cancer pain in children is much like management in adults, except that assessment is more difficult.
- For children who can verbalize and are older than 4 years, self-reporting is the most reliable way to assess pain. The self-report can be supplemented with behavioral observation to enhance accuracy.
- Preverbal and nonverbal children cannot self-report pain, and hence a less reliable assessment method must be used. The principal option is behavioral observation, a method that carries a significant risk of underassessment.
- When opioid abusers get cancer, they feel pain and need relief like everyone else. If pain is sufficient to justify opioids, then opioids should be used; nonopioids should not be substituted for opioids out of concern for addiction.
- Pain management standards from TJC are designed to make pain relief an institutional priority, and hence should greatly reduce the incidence of pain undertreatment.

30 Drugs for Headache

Headache is a common symptom that can be triggered by a variety of stimuli, including stress, fatigue, acute illness, and sensitivity to alcohol. Many people experience mild, episodic headaches that can be relieved with over-the-counter medications, such as aspirin, acetaminophen [Tylenol], and ibuprofen [Motrin, Advil]. For these individuals, medical intervention is unnecessary. In contrast, some people experience severe, recurrent, debilitating headaches that are frequently unresponsive to aspirin-like drugs. For these individuals, medical attention is merited. In this chapter, we focus on severe forms of headache—specifically, migraine, cluster, and tension-type headaches. Defining characteristics of these headaches are summarized in Table 30-1.

	Migraine	Cluster Headache	Tension-type Headache
Pain Location	Unilateral (60%) Bilateral (40%)	Unilateral, behind the right or left eye	Bilateral, in "headband" configuration
Pain Quality	Throbbing	Throbbing, sometimes piercing	Nonthrobbing
Pain Severity	Moderate to severe	Severe	Mild to moderate
Duration	4 hr to 3 days	15 min to 2 hr*	30 min to 7 days†
Impact of Activity	Makes pain worse	None	None
Associated Symptoms	Nausea, vomiting, photophobia, phonophobia	Conjunctival redness, lacrimation, nasal congestion, rhinorrhea, ptosis, miosis—all on the same side as the headache	Uncommon
Usual Time of Onset	Early morning	Nighttime	Daytime
Preceded by Aura	Yes, in 30% of cases	No	No
Triggers	Many (see Table 30-2)	Usually unidentified	Tension, anxiety
Gender Prevalence	More common in females (3:1)	More common in males (5:1)	Slightly (10%) more common in females
Family History	Likely	Unlikely	Unlikely
Impact on Daily Life	Often substantial	Usually substantial	Minimal

TABLE 30-1 Characteristics of Major Headache Syndromes

* Headaches occur in clusters that typically consist of one or more headaches (lasting 15 minutes to 2 hours) every day for 2 to 3 months, with a headache-free interval (months to years) between each cluster.

† *Chronic* tension headaches occur at least 15 days per month for 6 months or longer.

When attempting to treat headache, we must differentiate between headaches that have an identifiable underlying cause (eg, severe hypertension; hyperthyroidism; tumors; infection; disorders of the eye, ear, nose, sinuses, and throat) and headaches that have no identifiable cause (eg, migraine and cluster headaches). Obviously, if there is a clear cause, it should be treated directly.

As we consider drugs for headache, keep three basic principles in mind. First, anti-headache drugs may be used in two ways: to abort an ongoing attack or to prevent an attack from occurring. Second, not all patients with a particular type of headache respond to the same drugs; hence, therapy must be individualized. Third, several of the drugs employed to treat severe headaches (eg, ergotamine, opioids) can cause physical dependence. Accordingly, every effort should be made to keep dependence from developing. If dependence does develop, a withdrawal procedure is needed.

MIGRAINE HEADACHE I: CHARACTERISTICS AND OVERVIEW OF TREATMENT

Characteristics

Migraine headache is characterized by throbbing head pain of moderate to severe intensity that may be unilateral (60%) or bilateral (40%). Most patients also experience nausea and vomiting, along with sensitivity to light and sound. Physical activity intensifies the pain. Migraines usually develop in the morning after arising. Pain increases gradually and lasts 4 to 72 hours (median duration 24 hours). On average, attacks occur 1.5 times a month. Precipitating factors include anxiety, fatigue, stress, menstruation, alcohol, weather changes, and tyramine-containing foods (Table 30-2).

Migraine has two primary forms: migraine *with aura* (formerly called classic migraine) and migraine *without aura* (formerly called common migraine). In migraine with aura, the headache is preceded by visual symptoms (flashes of light,

a blank area in the field of vision, zigzag patterns). Of the two forms, migraine without aura is more common, affecting about 70% of migraineurs.

In the United States, 29.5 million people suffer from migraine. The disorder affects nearly 1 in 5 women and 1 in 20 men. About 65% of migraineurs are women in their late teens, 20s, or 30s. With some women, migraine attacks are worse during menstruation but subside during pregnancy and cease after menopause, indicating a hormonal component to the attacks. A family history of the disease is typical.

TABLE 30-2 Factors That Can Precipitate Migraine Headache

Emotions

Stress

Anticipation

Anxiety

Depression

Excitement

Frustration

Foods That Contain:

Tyramine (eg, aged cheeses, Chianti wine)

Nitrates (eg, cured meat products)

Phenylethylamine (eg, chocolate)

Monosodium glutamate (eg, Chinese food, canned soups)

Aspartame (eg, diet sodas, artificial sweeteners)

Yellow food coloring

Drugs

Alcohol

Analgesics (excessive use or withdrawal)

Caffeine (excessive use or withdrawal)

Cimetidine

Cocaine

Estrogens (eg, oral contraceptives)

Nitroglycerin

Weather

Low temperature and low humidity

High temperature and high humidity

Major weather change over 1–2 days

High or low barometric pressure

Others

Carbon monoxide

Hormonal changes in women

Flickering lights/glare

Loud noises

Hypoglycemia

Change in altitude

Migraine is highly debilitating. An attack can prevent participation in social and leisure activities, and can result in lost productivity at home, school, and work. According to the World Health Organization, disability caused by a severe migraine attack equals that caused by quadriplegia, psychosis, or dementia.

Pathophysiology

Migraine headache is a *neurovascular* disorder that involves *dilation* and *inflammation* of intracranial blood vessels. Headache generation begins with neural events that trigger vasodilation. Vasodilation then leads to pain, which leads to further neural activation, thereby amplifying pain-generating signals. Neurons of the trigeminal vascular system, which innervate intracranial blood vessels, are key components.

The exact cause of migraine pain is not completely understood—although vasodilation and inflammation are clearly involved. Available data suggest that two compounds—*calcitonin gene-related peptide* (CGRP) and *serotonin* (5-hydroxytryptamine [5-HT])—play important roles. The role of CGRP is to

promote migraine, and the role of 5-HT is to *suppress* migraine. Data that implicate CGRP as a cause of migraine include the following:

- Plasma levels of CGRP rise during a migraine attack.
- Stimulation of neurons of the trigeminal vascular system promotes release of CGRP, which in turn promotes vasodilation and release of inflammatory neuropeptides.
- Administration of sumatriptan, a drug that relieves migraine, lowers elevated levels of CGRP.
- Sumatriptan can suppress release of CGRP from cultured trigeminal neurons.

Data that support a suppressive role for 5-HT include the following:

- Plasma levels of 5-HT drop by 50% during a migraine attack.
- Depletion of 5-HT with reserpine can precipitate an attack in migraine-prone individuals.
- Administration of 5-HT or sumatriptan, both of which activate 5-HT receptors, can abort an ongoing attack.

Overview of Treatment

Drugs for migraine are employed in two ways: to abort an ongoing attack and to prevent attacks from occurring. Drugs used to abort an attack fall into two groups: nonspecific analgesics (aspirin-like drugs and opioid analgesics) and migraine-specific drugs (ergot alkaloids and serotonin***1B/1D*** receptor agonists [triptans]). Drugs employed for prophylaxis include beta blockers (eg, propranolol), tricyclic antidepressants (eg, amitriptyline), and antiepileptic drugs (eg, divalproex).

Nondrug measures can help. Patients should try to control or eliminate triggers (see Table 30-2) and should maintain a regular pattern of eating, sleeping, and exercise. Why? Because, in people with migraine, the brain seems to have a low tolerance for the ups and downs of life. Once an attack has begun, the migraineur should retire to a dark, quiet room. Placing an ice pack on the neck and scalp can help.

MIGRAINE HEADACHE II: ABORTIVE THERAPY

The objective of abortive therapy is to eliminate headache pain and suppress associated nausea and vomiting. Treatment should commence at the earliest sign of an attack. Because migraine causes GI disturbances (nausea, vomiting, and gastric stasis), oral therapy may be ineffective once an attack has begun. Hence, for treatment of an established attack, a drug that can be administered by injection, inhalation, or rectal suppository may be best. As noted, two types of drugs are used: nonspecific analgesics and migraine-specific agents. Representative drugs are listed in Table 30-3.

Drug selection depends on the intensity of the attack. For mild to moderate symptoms, an *aspirin-like drug* (eg, aspirin, naproxen, acetaminophen) may be sufficient. For moderate to severe symptoms, patients should take a migraine-specific drug—either an *ergot alkaloid* (ergotamine or dihydroergotamine) or a *serotonin**1B/1D** agonist*. If these agents fail to relieve pain, an *opioid analgesic* (eg, butorphanol, meperidine) may be needed.

Use of abortive medications (both nonspecific and migraine specific) should be limited to 1 or 2 days a week. Why? Because more frequent use can lead to *medication overuse headache* (MOH), also known as drug-induced headache or drug-rebound headache (Box 30-1).

Antiemetics are important adjuncts to migraine therapy. By reducing nausea and vomiting, these drugs can (1) make the patient more comfortable, and (2) permit therapy with oral antimigraine drugs. Two antiemetics—*metoclopramide* [Reglan] and *prochlorperazine* [Compazine]—are used most often. Of the two, metoclopramide is preferred. Why? Because, in addition to suppressing nausea and vomiting, metoclopramide can reverse gastric stasis caused by the attack, and can thereby facilitate absorption of oral antimigraine drugs. Like metoclopramide, prochlorperazine suppresses nausea and vomiting. However, because of its anticholinergic actions, prochlorperazine can make gastric stasis even worse.

Analgesics

Aspirin-like Drugs

Aspirin, acetaminophen, naproxen, and other aspirin-like analgesics can provide adequate relief of mild to moderate migraine attacks. In fact, when

combined with metoclopramide (to enhance absorption), aspirin may work as well as sumatriptan, a highly effective antimigraine drug. Moreover, the combination of aspirin plus metoclopramide costs less than sumatriptan and causes fewer adverse effects.

Acetaminophen should be used only in combination with other drugs. It should not be used alone. One effective combination, marketed as *Excedrin Migraine,* consists of acetaminophen, aspirin, and caffeine. An older and less effective product, marketed as *Midrin,* consists of acetaminophen, isometheptene (a sympathomimetic drug), and dichloralphenazone (a sedative).

Opioid Analgesics

Opioid analgesics are reserved for severe migraine that has not responded to first-line medications. The agents used most often are *meperidine* [Demerol] and *butorphanol nasal spray* [Stadol NS]. Of the two, butorphanol is preferred. Why? Because meperidine can cause all of the adverse effects associated with other pure opioid agonists (eg, respiratory depression, sedation, constipation) and also has significant abuse potential. These drawbacks are less of a problem with butorphanol.

TABLE 30-3 Migraine Headache: Drugs for Abortive Therapy

Nonspecific Analgesics

Aspirin-like Drugs

Nonsteroidal anti-inflammatory drugs (eg, aspirin, naproxen)

Acetaminophen + Aspirin + Caffeine [Excedrin Migraine]

Opioid Analgesics

Butorphanol [Stadol NS]

Meperidine [Demerol]

Migraine-Specific Drugs

Ergot Alkaloids

Dihydroergotamine [D.H.E. 45, Migranal]

Ergotamine [Ergomar]

Ergotamine + Caffeine [Cafergot, Ercaf]

Selective Serotonin*1B/1D* Receptor Agonists (Triptans)

Almotriptan [Axert]

Eletriptan [Relpax]

Frovatriptan [Frova]

Naratriptan [Amerge]

Rizatriptan [Maxalt]

Sumatriptan [Imitrex]

Zolmitriptan [Zomig]

Ergot Alkaloids

Ergotamine

Mechanism of Antimigraine Action.

The actions of ergotamine are complex, and the precise mechanism by which the drug aborts migraine attacks is unknown. Ergotamine can alter transmission at serotonergic, dopaminergic, and alpha-adrenergic junctions. Current evidence suggests that antimigraine effects are related to agonist activity at subtypes of serotonin receptors, specifically 5-HT*1B* and 5-HT*1D* receptors. Additional evidence indicates that ergotamine can block inflammation associated with the trigeminal vascular system, perhaps by suppressing release of CGRP. Relief may also be related to vascular effects. In cranial arteries, ergotamine acts directly to promote constriction and reduce the amplitude of pulsations. In addition, the drug can affect blood flow by depressing the vasomotor center.

Therapeutic Uses.

Ergotamine is a drug of choice for stopping an ongoing migraine attack. It is also used to treat cluster headaches. Because of the risk of dependence (see below), ergotamine should not be taken daily on a long-term basis.

Pharmacokinetics.

Administration may be oral, sublingual, rectal, or by inhalation. Bioavailability with oral and sublingual administration is low. Bioavailability with rectal and inhalation administration is higher. Although the half-life of ergotamine is only 2 hours, pharmacologic effects can still be observed 24 hours after dosing. Ergotamine undergoes metabolism by CYP3A4 (the 3A4 isozyme of cytochrome P450) followed by excretion in the bile.

Adverse Effects.

Ergotamine is well tolerated at usual therapeutic doses. The drug can stimulate the chemoreceptor trigger zone, causing *nausea and vomiting* in about 10% of patients, thereby augmenting nausea and vomiting caused by the migraine itself. Concurrent treatment with metoclopramide or a phenothiazine antiemetic (eg, prochlorperazine) can help reduce these responses. Other common side effects include *weakness in the legs, myalgia, numbness and tingling in fingers and toes, angina-like pain,* and *tachycardia or bradycardia*.

BOX 30-1 MEDICATION OVERUSE HEADACHE: TOO MUCH OF A GOOD THING

People who take headache medicine every day often develop medication overuse headaches (MOHs), also known as drug-rebound headaches or drug-induced headaches. What's a MOH? A chronic headache that develops in response to frequent use of headache medicines, and that resolves days to weeks after the overused drug is withdrawn. The stage for MOH is set when headache drugs are taken too often—especially if the dosage is high. Once the stage has been set, discontinuing the medication brings on the MOH, which causes the patient to resume taking medicine—thereby setting up a repeating cycle of MOH, followed by medication use and discontinuation, followed by another MOH, and so on. One reason the cycle gets established is that patients don't realize that the drugs they're taking to *treat* headache can, if taken too often, become the *cause* of headache. Failing to recognize MOH for what it is, patients take more and more medicine to make their headaches go away—but only succeed in making MOH worse.

Which drugs can cause MOH? Almost all of the medicines used for abortive headache therapy. Hence, MOH can be caused by overuse of analgesics

(aspirin-like drugs, opioids), ergotamine (but not dihydroergotamine), triptans, and caffeine.

How can MOH be treated? The only hope is to stop taking headache medicine. Unfortunately, when medication is withdrawn, headaches will increase for a while. Their duration and intensity depend on the drug that was overused. With triptans, withdrawal headaches are relatively mild and often resolve in a few days. In contrast, with analgesics or ergots, withdrawal headaches are more intense and may persist for 2 weeks or more.

Several measures can decrease the risk of MOH. The most important is limiting the use of abortive medicines. If possible, patients should take these drugs no more than 2 or 3 times a week—and doses should be no higher than actually needed. Alternating headache medicines may help too, since this would limit exposure to any one drug. If headaches begin to occur more than 2 or 3 times a month, prophylactic therapy should be tried. Implementing nondrug measures—stress reduction, avoidance of triggers, getting sufficient sleep, relaxation techniques, and biofeedback—can reduce the need for headache medicines, and can thereby decrease exposure to the drugs that cause MOH.

Overdose.

Acute or chronic overdose can cause serious toxicity referred to as *ergotism*. In addition to the adverse effects seen at therapeutic doses, overdose can cause ischemia secondary to constriction of peripheral arteries and arterioles: the extremities become cold, pale, and numb; muscle pain develops; and gangrene may eventually result. Patients should be informed about these responses and instructed to seek immediate medical attention if they develop. The risk of ergotism is highest in patients with sepsis, peripheral vascular disease, and renal or hepatic impairment. Management consists of discontinuing ergotamine, followed by measures to maintain circulation (treatment with anticoagulants, low-molecular-weight dextran, and/or intravenous nitroprusside as appropriate).

Drug Interactions.

Triptans.

Ergotamine should not be combined with triptans (eg, sumatriptan, zolmitriptan) because a prolonged vasospastic reaction could occur. To avoid this problem, dosing with ergotamine and serotonin agonists should be separated by at least 24 hours.

CYP3A4 Inhibitors.

Potent inhibitors of CYP3A4 can raise ergotaminine to dangerous levels, posing a risk of intense vasospasm. Cerebral and/or peripheral ischemia can result. Accordingly, concurrent use with CYP3A4 inhibitors is contraindicated. Drugs to avoid include certain HIV protease inhibitors (eg, ritonavir, nelfinavir), azole antifungal drugs (eg, ketoconazole, itraconazole), and macrolide antibiotics (eg, erythromycin, clarithromycin). Less potent inhibitors (eg, saquinavir, nefazodone, fluconazole, grapefruit juice) should be used with caution.

Physical Dependence.

Regular daily use of ergotamine, even in moderate doses, can cause physical dependence. The withdrawal syndrome is characterized by headache, nausea, vomiting, and restlessness. That is, withdrawal resembles a migraine attack. Patients who experience these symptoms are likely to resume taking the drug, thereby perpetuating the cycle of dependence. Hospitalization may be required to break the cycle. To avoid dependence, dosage and duration of treatment must be restricted (see dosing guidelines below).

Contraindications.

Ergotamine is contraindicated for patients with hepatic or renal impairment, sepsis (gangrene has resulted), coronary artery disease (CAD), and peripheral vascular disease, and for those taking potent inhibitors of CYP3A4. In addition, the drug should not be taken during pregnancy. Why? Because its ability to promote uterine contractions can cause fetal harm or abortion. In fact, because of its effects on the uterus, ergotamine is classified in Food and Drug Administration (FDA) Pregnancy Risk Category X: The risk of use by pregnant women clearly outweighs any possible benefits. Warn women of child-bearing age to avoid pregnancy while using this drug.

Preparations, Dosage, and Administration.

Ergotamine by itself is available in tablets for sublingual use. In addition, ergotamine is available in combination with other drugs for oral and rectal administration.

Sublingual.

Ergotamine tartrate [Ergomar] is supplied in 2-mg tablets for sublingual use. One tablet should be placed under the tongue immediately after onset of aura or headache. If needed, additional tablets can be administered at 30-minute intervals—up to a maximum of 3 tablets/24 hr or 5 tablets/wk.

Oral.

Two oral formulations—Cafergot Tablets and Ercaf Tablets—contain 1 mg ergotamine tartrate and 100 mg caffeine; a third—Cafatine-PB Tablets—contains 30 mg pentobarbital and 0.125 mg belladonna alkaloids in addition to the ergotamine and caffeine. Caffeine is present to enhance vasoconstriction and ergotamine absorption. Pentobarbital provides sedation. Belladonna alkaloids suppress emesis. With all three oral formulations, 2 tablets are taken immediately after onset of aura or headache. One additional tablet can be administered every 30 minutes—up to a maximum of 6 per attack or 10 per week.

Rectal.

Suppositories for rectal administration—Cafergot Supps—contain 2 mg ergotamine tartrate and 100 mg caffeine. No more than 2 suppositories should be administered per attack.

Dihydroergotamine

Therapeutic Uses.

Parenteral dihydroergotamine [D.H.E. 45, Migranal] is a drug of choice for terminating migraine and cluster headaches. Administration is by nasal spray or injection (IM, IV, subQ). Intranasal dihydroergotamine is less effective than intranasal sumatriptan (see below), but is associated with a lower rate of migraine recurrence.

Pharmacologic Effects.

The actions of dihydroergotamine are similar to those of ergotamine. Like ergotamine, dihydroergotamine alters transmission at serotonergic, dopaminergic, and alpha-adrenergic junctions. In contrast to ergotamine, dihydroergotamine causes little nausea and vomiting, no physical dependence, and minimal peripheral vasoconstriction (when used alone). Diarrhea, however, is prominent.

Pharmacokinetics.

Dihydroergotamine may be administered parenterally or by nasal spray—but not by mouth (owing to extensive first-pass metabolism). In the liver, the drug is metabolized by CYP3A4. An active metabolite (8′-hydroxydihydroergotamine) contributes to therapeutic effects. The half-life of dihydroergotamine plus the active metabolite is about 21 hours.

Drug Interactions.

As with ergotamine, dihydroergotamine should not be combined with potent inhibitors of CYP3A4, and should not be administered within 24 hours of a serotonin agonist (eg, sumatriptan).

Contraindications.

Like ergotamine, dihydroergotamine is contraindicated for patients with CAD, peripheral vascular disease, sepsis, pregnancy, and hepatic or renal impairment, and for patients taking triptans or potent inhibitors of CYP3A4.

Parenteral Administration.

Dihydroergotamine mesylate [D.H.E. 45] is available in solution (1 mg/mL) for IM, IV, and subQ administration.

Intramuscular and Subcutaneous.

The initial dose is 1 mg immediately after onset of symptoms. Additional 1-mg doses may be given hourly—but the total dose should not exceed 3 mg/24 hr for IM or subQ administration, or 2 mg/24 hr for IV administration. With all routes, the total dose should not exceed 6 mg/wk.

Intravenous.

One milligram is given initially, followed by 1 mg an hour later if needed. Dosage should not exceed 2 mg/24 hr or 6 mg/wk.

Intranasal Administration.

The nasal spray device [Migranal] delivers 0.5 mg of dihydroergotamine per actuation. The dosage is 1 spray in each nostril, repeated in 15 minutes, for a total of 2 mg. Pain is relieved in 60% of patients within 2 hours. The 24-hour recurrence rate is 15%.

Serotonin*1B/1D* Receptor Agonists (Triptans)

The serotonin*1B/1D* receptor agonists, also known as *triptans,* are first-line drugs for terminating a migraine attack. These agents relieve pain by constricting intracranial blood vessels and suppressing release of inflammatory neuropeptides. All are well tolerated. Rarely, they cause symptomatic coronary vasospasm.

Sumatriptan

Sumatriptan [Imitrex] was the first triptan available and will serve as our prototype for the group. The drug can be administered by mouth, nasal inhalation, or subQ injection.

Mechanism of Action.

Sumatriptan, an analog of 5-HT, causes selective activation of 5-HT*1B* and 5-HT*1D* receptors (5-HT*1B/1D* receptors). The drug has no affinity for 5-HT*2* or 5-HT*3* receptors, nor does it bind to adrenergic, dopaminergic, muscarinic, or histaminergic receptors. Binding to 5-HT*1B/1D* receptors on intracranial blood vessels causes vasoconstriction. Binding to 5-HT*1B/1D* receptors on sensory nerves of the trigeminal vascular system suppresses release of CGRT, a compound that promotes release of inflammatory neuropeptides. As a result, sumatriptan reduces release of inflammatory neuropeptides, and thereby diminishes perivascular inflammation. Both actions—vasoconstriction and decreased perivascular inflammation—help relieve migraine pain.

Therapeutic Use.

Sumatriptan is taken to abort an ongoing migraine attack. The drug relieves headache and associated symptoms (nausea, photophobia, phonophobia). In clinical trials, sumatriptan gave complete relief to the majority of patients. Beneficial effects begin about 15 minutes after subQ or intranasal dosing, and 30 to 60 minutes after oral dosing. Complete relief occurs in 70% to 80% of patients 2 hours after subQ dosing, in 60% of patients 2 hours after intranasal dosing, and in 50% to 60% of patients 4 hours after oral dosing. Unfortunately, headache returns in about 40% of patients within 24 hours. In comparison, the 24-hour recurrence rate with dihydroergotamine is only 18%. In patients who respond to subQ sumatriptan, subsequent administration of oral sumatriptan can delay recurrence but does not prevent it. In addition to use in migraine, sumatriptan is approved for cluster headaches.

Pharmacokinetics.

With oral or intranasal administration, bioavailability is low (about 15%), whereas subQ bioavailability is high (97%). As a result, oral and intranasal doses are considerably higher than subQ doses. Once in the blood, sumatriptan undergoes hepatic metabolism followed by excretion in the urine. The half-life is short—about 2.5 hours.

Adverse Effects.

Sumatriptan is generally well tolerated. Most side effects are transient and mild. Coronary vasospasm is the biggest concern.

Chest Symptoms.

About 50% of patients experience unpleasant chest symptoms, usually described as “heavy arms” or “chest pressure” rather than pain. These symptoms are transient and *not* related to ischemic heart disease. Possible causes are pulmonary vasoconstriction, esophageal spasm, intercostal muscle spasm, and bronchoconstriction. Patients should be forewarned of these symptoms and reassured they are not dangerous.

Coronary Vasospasm.

Rarely, sumatriptan causes angina secondary to coronary vasospasm. Electrocardiographic changes have been observed in patients with CAD or Prinzmet-

al's (vasospastic) angina. To reduce the risk of angina, avoid sumatriptan in patients with risk factors for CAD until CAD has been ruled out. These patients include postmenopausal women, men over 40, smokers, and patients with hypertension, hypercholesterolemia, obesity, diabetes, or a family history of CAD. Because of the risk of coronary vasospasm, sumatriptan is contraindicated for patients with a history of ischemic heart disease, myocardial infarction (MI), uncontrolled hypertension, or other heart disease.

Teratogenesis.

Sumatriptan should be avoided during pregnancy. When given daily to pregnant rabbits, the drug was embryolethal at blood levels only 3 times higher than those achieved with a 6-mg subQ injection in humans (a typical dose). Accordingly, unless the prescriber directs otherwise, women should be instructed to avoid the drug if they are pregnant or think they might be, if they are trying to become pregnant, or if they are not using an adequate form of contraception. Sumatriptan is classified in FDA Pregnancy Risk Category C.

Other Adverse Effects.

Mild reactions include *vertigo, malaise, fatigue,* and *tingling sensations*. Transient pain and redness may occur at sites of subQ injection. The intranasal formulation tastes bad and may irritate the nose and throat.

Drug Interactions.

Ergot Alkaloids and Other Triptans.

Sumatriptan, other triptans, and ergot alkaloids (eg, ergotamine, dihydroergotamine) all cause vasoconstriction. Accordingly, if one triptan is combined with another or with an ergot alkaloid, excessive and prolonged vasospasm could result. Accordingly, sumatriptan should not be used within 24 hours of an ergot derivative or another triptan.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) can suppress degradation of sumatriptan, causing its plasma level to rise. Toxicity can result. Accordingly,

sumatriptan and MAOIs should not be used together. Furthermore, sumatriptan should not be administered within 2 weeks of stopping an MAOI.

Preparations, Dosage, and Administration.

Subcutaneous.

Sumatriptan succinate [Imitrex] for subQ injection is available in two strengths: 4 mg and 6 mg. The 4-mg strength is supplied in a STATdose Pen for self-injection. The 6-mg strength is supplied in single-dose vials as well as in a STATdose Pen. The maximum single dose is 6 mg. The maximum that may be given in 24 hours is two 6-mg doses, separated by at least 1 hour.

Oral.

Sumatriptan [Imitrex], by itself, is available in 25-, 50-, and 100-mg tablets for oral use. The usual dose is 25 mg, but doses as high as 100 mg may be tried. If, after 2 hours, the response to the first dose is unsatisfactory, a second dose may be given.

Oral sumatriptan is also available with naproxen in fixed-dose combination tablets marketed as *Treximet* (see below).

Nasal Spray.

Sumatriptan [Imitrex] is available in 5- and 20-mg unit-dose spray devices. The initial dose is 5 or 20 mg, which can be repeated in 2 hours if needed. The maximum 24-hour dose is 40 mg.

Other Serotonin ***1B/1D*** Receptor Agonists

In addition to sumatriptan, the triptan family includes six other drugs: naratriptan [Amerge], rizatriptan [Maxalt], zolmitriptan [Zomig], almotriptan [Axert], frovatriptan [Frova], and eletriptan [Relpax]. All six are administered orally, and one—zolmitriptan—is also given by nasal spray. All six are essentially equal to sumatriptan with respect to efficacy and safety, and all have the same mechanism of action: activation of 5-HT***1B/1D*** receptors with subsequent intracranial vasoconstriction and decreased perivascular inflammation. All are in FDA Pregnancy Risk Category C. Because the triptans are very similar, se-

lection among them is based on differences in kinetics, side effects, and drug interactions. Dosage and time course are summarized in Table 30-4.

Drug	Route	Onset (min)	Duration	Half-Life (hr)	Dosage	Comments
Sumatriptan [Imitrex]	Oral	30–60	Short	2.5	25, 50, or 100 mg; may repeat in 2 hr (max. 200 mg/24 hr)	First triptan available. Most widely used and best understood. Available in nasal and subQ formulations, which act faster than oral triptans.
	Nasal	15–20			5 or 20 mg; may repeat in 2 hr (max. 40 mg/24 hr)	
	SubQ	10–15			4–6 mg; may repeat in 1 hr (max. 12 mg/24 hr)	Don't combine with an MAOI.
Almotriptan [Axert]	Oral	30–120	Short	3.1	6.25 or 12.5 mg; may repeat in 2 hr (max. 25 mg/24 hr)	Incidence of chest discomfort (pain, tightness, pressure) is lower than with other triptans. Safe for use with MAOIs.
Frovatriptan [Frova]	Oral	120–180	Long	26	2.5 mg; may repeat in 2 hr	Longest half-life, slowest onset—but also lowest rate of headache recurrence. Decrease dose if combined with propranolol. Safe for use with MAOIs.
Eletriptan [Relpax]	Oral	60	Short	4	20 or 40 mg; may repeat in 2 hr (max. 80 mg/24 hr)	Bioavailability increased by high-fat meal. Safe for use with MAOIs. Don't take within 72 hr of a CYP3A4 inhibitor.
Naratriptan [Amerge]	Oral	60–180	Long	6	1 or 2.5 mg; may repeat in 4 hr (max. 5 mg/24 hr)	Available in melt-in-the-mouth form that can be taken without water. Safe for use with MAOIs.
Rizatriptan [Maxalt]	Oral	30–120	Short	2–3	5 or 10 mg; may repeat in 2 hours (max. 30 mg/24 hr)	May be the most consistently effective triptan. Decrease dose if combined with propranolol. Available in melt-in-the-mouth tablets that can be taken without water. Don't combine with an MAOI.
Zolmitriptan [Zomig]	Oral	45	Short	3	2.5 or 5 mg; may repeat in 2 hr (max. 10 mg/24 hr)	Available in melt-in-the-mouth form that can be taken without water, and in a single-dose nasal spray. Don't combine with an MAOI.
	Nasal	15			5 mg; may repeat in 2 hr (max. 10 mg/24 hr)	

MAOI = monoamine oxidase inhibitor.

TABLE 30-4 Clinical Pharmacology of the Triptans

Zolmitriptan.

Zolmitriptan [Zomig, Zomig ZMT] is indicated for terminating an ongoing migraine attack. The drug is similar to sumatriptan with regard to mechanism, efficacy, time course, side effects, and interactions. Zolmitriptan is formulated for oral and intranasal use. Two oral preparations are available: standard tablets (2.5 and 5 mg), sold as *Zomig,* and melt-in-the-mouth tablets (2.5 mg), sold as *Zomig ZMT*. Zomig ZMT dissolves in saliva on the tongue; no water is needed, and hence the drug can be taken conveniently as soon as an aura is perceived. Be aware, however, that onset of effects is no faster than with standard Zomig tablets. With either formulation, a 2.5-mg dose produces the most favorable response/tolerability ratio. Intranasal zolmitriptan, sold as *Zomig,* is available in a 5-mg single-dose spray device. Effects begin in 15 minutes, compared with 30 to 45 minutes for the oral products. However, although the nasal spray is faster, it does have two drawbacks: it tastes bad (albeit not as bad as sumatriptan nasal spray) and only one strength (5 mg/spray) is available. If a smaller dose is needed, an oral formulation must be used. Regardless of the formulation used, about 65% of patients respond within 2 hours. If headache persists, dosing can be repeated 2 hours after the initial dose. The maximum dose per

24 hours is 10 mg. Headache recurs in 8% to 32% of patients. Adverse effects are generally mild and transient. Like sumatriptan, zolmitriptan causes harmless, transient chest discomfort. Of much greater concern, the drug can cause coronary vasospasm, and hence is contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension. To avoid excessive vasospasm, zolmitriptan should not be administered within 24 hours of an ergot alkaloid or another triptan, or within 2 weeks of stopping an MAOI.

Naratriptan.

Naratriptan [Amerge] is indicated for oral therapy of an ongoing migraine attack. The drug differs from most other triptans in two respects: (1) it has a relatively long half-life (6 hours versus 2 to 3 hours for most other triptans), and (2) it can be safely combined with an MAOI. Onset of effects is slower than with other triptans, but the duration is longer. Because effects persist, the 24-hour migraine recurrence rate may be reduced. Naratriptan is available in 1- and 2.5-mg tablets. The 2.5-mg strength is more effective but causes more side effects. The initial dose is 1 or 2.5 mg. Dosing may be repeated in 4 hours if needed. The maximum daily dose is 5 mg. Like other triptans, naratriptan causes transient chest discomfort. Also like other triptans, the drug can cause coronary vasospasm, and hence is contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension. To avoid excessive vasospasm, naratriptan should not be administered within 24 hours of an ergot alkaloid or another triptan.

Rizatriptan.

Rizatriptan [Maxalt, Maxalt MLT] is used to terminate an ongoing migraine attack. The drug is similar to sumatriptan with regard to mechanism, efficacy, time course, side effects, and interactions. Rizatriptan is available in two oral formulations: standard tablets [Maxalt] and melt-in-the-mouth tablets [Maxalt MLT] that can be taken without water. Both formulations come in 5- and 10-mg strengths. The initial dose is 5 or 10 mg. Dosing may be repeated in 2 hours if needed. No more than 30 mg should be taken per day. Adverse effects are generally mild and transient. Like other triptans, rizatriptan causes harmless, transient chest discomfort. Also like other triptans, the drug can cause coronary vasospasm, and hence is contraindicated for patients with ischem-

ic heart disease, prior MI, or uncontrolled hypertension. To avoid excessive vasospasm, rizatriptan should not be administered within 24 hours of an ergot alkaloid or another triptan, or within 2 weeks of stopping an MAOI. Propranolol can raise levels of rizatriptan; a dosage reduction may be needed. Rizatriptan may harm the developing fetus: In rats, the drug increased perinatal mortality, reduced learning capacity, and decreased pre and post-weaning weight. However, postmarketing surveillance data suggest that, in humans, rizatriptan may not increase the risk of congenital anomalies or spontaneous abortion. Until more is known, the drug should be used with caution in pregnant women.

Almotriptan.

Almotriptan [Axert] is indicated for oral therapy of an ongoing migraine attack. The drug is similar to sumatriptan with regard to mechanism, efficacy, and time course—and is better tolerated. Almotriptan is available in 6.25- and 12.5-mg tablets for oral use. The initial dose is 6.25 or 12.5 mg. Dosing can be repeated in 2 hours if headache persists. The maximum dose per 24 hours is 25 mg. Adverse effects are minimal. Like other triptans, almotriptan can cause harmless, transient chest discomfort—but the incidence is very low (only 0.3%). Also like other triptans, the drug can cause coronary vasospasm, and hence is contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension. To avoid excessive vasospasm, zolmitriptan should not be administered within 24 hours of an ergot alkaloid or another triptan. In contrast to some triptans, almotriptan can be combined safely with an MAOI.

Frovatriptan.

Frovatriptan [Frova] is indicated for oral therapy of an ongoing migraine attack. The drug is similar to other triptans with regard to mechanism and side effects—but is less effective and has very different kinetics. Effects begin slowly, but are sustained—thanks to the drug's long half-life (26 hours). Although the number of patients responding at 2 hours is low (37% to 46%), rates of headache recurrence are low too (7% to 23%)—lower than with any other triptan. Frovatriptan is available in 2.5-mg tablets. The initial dose is 2.5 mg. If headache recurs after initial relief, dosing can be repeated—but no

sooner than 2 hours after the first dose. If there was no response to the first dose, repeat dosing is unlikely to help. The maximum dose per 24 hours is 7.5 mg. Adverse effects are mild and transient. Like sumatriptan, frovatriptan can cause harmless, transient chest discomfort. In addition, the drug can cause coronary vasospasm, and hence is contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension. To avoid excessive vasospasm, frovatriptan should not be administered within 24 hours of an ergot alkaloid or another triptan. However, it can be used concurrently with an MAOI. Dosage should be reduced in patients receiving propranolol.

Eletriptan.

Eletriptan [Relpax] is indicated for oral therapy of an ongoing migraine attack. The drug is at least as effective as oral sumatriptan, and may have a faster onset. Eletriptan is available in 20- and 40-mg tablets. The initial dose is 20 or 40 mg, which can be repeated in 2 hours if needed. The total dose in 24 hours should not exceed 80 mg. Like other triptans, eletriptan can cause transient chest discomfort. Also like other triptans, it can cause coronary vasospasm, and hence is contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension. To avoid excessive vasospasm, eletriptan should not be administered within 24 hours of an ergot alkaloid or another triptan. However, the drug may be used concurrently with an MAOI. Eletriptan is metabolized in the liver by CYP3A4, and hence strong inhibitors of CYP3A4 (eg, ketoconazole, itraconazole, clarithromycin, ritonavir) may cause toxicity by raising eletriptan levels. Accordingly, eletriptan should not be used within 72 hours of these drugs. Eletriptan levels may also be raised by verapamil, a moderate CYP3A4 inhibitor used for migraine prophylaxis; caution is advised.

Other Abortive Agents

Sumatriptan/Naproxen.

Sumatriptan and naproxen (a nonsteroidal anti-inflammatory drug) are now available in a fixed-dose combination under the trade name *Treximet*. Each tablet contains 85 mg sumatriptan and 500 mg naproxen. In clinical trials, the combination was better than either agent alone at relieving the pain of a migraine attack. In addition, the combination effectively reduced nausea

and sensitivity to both light and sound. Presumably, the superior benefits of the combination derive from attacking migraine by multiple mechanisms: naproxen reduces pain and inflammation, while sumatriptan causes vasoconstriction and inhibits release of inflammatory neuropeptides.

Haloperidol.

Haloperidol [Haldol], a neuroleptic drug developed for schizophrenia, can relieve pain of migraine. In a small, placebo-controlled trial, 5 mg of intravenous haloperidol decreased migraine pain dramatically. As measured on a visual analog scale, pain intensity dropped from 7.7 to 2.2 with haloperidol, versus only 7.2 to 6.3 with placebo. Furthermore, the relapse rate with haloperidol was low—only 3%. The effects of haloperidol are even more impressive considering that most of the patients in this trial had been unresponsive to conventional antimigraine drugs. The major adverse effects of haloperidol were sedation and akathisia (a sense of restlessness and a compelling need to be in motion). The basic pharmacology of haloperidol is discussed in Chapter 31 (Antipsychotic Agents and Their Use in Schizophrenia).

Telcagepant.

Telcagepant, an experimental *CGRP receptor antagonist*, has the same efficacy as zolmitriptan—and is better tolerated. In a randomized, double-blind, placebo-controlled trial that enrolled 1388 patients with moderate to severe migraine, 300 mg of telcagepant produced the same reductions in pain, phonophobia, photophobia, and nausea as did 5 mg of zolmitriptan. Furthermore, side effects with telcagepant—which were limited to dry mouth, fatigue, and vomiting—occurred only slightly more often than with placebo.

MIGRAINE HEADACHE III: PREVENTIVE THERAPY

Prophylactic therapy can reduce the frequency and intensity of migraine attacks. Preventive treatment is indicated for patients who have frequent attacks (two or more a month), attacks that are especially severe, or attacks that do not respond adequately to abortive agents. Preferred drugs for prophylaxis include propranolol, divalproex, and amitriptyline. All three are effective and well tolerated. Major preventive agents are listed in Table 30-5.

Beta Blockers

Beta blockers are preferred drugs for migraine prevention. Of the available beta blockers, *propranolol* [Inderal] is used most often. Treatment can reduce the number and intensity of attacks in 70% of patients. Benefits take a few weeks to develop. The most common side effects are extreme tiredness and fatigue, which occur in about 10% of patients. In addition, the drug can exacerbate symptoms of asthma, and might promote depression. The usual maintenance dosage is 80 to 240 mg/day, taken either as a single dose (using a long-acting formulation) or in two divided doses (using a short-acting formulation). In addition to propranolol, four other beta blockers—*timolol, atenolol, metoprolol,* and *nadolol*—can help prevent migraine attacks. In contrast, beta blockers that possess intrinsic sympathomimetic activity (eg, acebutolol, pindolol) are *not* effective. The basic pharmacology of the beta blockers is discussed in Chapter 18.

TABLE 30-5 Migraine Headache: Drugs for Preventive Therapy

Beta-Adrenergic Blocking Agents

Propranolol [Inderal]

Timolol [Blocadren]

Antiepileptic Drugs

Divalproex [Depakote ER]

Topiramate [Topamax]

Tricyclic Antidepressants

Amitriptyline [Elavil]

Calcium Channel Blockers

Verapamil [Calan]

Flunarizine*

Estrogens (for menstrual migraine)

Estrogen gel

Estrogen patch [Alora, Climara, Esclim, Estraderm, Vivelle]

* Not available in the United States.

Tricyclic Antidepressants

Tricyclic antidepressants can prevent migraine and tension-type headaches in some patients. The underlying mechanism has not been established, but may involve inhibiting reuptake of serotonin, making more of the transmitter available for action. The tricyclic agent used most often is *amitriptyline* [Elavil]. Benefits equal those of propranolol. The dosage range is 25 to 150 mg once daily at bedtime. Since amitriptyline is effective in patients who are not depressed, it would seem that benefits do not depend on elevation of mood. Like other tricyclic antidepressants, amitriptyline can cause hypotension and anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision, tachycardia). Excessive doses can cause dysrhythmias. The basic pharmacology of amitriptyline is discussed in Chapter 32.

Antiepileptic Drugs

Several drugs that were developed for epilepsy can reduce migraine attacks. Proof of efficacy is strongest for divalproex [Depakote ER] and topiramate [Topamax]. Gabapentin [Neurontin] and tiagabine [Gabitril] appear promising, although extensive proof of efficacy is lacking.

Divalproex.

Divalproex [Depakote ER], employed first for epilepsy and later for bipolar disorder (manic-depressive illness), is now approved for prophylaxis of migraine too. The drug is a form of valproic acid (see Chapter 24). Divalproex reduces the incidence of attacks by 50% or more in 30% to 50% of patients. However, when attacks do occur, their intensity and duration are not diminished. In migraineurs, the most common side effect is nausea. Other side effects include fatigue, weight gain, tremor, and reversible hair loss. Potentially fatal pancreatitis and hepatitis occur rarely. Divalproex can cause neural tube defects in the developing fetus, and hence is contraindicated during pregnancy. The drug is available in standard and extended-release (ER) tablets. Only the ER tablets are approved for preventing migraine. The dosage range is 800 to 1500 mg once a day.

Topiramate.

Topiramate [Topamax], originally developed for epilepsy, was approved for migraine prophylaxis in 2004. Benefits take several weeks to develop, and appear equal to those of beta blockers, tricyclic antidepressants, or divalproex. However, topiramate costs much more than these drugs. In clinical trials, topiramate reduced migraine frequency by at least 50% in 83% of adolescents and about 50% of adults. The drug also reduced the need for rescue medication. Unfortunately, side effects are common, especially paresthesias, fatigue, and cognitive dysfunction (psychomotor slowing, word-finding difficulty, impairment of concentration and memory). Other side effects include metabolic acidosis and moderate weight loss (owing to anorexia, nausea, and diarrhea). To minimize side effects, dosage should be low initially and then gradually increased. The recommended titration schedule is 25 mg in the evening the first week, 25 mg in the morning and evening the second week, 25 mg in the morning and 50 mg in the evening the third week, and 50 mg in the morning and evening thereafter. The basic pharmacology of topiramate is discussed in Chapter 24.

Estrogens (for Menstrual Migraine)

Menstrual migraine is defined as migraine that routinely occurs within 2 days of the onset of menses. An important trigger is the decline in estrogen levels that precedes menstruation. For many women, menstrual migraine can be prevented by taking estrogen supplements, which compensate for the premenstrual estrogen drop. Topical preparations—estrogen gel and estrogen patches [eg, Climara, Estraderm]—work well. Effective dosages are 1.5 mg/day for the gel and 100 mg/day for the patches. Dosing is done for 7 days each month, beginning 2 days before the expected attack.

There is evidence that frovatriptan [Frova] can significantly reduce the frequency, intensity, and duration of menstrual migraine. The dosage is 2.5 mg taken once or twice daily for 6 days, beginning 2 days before the expected attack.

Other Drugs for Prophylaxis

Calcium Channel Blockers

Of the calcium channel blockers (CCBs) evaluated for migraine prevention, two appear especially useful: *verapamil* and *flunarizine* (a drug not yet available in the United States). Both agents are less effective than propranolol or divalproex, and their effects develop slowly, reaching a maximum in 1 to 2 months. Although CCBs can relieve vasospasm, it is not clear that vasodilation explains antimigraine effects. Another possible mechanism is modulation of neurotransmitter release, a calcium-dependent process that CCBs are known to affect. It is noteworthy that benefits take several weeks to develop, suggesting benefits may result from central nervous system *adaptation* to CCBs, and not directly from blockade of calcium channels on blood vessels or neurons. When used for prophylaxis, CCBs cause side effects in 20% to 60% of patients. Constipation and orthostatic hypotension are most common. The basic pharmacology of CCBs is discussed in Chapter 44.

Candesartan, an Angiotensin II Receptor Blocker (ARB)

For prophylaxis of migraine, candesartan [Atacand] appears about as effective as more established therapies (beta blockers, divalproex, amitriptyline) and is much better tolerated. In a double-blind, placebo-controlled trial, about half of the patients receiving candesartan (16 mg/day) experienced 47% fewer migraine days and 46% fewer migraine hours. Treatment also reduced the need for rescue therapy with triptans and analgesics. Adverse effects were equivalent to those of placebo. How candesartan reduces migraine attacks is unknown. The basic pharmacology of the ARBs is discussed in Chapter 43.

Supplements

Riboflavin.

Riboflavin (vitamin B2) can reduce the number and severity of migraine attacks, but benefits are modest and develop slowly. In one study, migraineurs with frequent attacks took 400 mg of riboflavin a day. After 3 months, the number of attacks was decreased by 37%. In addition, the average duration of each attack also declined. Side effects were minimal.

Coenzyme Q-10.

In a preliminary study, daily therapy with coenzyme Q-10 (CoQ-10) produced a significant reduction in the occurrence of migraine attacks. Subjects took 150 mg of CoQ-10 each morning. After 3 months, the number of days on which headaches occurred declined by at least 50% in 61% of study participants. However, although headache frequency declined, headache intensity was not affected. CoQ-10 was well tolerated.

Butterbur.

Extracts made from the root of *Petasites hybridus,* a plant whose common name is butterbur, can reduce the frequency of migraine attacks. In a double-blind, placebo-controlled trial, about 1 in 5 patients taking 75 mg of extract twice daily experienced a 50% or greater reduction in migraine frequency. The only side effects were mild GI symptoms (eg, nausea, burping, stomach pain). However, butterbur root contains pyrrolizidine alkaloids, which, if not removed during processing, can cause liver damage and cancer. In the study noted, the preparation employed, sold as Petadolex, is pyrrolizidine free.

CLUSTER HEADACHES

Characteristics

Cluster headaches occur in a series or "cluster" of attacks. Each attack lasts 15 minutes to 2 hours and is characterized by severe, throbbing, unilateral pain in the orbital-temporal area (ie, near the eye). A typical cluster consists of one or two such attacks every day for 2 to 3 months. An attack-free interval of months to years separates each cluster. Along with headache, patients usually experience lacrimation, conjunctival redness, nasal congestion, rhinorrhea, ptosis (drooping eyelid), and miosis (constriction of the pupil)—all on the same side as the headache. Although related to migraine, cluster headaches differ in several ways: (1) they are not preceded by an aura, (2) they do not cause nausea and vomiting, (3) they can be more debilitating, (4) they are less common and occur mostly in males (5:1), (5) they are not associated with a family history of attacks, and (6) management is different.

Drug Therapy

Prophylaxis.

Primary therapy is directed at prophylaxis. Effective agents include *prednisone, lithium,* and *verapamil.* High-dose prednisone (40 to 80 mg/day) acts rapidly, producing results in 48 hours. However, because long-term use of glucocorticoids carries serious risks (see Chapter 71), treatment should stop in 1 to 2 months. Lithium is a drug of choice for preventing chronic cluster headache. Benefits begin in 1 to 2 weeks. To ensure therapeutic effects and minimize toxicity, blood levels of lithium must be monitored. The target range is 0.6 to 1.2 mEq/L. Verapamil (160 to 480 mg/day) is less effective than lithium but safer and easier to use. Prophylactic therapy should be limited to the cluster cycle, and then discontinued when the current cycle is over. Drugs for prophylaxis are listed in Table 30-6.

Drug*	Usual Daily Dosage (mg)
Calcium Channel Blockers	
Verapamil [Calan, others]	160–480
Neurostabilizers	
Divalproex [Depakote]	500–1500
Topiramate [Topamax]	50–200
Lithium [Lithobid]	600–1200†
Nonsteroidal Anti-inflammatory Drugs	
Indomethacin	100–150
Naproxen	1000–1500
Glucocorticoids	
Prednisone	40–80
Ergot Alkaloids	
Ergotamine	1.2

TABLE 30-6 Drugs Used for Prophylaxis of Cluster Headache

* None of the drugs listed is approved by the FDA for cluster headache prophylaxis.

† Dosage is adjusted on the basis of serum lithium levels.

Treatment.

If an attack occurs despite preventive therapy, it can be aborted with *oxygen, sumatriptan,* or an *ergot preparation*. Inhaling 100% oxygen for 10 minutes or

less brings rapid relief to most patients. The mechanism is unknown. Speedy relief can also be achieved with *sublingual* ergotamine tartrate, *intranasal* dihydroergotamine, or *subcutaneous* sumatriptan. Slower relief can be achieved with an ergotamine-caffeine *suppository. Oral* ergotamine acts too slowly to be of much help.

TENSION-TYPE HEADACHE

Characteristics

Tension-type headaches (formerly called muscle-contraction headaches) are the most common headache type. These headaches are characterized by moderate, nonthrobbing pain, usually located in a "headband" distribution. Headache is often associated with scalp formication and a sense of tightness or pressure in the head and neck. Precipitating factors include eye strain, aggravation, frustration, and life's daily stresses. Depressive symptoms (sleep disturbances, including early and frequent awakening) are often present. Tension headaches may be episodic or chronic. By definition, chronic tension-type headaches occur 15 or more days per month for at least 6 months.

Treatment

An acute attack of mild to moderate intensity can be relieved with a nonopioid analgesic: acetaminophen or a nonsteroidal anti-inflammatory drug (eg, aspirin, ibuprofen, naproxen). An analgesic-sedative combination (eg, aspirin-butalbital) may also be used. However, because of their potential for dependence and abuse, these combinations should be reserved for acute therapy of episodic attacks; they are inappropriate for patients with chronic headache syndrome.

For prophylaxis, *amitriptyline* [Elavil], a tricyclic antidepressant, is the drug of choice. Dosing at bedtime will help relieve any depression-related sleep disturbances in addition to protecting against headache. Amitriptyline can cause anticholinergic side effects (eg, dry mouth, constipation) and poses a risk of cardiotoxicity at high doses (see Chapter 32).

In addition to receiving drugs, patients should be taught how to manage stress. Instruction should include cognitive coping skills and information on

relaxation techniques (eg, massage, hot baths, biofeedback, deep muscle relaxation).

KEY POINTS

- Migraine is a neurovascular disorder involving dilation and inflammation of intracranial arteries.
- Antimigraine drugs are used in two ways: abortive and prophylactic.
- The goal of abortive therapy is to eliminate headache pain and associated nausea and vomiting.
- The goal of prophylactic therapy is to reduce the incidence and intensity of migraine attacks.
- There are two kinds of drugs for abortive therapy: nonspecific analgesics (aspirin-like drugs and opioids) and migraine-specific drugs (ergot alkaloids and triptans).
- Aspirin-like analgesics (eg, acetaminophen, aspirin, naproxen) are effective for abortive therapy of mild to moderate migraine.
- Opioid analgesics (eg, butorphanol) are reserved for severe migraine that has not responded to other drugs.
- Ergotamine is a first-line drug for abortive therapy of severe migraine.
- Overdose with ergotamine can cause ergotism, a serious condition characterized by severe tissue ischemia secondary to generalized constriction of peripheral arteries.
- Ergotamine must not be taken routinely because physical dependence will occur.
- Ergotamine can cause uterine contractions and must not be taken during pregnancy.
- Ergotamine must not be combined with potent inhibitors of CYP3A4, owing to a risk of intense vasoconstriction and associated ischemia.

- Triptans (eg, sumatriptan) are first-line drugs for abortive therapy of moderate to severe migraine.
- Triptans activate 5-HT***1B/1D*** receptors and thereby constrict intracranial blood vessels and suppress release of inflammatory neuropeptides.
- All triptans are available in oral formulations, which have a relatively slow onset. Two triptans—sumatriptan and zolmitriptan—are available in fast-acting formulations (either nasal spray, subQ injection, or both).
- Triptans can cause coronary vasospasm, and hence are contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension.
- Triptans should not be combined with one another or with ergot derivatives because excessive vasoconstriction could occur.
- Prophylactic therapy is indicated for migraineurs who have frequent attacks (two or more a month), especially severe attacks, or attacks that do not respond adequately to abortive agents.
- Propranolol, divalproex, and amitriptyline are preferred drugs for migraine prophylaxis.
- Estrogen supplements can help prevent menstrual-associated migraine.

Summary of Major Nursing Implications*

ERGOTAMINE AND DIHYDROERGOTAMINE

Preadministration Assessment

Therapeutic Goal

Termination of migraine or cluster headache.

Baseline Data.

Determine the age of onset, frequency, location, intensity, and quality (throbbing or nonthrobbing) of headaches as well as the presence or absence of a

prodromal aura. Assess for trigger factors (eg, stress, anxiety, fatigue) and for a family history of severe headache.

Assess for possible underlying causes of headache (eg, severe hypertension; hyperthyroidism; infection; tumors; disorders of the eye, ear, nose, sinuses, or throat), which should be treated if present.

Identifying High-Risk Patients

Ergot alkaloids are *contraindicated* in patients with hepatic or renal impairment, sepsis, CAD, or peripheral vascular disease, and for patients who are pregnant, taking triptans, or taking potent inhibitors of CYP3A4.

Implementation: Administration

Routes

Ergotamine Alone.

Sublingual.

Ergotamine Plus Caffeine.

Oral, rectal.

Dihydroergotamine.

Nasal spray, IM, IV, and subQ.

Dosage and Administration

Instruct patients to commence dosing immediately after onset of symptoms.

Nausea and vomiting from the headache and from ergotamine itself may prevent complete absorption of oral ergotamine. Concurrent treatment with metoclopramide or another antiemetic can minimize these effects. (Nausea and vomiting are minimal with dihydroergotamine.)

Ergotamine (but not dihydroergotamine) can cause physical dependence and serious toxicity if dosage is excessive. **Inform patients about the risks of**

dependence and toxicity and the importance of not exceeding the prescribed dosage.

Implementation: Measures to Enhance Therapeutic Effects

Educate patients in ways to control, avoid, or eliminate trigger factors (eg, stress, fatigue, anxiety, alcohol, tyramine-containing foods).

Teach patients about relaxation techniques (eg, biofeedback, deep muscle relaxation). Advise patients to rest in a quiet, dark room for 2 to 3 hours after drug administration and to apply an ice pack to the neck and scalp.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Determine the size and frequency of doses used and the extent to which therapy has reduced the intensity and duration of attacks.

Minimizing Adverse Effects

Nausea and Vomiting.

Ergotamine promotes nausea and vomiting. Minimize these by concurrent therapy with metoclopramide or a phenothiazine-type antiemetic.

Ergotism.

Toxicity (ergotism) can result from acute or chronic overdose. **Teach patients the early manifestations of ergotism (muscle pain; paresthesias in fingers and toes; extremities become cold, pale, and numb) and instruct them to seek immediate medical attention if they develop.** Treat by withdrawing ergotamine and administering drugs (anticoagulants, low-molecular-weight dextran, intravenous nitroprusside) as appropriate to maintain circulation.

Physical Dependence.

Ergotamine can cause physical dependence. **Warn patients not to overuse the drug, since physical dependence can result. Teach patients the signs and symptoms of withdrawal (headache, nausea, vomiting, restlessness) and instruct them to inform the prescriber if these develop during a drug-**

free interval. Patients who become dependent may require hospitalization to bring about withdrawal.

Abortion.

Ergot alkaloids are uterine stimulants that can cause abortion in high doses. **Warn women of child-bearing age to avoid pregnancy while using these drugs.**

Minimizing Adverse Interactions

Inhibitors of CYP3A4.

Ergotamine and *dihydroergotamine* must not be combined with potent inhibitors of CYP3A4, which can raise these drugs to toxic levels, thereby posing a risk of intense vasoconstriction and associated ischemia. Drugs to avoid include certain HIV protease inhibitors (eg, ritonavir, nelfinavir), azole antifungal drugs (eg, ketoconazole, itraconazole), and macrolide antibiotics (eg, erythromycin, clarithromycin).

SEROTONIN*1B/1D* RECEPTOR AGONISTS (TRIPTANS)

Almotriptan

Eletriptan

Frovatriptan

Naratriptan

Rizatriptan

Sumatriptan

Zolmitriptan

Preadministration Assessment

Therapeutic Goal

Termination of migraine headache.

Baseline Data

See *Ergotamine and Dihydroergotamine*.

Identifying High-Risk Patients

All triptans are *contraindicated* for patients with ischemic heart disease, prior MI, or uncontrolled hypertension, and for patients taking ergot alkaloids or other triptans. *Sumatriptan, rizatriptan,* and *zolmitriptan* are *contraindicated* for patients taking MAOIs.

Implementation: Administration

Routes

Oral.

All triptans.

Subcutaneous.

Sumatriptan.

Intranasal.

Sumatriptan and zolmitriptan.

Dosage and Administration

Instruct patients to administer triptans immediately after onset of symptoms.

Teach patients how to use the sumatriptan auto-injector.

Implementation: Measures to Enhance Therapeutic Effects

Educate patients in ways to control, avoid, or eliminate trigger factors (eg, stress, fatigue, anxiety, alcohol, tyramine-containing foods).

Teach patients biofeedback or another relaxation technique. Advise patients to rest in a quiet, dark room for 2 to 3 hours after drug administration and to apply an ice pack to the neck and scalp.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Determine the size and frequency of doses used and the extent to which therapy has reduced the intensity and duration of attacks.

Minimizing Adverse Effects

Coronary Vasospasm.

All triptans can cause coronary vasospasm with resultant anginal pain. Avoid these drugs in patients with ischemic heart disease, prior MI, or uncontrolled hypertension. In patients with risk factors for CAD, rule out CAD before giving triptans.

Teratogenesis.

Sumatriptan can cause birth defects in laboratory animals, and hence must not be used during pregnancy. *Rizatriptan* may also pose fetal risk.

Minimizing Adverse Interactions

Ergot Alkaloids and Other Triptans.

Combining a triptan with an ergot alkaloid (eg, ergotamine, dihydroergotamine) or another triptan can cause prolonged vasospasm. Do not administer a triptan within 24 hours of an ergot alkaloid or another triptan.

MAOIs.

MAOIs can intensify the effects of *sumatriptan, rizatriptan,* and *zolmitriptan*. Do not give these triptans to patients who are taking MAOIs or who stopped taking MAOIs within the last 14 days.

Propranolol.

Propranolol can raise levels of *frovatriptan* and *rizatriptan*. Dosage of the triptan should be reduced.

Psychotherapeutic Drugs

31 Antipsychotic Agents and Their Use in Schizophrenia

The antipsychotic agents are a chemically diverse group of compounds used for a broad spectrum of psychotic disorders. Specific indications include schizophrenia, delusional disorders, bipolar disorder, depressive psychoses, and drug-induced psychoses. In addition to their psychiatric applications, the antipsychotics are used to suppress emesis and to treat Tourette's syndrome and Huntington's chorea. As a rule, antipsychotics should not be used to treat dementia in the elderly, owing to a risk of increased mortality.

Since their introduction in the early 1950s, the antipsychotic agents have catalyzed revolutionary change in the management of psychotic illnesses. Before these drugs were available, psychoses were largely untreatable and patients were fated to a life of institutionalization. With the advent of antipsychotic medications, many patients with schizophrenia and other severe psychotic disorders have been able to leave psychiatric hospitals and return to the community. Others have been spared hospitalization entirely. For those who must be institutionalized, antipsychotic drugs have at least reduced suffering.

The antipsychotic drugs fall into two major groups: (1) *first-generation antipsychotics* (FGAs), also known as *conventional antipsychotics,* and (2) *second-generation antipsychotics* (SGAs), also known as *atypical antipsychotics*. All of the FGAs block receptors for dopamine in the central nervous system (CNS). As a result, they all can cause serious movement disorders, known as *extrapyramidal symptoms* (EPS). The SGAs produce only moderate blockade of receptors for dopamine and much stronger blockade of receptors for serotonin. Because dopamine receptor blockade is low, the risk of EPS is low as well. However, although the SGAs carry little risk of EPS, they do pose a risk of *metabolic effects*—weight gain, diabetes, and dyslipidemia—that can cause cardiovascular events and early death. Nonetheless, owing to aggressive marketing and a *perception* of clinical superiority, SGAs have become our most widely prescribed antipsychotic drugs, outselling the FGAs by 10 to 1.

SCHIZOPHRENIA: CLINICAL PRESENTATION AND ETIOLOGY

Clinical Presentation

Schizophrenia is a chronic psychotic illness characterized by disordered thinking and a reduced ability to comprehend reality. Symptoms usually emerge during adolescence or early adulthood. In the United States, about 3.2 million people are affected. Diagnostic criteria for schizophrenia are presented in Table 31-1.

Three Types of Symptoms

Symptoms of schizophrenia can be divided into three groups: positive symptoms, negative symptoms, and cognitive symptoms. Positive and negative symptoms are summarized in Table 31-2.

Positive Symptoms	Negative Symptoms
Hallucinations	Social withdrawal
Delusions	Emotional withdrawal
Disordered thinking	Lack of motivation
Disorganized speech	Poverty of speech
Combativeness	Blunted affect
Agitation	Poor insight
Paranoia	Poor judgment
	Poor self-care

TABLE 31-2 Positive and Negative Symptoms of Schizophrenia

Positive Symptoms and Negative Symptoms.

Positive symptoms can be viewed as an exaggeration or distortion of normal function, whereas negative symptoms can be viewed as a loss or diminution of normal function. Positive symptoms include hallucinations, delusions, agitation, tension, and paranoia. Negative symptoms include lack of motivation, poverty of speech, blunted affect, poor self-care, and social withdrawal. Positive symptoms respond equally to FGAs and SGAs. Negative symptoms may respond better to SGAs.

Cognitive Symptoms.

Cognitive symptoms include disordered thinking, reduced ability to focus attention, and prominent learning and memory difficulties. Subtle changes may appear years before symptoms become florid, when thinking and speech may be completely incomprehensible to others. Cognitive symptoms may respond better to SGAs than to FGAs.

TABLE 31-1 DSM-IV-TR Diagnostic Criteria for Schizophrenia

A. Characteristic Symptoms

At least two of the following are present for a significant time during a 1-month period (or less if successfully treated):

- Delusions
- Hallucinations
- Disorganized speech (eg, frequent derailment or incoherence)
- Grossly disorganized or catatonic behavior
- Negative symptoms (affective flattening, alogia, or avolition)

Note: Only one symptom is required if delusions are bizarre or if hallucinations consist of either (1) a voice making running comments on the person's behavior or thoughts or (2) voices conversing with each other.

B. Social/Occupational Dysfunction

For a significant time since the onset of the disturbance, at least one major area of functioning (eg, work, interpersonal relations, self-care) is markedly below the pre-onset level *or*, if the onset occurred in childhood or adolescence, the individual failed to achieve the expected level of inter-personal, academic, or occupational functioning.

C. Duration

Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (ie, active-phase symptoms). It may also include periods of prodromal or residual symptoms; during these times the disturbance is manifested only by negative symptoms or by at least two symptoms from Criterion A that are present in attenuated form (eg, odd beliefs, unusual perceptual experience).

D. Schizoaffective and Mood Disorder Exclusion

Schizoaffective Disorder and Mood Disorder with Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/General Medical Condition Exclusion

The disturbance is not due to the direct physiologic effects of a substance (eg, drug of abuse, medication) or a general medical condition.

F. Relationship to a Pervasive Developmental Disorder

If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are present for at least 1 month (or less if successfully treated).

Acute Episodes

During an acute schizophrenic episode, delusions (fixed false beliefs) and hallucinations are frequently prominent. Delusions are typically religious, grandiose, or persecutory. Auditory hallucinations, which are more common than visual hallucinations, may consist of voices arguing or commenting on one's behavior. The patient may feel controlled by external influences. Disordered thinking and loose association may render rational conversation impossible. Affect may be blunted or labile. Misperception of reality may result in hostility and lack of cooperation. Impaired self-care skills may leave the patient disheveled and dirty. Patterns of sleeping and eating are usually disrupted.

Residual Symptoms

After florid symptoms (eg, hallucinations, delusions) of an acute episode remit, less vivid symptoms may remain. These include suspiciousness, poor anxiety management, and diminished judgment, insight, motivation, and capacity for self-care. As a result, patients frequently find it difficult to establish close relationships, maintain employment, and function independently in society. Suspiciousness and poor anxiety management contribute to social with-

drawal. An inability to appreciate the need for continued drug therapy may cause nonadherence, resulting in relapse and perhaps hospital readmission.

Long-Term Course

The long-term course of schizophrenia is characterized by episodic acute exacerbations separated by intervals of partial remission. As the years pass, some patients experience progressive decline in mental status and social functioning. However, many others stabilize, or even improve. Maintenance therapy with antipsychotic drugs reduces the risk of acute relapse, but may fail to prevent long-term deterioration.

Etiology

Although there is strong evidence that schizophrenia has a biologic basis, the exact etiology is unknown. Genetic, perinatal, neurodevelopmental, and neuroanatomic factors may all be involved. Possible primary defects include excessive activation of CNS receptors for dopamine, and insufficient activation of CNS receptors for glutamate. Although psychosocial stressors can precipitate acute exacerbations in susceptible patients, they are not considered causative.

FIRST-GENERATION (CONVENTIONAL) ANTIPSYCHOTICS: GROUP PROPERTIES

In this section we discuss pharmacologic properties shared by all of the FGAs. Much of our attention focuses on adverse effects. Of these, extrapyramidal side effects are of particular concern. Because of these neurologic side effects, the FGAs are also known as *neuroleptics*.

Classification

The FGAs can be classified by potency or chemical structure. From a clinical viewpoint, classification by potency is more helpful.

Classification by Potency

First-generation antipsychotics can be classified as *low potency, medium potency,* or *high potency* (Table 31-3). The low-potency drugs, represented by

chlorpromazine [Thorazine], and the high-potency drugs, represented by haloperidol [Haldol], are of particular interest.

It is important to note that, although the FGAs differ from one another in potency, they all have the same ability to relieve symptoms of psychosis. Recall that the term *potency* refers only to the size of the dose needed to elicit a given response; potency implies nothing about the maximal effect a drug can produce. Hence, when we say that haloperidol is more potent than chlorpromazine, we mean only that the dose of haloperidol required to relieve psychotic symptoms is smaller than the required dose of chlorpromazine; we do not mean that haloperidol can produce greater effects. When administered in therapeutically equivalent doses, both drugs elicit an equivalent antipsychotic response.

If low-potency and high-potency neuroleptics are equally effective, why distinguish between them? The answer is that, although these agents produce identical *antipsychotic* effects, they differ significantly in *side effects*. Hence, by knowing the potency category to which a particular neuroleptic belongs, we can better predict its undesired responses. This knowledge is useful in drug selection and providing patient care and education.

Drug	Trade Name	Equivalent Oral Dose (mg)*	Incidence of Side Effects: Extrapyramidal Effects†	Sedation	Ortho-static Hypo-tension	Anticho-linergic Effects	Weight Gain, Diabetes, Dyslipidemia	Significant QT Prolongation
First-Generation (Conventional) Antipsychotics								
Low Potency								
Chlorpromazine	Thorazine	100	Moderate	High	High	Moderate	Moderate	Yes
Thioridazine	Mellaril	100	Low	High	High	High	Moderate	Yes
Medium Potency								
Loxapine	Loxitane	10	Moderate	Moderate	Low	Low	Low	—
Molindone	Moban	10	Moderate	Moderate	Low	Low	Low	—
Perphenazine	generic only	10	Moderate	Moderate	Low	Low	—	—
High Potency								
Trifluoperazine	generic only	5	High	Low	Low	Low	—	—
Thiothixene	Navane	2	High	Low	Moderate	Low	Moderate	—
Fluphenazine	Prolixin	2	High	Low	Low	Low	—	—
Haloperidol	Haldol	2	High	Low	Low	Low	Moderate	Yes
Pimozide	Orap	0.5	High	Moderate	Low	Moderate	—	Yes
Second-Generation (Atypical) Antipsychotics								
Clozapine	Clozaril, FazaClo	50	Very low	High	Moderate	High	High	—
Olanzapine	Zyprexa	5	Very low	High	Moderate	High	High	—
Risperidone	Risperdal	4	Moderate	Low	Low	None	Moderate	—
Paliperidone	Invega	—	Moderate	Low	Low	None	Moderate	?
Quetiapine	Seroquel	150	Very low	Moderate	Moderate	None	Moderate	—
Ziprasidone	Geodon	—	Moderate	Moderate	Moderate	None	Low	Yes
Aripiprazole	Abilify	—	Very low	Low	Low	None	Low	—

TABLE 31-3 Antipsychotic Drugs: Relative Potency and Incidence of Side Effects

* Doses listed are the therapeutic equivalent of 100 mg of oral chlorpromazine.

† Incidence refers to *early* extrapyramidal reactions (acute dystonia, parkinsonism, akathisia). The incidence of *late* reactions (tardive dyskinesia) is the same for all traditional antipsychotics; tardive dyskinesia has not been reported with second-generation antipsychotics.

Chemical Classification

The FGAs fall into six major chemical categories (Table 31-4). One of these categories, the phenothiazines, has three subgroups. Drugs in all groups are

equivalent with respect to antipsychotic actions. Because of this equivalence, chemical classification is not emphasized in this chapter.

Two chemical categories—*phenothiazines* and *butyrophenones*—deserve special attention. The phenothiazines were the first of the modern antipsychotic agents. Chlorpromazine, our prototype of the low-potency neuroleptics, belongs to this family. The butyrophenones stand out because they are the family to which haloperidol belongs. Haloperidol is the prototype of the high-potency FGAs.

Chemical Group and Generic Name	Trade Name	Route	Usual Total Daily Dose (mg)	
			Short Term	Maintenance
First-Generation (Conventional) Antipsychotics				
Phenothiazine: Aliphatic				
Chlorpromazine	Thorazine	PO, IM, IV, R*	200–1000	50–400
Phenothiazine: Piperidine				
Thioridazine	Mellaril	PO	200–800	50–400
Phenothiazine: Piperazine				
Fluphenazine	Prolixin	PO, IM	5–30	1–15
Perphenazine	generic only	PO	12–64	8–24
Trifluoperazine	generic only	PO, IM	10–60	4–30
Thioxanthene				
Thiothixene	Navane	PO	10–60	6–30
Butyrophenone				
Haloperidol	Haldol	PO, IM	5–50	1–5
Dihydroindolone				
Molindone	Moban	PO	40–225	15–100
Dibenzoxazepine				
Loxapine	Loxitane	PO	20–160	20–60
Diphenylbutylpiperadine				
Pimozide	Orap	PO	1–2‡	10‡
Second-Generation (Atypical) Antipsychotics				
Dibenzodiazepine				

TABLE 31-4 Antipsychotic Drugs: Routes and Dosages

* R = rectal (suppository).

† Dosage for Tourette's syndrome.

Mechanism of Action

The FGAs block a variety of receptors within and outside the CNS. To varying degrees, they block receptors for dopamine, acetylcholine, histamine, and norepinephrine. There is little question that blockade at these receptors is responsible for the major *adverse effects* of the antipsychotics. However, since the etiology of psychotic illness is unclear, the relationship of receptor blockade to *therapeutic effects* can only be guessed. The current dominant theory suggests that FGA drugs suppress symptoms of psychosis by blocking dopamine**2** (D**2**) receptors in the mesolimbic area of the brain. In support of this theory is the observation that all of the FGAs produce D**2** receptor blockade. Furthermore, there is a close correlation between the clinical potency of these drugs and their potency as D**2** receptor antagonists.

Therapeutic Uses

Schizophrenia.

Schizophrenia is the primary indication for antipsychotic drugs. These agents effectively suppress symptoms during acute psychotic episodes and, when taken chronically, can greatly decrease the risk of relapse. Initial effects may be seen in 1 to 2 days, but substantial improvement usually takes 2 to 4 weeks, and full effects may not develop for several months. Positive symptoms (eg, delusions, hallucinations) respond better than either negative symptoms (eg, social and emotional withdrawal, blunted affect, poverty of speech) or cognitive dysfunction (eg, disordered thinking, learning and memory difficulties). All of the FGA agents are equally effective, although individual patients may respond better to one FGA than to another. Consequently, selection among these drugs is based primarily on their side effect profiles, rather than on therapeutic effects. It must be noted that antipsychotic drugs do not alter the underlying pathology of schizophrenia. Hence, treatment is not curative—it offers only symptomatic relief. Management of schizophrenia is discussed in depth later in the chapter.

Bipolar Disorder (Manic-Depressive Illness).

Most patients with bipolar disorder are managed with a mood-stabilizing agent (eg, lithium, valproic acid). Neuroleptics may be employed acutely, usually in combination with lithium or valproic acid, to help manage patients going through a severe manic phase. Bipolar disorder and its treatment are the subject of Chapter 33.

Tourette's Syndrome.

This rare inherited disorder is characterized by severe motor tics, barking cries, grunts, and outbursts of obscene language, all of which are spontaneous and beyond control of the patient. In addition to these core symptoms, patients frequently have symptoms resembling those of obsessive-compulsive disorder (OCD) or attention-deficit/hyperactivity disorder (ADHD). Neuroleptic drugs (eg, pimozide, fluphenazine, haloperidol) are the most effective agents for managing core symptoms. When core symptoms are mild, clonidine is the drug of choice. Symptoms of OCD can be managed with a selective serotonin reuptake inhibitor (eg, fluoxetine [Prozac]). Symptoms of ADHD can be controlled with a CNS stimulant (eg, methylphenidate [Ritalin]).

Prevention of Emesis.

Neuroleptics suppress emesis by blocking dopamine receptors in the chemoreceptor trigger zone of the medulla. These drugs can be employed to suppress vomiting associated with cancer chemotherapy, gastroenteritis, uremia, and other conditions.

Other Applications.

Neuroleptics can be used for *delusional disorders, schizoaffective disorder,* and *dementia and other organic mental syndromes* (ie, psychiatric syndromes resulting from organic causes, such as infection, metabolic disorders, poisoning, and structural injury to the brain). In addition, neuroleptics can relieve symptoms of *Huntington's chorea*.

Adverse Effects

The antipsychotic drugs block several kinds of receptors, and hence produce an array of side effects. Side effects associated with blockade of specific receptors are summarized in Table 31-5.

Although antipsychotic agents produce a variety of undesired effects, these drugs are, on the whole, very safe; death from overdose is practically unheard of. Among the many side effects FGAs can produce, the most troubling are the extrapyramidal reactions—especially tardive dyskinesia (TD).

Receptor Type	Consequence of Blockade
D_2 dopaminergic	EPS'; prolactin release
H_1 histaminergic	Weight gain, sedation
Muscarinic cholinergic	Dry mouth, blurred vision, urinary retention, constipation, tachycardia
$Alpha_1$-adrenergic	Orthostatic hypotension, reflex tachycardia

EPS = extrapyramidal symptoms.

TABLE 31-5 Receptor Blockade and Side Effects of Antipsychotic Drugs

Extrapyramidal Symptoms

Extrapyramidal symptoms (EPS) are movement disorders resulting from effects of antipsychotic drugs on the extrapyramidal motor system. The extrapyramidal system is the same neuronal network whose malfunction is responsible for the movement disorders of Parkinson's disease (PD). Although the exact cause of EPS is unclear, blockade of D2 receptors is strongly suspected.

Four types of EPS occur. They differ with respect to time of onset and management. Three of these reactions—acute dystonia, parkinsonism, and akathisia—occur early in therapy and can be managed with a variety of drugs. The fourth reaction—tardive dyskinesia—occurs late in therapy and has no satisfactory treatment. Characteristics of EPS are summarized in Table 31-6.

The *early* reactions occur *less frequently* with *low-potency* agents (eg, chlorpromazine) than with high-potency agents (eg, haloperidol). In contrast, the risk of TD is equal with all FGAs.

Type of Reaction	Time of Onset	Features	Management
Early Reactions			
Acute dystonia	A few hours to 5 days	Spasm of muscles of tongue, face, neck, and back; opisthotonus	Anticholinergic drugs (eg, benztropine) IM or IV.
Parkinsonism	5–30 days	Bradykinesia, mask-like facies, tremor, rigidity, shuffling gait, drooling, cogwheeling, stooped posture	Anticholinergics (eg, benztropine, diphenhydramine), amantadine, or both. For severe symptoms, switch to a second-generation antipsychotic.
Akathisia	5–60 days	Compulsive, restless movement; symptoms of anxiety, agitation	Reduce dosage or switch to a low-potency antipsychotic. Treat with a benzodiazepine, beta blocker, or anticholinergic drug.
Late Reaction			
Tardive dyskinesia	Months to years	Oral-facial dyskinesias, choreoathetoid movements	Best approach is prevention; no reliable treatment. Discontinue all anticholinergic drugs. Give benzodiazepines. Reduce anti-psychotic dosage. For severe TD, switch to a second-generation antipsychotic.

TABLE 31-6 Extrapyramidal Side Effects of Antipsychotic Drugs

Acute Dystonia.

Acute dystonia can be both disturbing and dangerous. The reaction develops within the first few days of therapy, and frequently within hours of the first dose. Typically, the patient develops severe spasm of the muscles of the tongue, face, neck, or back. Oculogyric crisis (involuntary upward deviation of the eyes) and opisthotonus (tetanic spasm of the back muscles causing the trunk to arch forward, while the head and lower limbs are thrust backward) may also occur. Severe cramping can cause joint dislocation. Laryngeal dystonia can impair respiration.

Intense dystonia is a crisis that requires rapid intervention. Initial treatment consists of anticholinergic medication (eg, benztropine, diphenhydramine) administered IM or IV. As a rule, symptoms resolve within 5 minutes of IV dosing and within 15 to 20 minutes of IM dosing.

It is important to differentiate between acute dystonia and psychotic hysteria. Why? Because misdiagnosis of acute dystonia as hysteria could result in escalation of antipsychotic dosage, thereby causing the acute dystonia to become even worse.

Parkinsonism.

Antipsychotic-induced parkinsonism is characterized by bradykinesia, masklike facies, drooling, tremor, rigidity, shuffling gait, cogwheeling, and stooped posture. Symptoms develop within the first month of therapy and are indistinguishable from those of idiopathic PD.

Neuroleptics cause parkinsonism by blocking dopamine receptors in the striatum. Since idiopathic PD is also due to reduced activation of striatal dopamine receptors (see Chapter 21), it is no wonder that PD and neuroleptic-induced parkinsonism share the same symptoms.

Neuroleptic-induced parkinsonism is treated with some of the drugs used for idiopathic PD. Specifically, centrally acting *anticholinergic drugs* (eg, benztropine, diphenhydramine) and *amantadine* [Symmetrel] may be employed. Levodopa and direct dopamine agonists (eg, bromocriptine) should be avoided.

Why? Because these drugs activate dopamine receptors, and might thereby counteract the beneficial effects of antipsychotic treatment.

Use of antiparkinsonism drugs should not continue indefinitely. Antipsychotic-induced parkinsonism tends to resolve spontaneously, usually within months of its appearance. Accordingly, antiparkinsonism drugs should be withdrawn after a few months to determine if they are still needed.

If parkinsonism is severe, switching to an SGA is likely to help. As discussed below, the risk of parkinsonism with the SGAs is much lower than with FGAs.

Akathisia.

Akathisia is characterized by pacing and squirming brought on by an uncontrollable need to be in motion. This profound sense of restlessness can be very disturbing. The syndrome usually develops within the first 2 months of treatment. Like other early EPS, akathisia occurs most frequently with high-potency FGAs.

Three types of drugs have been used to suppress symptoms: *beta blockers, benzodiazepines,* and *anticholinergic drugs*. Although these drugs can help, reducing antipsychotic dosage or switching to a low-potency FGA may be more effective.

It is important to differentiate between akathisia and exacerbation of psychosis. If akathisia were to be confused with anxiety or psychotic agitation, it is likely that antipsychotic dosage would be increased, thereby making akathisia more intense.

Tardive Dyskinesia.

Tardive dyskinesia, the most troubling EPS, develops in 15% to 20% of patients during long-term therapy. The risk is related to duration of treatment and dosage size. For many patients, symptoms are irreversible.

Tardive dyskinesia is characterized by involuntary choreoathetoid (twisting, writhing, worm-like) movements of the tongue and face. Patients may also present with lip-smacking movements, and their tongues may flick out in a "fly-catching" motion. One of the earliest manifestations of TD is slow, worm-like movement of the tongue. Involuntary movements that involve the tongue and mouth can interfere with chewing, swallowing, and speaking. Eating diffi-

culties can result in malnutrition and weight loss. Over time, TD produces involuntary movements of the limbs, toes, fingers, and trunk. For some patients, symptoms decline following a dosage reduction or drug withdrawal. For others, TD is irreversible.

The cause of TD is complex and incompletely understood. One theory suggests that symptoms result from excessive *activation* of dopamine receptors. It is postulated that, in response to chronic receptor blockade, dopamine receptors of the extrapyramidal system undergo a functional change such that their sensitivity to activation is increased. Stimulation of these "supersensitive" receptors produces an imbalance in favor of dopamine, and thereby produces abnormal movement. In support of this theory is the observation that symptoms of TD can be reduced (temporarily) by *increasing* antipsychotic dosage, which increases dopamine receptor blockade. (Since symptoms eventually return even though antipsychotic dosage is kept high, dosage elevation cannot be used to treat TD.)

There is no reliable management for TD. Measures that may be tried include gradual withdrawal of anticholinergic drugs, administration of benzodiazepines, and reducing the dosage of the offending FGA. For patients with severe TD, switching to an SGA agent may be beneficial. These drugs do not seem to cause TD, and may actually suppress symptoms in patients who have developed the disorder.

Since TD has no reliable means of treatment, prevention is the best approach. Antipsychotic drugs should be used in the lowest effective dosage for the shortest time required. After 12 months, the need for continued therapy should be assessed. If drug use must continue, a neurologic evaluation should be done at least every 3 months to detect early signs of TD. For patients with chronic schizophrenia, dosage should be tapered periodically (at least annually) to determine the need for continued treatment.

Other Adverse Effects

Neuroleptic Malignant Syndrome.

Neuroleptic malignant syndrome (NMS) is a rare but serious reaction that carries a 4% risk of mortality—down from 30% in the past, thanks to early dia-

gnosis and intervention. Primary symptoms are "lead pipe" rigidity, sudden high fever (temperature may exceed 41°C), sweating, and autonomic instability, manifested as dysrhythmias and fluctuations in blood pressure. Level of consciousness may rise and fall, the patient may appear confused or mute, and seizures or coma may develop. Death can result from respiratory failure, cardiovascular collapse, dysrhythmias, and other causes. NMS is more likely with high-potency agents than with low-potency agents.

Treatment consists of supportive measures, drug therapy, and immediate withdrawal of antipsychotic medication. Hyperthermia should be controlled with cooling blankets and antipyretics (eg, aspirin, acetaminophen). Hydration should be maintained with fluids. Benzodiazepines may relieve anxiety and help reduce blood pressure and tachycardia. Two drugs—*dantrolene* and *bromocriptine*—may be especially helpful. Dantrolene is a direct-acting muscle relaxant (see Chapter 25). In patients with NMS, this drug reduces rigidity and hyperthermia. Bromocriptine is a dopamine receptor agonist (see Chapter 21) that may relieve CNS toxicity.

Resumption of antipsychotic therapy carries a small risk of NMS recurrence. The risk can be minimized by (1) waiting at least 2 weeks before resuming antipsychotic treatment, (2) using the lowest effective dosage, and (3) avoiding high-potency agents. If a second episode occurs, switching to an SGA may be helpful.

Anticholinergic Effects.

First-generation agents produce varying degrees of muscarinic cholinergic blockade (see Table 31-3). By blocking muscarinic receptors, these drugs can elicit the full spectrum of anticholinergic responses (dry mouth, blurred vision, photophobia, urinary hesitancy, constipation, tachycardia). Patients should be informed about these responses and taught how to minimize danger and discomfort. As indicated in Table 31-3, anticholinergic effects are more likely with low-potency FGAs than with high-potency FGAs. Anticholinergic effects and their management are discussed in detail in Chapter 14.

Orthostatic Hypotension.

Antipsychotic drugs promote orthostatic hypotension by blocking alpha*1*-adrenergic receptors on blood vessels. Alpha-adrenergic blockade prevents compensatory vasoconstriction when the patient stands, thereby causing blood pressure to fall. Patients should be informed about signs of hypotension (lightheadedness, dizziness) and advised to sit or lie down if these occur. In addition, patients should be informed that hypotension can be minimized by moving slowly when assuming an erect posture. With hospitalized patients, blood pressure and pulses should be checked before drug administration and 1 hour after. Measurements should be made while the patient is lying down and again after the patient has been sitting or standing for 1 to 2 minutes. If blood pressure is low, or if pulse rate is high, the drug should be withheld and the prescriber consulted. Hypotension is more likely with low-potency FGAs than with the high-potency FGAs (see Table 31-3). Tolerance to hypotension develops in 2 to 3 months.

Sedation.

Sedation is common during the early days of treatment but subsides within a week or so. Neuroleptic-induced sedation is thought to result from blockade of histamine*1* receptors in the CNS. Daytime sedation can be minimized by giving the entire daily dose at bedtime. Patients should be warned against participating in hazardous activities (eg, driving) until sedative effects diminish.

Neuroendocrine Effects.

Antipsychotics increase levels of circulating prolactin by blocking the inhibitory action of dopamine on prolactin release. Elevation of prolactin levels promotes *gynecomastia* (breast growth) and *galactorrhea* in up to 57% of women. Up to 97% of women experience menstrual irregularities. Gynecomastia and galactorrhea can also occur in males. Since prolactin can promote growth of prolactin-dependent carcinoma of the breast, neuroleptics should be avoided in patients with this form of cancer. (It should be noted that, although FGAs can promote the growth of cancers that already exist, there is no evidence that FGAs actually *cause* cancer.)

Seizures.

First-generation agents can reduce seizure threshold, thereby increasing the risk of seizure activity. The risk of seizures is greatest in patients with epilepsy and other seizure disorders. These patients should be monitored, and, if loss of seizure control occurs, the dosage of their antiseizure medication must be increased.

Sexual Dysfunction.

First-generation agents can cause sexual dysfunction in women and men. In women, these drugs can suppress libido and impair the ability to achieve orgasm. In men, FGAs can suppress libido and cause erectile and ejaculatory dysfunction; the incidence of these effects is 25% to 60%. Drug-induced sexual dysfunction can make treatment unacceptable to sexually active patients, thereby leading to poor compliance. A reduction in dosage or switching to a high-potency FGA may reduce effects on sexual function. Patients should be counseled about possible sexual dysfunction and encouraged to report problems.

Dermatologic Effects.

Drugs in the *phenothiazine* class can sensitize the skin to ultraviolet light, thereby increasing the risk of severe sunburn. Patients should be warned against excessive exposure to sunlight and advised to apply a sunscreen and wear protective clothing. Phenothiazines can also produce pigmentary deposits in the skin, cornea, and lens of the eye.

Handling antipsychotics can cause contact dermatitis in patients and healthcare workers. Dermatitis can be prevented by avoiding direct contact with these drugs.

Agranulocytosis.

Agranulocytosis is a rare but serious reaction. Among the FGAs, the risk is highest with chlorpromazine and certain other phenothiazines. Since agranulocytosis severely compromises the ability to fight infection, a white blood cell count (WBC) should be done whenever signs of infection (eg, fever, sore throat) appear. If agranulocytosis is diagnosed, the neuroleptic should be withdrawn. Agranulocytosis reverses upon cessation of treatment.

Severe Dysrhythmias.

Four FGAs—*chlorpromazine, thioridazine, haloperidol,* and *pimozide*—pose a risk of fatal cardiac dysrhythmias. The mechanism is prolongation of the QT interval, an index of cardiac function that can be measured with an electrocardiogram (ECG). As discussed in Chapter 7 (Adverse Drug Reactions and Medication Errors), drugs that prolong the QT interval increase the risk of torsades de pointes, a dysrhythmia than can progress to fatal ventricular fibrillation. To reduce the risk of dysrhythmias, patients should undergo an ECG and serum potassium determination prior to treatment and periodically thereafter. In addition, they should avoid other drugs that cause QT prolongation (see Chapter 7, Table 7-2), as well as drugs that can increase levels of the drugs under consideration.

Physical and Psychologic Dependence

Development of physical and psychologic dependence is rare. Patients should be reassured that addiction and dependence are not likely.

Although physical dependence is minimal, abrupt withdrawal of FGAs *can* precipitate a mild abstinence syndrome. Symptoms, which are related to chronic cholinergic blockade, include restlessness, insomnia, headache, gastric distress, and sweating. The syndrome can be avoided by withdrawing FGAs gradually.

Drug Interactions

Anticholinergic Drugs.

Drugs with anticholinergic properties will intensify anticholinergic responses to neuroleptics. Patients should be advised to avoid all drugs with anticholinergic actions, including antihistamines and certain over-the-counter sleep aids.

CNS Depressants.

Neuroleptics can intensify CNS depression caused by other drugs. Patients should be warned against using alcohol and all other drugs with CNS-depressant actions (eg, antihistamines, benzodiazepines, barbiturates).

Levodopa and Direct Dopamine Receptor Agonists.

Levodopa (a drug for Parkinson's disease) may counteract the antipsychotic effects of neuroleptics. Conversely, neuroleptics may counteract the therapeutic effects of levodopa. These interactions occur because levodopa and neuroleptics have opposing effects on receptors for dopamine: Levodopa activates dopamine receptors, whereas neuroleptics cause receptor blockade. Like levodopa, the direct dopamine receptor agonists (eg, bromocriptine) activate dopamine receptors, and hence have interactions with neuroleptics identical to those of levodopa.

Toxicity

First-generation antipsychotics are very safe; death by overdose is extremely rare. With chlorpromazine, for example, the therapeutic index is about 200. That is, the lethal dose is 200 times the therapeutic dose.

Overdose produces hypotension, CNS depression, and extrapyramidal reactions. Extrapyramidal reactions can be treated with antiparkinsonism drugs. Hypotension can be treated with IV fluids plus an alpha-adrenergic agonist (eg, phenylephrine). There is no specific antidote to CNS depression. Excess drug should be removed from the stomach by gastric lavage. Emetics cannot be used because their effects would be blocked by the antiemetic action of the neuroleptic.

FIRST-GENERATION (CONVENTIONAL) ANTIPSYCHOTICS: INDIVIDUAL AGENTS

All of the FGAs are equally effective at alleviating symptoms of schizophrenia, although individual patients may respond better to one FGA than to another. Differences among these agents relate primarily to side effects (see Table 31-3). Because the high-potency agents produce fewer side effects than the low-potency agents, high-potency agents are generally preferred.

Low-Potency Agents

Chlorpromazine

Chlorpromazine [Thorazine] was the first modern antipsychotic medication and is the prototype for all that followed. None of the newer FGAs is superior at relieving symptoms of psychotic illnesses. Chlorpromazine is a low-potency FGA and belongs to the phenothiazine family of compounds.

Therapeutic Uses.

Principal indications are schizophrenia and other psychotic disorders. Additional psychiatric indications are schizoaffective disorder and the manic phase of bipolar disorder. Other uses include suppression of emesis and relief of intractable hiccups.

Pharmacokinetics.

Chlorpromazine may be administered PO, IM, IV, and by rectal suppository. Following oral administration, the drug is well absorbed but undergoes extensive first-pass metabolism. As a result, oral bioavailability is only 30%. When chlorpromazine is given IM or IV, peak plasma levels are 10 times those achieved with an equal oral dose. Excretion is renal, almost entirely as metabolites.

Adverse Effects.

The most common adverse effects are sedation, orthostatic hypotension, and anticholinergic effects (dry mouth, blurred vision, urinary retention, photophobia, constipation, tachycardia). Neuroendocrine effects—galactorrhea, gynecomastia, menstrual irregularities—occur occasionally. Photosensitivity reactions are possible, and patients should be advised to minimize unprotected exposure to sunlight. Because chlorpromazine is a low-potency neuroleptic, the risk of early extrapyramidal reactions (dystonia, akathisia, parkinsonism) is relatively low. However, the risk of TD is the same as with all other FGAs. Chlorpromazine lowers seizure threshold. Accordingly, patients with seizure disorders should be especially diligent about taking antiseizure medication. Agranulocytosis and NMS occur rarely.

Drug Interactions.

Chlorpromazine can intensify responses to CNS depressants (eg, antihistamines, benzodiazepines, barbiturates) and anticholinergic drugs (eg, antihistamines, tricyclic antidepressants, atropine-like drugs).

Preparations, Dosage, and Administration.

Chlorpromazine [Thorazine] is available in four formulations: *tablets* (10, 25, 50, 100, and 200 mg), *oral concentrate* (30 and 100 mg/mL), *rectal suppositories* (25 and 100 mg), and *solution for injection* (25 mg/mL).

Oral Therapy.

The initial dosage for adults is 25 mg 3 times a day. Dosage should be gradually increased until symptoms are controlled. The usual maintenance dosage is 400 mg/day. Elderly patients require less drug than younger patients.

Parenteral Therapy.

Parenteral therapy is indicated for acutely psychotic, hospitalized patients. Intramuscular administration is preferred to IV administration. (Intravenous chlorpromazine is highly irritating and generally avoided.) The initial dose is 25 to 50 mg. Dosage may be increased gradually to a maximum of 400 mg every 4 to 6 hours. Once symptoms are controlled, oral therapy should be substituted for parenteral therapy.

Thioridazine

Thioridazine [Mellaril] is a low-potency FGA that prolongs the QT interval, and hence can cause fatal cardiac dysrhythmias. Because of this danger, the drug should be reserved for treating schizophrenia in patients who have not responded to safer agents. The most common adverse effects are sedation, orthostatic hypotension, anticholinergic effects, weight gain, and inhibition of ejaculation. Effects seen occasionally include extrapyramidal reactions (dystonia, parkinsonism, akathisia, TD), galactorrhea, gynecomastia, menstrual irregularities, and photosensitivity reactions. NMS, convulsions, agranulocytosis, and pigmentary retinopathy occur rarely. Principal interactions are with anticholinergic drugs and CNS depressants. Thioridazine is available in two oral formulations: tablets (10, 15, 25, 50, 100, 150, and 200 mg) and a liquid concentrate (30 and 100 mg/mL). The initial dosage is 50 to 100 mg 3 times a day.

Dosage may be gradually increased until symptoms are controlled, but should not exceed 800 mg/day. The usual maintenance dosage is 200 to 800 mg/day in two to four divided doses.

Medium-Potency Agents

Loxapine.

Loxapine [Loxitane] is a medium-potency agent indicated only for schizophrenia. The side effect profile is similar to that of fluphenazine (see below). The drug is available in capsules (5, 10, 25, and 50 mg) for oral use. The initial dosage is 10 mg twice a day. Dosage is increased until symptoms are controlled, typically with 60 to 100 mg/day in divided doses. The dosage should be reduced for maintenance therapy; the usual range is 20 to 60 mg/day.

Molindone.

Molindone [Moban] is a medium-potency agent approved only for schizophrenia. The most common adverse effects are early extrapyramidal reactions (dystonia, parkinsonism, akathisia) and anticholinergic effects (dry mouth, blurred vision, photophobia, urinary retention, constipation, tachycardia). Effects seen occasionally include sedation, menstrual irregularities, weight loss, and TD. Orthostatic hypotension and NMS occur rarely. Molindone is available in tablets (5, 10, 25, 50, and 100 mg) for oral use. The initial dosage is 50 to 75 mg/day in divided doses. Dosage is then increased until symptoms are controlled. As much as 225 mg/day has been given. Dosage should be reduced to the lowest effective amount for maintenance.

Perphenazine.

Perphenazine, formerly available as *Trilafon*, is a medium-potency agent used for schizophrenia and other psychotic disorders. Its side effect profile is like that of fluphenazine (see below). The drug is available in tablets (2, 4, 8, and 16 mg) and an oral concentrate (16 mg/5 mL). The initial dosage is 4 to 8 mg 3 times daily. Once symptoms have been controlled, the dosage should be reduced to the lowest effective amount.

High-Potency Agents

High-potency agents differ from low-potency agents primarily in that high-potency agents cause more early EPS but less sedation, orthostatic hypotension, and anticholinergic effects. Because they cause fewer side effects, high-potency agents are generally preferred for initial therapy.

Haloperidol

Actions and Uses.

Haloperidol [Haldol], a member of the *butyrophenone* family, is the prototype of the high-potency FGAs. Antipsychotic actions are equivalent to those of chlorpromazine. Principal indications are schizophrenia and acute psychosis. In addition, haloperidol is a preferred agent for Tourette's syndrome. The drug is also effective in refractory migraine, although it is not approved for this use.

Pharmacokinetics.

Haloperidol may be administered PO or IM. Oral bioavailability is about 60%. Hepatic metabolism is extensive. Parent drug and metabolites are excreted in the urine.

Adverse Effects.

As indicated in Table 31-3, early extrapyramidal reactions (acute dystonia, parkinsonism, akathisia) occur frequently, whereas sedation, hypotension, and anticholinergic effects are uncommon. Note that the incidence of these reactions is opposite to that seen with chlorpromazine and other low-potency agents. The incidence of TD with haloperidol is the same as with the low-potency drugs. Like chlorpromazine, haloperidol occasionally causes gynecomastia, galactorrhea, and menstrual irregularities. NMS, photosensitivity, convulsions, and impotence are rare.

Haloperidol can prolong the QT interval, and hence may pose a risk of *serious dysrhythmias,* especially when given IV and/or in high doses. The drug should be used with caution in patients with dysrhythmia risk factors, including long QT syndrome, hypokalemia or hyperkalemia, or a history of dysrhythmias, heart attack, or severe heart failure. Combined use with other QT-prolonging drugs (eg, amiodarone, erythromycin, quinidine) should be avoided.

Preparations, Dosage, and Administration.

Preparations.

Haloperidol [Haldol] is available in tablets (0.5, 1, 2, 5, 10, and 20 mg) and a liquid concentrate (2 mg/mL) for oral use. Two injectable forms—*haloperidol lactate* (5 mg/mL) and *haloperidol decanoate* (50 and 100 mg/mL)—are available for parenteral (IM) administration. Haloperidol lactate is employed for acute therapy. Haloperidol decanoate is a depot preparation used for long-term therapy.

Oral Therapy.

The initial dosage for adults is 0.5 to 2 mg taken 2 or 3 times a day. For severe illness, daily doses up to 100 mg have been employed. Once symptoms have been controlled, the dosage should be reduced to the lowest effective amount.

Intramuscular Therapy.

For *acute therapy* of severe psychosis, haloperidol lactate is administered IM in doses of 2 to 5 mg. Dosing may be repeated as often as every 60 minutes, although intervals of 4 to 8 hours may be satisfactory. Once symptoms are under control, the patient should be switched to oral therapy.

For *long-term therapy*, haloperidol decanoate is given once every 4 weeks by deep IM injection—but only to patients already stabilized on oral haloperidol. The initial dose is 10 to 20 times the current oral dose—but no greater than 100 mg. Maintenance doses are 10 to 15 times the previous oral dose.

Other High-Potency Agents

Fluphenazine.

Fluphenazine [Prolixin] is a high-potency agent indicated for schizophrenia and other psychotic disorders. The drug belongs to the piperazine subclass of phenothiazines. As with other high-potency agents, the most common adverse effects are early extrapyramidal reactions (acute dystonia, parkinsonism, akathisia). The risk of TD equals that of other FGAs. Effects seen occasionally include sedation, orthostatic hypotension, anticholinergic effects,

gynecomastia, galactorrhea, and menstrual irregularities. NMS, convulsions, and agranulocytosis are rare.

Fluphenazine may be given PO or IM. For oral use, the drug is available in tablets (1, 2.5, 5, and 10 mg) and an elixir (2.5 mg/5 mL). The initial *oral* dosage is 2.5 to 10 mg/day, given in divided doses every 6 to 8 hours. Daily dosages greater than 3 mg are rarely needed, although some patients may require as much as 30 mg. Once symptoms have been controlled, the dosage should be reduced to the lowest effective amount, typically 1 to 5 mg/day taken as a single dose.

Two injectable preparations are available: *fluphenazine hydrochloride* (2.5 mg/mL) and *fluphenazine decanoate* (25 mg/mL). Both are given IM. Fluphenazine hydrochloride is a fast-acting preparation used for acute therapy. The usual dosage is 2.5 to 10 mg/day, given in divided doses every 6 to 8 hours. Fluphenazine decanoate [Prolixin Decanoate] is a depot preparation used for long-term therapy—but only in patients already stabilized on oral fluphenazine (or another phenothiazine antipsychotic). Intramuscular doses are based on the oral dosage. A reasonable conversion ratio is 12.5 mg of IM fluphenazine every 3 weeks for each 10 mg of oral fluphenazine taken daily.

Trifluoperazine.

Trifluoperazine (formerly available as *Stelazine*) is a high-potency agent used for schizophrenia and other psychotic disorders. The drug belongs to the piperazine subclass of phenothiazines. The most common adverse effects are early extrapyramidal reactions (acute dystonia, parkinsonism, akathisia). Effects seen occasionally include sedation, orthostatic hypotension, anticholinergic effects, gynecomastia, galactorrhea, menstrual irregularities, and TD. NMS, convulsions, and agranulocytosis are rare. Trifluoperazine is available in tablets (1, 2, 5, and 10 mg) for oral use. Dosing is begun at 2 to 5 mg twice daily, and then increased until an optimal response has been produced, usually with 15 to 20 mg/day.

Thiothixene.

Thiothixene [Navane] is a high-potency agent approved only for schizophrenia. The most common adverse effects are early extrapyramidal reactions

(acute dystonia, parkinsonism, akathisia) and anticholinergic responses. Side effects seen occasionally include galactorrhea, gynecomastia, menstrual irregularities, sedation, orthostatic hypotension, and TD. Agranulocytosis, NMS, and convulsions are rare. Thiothixene is available in capsules (1, 2, 5, 10, and 20 mg) for oral use. The initial dosage is 2 mg 3 times daily. Dosage is increased until an optimal response has been achieved, usually with 20 to 30 mg/day.

Pimozide.

Pimozide [Orap] is a high-potency FGA approved only for suppressing symptoms of *Tourette's syndrome,* a rare disorder characterized by severe motor tics and uncontrollable grunts, barking cries, and outbursts of obscene language. Like other neuroleptics, pimozide can cause sedation, postural hypotension, and extrapyramidal reactions (acute dystonia, parkinsonism, akathisia, TD). Pimozide can prolong the QT interval, and hence poses a risk of fatal cardiac dysrhythmias. Sertraline [Zoloft] increases this risk by raising pimozide levels, and hence the two drugs should not be combined. Pimozide is available in tablets (1 and 2 mg) for oral therapy. The initial dosage is 1 to 2 mg/day in divided doses. Dosage should be slowly increased to a maintenance level of 10 mg/day or 0.2 mg/kg/day (whichever is less).

SECOND-GENERATION (ATYPICAL) ANTIPSYCHOTICS

The second-generation antipsychotics (SGAs), also known as *atypical antipsychotics,* were introduced in the 1990s and quickly took over 90% of the market, owing to the *perception* of superior efficacy and greater safety. However, neither initial perception has held up. Thanks to two large, government-sponsored studies, one in the United States and the other in Great Britain, we now know that, in most cases, SGAs and FGAs are equally effective. As for major side effects, the SGAs *are* less likely to cause EPS, including TD. However, the SGAs carry an even greater risk of their own, namely, potentially fatal metabolic effects—weight gain, diabetes, and dyslipidemia—that can lead to cardiovascular events and premature death. Furthermore, like the FGAs, the SGAs can cause sedation and orthostatic hypotension, and can increase the risk of death when used to treat dementia in the elderly. Lastly, even though SGAs have no clear clinical advantage over FGAs, the SGAs cost *ten* times as much.

In addition to their use in schizophrenia, all of the SGAs are approved for bipolar disorder (see Chapter 33).

Clozapine

Clozapine [Clozaril, FazaClo] was the first SGA and will serve as our prototype for the group—even though other SGAs are now used more widely. Most authorities agree that clozapine is our most effective drug for schizophrenia, the only indication that clozapine has. However, because it can cause agranulocytosis, clozapine should be reserved for patients who have not responded to safer alternatives.

Mechanism of Action

Antipsychotic effects result from blockade of receptors for dopamine and serotonin (5-hydroxytryptamine [5-HT]). Like the FGAs, clozapine blocks D2 dopamine receptors, but its affinity for these receptors is relatively low. In contrast, the drug produces strong blockade of 5-HT2 serotonin receptors. Combined blockade of D2 receptors and 5-HT2 receptors is thought to underlie therapeutic effects. Low affinity for D2 receptors may explain why EPS are uncommon. In addition to blocking receptors for dopamine and serotonin, clozapine blocks receptors for norepinephrine (alpha1), histamine, and acetylcholine.

Therapeutic Use

Schizophrenia.

Clozapine is approved for relieving general symptoms of schizophrenia and for reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder who are at chronic suicide risk. Because of the risk of fatal agranulocytosis (see below), clozapine should be reserved for patients with severe disease who have not responded to safer alternatives. Like the FGAs, clozapine improves positive symptoms of schizophrenia. However, in contrast to FGAs, clozapine also improves negative symptoms. Patients become more animated, behavior is more socially acceptable, and rates of rehospitalization are reduced. Because the incidence of EPS with clozapine is low, the drug is well suited for patients who have experienced severe EPS with an FGA.

Levodopa-Induced Psychosis.

Psychosis is a common side effect of levodopa, a drug used for Parkinson's disease (PD). Clozapine is preferred to FGAs for treatment. As discussed in Chapter 21, the movement disorders of PD result from insufficient dopamine in the striatum, a component of the extrapyramidal system. Levodopa reduces symptoms of PD by increasing dopamine availability. Since FGAs cause profound blockade of dopamine receptors in the striatum, they will intensify symptoms of PD. In contrast, clozapine causes little or no blockade of striatal dopamine receptors, and hence can alleviate levodopa-induced psychosis without making symptoms of PD worse. The dosage of clozapine required is only 25 mg a day—about 20 times less than the dosage for schizophrenia.

Pharmacokinetics

Clozapine is rapidly absorbed following oral administration. Plasma levels peak in 3.2 hours. About 95% of the drug is bound to plasma proteins. Clozapine undergoes extensive metabolism followed by fecal and urinary excretion. Its half-life is approximately 12 hours.

Adverse Effects and Interactions

Common adverse effects include sedation and weight gain (from blocking H***1*** histamine receptors); orthostatic hypotension (from blocking alpha-adrenergic receptors); and dry mouth, blurred vision, urinary retention, constipation, and tachycardia (from blocking muscarinic cholinergic receptors). Neuroendocrine effects (galactorrhea, gynecomastia, amenorrhea) and interference with sexual function are minimal.

In contrast to FGAs, clozapine carries a low risk of extrapyramidal effects. TD has not been reported. In fact, TD may improve when patients switch to clozapine from an FGA.

Agranulocytosis.

Clozapine produces agranulocytosis in 1% to 2% of patients. The overall risk of death is about 1 in 5000. The usual cause is gram-negative septicemia. Agranulocytosis typically occurs during the first 6 months of treatment, and the onset is usually gradual. Why agranulocytosis occurs is unknown.

Because of the risk of fatal agranulocytosis, monitoring of the WBC *and* absolute neutrophil count (ANC) is mandatory. Prior to starting clozapine, both the total WBC and ANC must be in the normal range (ie, 3500/mm^3 or greater and 2000/mm^3 or greater, respectively). During treatment, the WBC and ANC must be monitored weekly for the first 6 months, every 2 weeks for the next 6 months, and monthly thereafter. If the total WBC count falls below 3000/mm^3 or if the ANC falls below 1500/mm^3, treatment should be interrupted. When subsequent *daily* monitoring indicates that counts have risen above these values, clozapine can be resumed. If the total WBC count falls below 2000/mm^3 or if the ANC falls below 1000/mm^3, clozapine should be permanently discontinued. Blood counts should be monitored for 4 weeks after drug withdrawal.

Patients should be informed about the risk of agranulocytosis and told that clozapine will not be dispensed if the blood tests have not been done. Also, patients should be informed about early signs of infection (fever, sore throat, fatigue, mucous membrane ulceration) and instructed to report these immediately.

Metabolic Effects: Weight Gain, Diabetes, and Dyslipidemia.

Clozapine and the other SGAs can cause a group of closely linked metabolic effects—obesity, diabetes, and dyslipidemia—all of which increase the risk of cardiovascular events. As indicated in Table 31-3, risk is highest with clozapine and olanzapine, lower with risperidone, paliperidone, and quetiapine, and lowest with ziprasidone and aripiprazole.

Weight gain is the metabolic effect of greatest concern. Why? Because it seems to underlie development of diabetes and dyslipidemia. Among patients taking clozapine, weight gain can be significant. Increases in excess of 30 pounds have been reported. Patients should be informed about the possibility of weight gain and encouraged to get regular exercise, monitor their weight, and control caloric intake. Weight should be measured at baseline; 4, 8, and 12 weeks later; and every 3 months thereafter. In addition, waist circumference should be measured at baseline and annually thereafter. If significant weight gain occurs, it can be managed with a combination of lifestyle measures (diet and exercise) and *metformin,* an oral hypoglycemic agent used for diabetes. In a recent study, metformin was more effective than lifestyle measures, and the combination of metformin plus lifestyle measures was more effective than

either intervention alone. Why do antipsychotic drugs promote weight gain? Probably through blockade of histamine H*1* receptors in the brain.

Clozapine and all other SGAs can cause *new-onset diabetes*. Patients taking these drugs have developed typical diabetes symptoms, including hyperglycemia, polyuria, polydipsia, polyphagia, and dehydration. In extreme cases, hyperglycemia has led to ketoacidosis, hyperosmolar coma, and even death. Because of diabetes risk, fasting blood sugar should be measured before starting clozapine, 12 weeks later, and annually thereafter. Patients with documented diabetes at treatment onset should be monitored for worsening of glucose control. All patients should be informed about symptoms of diabetes and instructed to report them. If diabetes develops, it can be managed with insulin or an oral hypoglycemic drug, such as metformin. Discontinuing clozapine is also an option. However, if the drug has produced control of psychotic symptoms, continuing clozapine and treating the diabetes would seem preferable.

Dyslipidemia associated with clozapine and other SGAs can manifest as increased total cholesterol, LDL cholesterol, and triglycerides, along with decreased HDL cholesterol. This lipid profile increases the risk of atherosclerosis and coronary heart disease. To monitor effects on lipids, a fasting lipid profile should be obtained at baseline, 12 weeks later, and every 5 years thereafter.

Seizures.

Generalized tonic-clonic convulsions occur in 3% of patients. The risk of seizures is dose related. Patients should be warned not to drive or to participate in other potentially hazardous activities if a seizure has occurred. Patients with a history of seizure disorders should use the drug with great caution.

Myocarditis.

Very rarely, clozapine has been associated with myocarditis (inflammation of the heart muscle), which can be fatal. If a patient develops signs and symptoms (eg, unexplained fatigue, dyspnea, tachypnea, chest pain, palpitations), clozapine should be withheld until myocarditis has been ruled out. If myocarditis is diagnosed, clozapine should not be used again.

Orthostatic Hypotension.

Clozapine can cause orthostatic hypotension, sometimes with fainting. Rarely, collapse is severe, and accompanied by respiratory and/or cardiac arrest. Hypotension is most likely during initial dosage titration, especially if dosage escalation is rapid.

Effects in Elderly Dementia Patients.

When used off-label to treat elderly patients with dementia, FGAs and SGAs about double the rate of mortality. Most deaths result from heart-related events (eg, heart failure, sudden death) or from infection (mainly pneumonia). Since FGAs and SGAs are not approved for treating dementia, and since doing so increases the risk of death, it would seem that such use is ill advised.

Drug Interactions.

Because of its ability to cause agranulocytosis, clozapine is contraindicated for patients taking other drugs that can suppress bone marrow function (eg, many anticancer drugs).

Preparations, Dosage, and Administration

Clozapine is available in standard tablets (12.5, 25, 50, 100, and 200 mg), sold as *Clozaril,* and in orally disintegrating tablets (25 and 100 mg), sold as *FazaClo*. To minimize side effects, treatment should begin with a 12.5-mg dose, followed by 25 mg once or twice daily. Dosage is then increased by 25 mg/day until it reaches 300 to 450 mg/day. Further increases can be made once or twice weekly in increments no larger than 100 mg. The usual maintenance dosage is 300 to 600 mg/day in three divided doses. The maximum dosage is 900 mg/day. If therapy is interrupted, it should resume with a 12.5-mg dose and then follow the original escalation guidelines. Because of the risk of agranulocytosis, dispensing is normally limited to a 1-week supply.

Other Atypical Antipsychotics

Risperidone

Risperidone [Risperdal] is a rapid-acting drug originally approved for schizophrenia and then later approved for acute bipolar mania. Most recently, the drug was approved for children with autistic disorder, with the goal of re-

ducing irritability-associated symptoms, such as tantrums, aggression, mood swings, and self-injury. In patients with schizophrenia, the drug improves positive symptoms, negative symptoms, and cognitive function. Like other SGAs, it causes fewer EPS than FGAs. Risperidone is structurally unrelated to clozapine.

Mechanism of Action.

We know that risperidone binds to multiple receptors, but we don't know with certainty how clinical benefits are produced. Risperidone is a powerful antagonist at 5-HT2 receptors and a less powerful antagonist at D2 receptors. Antagonism at both sites probably underlies therapeutic effects. Risperidone does not block cholinergic receptors but does block H1 receptors as well as alpha-adrenergic receptors.

Pharmacokinetics.

Absorption is rapid and not affected by food. Plasma levels peak about 1 hour after oral dosing. Much of each dose is metabolized to 9-hydroxyrisperidone, whose activity equals that of risperidone itself. Parent drug and metabolite are excreted primarily in the urine. The effective half-life is 24 hours. In patients with hepatic or renal dysfunction, the half-life is prolonged.

Therapeutic Effects.

Risperidone relieves positive and negative symptoms of schizophrenia and improves cognitive function. Significant improvement may be seen in 1 week. By contrast, benefits of haloperidol develop more slowly and are limited primarily to positive symptoms. In patients with severe TD, risperidone may have an antidyskinetic effect.

Adverse Effects.

Side effects are generally infrequent and mild, and only rarely require discontinuation of treatment. The incidence of EPS is very low at the recommended dosage. However, at dosages above 10 mg/day, there is a dose-related increase in EPS. With the long-acting IM formulation, the incidence of EPS is substantial (about 25%). TD has not been observed. Risperidone increases prolactin levels, but symptoms (gynecomastia, galactorrhea) are uncommon. Like oth-

er SGAs, risperidone can cause metabolic effects: weight gain, diabetes, and dyslipidemia. Adverse effects that have led to discontinuing the drug include agitation, dizziness, somnolence, and fatigue. Excessive doses have caused difficulty concentrating, sedation, and disruption of sleep. When used off-label to treat elderly dementia patients, risperidone doubles or triples the risk of stroke, and nearly doubles the risk of death (usually from cardiac events or pneumonia).

Preparations, Dosage, and Administration.

Schizophrenia, Oral Therapy.

For oral therapy, risperidone is available in standard tablets (0.25, 0.5, 1, 2, 3, and 4 mg) and solution (1 mg/mL), both sold as *Risperdal,* and in orally disintegrating tablets (0.5, 1, and 2 mg), sold as *Risperdal M-TAB*. The recommended dosage is 1 mg twice daily the first day, 2 mg twice daily the second day, and 3 mg twice daily thereafter. Dosages above 2 or 3 mg twice daily do not increase therapeutic effects, but do increase the risk of EPS and other side effects. Dosage should be reduced in patients with renal or hepatic impairment.

Schizophrenia, Intramuscular Therapy.

Intramuscular risperidone [Risperdal Consta] is a depot preparation used for *long-term* therapy, not for acute therapy. In this formulation, risperidone is bound to a matrix that has been encapsulated within microspheres. Following IM injection, the matrix gradually breaks down to release free drug. Importantly, main release doesn't begin until 2 to 3 weeks after the injection, producing therapeutic levels 4 to 6 weeks after the injection. Because effects are delayed, patients should take an oral antipsychotic during the first 3 weeks of Risperdal Consta use. The IM dosage range is 25 to 50 mg every 2 weeks.

Bipolar Disorder.

Dosage for bipolar disorder is presented in Chapter 33 (Table 33-5).

Irritability Associated with Autistic Disorder.

The initial dosage is 0.25 mg/day (for children under 20 kg) and 0.5 mg/day (for children 20 kg and over). After a minimum of 4 days, dosage may be in-

creased to the recommended maintenance level of 0.5 mg/day (for children under 20 kg) or 1 mg/day (for children 20 kg and over). If needed, dosage may be slowly titrated higher. For all children, the total daily dose can be administered as a single dose or as two divided doses of equal size.

Paliperidone

Paliperidone [Invega] is the active metabolite of risperidone (9-hydroxyrisperidone), and hence has the same adverse and therapeutic effects as risperidone itself. The two drugs differ primarily in that paliperidone is not extensively metabolized, and has no significant kinetic interactions with other drugs. Also, in contrast to risperidone, paliperidone is dosed just once a day, and doesn't require initial dosage titration. Paliperidone can prolong the QT interval, and hence should not be combined with other QT-prolonging drugs. Paliperidone is approved for acute therapy and maintenance therapy of schizophrenia.

Paliperidone is available in extended-release tablets (3, 6, and 9 mg) that employ the osmotic-release oral system (OROS) for delivery. Dosing is done once daily in the morning, with or without food. Patients should be instructed to swallow the tablets whole, without crushing, chewing, or dividing. Also, they should be informed that Invega tablets have a nonabsorbable shell that passes intact into the stool. For patients with normal renal function, the usual dosage is 6 mg/day. For patients with moderate renal impairment (creatinine clearance 50 to 80 mL/min), dosage must not exceed 6 mg/day. For patients with severe renal impairment (creatinine clearance 10 to 50 mL/min), dosage should not exceed 3 mg/day.

Olanzapine

Olanzapine [Zyprexa] is an SGA approved for (1) schizophrenia, (2) maintenance therapy of bipolar disorder, and (3) acute agitation associated with schizophrenia and bipolar mania. In addition, olanzapine is used off-label to suppress nausea and vomiting in cancer patients. The drug is similar to clozapine in structure and actions, but does not cause agranulocytosis. The risk of metabolic effects with this drug is higher than with most other SGAs.

Mechanism of Action.

Olanzapine blocks receptors for serotonin, dopamine, histamine, acetylcholine, and norepinephrine. Therapeutic effects are believed to result from blocking 5-HT2 receptors and D2 receptors. Adverse effects result in part from blocking receptors for histamine, acetylcholine, and norepinephrine.

Pharmacokinetics.

Olanzapine is well absorbed following oral administration. Food does not alter the rate or extent of absorption. Plasma levels peak 6 hours after dosing and decline with a half-life of 30 hours. Hepatic metabolism is extensive.

Therapeutic Uses.

Schizophrenia.

In patients with schizophrenia, olanzapine is at least as effective as haloperidol or risperidone and produces fewer EPS than either drug. Comparative trials with clozapine have not been done. Interestingly, olanzapine can relieve psychosis induced by drugs taken for Parkinson's disease without reversing antiparkinsonism effects.

Bipolar Disorder.

Olanzapine is approved for monotherapy of acute mania in patients with bipolar disorder. Benefits appear equal to those of lithium, a drug of choice for this condition (see Chapter 33).

Adverse Effects.

Regarding serious adverse effects, olanzapine is a mixed blessing: the drug carries a low risk of EPS and high risk of metabolic effects. Acute EPS are minimal when the drug is used at the recommended dosage. TD has not been reported. Among the SGAs, olanzapine (along with clozapine) poses the highest risk of serious metabolic effects: weight gain, diabetes, and dyslipidemia—all of which can lead to adverse cardiovascular events and premature death. Unlike clozapine, olanzapine does not cause agranulocytosis. But, like all other antipsychotic drugs, olanzapine can increase mortality in elderly patients with dementia.

Mild effects are relatively common. Olanzapine causes somnolence in 26% of patients, presumably by blocking H*1* receptors. Blockade of muscarinic receptors causes constipation and other anticholinergic effects. Alpha*1*-adrenergic blockade causes orthostatic hypotension. In addition, case reports indicate that olanzapine can cause sleepwalking and writer's cramp. Following overdose, the only signs are slurred speech and drowsiness.

Preparations, Dosage, and Administration.

Preparations.

For oral therapy, olanzapine [Zyprexa, Zyprexa Zydis] is available in standard tablets (2.5, 5, 7.5, 10, and 25 mg), sold as *Zyprexa,* and in orally disintegrating tablets (5, 10, 15, and 20 mg), sold as *Zyprexa Zydis*. For IM therapy, olanzapine [Zyprexa IntraMuscular] is available as a powder (10 mg) to be reconstituted with 2.1 mL of sterile water.

Schizophrenia Dosage.

The recommended *oral* dosage is 5 to 10 mg once a day for the first few days, and 10 mg once a day thereafter. Dosages greater than 10 mg/day are no more effective, but do increase the risk of side effects. *Intramuscular* doses range from 2.5 to 10 mg.

Bipolar Disorder Dosage.

For treatment of bipolar disorder, olanzapine is available in two oral formulations: olanzapine alone [Zyprexa, Zyprexa Zydis] and olanzapine plus fluoxetine [Symbyax]. The dosage for olanzapine alone is presented in Chapter 33 (Table 33-5). The dosage range for olanzapine plus fluoxetine is 6 to 12 mg/day of olanzapine plus 25 to 50 mg/day of fluoxetine.

Quetiapine

Actions and Uses.

Quetiapine [Seroquel] is an SGA indicated for schizophrenia and acute bipolar mania. In patients with schizophrenia, the drug can improve both positive and negative symptoms, although negative symptoms respond less consist-

ently. The drug also improves cognitive function. Like other SGAs, quetiapine produces strong blockade of 5-HT2 receptors and weaker blockade of D2 receptors. Blockade of both receptor types is believed responsible for beneficial effects. In addition to blocking receptors for serotonin and dopamine, quetiapine blocks H1 receptors and alpha-adrenergic receptors, but does not block receptors for acetylcholine.

Pharmacokinetics.

Quetiapine is well absorbed following oral administration. The drug undergoes hepatic metabolism followed by excretion in the urine and feces. The half-life is 6 hours.

Adverse Effects.

Quetiapine carries a moderate risk of serious metabolic effects: weight gain, diabetes, and dyslipidemia. As with other SGAs, the risk of EPS is low at therapeutic doses. Tardive dyskinesia has not been reported. Despite structural similarity to clozapine, quetiapine does not pose a risk of agranulocytosis. However, quetiapine does share the ability to increase mortality in elderly patients with dementia. Common side effects include sedation (from H1 blockade) and orthostatic hypotension (from alpha blockade).

Cataracts are a concern. Cataracts developed in dogs fed 4 times the maximum human dose for 6 or 12 months. Lens changes have also developed in patients; quetiapine may have been the cause. Because quetiapine may pose a risk of cataracts, the manufacturer recommends examination of the lens for cataracts prior to treatment and every 6 months thereafter.

Drug Interactions.

Metabolism of quetiapine is accelerated by phenytoin, a drug that induces CYP3A4, an isozyme of hepatic cytochrome P450 (CYP) drug-metabolizing enzymes. As a result, a larger dose of quetiapine may be needed to maintain antipsychotic effects. Other inducers of CYP3A4 (eg, barbiturates, carbamazepine, rifampin) may have the same effect.

Although clinical data are not yet available, it seems likely that inhibitors of CYP3A4 (eg, ketoconazole, itraconazole, fluconazole, erythromycin) will in-

crease levels of quetiapine, thereby posing a risk of toxicity. Caution is advised.

Preparations, Dosage, and Administration.

Preparations.

Quetiapine is available in immediate-release tablets (25, 50, 100, 200, 300, and 400 mg), marketed as *Seroquel,* and in extended-release tablets (200, 300, and 400 mg), marketed as *Seroquel XR.*

Schizophrenia Dosage.

With the *immediate-release* tablets, the initial dosage is low—25 mg twice a day—to minimize orthostatic hypotension. Dosage is gradually increased over the next 3 days to a maintenance level of 400-800 mg/day, given in two or three divided doses. For patients who may be especially sensitive to quetiapine (eg, the elderly, those with hepatic impairment, those predisposed to hypotension), a slower titration rate and lower maintenance dosage may be advisable.

With the *extended-release* tablets, dosing begins at 300 mg once daily, and is later increased to a maintenance level of 400 to 800 mg once daily. Patients currently using immediate-release quetiapine may be switched to extended-release quetiapine at the equivalent total daily dosage.

Bipolar Disorder Dosage.

Dosage for bipolar disorder is presented in Chapter 33 (Table 33-5).

Ziprasidone

Ziprasidone [Geodon] is an SGA indicated for schizophrenia and acute bipolar mania. In patients with schizophrenia, ziprasidone can improve positive symptoms, negative symptoms, and cognitive function, while causing fewer EPS than FGAs. Ziprasidone stands out from other SGAs in that it can cause significant prolongation of the QT interval, thereby posing a risk of potentially fatal dysrhythmias.

Mechanism of Action.

Ziprasidone blocks multiple receptor types, including D2, 5-HT2, H1, and alpha-adrenergic receptors. In addition, it blocks reuptake of two transmitters: serotonin and norepinephrine. As with other SGAs, therapeutic effects are believed to result from blockade of D2 and 5-HT2 receptors. Blockade of serotonin and norepinephrine uptake may provide antidepressant effects.

Pharmacokinetics.

Oral ziprasidone is well absorbed, especially in the presence of food. Binding to plasma proteins is extensive. Ziprasidone undergoes hepatic metabolism (primarily by CYP3A4) followed by excretion in the urine and feces. The elimination half-life is about 7 hours.

Adverse Effects.

Ziprasidone is generally well tolerated. The most common side effects are somnolence (perhaps from H1 blockade), orthostatic hypotension (perhaps from alpha-adrenergic blockade), and rash (the side effect most responsible for discontinuing the drug). EPS develop in about 5% of patients. Like other SGAs, ziprasidone can promote weight gain, diabetes, and dyslipidemia. However, the risk is low. In contrast to clozapine, ziprasidone does not cause agranulocytosis. Like other antipsychotic drugs, ziprasidone may increase mortality in elderly patients with dementia.

Ziprasidone *prolongs the QT interval*, and thereby poses a risk of torsades de pointes, a dysrhythmia that can progress to fatal ventricular fibrillation. QT prolongation is greater than with haloperidol but less than with thioridazine [Mellaril]. Because of QT prolongation, ziprasidone should not be given to patients with risk factors for torsades de pointes, the most important being hypokalemia, hypomagnesemia, bradycardia, congenital QT prolongation, or a history of dysrhythmias, myocardial infarction, or severe heart failure.

Drug Interactions.

Ziprasidone should not be combined with other drugs that prolong the QT interval. Among these are tricyclic antidepressants, thioridazine, several antidysrhythmic drugs (eg, amiodarone, dofetilide, quinidine), and certain antibiotics (eg, clarithromycin, erythromycin, moxifloxacin, gatifloxacin, sparfloxacin).

Drugs that induce CYP3A4 (eg, carbamazepine, phenytoin) can accelerate the metabolism of ziprasidone, and may thereby decrease its levels. Conversely, drugs that inhibit CYP3A4 (eg, ketoconazole) may increase ziprasidone levels.

Preparations, Dosage, and Administration.

Preparations.

Ziprasidone [Geodon] is available in capsules (20, 40, 60, and 80 mg) for oral dosing and 20-mg single-use vials for IM injection.

Schizophrenia, Oral Dosage.

The initial dosage is 20 mg twice daily taken with food. The maximum is 80 mg twice daily.

Schizophrenia, Intramuscular Dosage.

Two dosing schedules may be employed: (1) 10-mg doses given at least 2 hours apart up to a maximum of 40 mg/day or (2) 20-mg doses administered at least 4 hours apart up to a maximum of 40 mg/day. Intramuscular therapy for more than 3 days has not been studied. If long-term treatment is indicated, switch to oral ziprasidone.

Bipolar Disorder.

Dosage for bipolar disorder is presented in Chapter 33 (Table 33-5).

Aripiprazole

Contrasts with Other Atypical Antipsychotic Agents.

Aripiprazole [Abilify, Abilify Discmelt] is the first representative of a new class of antipsychotic drugs, referred to by some as *dopamine system stabilizers* (DSSs). Approved indications are schizophrenia, acute bipolar mania, major depressive disorder, and agitation associated with schizophrenia or bipolar mania. Aripiprazole has a more favorable safety profile than other SGAs, but is less effective than some (see Table 31-7). In patients with schizophrenia, aripiprazole is like other SGAs: it improves cognitive function, positive symptoms, and negative symptoms, while posing little or no risk of EPS or TD. In con-

trast to other SGAs, aripiprazole is unlikely to cause significant metabolic effects, hypotension, or prolactin release, and poses no risk of anticholinergic effects or dysrhythmias. However, like all other antipsychotics, the drug may increase mortality in elderly patients with dementia.

Generic Name	Trade Name	Effectiveness
Aripiprazole	Abilify	+ +
Clozapine	Clozaril, FazaClo	+ + + +
Olanzapine	Zyprexa	+ + +
Paliperidone	Invega	+ + +
Quetiapine	Seroquel	+ +
Risperidone	Risperdal	+ + +
Ziprasidone	Geodon	+ +

TABLE 31-7 Relative Effectiveness of Second-Generation Antipsychotics

Mechanism of Action.

Like other antipsychotic drugs, aripiprazole can affect multiple receptor types. It blocks H*1*, 5-HT*2*, and alpha*1* receptors, and has mixed effects on 5-HT*1* and D*2* receptors. The drug does not block cholinergic receptors.

As with other SGAs, therapeutic effects are believed to result from interaction with dopamine and serotonin receptors. However, the nature of the interaction differs: Whereas other SGAs act as *pure antagonists* at dopamine and serotonin receptors, aripiprazole acts as a *partial agonist* at 5-HT*1* and D*2* recept-

ors, and as a pure antagonist only at 5-HT2 receptors. Because aripiprazole is a partial agonist at 5-HT1 and D2 receptors, net effects on receptor activity will depend on how much transmitter (dopamine or serotonin) is present. Specifically, at synapses where transmitter concentrations are *low,* aripiprazole will bind to receptors and thereby cause *moderate activation*. Conversely, at synapses where transmitter concentrations are *high,* aripiprazole will compete with the transmitter for receptor binding, and hence will *reduce receptor activation*. It is because of this ability to modulate the activity of dopamine receptors—rather than simply cause receptor activation or blockade—that aripiprazole has been dubbed a DSS. Researchers suggest that dopamine system stabilization explains why aripiprazole can improve positive and negative symptoms of schizophrenia while having little or no effect on the extrapyramidal system or prolactin release.

Pharmacokinetics.

Aripiprazole is well absorbed following oral administration, both in the presence and absence of food. Plasma levels peak 3 to 5 hours after dosing. Protein binding in blood is high—more than 99%. In the liver, aripiprazole undergoes metabolism by two isozymes of cytochrome P450, designated CYP3A4 and CYP2D6. Aripiprazole and its active metabolite—dihydro-aripiprazole—have prolonged half-lives: 75 hours and 94 hours, respectively. Because elimination is slow, (1) dosing can be done once a day and (2) about 14 days (four half-lives) are required to achieve steady-state (plateau) plasma drug levels.

Adverse Effects.

In clinical trials, aripiprazole was well tolerated. The most common side effects were headache, agitation, nervousness, anxiety, insomnia, nausea, vomiting, dizziness, and somnolence. The incidence of EPS was the same as in patients taking placebo. Tardive dyskinesia has not been observed. To date, only a few cases of NMS have been reported. Among the SGAs, aripiprazole (along with ziprasidone) poses the lowest risk of weight gain, diabetes, and dyslipidemia. Although aripiprazole can block alpha1adrenergic receptors, the incidence of orthostatic hypotension is low (1.9% vs. 1% in patients on placebo). Aripiprazole does not prolong the QT interval, and hence does not

pose a risk of dysrhythmias. Also, the drug does not increase prolactin levels, and hence does not cause gynecomastia or galactorrhea.

Drug Interactions.

Drugs that induce CYP3A4 (eg, barbiturates, carbamazepine, phenytoin, rifampin) can accelerate metabolism of aripiprazole, and can thereby reduce its blood level. Conversely, drugs that inhibit CYP3A4 (eg, ketoconazole, itraconazole, fluconazole, erythromycin) can increase aripiprazole levels, as can drugs that inhibit CYP2D6 (eg, quinidine, fluoxetine, paroxetine).

Preparations, Dosage, and Administration.

Preparations.

Aripiprazole for *oral therapy* is available in standard tablets (2, 5, 10, 15, 20, and 30 mg) and solution (1 mg/mL), both sold as *Abilify,* and in orally disintegrating tablets (10 and 15 mg) sold as *Abilify Discmelt*. Aripiprazole for IM therapy is available in single-use vials (7.5 mg/mL) sold as *Abilify*.

Oral Dosage for Schizophrenia.

The recommended dosage—both initial and maintenance—is 10 or 15 mg once a day, administered with or without food. Dosages above 15 mg/day do not increase therapeutic effects, but can intensify side effects. Dosage should be doubled for patients taking inducers of CYP3A4, and cut in half for patients taking inhibitors of CYP3A4 or CYP2D6.

Oral Dosage for Major Depressive Disorder.

The recommended initial dosage is 2 to 5 mg/day. Dosage may be increased by up to 5 mg/day, but at intervals of no less than 1 week. Dosages above 15 mg/day have not been studied. As with oral therapy of schizophrenia, dosage should be doubled for patients taking inducers of CYP3A4, and cut in half for patients taking inhibitors of CYP3A4 or CYP2D6.

Oral Dosage for Bipolar Disorder.

Dosage for bipolar disorder is presented in Chapter 33 (Table 33-5).

Intramuscular Dosage for Agitation Associated with Schizophrenia or Bipolar Mania.

The recommended dosage is 9.75 mg once. As with oral therapy, dosage should be doubled for patients taking inducers of CYP3A4, and cut in half for patients taking inhibitors of CYP3A4 or CYP2D6.

DEPOT ANTIPSYCHOTIC PREPARATIONS

Depot antipsychotics are long-acting, injectable formulations used for long-term maintenance therapy of schizophrenia. The objective is to prevent relapse and maintain the highest possible level of functioning. The rate of relapse is lower with depot therapy than with oral therapy. Depot preparations are valuable for all patients who need long-term treatment—not just for patients who have difficulty with adherence. There is no evidence that depot preparations pose an increased risk of side effects, including NMS and TD. In fact, because depot therapy permits a reduction in the total drug burden (the dose per unit time is lower than with oral therapy), the risk of TD is actually reduced.

Three depot preparations are currently available—*haloperidol decanoate* [Haldol Decanoate], *fluphenazine decanoate* [Prolixin Decanoate], and *risperidone microspheres* [Risperdal Contra]—and at least two more preparations—*paliperidone palmitate* and *iloperidone*—are in development. Following IM or subQ injection, active drug (fluphenazine, haloperidol, or risperidone) is slowly absorbed into the blood. Because of this slow, steady absorption, plasma levels remain relatively constant between injections. The dosing interval is 2 to 4 weeks. Typical maintenance dosages are presented in Table 31-8.

Generic Name [Trade Name]	Route	Typical Maintenance Dosage
Haloperidol decanoate [Haldol Decanoate]	IM	50–200 mg every 4 wk
Fluphenazine decanoate [Prolixin Decanoate]	IM, subQ	12.5–50 mg every 2 wk
Risperidone microspheres [Risperdal Contra]	IM	25–50 mg every 2 wk

TABLE 31-8 Depot Antipsychotic Preparations

MANAGEMENT OF SCHIZOPHRENIA

Drug Therapy

Drug therapy of schizophrenia has three major objectives: (1) suppression of acute episodes, (2) prevention of acute exacerbations, and (3) maintenance of the highest possible level of functioning.

Drug Selection

Like all other drugs, antipsychotics should be selected on the basis of effectiveness, tolerability, and cost. Currently, SGAs are prescribed 10 times more often than FGAs, but that may change. When the SGAs were introduced, available data suggested they were more effective than FGAs and also safer. However, we now know otherwise. The *Clinical Antipsychotic Trials in Intervention Effectiveness* (CATIE) study, published in 2005, compared four SGAs—olanzapine [Zyprexa], quetiapine [Seroquel], risperidone [Risperdal], and ziprasidone [Geodon]—with the FGA perphenazine. This result? The SGAs were no more effective than perphenazine. These data were confirmed by a second study, conducted in Great Britain, which showed again that perphenazine was just as effective as several SGAs. These two trials were the first large studies to directly compare FGAs and SGAs—and their surprising results were completely unexpected. Regarding serious side effects, SGAs were initially thought safer than FGAs. Why? Because SGAs posed a low risk of EPS. However, over time, it became clear that SGAs posed a serious risk of their own: potentially fatal metabolic effects. Hence, rather than being *free* of serious side effects, the SGAs

simply substituted a new serious effect for the old one. As for cost, the FGAs are much cheaper. For example, whereas haloperidol costs only $50 a year, risperidone costs about $2000 a year, and olanzapine costs about $4000. In summary, here's what we know:

- Most FGAs and SGAs are equally effective, except for clozapine, which is more effective than the rest.
- Whereas FGAs pose a significant risk of EPS, SGAs pose a significant risk of metabolic effects, which may be more detrimental than EPS.
- FGAs cost about 10 times less than SGAs.

Given this information, which drug should we choose? That's still hard to answer. With regard to efficacy and safety, no single agent is clearly superior to the others. So we're back to our initial selection criteria: efficacy, safety, and cost. For a patient who is treatment resistant, a trial with clozapine might be reasonable. For a patient with a history of diabetes or dyslipidemia, an FGA might be a good choice, as might aripiprazole or ziprasidone, two SGAs with a low risk of metabolic effects. If there's no clinical reason to select an SGA over an FGA, cost considerations would suggest choosing the FGA.

Dosing

Dosing with antipsychotics is highly individualized. Elderly patients require relatively small doses—typically 30% to 50% of those for younger patients. Poorly responsive patients may need larger doses. However, very large doses should generally be avoided. Why? Because huge doses are probably no more effective than moderate doses, and will increase the risk of side effects.

Dosage size and timing are likely to change over the course of therapy. During the initial phase, antipsychotics should be administered in divided daily doses. Once an effective dosage has been determined, the entire daily dose can often be given at bedtime. Since antipsychotics cause sedation, bedtime dosing helps promote sleep while decreasing daytime drowsiness. Doses used early in therapy to gain rapid control of behavior are often very high. For long-term therapy, the dosage should be reduced to the lowest effective amount.

Routes

Oral.

Oral administration is preferred for most patients. Antipsychotics are available in tablets, capsules, and liquids for oral dosing.

The liquid formulations require special handling. These preparations are concentrated and must be diluted prior to use. Dilution may be performed with a variety of fluids, including milk, fruit juices, and carbonated beverages. Some oral liquids are light sensitive and must be stored in amber or opaque containers. Liquid formulations of *phenothiazines* can cause contact dermatitis; nurses and patients should take care to avoid skin contact with these preparations.

Intramuscular.

Intramuscular injection is generally reserved for patients with severe, acute schizophrenia and for long-term maintenance. Depot preparations are given every 2 to 4 weeks (see Table 31-8).

Initial Therapy

With adequate dosing, symptoms begin to resolve within 1 to 2 days. However, significant improvement takes 1 to 2 weeks, and a full response may not be seen for several months.

Some symptoms resolve sooner than others. During the first week, the goal is to reduce agitation, hostility, anxiety, and tension and to normalize patterns of sleeping and eating. Over the next 6 to 8 weeks, symptoms should continue to steadily improve. The goals over this interval are increased socialization and improved self-care, mood, and formal thought processes. Of the patients who have not responded within 6 weeks, 50% are likely to respond by the end of 12 weeks.

It is important to note that not all symptoms respond equally. With FGAs, positive symptoms respond better than negative symptoms or cognitive dysfunction. However, with the SGAs, all three types of symptoms may respond well.

Maintenance Therapy

Schizophrenia is a chronic disorder that usually requires prolonged treatment. The purpose of long-term therapy is to reduce the recurrence of acute florid episodes and to maintain the highest possible level of functioning. Un-

fortunately, although long-term treatment can be very effective, it also carries a risk of adverse effects, especially TD.

Following control of an acute episode, antipsychotic therapy should continue for at least 12 months. Withdrawal of medication prior to this time is associated with a 55% incidence of relapse, compared with only 20% in patients who continue drug use. Accordingly, patients must be convinced to continue therapy for the entire 12-month course, even though they may be symptom free and consider themselves "cured."

After 12 months, an attempt should be made to discontinue drug use, provided symptoms are absent. About 25% of patients do not need drugs beyond this time. To avoid a withdrawal reaction, dosage should be tapered gradually. It is important that medication not be withdrawn at a time of stress (eg, when the patient is being discharged following hospitalization). If relapse occurs in response to withdrawal, treatment should be reinstituted. For many patients, resumption of therapy controls symptoms and prevents further deterioration.

When long-term therapy is conducted, dosage should be adjusted with care. To reduce the risk of TD and other adverse effects, a minimum effective dosage should be established. Annual attempts should be made to lower the dosage or to discontinue treatment entirely.

Long-acting (depot) antipsychotics are especially well suited for prolonged treatment. Depot therapy has three major advantages compared with oral therapy: (1) the relapse rate is lower, (2) drug levels are more stable between doses, and (3) the total dose per unit time is lower, thereby reducing the risk of adverse effects, including TD. In the United States, only 10% of patients receive depot therapy. This low rate is based in large part on the widely held (but unfounded) perception that depot therapy is for "losers"—patients who suffer recurrent relapse because of persistent nonadherence with oral therapy.

Adjunctive Drugs

Benzodiazepines (eg, lorazepam, alprazolam) can suppress anxiety and promote sleep. Whether they also improve core symptoms of schizophrenia is uncertain. In patients experiencing an acute psychotic episode, benzodiazepines can help suppress anxiety, irritability, and agitation. In addition, benzodiazepines may allow the dosage of antipsychotic medication to be reduced.

Antidepressants are appropriate when schizophrenia is associated with depressive symptoms. A tricyclic antidepressant (eg, imipramine) is usually chosen. Antidepressant dosage is the same as for major depression. The ideal duration is unknown.

Promoting Adherence

Poor adherence is a common cause of therapeutic failure, and underlies a significant proportion of hospital readmissions. Adherence can be difficult to achieve because treatment is prolonged and because patients may fail to appreciate the need for therapy, or they may be unwilling or unable to take medicine as prescribed. In addition, side effects can discourage adherence. Adherence can be enhanced by

- Ensuring that the medication given to hospitalized patients is actually swallowed and not "cheeked"
- Encouraging family members to oversee medication for outpatients
- Providing patients with written and verbal instructions on dosage size and timing, and encouraging them to take their medicine exactly as prescribed
- Informing patients and their families that antipsychotics must be taken on a regular schedule to be effective, and hence cannot be used PRN
- Informing patients about side effects of treatment and teaching them how to minimize undesired responses
- Assuring patients that antipsychotic drugs do not cause addiction
- Establishing a good therapeutic relationship with the patient and family
- Using an IM depot preparation (fluphenazine decanoate, haloperidol decanoate, risperidone microspheres) for long-term therapy

Nondrug Therapy

Although drugs can be of great benefit in schizophrenia, medication alone does not constitute optimal treatment. The acutely ill patient needs care, support, and protection; a period of hospitalization may be essential. Counseling can offer the patient and family insight into the nature of schizophrenia and can facilitate adjustment and rehabilitation. Although conventional psycho-

therapy is of little value in reducing symptoms of schizophrenia, establishing a good therapeutic relationship can help promote adherence and can help the prescriber evaluate the patient, which in turn can facilitate dosage adjustment and drug selection. Behavioral therapy can help reduce stress. Vocational training in a sheltered environment offers the hope of productivity and some measure of independence. Ideally, the patient will be provided with a comprehensive therapeutic program to complement the benefits of medication. Unfortunately, ideal situations don't always exist, leaving many patients to rely on drugs as their sole treatment modality.

KEY POINTS

- Schizophrenia is the principal indication for antipsychotic drugs, although many are also used for bipolar disorder.
- Schizophrenia is a chronic illness characterized by disordered thinking and reduced comprehension of reality. Positive symptoms include hallucinations, delusions, and agitation. Negative symptoms include blunted affect, poverty of speech, and social withdrawal. Cognitive dysfunction manifests as disordered thinking, reduced ability to focus attention, plus learning and memory difficulties.
- Antipsychotic drugs fall into two major groups: first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs).
- First-generation antipsychotics are thought to relieve symptoms of schizophrenia by blocking D2 receptors.
- First-generation antipsychotics improve positive symptoms of schizophrenia more effectively than negative symptoms or cognitive dysfunction.
- Therapeutic responses to antipsychotic drugs develop slowly, often taking several months to become maximal.
- Low-potency FGAs and high-potency FGAs produce equal therapeutic effects.
- First-generation antipsychotic drugs produce three types of early EPS: acute dystonia, parkinsonism, and akathisia.

- Acute dystonia and parkinsonism respond to anticholinergic drugs (eg, benztropine). Akathisia is harder to treat, but may respond to anticholinergic drugs, benzodiazepines, or beta blockers.
- Tardive dyskinesia (TD), a late EPS, has no reliable treatment. For patients with severe TD, switching to an SGA may help.
- The risk of early EPS is much greater with high-potency FGAs than with low-potency FGAs, whereas the risk of TD is equal with both groups.
- Neuroleptic malignant syndrome, which can be fatal, is characterized by muscular rigidity, high fever, and autonomic instability. Dantrolene and bromocriptine are used for treatment.
- Low-potency FGAs produce more sedation, orthostatic hypotension, and anticholinergic effects than high-potency FGAs.
- Antipsychotic drugs increase levels of circulating prolactin by blocking the inhibitory action of dopamine on prolactin release.
- Levodopa can counteract the beneficial effects of FGA drugs and vice versa. Why? Because levodopa activates dopamine receptors, whereas FGAs block dopamine receptors.
- Chlorpromazine [Thorazine] is the prototype of the low-potency FGAs.
- Haloperidol [Haldol] is the prototype of the high-potency FGAs.
- Second-generation antipsychotics differ from FGAs in three important ways: (1) they block receptors for serotonin in addition to receptors for dopamine; (2) they cause few or no EPS, including TD; and (3) they carry a higher risk of serious metabolic effects—weight gain, diabetes, and dyslipidemia—that can lead to adverse cardiovascular events and premature death.
- Among the SGAs, the risk of metabolic effects is greatest with clozapine and olanzapine.
- Like FGAs, the SGAs increase the risk of mortality in elderly patients with dementia.
- Clozapine, the first SGA, is the most effective antipsychotic drug available.

- Clozapine can cause potentially fatal agranulocytosis. Hence, (1) regular blood tests are mandatory and (2) this drug is reserved for patients who have not responded to other SGAs or FGAs.
- Antipsychotic depot preparations—haloperidol decanoate, fluphenazine decanoate, and risperidone microspheres—are used for long-term maintenance therapy of schizophrenia.
- In general, and despite initial impressions, the SGAs are neither safer nor more effective than FGAs.

Summary of Major Nursing Implications*

FIRST-GENERATION (CONVENTIONAL) ANTIPSYCHOTICS

Chlorpromazine

Fluphenazine

Haloperidol

Loxapine

Molindone

Perphenazine

Pimozide

Thioridazine

Thiothixene

Trifluoperazine

Except where indicated, the nursing implications below apply to all FGAs.

Preadministration Assessment

Therapeutic Goal

Treatment of schizophrenia has three goals: suppression of acute episodes, prevention of acute exacerbations, and maintenance of the highest possible level of functioning.

Baseline Data

Patients should receive a thorough mental status examination and a physical examination.

Observe and record such factors as overt behavior (eg, gait, pacing, restlessness, volatile outbursts), emotional state (eg, depression, agitation, mania), intellectual function (eg, stream of thought, coherence, hallucinations, delusions), and responsiveness to the environment.

Obtain a complete family and social history.

Determine vital signs and obtain complete blood counts, electrolytes, and evaluations of hepatic, renal, and cardiovascular function.

Identifying High-Risk Patients

First-generation antipsychotics are *contraindicated* for patients who are comatose or severely depressed and for patients with Parkinson's disease, prolactin-dependent carcinoma of the breast, bone marrow depression, and severe hypotension or hypertension. Use with *caution* in patients with glaucoma, adynamic ileus, prostatic hypertrophy, cardiovascular disease, hepatic or renal dysfunction, and seizure disorders.

Avoid *chlorpromazine, thioridazine, haloperidol,* and *pimozide* in patients with risk factors for torsades de pointes (eg, hypokalemia, hypomagnesemia, bradycardia, congenital QT prolongation, or a history of dysrhythmias, myocardial infarction, or severe heart failure) and for those taking drugs that prolong the QT interval.

Generally *avoid all FGAs* in elderly patients with dementia.

Implementation: Administration

Routes

Oral, IM, IV, subQ, rectal (suppository). Routes for individual agents are summarized in Tables 31-4 and 31-8.

Administration

Dosing.

Divided daily doses are employed initially. Once an effective dosage has been determined, the entire daily dose is usually administered at bedtime, thereby promoting sleep and minimizing daytime sedation. For long-term therapy, the smallest effective dosage should be employed.

Oral Liquids.

Oral liquid formulations must be protected from light. Concentrated formulations should be diluted just prior to use. Dilution in fruit juice improves palatability.

Oral liquids can cause contact dermatitis. **Warn patients against making skin contact with these drugs, and instruct them to flush the affected area with water if a spill occurs.** Take care to avoid skin contact with these preparations yourself.

Intramuscular.

Make injections into the deltoid or gluteal muscle. Rotate the injection site. Depot preparations are administered every 2 to 4 weeks (see Table 31-8).

Implementation: Measures to Enhance Therapeutic Effects

Promoting Adherence

Poor adherence is a common cause of therapeutic failure and rehospitalization. Adherence can be improved by

- Ensuring that medication is actually swallowed and not "cheeked"
- **Encouraging family members to oversee medication for outpatients**
- **Providing patients with written and verbal instructions on dosage size and timing, and encouraging them to take their medicine as prescribed**
- **Informing patients and their families that antipsychotic drugs must be taken on a regular schedule**
- **Informing patients about side effects and teaching them how to minimize undesired responses**
- **Assuring patients that antipsychotic drugs do not cause addiction**
- Establishing a good therapeutic relationship with the patient and family

- Using a depot preparation (eg, fluphenazine decanoate) for long-term therapy

Nondrug Therapy

Acutely ill patients need care, support, and protection; hospitalization may be essential. **Educate the patient and family about the nature of schizophrenia to facilitate adjustment and rehabilitation.** Behavioral therapy can help reduce stress. Vocational training in a sheltered environment offers the hope of productivity and some measure of independence.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Success is indicated by improvement in psychotic symptoms. Evaluate for suppression of hallucinations, delusions, agitation, tension, and hostility, and for improvement in judgment, insight, motivation, affect, self-care, social skills, anxiety management, and patterns of sleeping and eating.

Minimizing Adverse Effects

Early EPS: Acute Dystonia, Parkinsonism, and Akathisia.

These reactions develop within hours to months of the onset of treatment. The risk is greatest with high-potency FGAs. Take care to differentiate these reactions from worsening of psychotic symptoms. **Inform patients and their families about symptoms (eg, muscle spasm of tongue, face, neck, or back; tremor; rigidity; restless movement), and instruct them to notify the prescriber if these appear.** Acute dystonia and parkinsonism respond to anticholinergic drugs (eg, benztropine). Akathisia may respond to anticholinergic drugs, beta blockers, or benzodiazepines. For severe parkinsonism, switch to an SGA.

Late EPS: Tardive Dyskinesia.

TD develops after months or years of continuous therapy. The risk is equal with all FGAs. **Inform patients and their families about early signs (eg, fine, worm-like movements of the tongue), and instruct them to notify**

the prescriber if these develop. Although there is no reliable treatment, the following measures are recommended: discontinue all anticholinergic drugs; give a benzodiazepine; and discontinue the antipsychotic, or at least reduce the dosage. For severe TD, switch to an SGA.

Neuroleptic Malignant Syndrome.

NMS is a rare reaction that carries a 4% risk of mortality. Symptoms include rigidity, fever, sweating, dysrhythmias, and fluctuations in blood pressure. NMS is most likely with high-potency FGAs.

Treatment consists of supportive measures (use of cooling blankets, rehydration), drug therapy (dantrolene, bromocriptine), and immediate withdrawal of the neuroleptic. If neuroleptic therapy is resumed after symptoms have subsided, the lowest effective dosage of a low-potency drug should be employed. If a second episode occurs, switching to an SGA may be helpful.

Anticholinergic Effects.

Inform patients about possible anticholinergic reactions (dry mouth, blurred vision, photophobia, urinary hesitancy, constipation, tachycardia, suppression of sweating), and teach them how to minimize discomfort. A complete summary of nursing implications for anticholinergic effects is given in Chapter 14. Anticholinergic effects are most likely with low-potency FGAs.

Orthostatic Hypotension.

Inform patients about signs of hypotension (lightheadedness, dizziness) and advise them to sit or lie down if these occur. Inform patients that hypotension can be minimized by moving slowly when assuming an erect posture. Orthostatic hypotension is most likely with low-potency FGAs.

In hospitalized patients, measure blood pressure and pulses before dosing and 1 hour after. Make these measurements while the patient is lying down and again after he or she has been sitting or standing for 1 to 2 minutes. If blood pressure is low, withhold medication and consult the prescriber.

Sedation.

Sedation is most intense during the first weeks of therapy and declines with continued drug use. **Warn patients about sedative effects, and advise them to avoid hazardous activity until sedation subsides.** Sedation is most likely with low-potency FGAs.

Seizures.

Neuroleptics reduce seizure threshold, thereby increasing the risk of seizures, especially in patients with epilepsy and other seizure disorders. For patients with seizure disorders, adequate doses of antiseizure medication must be employed. Monitor the patient for seizure activity; if loss of seizure control occurs, dosage of antiseizure medication must be increased.

Sexual Dysfunction.

In women, FGAs can suppress libido and impair the ability to achieve orgasm. In men, FGAs can suppress libido and cause erectile and ejaculatory dysfunction. **Counsel patients about possible sexual dysfunction and encourage them to report problems.** Dosage reduction or switching to a high-potency FGA may be helpful.

Dermatologic Effects.

Inform patients that phenothiazines can sensitize the skin to ultraviolet light, thereby increasing the risk of sunburn. Advise them to avoid excessive exposure to sunlight, apply a sunscreen, and wear protective clothing.

Oral liquid formulations can cause contact dermatitis. **Warn patients to avoid skin contact with these drugs.**

Neuroendocrine Effects.

Inform patients that FGAs can cause galactorrhea, gynecomastia, and menstrual irregularities.

Antipsychotics can promote growth of prolactin-dependent carcinoma of the breast and must not be used by patients with this cancer.

Agranulocytosis.

Agranulocytosis greatly diminishes the ability to fight infection. **Inform patients about early signs of infection (fever, sore throat), and instruct them to notify the prescriber if these develop.** If blood tests indicate agranulocytosis, the antipsychotic should be withdrawn.

Severe Dysrhythmias.

Chlorpromazine, *thioridazine, haloperidol,* and *pimozide* prolong the QT interval, and can thereby induce torsades de pointes, a dysrhythmia that can progress to fatal ventricular fibrillation. The risk of dysrhythmias can be reduced by (1) ensuring that potassium and magnesium levels are normal, (2) avoiding other drugs that cause QT prolongation, and (3) avoiding drugs that can increase levels of the antipsychotic drug being used.

Death in Elderly Dementia Patients.

All FGAs increase the risk of mortality when used to treat dementia in elderly patients, an application use for which these drugs are not approved. Avoid FGAs in these patients.

Minimizing Adverse Interactions

Anticholinergics.

Drugs with anticholinergic properties will intensify anticholinergic responses to FGAs. **Instruct patients to avoid all drugs with anticholinergic properties, including the antihistamines and certain over-the-counter sleep aids.**

CNS Depressants.

First-generation agents will intensify CNS depression caused by other drugs. **Warn patients against use of alcohol and all other drugs with CNS-depressant properties (eg, barbiturates, opioids, antihistamines, benzodiazepines).**

Levodopa and Direct Dopamine Receptor Agonists.

Levodopa and the dopamine receptor agonists (eg, bromocriptine) promote activation of dopamine receptors, and may thereby diminish the therapeutic effects of FGAs. Accordingly, patients taking FGAs should not use these drugs.

QT-Prolonging Drugs.

Drugs that prolong the QT interval increase the risk of dysrhythmias in patients taking *chlorpromazine, thioridazine, haloperidol,* and *pimozide,* and hence must be avoided. Agents to avoid include tricyclic antidepressants, thioridazine, several antidysrhythmic drugs (eg, amiodarone, dofetilide, quinidine), and certain antibiotics (eg, clarithromycin, erythromycin, moxifloxacin, gatifloxacin, sparfloxacin).

SECOND-GENERATION (ATYPICAL) ANTIPSYCHOTICS

Aripiprazole

Clozapine

Olanzapine

Paliperidone

Quetiapine

Risperidone

Ziprasidone

Except where indicated, the nursing implications below apply to all SGAs.

Preadministration Assessment

Therapeutic Goal

See *First-Generation (Conventional) Antipsychotics*.

Baseline Data

See *First-Generation (Conventional) Antipsychotics*. Also, obtain baseline measurements of weight, waist circumference, fasting blood glucose, and fasting lipid levels. For patients taking *quetiapine,* examine the lens for cataracts. For patients taking *clozapine,* obtain baseline values for total WBC and ANC.

Identifying High-Risk Patients

Use all SGAs, and especially *clozapine* and *olanzapine,* with *caution* in patients with diabetes.

Clozapine is *contraindicated* for patients with a history of bone marrow depression or clozapine-induced agranulocytosis, and for those taking myelosuppressive drugs (eg, many anticancer drugs).

Use *clozapine* with *caution* in patients with seizure disorders.

Ziprasidone is *contraindicated* for patients with risk factors for torsades de pointes (eg, hypokalemia, hypomagnesemia, bradycardia, congenital QT prolongation, or a history of dysrhythmias, myocardial infarction, or severe heart failure) and for those taking drugs that prolong the QT interval.

Generally *avoid all SGAs* in elderly patients with dementia.

Implementation: Administration

Routes

Oral, IM. Routes for individual agents are summarized in Tables 31-4 and 31-8.

Dosing

To minimize side effects, dosage should be low initially and then gradually increased.

Implementation: Measures to Enhance Therapeutic Effects

Promoting Adherence

See *First-Generation (Conventional) Antipsychotics*.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

See *First-Generation (Conventional) Antipsychotics*.

Minimizing Adverse Effects

In contrast to FGAs, the SGAs carry a low risk of sexual dysfunction, neuroendocrine effects, and extrapyramidal reactions, including TD.

Orthostatic Hypotension and Anticholinergic Effects.

See *First-Generation (Conventional) Antipsychotics*.

Agranulocytosis.

Clozapine produces agranulocytosis in 1% to 2% of patients, typically during the first 6 months of treatment. Deaths from gram-negative septicemia have occurred.

Regular hematologic monitoring is mandatory: WBC and ANC must be determined weekly for the first 6 months, every 2 weeks for the next 6 months, and monthly thereafter. If the total WBC count falls below 3000/mm^3 or if the ANC falls below 1500/mm^3, treatment should be interrupted. When subsequent *daily* monitoring indicates that cell counts have risen above these values, clozapine can be resumed. If the total WBC count falls below 2000/mm^3 or if the ANC falls below 1000/mm^3, clozapine should be permanently discontinued. Continue monitoring blood counts for 4 weeks.

Warn patients about the risk of agranulocytosis, and inform them that clozapine will not be dispensed without repeated proof of blood counts. Inform patients about early signs of infection (fever, sore throat, fatigue, mucous membrane ulceration), and instruct them to report these immediately.

Metabolic Effects: Weight Gain, Diabetes, and Dyslipidemia.

All SGAs—and especially *clozapine* and *olanzapine*—can promote weight gain, which can lead to diabetes and dyslipidemia. To monitor weight gain, determine weight at baseline; 4, 8, and 12 weeks later; and every 3 months thereafter. Also, determine waist circumference at baseline and annually thereafter. **Inform patients about the risk of weight gain and encourage them to control caloric intake and get regular exercise.** If significant weight gain occurs, it can be managed with a combination of diet, exercise, and metformin.

To monitor for diabetes, measure fasting blood glucose at baseline, 12 weeks later, and annually thereafter. In patients with documented diabetes at

baseline, monitor for worsening of glucose control. **Inform all patients about symptoms of diabetes—hyperglycemia, polyuria, polydipsia, polyphagia, dehydration—and instruct them to tell the prescriber if they occur.** If diabetes develops, it can be managed with insulin or an oral hypoglycemic drug (eg, metformin).

To monitor for *dyslipidemia,* obtain a fasting lipid profile at baseline, 12 weeks later, and every 5 years thereafter.

Seizures.

Clozapine causes generalized tonic-clonic seizures in 3% of patients. **Warn patients against driving and other hazardous activities if seizures have occurred.**

Sedation.

All SGAs—and especially *clozapine* and *olanzapine*—can cause sedation. **Warn patients against driving and participating in other hazardous activities if impairment is significant.**

Myocarditis.

Very rarely, *clozapine* causes myocarditis. **Inform patients about signs and symptoms (eg, unexplained fatigue, dyspnea, tachypnea, chest pain, palpitations), and advise them to seek immediate medical attention if these develop.** Withhold clozapine until myocarditis has been ruled out. If myocarditis is diagnosed, the drug should never be used again.

Dysrhythmias.

Ziprasidone prolongs the QT interval, posing a risk of torsades de pointes, a potentially fatal dysrhythmia. The risk of dysrhythmias can be reduced by (1) ensuring that potassium and magnesium levels are normal, (2) avoiding other drugs that cause QT prolongation, and (3) avoiding drugs that can increase levels of ziprasidone.

Death in Elderly Dementia Patients.

All SGAs increase the risk of mortality when used to treat dementia in elderly patients, an application for which these drugs are not approved. Avoid SGAs in these patients.

Cataracts.

Quetiapine may pose a risk of cataracts. Examine the lens for cataracts at baseline and every 6 months thereafter.

Minimizing Adverse Interactions

CNS Depressants.

Second-generation antipsychotics may intensify CNS depression caused by other drugs. **Warn patients against use of alcohol and all other drugs with CNS-depressant properties (eg, barbiturates, opioids, antihistamines, benzodiazepines).**

Levodopa and Direct Dopamine Receptor Agonists.

Levodopa and the dopamine receptor agonists (eg, bromocriptine) promote activation of dopamine receptors, and may thereby diminish therapeutic effects of the SGAs. Patients taking antipsychotics should not use these drugs.

Myelosuppressive Drugs.

Clozapine must not be given to patients taking other drugs that can suppress bone marrow function (eg, many anticancer agents).

QT-Prolonging Drugs.

Drugs that prolong the QT interval increase the risk of dysrhythmias in patients taking *ziprasidone,* and hence must be avoided. Agents to avoid include tricyclic antidepressants, thioridazine, several antidysrhythmic drugs (eg, amiodarone, dofetilide, quinidine), and certain antibiotics (eg, clarithromycin, erythromycin, moxifloxacin, gatifloxacin, sparfloxacin).

Inducers and Inhibitors of CYP3A4.

Drugs that induce CYP3A4 (eg, barbiturates, carbamazepine, phenytoin, rifampin) can accelerate metabolism of *aripiprazole, quetiapine,* and *ziprasidone,*

and can thereby reduce blood levels of these three drugs. Conversely, drugs that inhibit CYP3A4 (eg, ketoconazole, itraconazole, fluconazole, erythromycin) can increase levels of these three drugs.

32 Antidepressants

As their name suggests, the antidepressants are used primarily to relieve symptoms of depression. In addition, these drugs can help patients with anxiety disorders. As a rule, antidepressants are not indicated for uncomplicated bereavement. The antidepressants fall into five major groups: tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and atypical antidepressants.

MAJOR DEPRESSION: CLINICAL FEATURES, PATHOGENESIS, AND TREATMENT MODALITIES

Depression is the most common psychiatric disorder. In the United States, about 30% of the population will experience some form of depression during their lives. At any given time, about 5% of the adult population is depressed. The incidence in women is twice that in men. The risk of suicide among depressed people is high. Unfortunately, depression is underdiagnosed and undertreated: Only 30% of depressed individuals receive treatment. This is especially sad in that treatment can help many people: about 40% of those given antidepressants achieve full remission; another 20% to 30% achieve at least a 50% reduction in symptom severity.

TABLE 32-1 DSM-IV-TR Diagnostic Criteria for a Major Depressive Episode

A. For a diagnosis of major depression, at least five of the following symptoms must be present for 2 weeks or more, and must represent a change from previous functioning. Furthermore, at least one symptom must be (1) depressed mood or (2) loss of interest or pleasure. (*Note:* Do not include mood-incongruent delusions or hallucinations, or symptoms that are due to a general medical condition.)

- Depressed mood most of the day, nearly every day (*Note:* In children and adolescents, can be irritable mood.)
- Loss of interest or pleasure in all or almost all activities
- Significant weight loss or weight gain without dieting *or* decrease or increase in appetite (*Note:* In children, consider failure to make expected weight gains.)

- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Diminished ability to think or concentrate *or* indecisiveness
- Recurrent thoughts of death, recurrent suicidal ideation, a suicide attempt, or a specific suicide plan

B. The symptoms do not meet the criteria for a Mixed Episode (ie, an episode in which criteria are met for a Major Depressive Episode *and* a Manic Episode).

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiologic effects of a substance (eg, drug of abuse, medication) or a general condition (eg, hypothyroidism).

E. Major depression should not be diagnosed in the context of bereavement (ie, after the loss of a loved one), unless the symptoms persist for longer than 2 months, or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Clinical Features

Diagnostic criteria for a major depressive episode are summarized in Table 32-1. As indicated, the principal symptoms are *depressed mood* and *loss of pleasure or interest in all or nearly all of one's usual activities and pastimes*. Associated symptoms include insomnia (or sometimes hypersomnia); anorexia and weight loss (or sometimes hyperphagia and weight gain); mental slowing and loss of concentration; feelings of guilt, worthlessness, and helplessness; thoughts of death and suicide; and overt suicidal behavior. For a diagnosis to be made, symptoms must be present most of the day, nearly every day, for at least 2 weeks.

It is important to distinguish between major depression and normal grief or sadness. Whereas major depression is an illness, grief or sadness is not. Rather,

grief and sadness are appropriate reactions to a major life stressor (eg, death of a loved one, loss of a job). In most cases, grief and sadness resolve spontaneously over several weeks and do not require medical intervention. However, if symptoms are unusually intense, and if they fail to abate within an appropriate time, a major depressive episode may have been superimposed. If this occurs, treatment is indicated.

Pathogenesis

The etiology of major depression is complex and incompletely understood. For some individuals, depression seems to descend "out of the blue"; otherwise healthy people—unexpectedly and without apparent cause—find themselves feeling profoundly depressed. For many others, depressive episodes are brought on by stressful life events, such as bereavement, loss of a job, or childbirth (Box 32-1). Since depression does not occur in everyone, it would appear that some people are more vulnerable than others. Factors that may contribute to vulnerability include genetic heritage, a difficult childhood, and chronic low self-esteem.

Clinical observations made in the 1960s led to formulation of the *monoamine-deficiency hypothesis of depression,* which asserts that depression is caused by a functional deficiency of monoamine neurotransmitters (norepinephrine, serotonin, or both). Findings that support the hypothesis include (1) induction of depression with reserpine, a drug that depletes monoamines from the brain; (2) induction of depression with inhibitors of tyrosine hydroxylase, an enzyme needed for monoamine transmitter synthesis; and (3) relief of depression with drugs that intensify monoamine-mediated neurotransmission. Although these observations lend support to the monoamine-deficiency hypothesis, it is clear that the hypothesis is too simplistic. However, despite its shortcomings, the monoamine-deficiency hypothesis does provide a useful conceptual framework for understanding antidepressant drugs.

Treatment Modalities

Depression can be treated with four modalities: (1) pharmacotherapy, (2) depression-specific psychotherapy (eg, cognitive behavioral therapy), (3) electroconvulsive therapy (ECT), and (4) vagus nerve stimulation. The first three modalities offer clear benefits. Benefits of vagus nerve stimulation are ques-

tionable. For patients with mild to moderate depression, drug therapy and psychotherapy can be equally effective. For those with more severe depression, a combination of drugs and psychotherapy is better than either intervention alone. ECT is used when a rapid response is needed, or when drugs and psychotherapy have not worked. Vagus nerve stimulation is tried only after treatment with at least four drugs has failed.

Drugs are the primary therapy for major depression. Available antidepressants are listed in Table 32-2. For many patients, the *tricyclic antidepressants* (TCAs) are drugs of first choice. These agents are inexpensive, effective, relatively safe, and easy to administer. *Selective serotonin reuptake inhibitors* (SSRIs) are just as effective as the tricyclics and better tolerated. Because of these qualities—and despite their high cost—the SSRIs have become our most widely prescribed antidepressant drugs. *Monoamine oxidase inhibitors* (MAOIs) are generally reserved for patients who have not responded to TCAs or SSRIs. However, for patients with *atypical* depression, MAOIs are drugs of choice.

	Transmitters Affected[a]	Adverse Effects: Agitation/Insomnia	Anticholinergic Activity	Sedation	Hypotension	Seizure Risk	Cardiac Toxicity	Weight Gain	Sexual Dysfunction	Other Adverse Effects
Tricyclic Antidepressants (TCAs)										
Amitriptyline	NE, 5-HT	0/+	+ + + +	+ + +	+ +	+ +	+ + +	+ + +	+ +	
Clomipramine	NE, 5-HT	+	+ +	+ +	+ +	+ + +	+ + +	++	+ +	
Doxepin	NE, 5-HT	0/+	+ +	+ + +	+ +	+ +	+ ++	+ + +	+ +	
Imipramine	NE, 5-HT	+	+ +	+ +	+ +	+ +	+ + +	+ +	+ +	
Trimipramine	NE, 5-HT	0/+	+ + +	+ + +	+ +	+ +	+ + +	+ +	+ +	
Desipramine	NE	+	+	b	+	+	+ +	+	+ +	
Maprotiline	NE	+	+ +	+ +	+	+ + +	+ +	+	+ +	
Nortriptyline	NE	+	+	+	+	+	+ +	+ +	+ +	
Protriptyline	NE	+ +	+ +	b	+	+ +	+ + +	+	+ +	
Selective Serotonin Reuptake Inhibitors (SSRIs)										
Citalopram	5-HT	+ +	0/+	0/+	0	0/+	0	+	+ + +	GI bleeding, hyponatremia, NAS and PPHN in newborns[c]
Escitalopram	5-HT	+ +	0/+	0/+	0	0/+	0	+	+ + +	
Fluoxetine	5-HT	+ +	0	b	0	0/+	0/+	+	+ + +	
Fluvoxamine	5-HT	+ +	0/+	0/+	0	0/+		+	+ + +	
Paroxetine	5-HT	+ +	0/+	b	0	0/+	0	+	+ + +	
Sertraline	5-HT	+ +	0	b	0	0/+	0	+	+ + +	
Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)										
Venlafaxine	NE, 5-HT	+ +	0	0	0	0/+	0/+	0	+ + +	
Desvenlafaxine	NE, 5-HT	+ +	0	0	0	0/+	0/+	0	+ +	
Duloxetine	NE, 5-HT	+ +	0	0	0/+	0/+	0/+	0/+	+	Hepatotoxicity
Monoamine Oxidase Inhibitors (MAOIs)										
Isocarboxazid	NE, 5-HT, DA	+ +	0	+	+	0	0	+	+ +	Hypertensive crisis from tyramine in food[d]
Phenelzine	NE, 5-HT, DA	+ +	0	+	+	0	0	+	+ +	
Selegiline	NE, 5-HT, DA	+ +	0	0	0	0	0	0	+	
Tranylcypromine	NE, 5-HT, DA	+ +	0	b	+	0	0	+	+ +	
Atypical Antidepressants										
Amoxapine	NE, ↓ DA[e]	0/+	+	+	+	+ +	++	+	+ +	Parkinsonism
Bupropion	DA	+ +	0/+	b	0	+ + +	0	0	[f]	Seizures
Mirtazapine	NE, 5-HT	0/+	0/+	+ + + +	0/+	0	0	++++	0	
Nefazodone	5-HT	0/+	0/+	+ +	0	0	0/+	0/+	0/+	
Trazodone	5-HT	0/+	0/+	+ + + +	+	0	0/+	+	+[g]	Priapism

TABLE 32-2 Antidepressants: Adverse Effects and Impact on Neurotransmitters

a NE = norepinephrine; 5-HT = serotonin; DA = dopamine. All of the antidepressants *increase* synaptic activity of the transmitters indicated—with the exception of amoxapine, which increases activity of NE, but *blocks* receptors for DA. The TCAs, SSRIs, SNRIs, amoxapine, bupropion, nefazodone, and trazodone decrease transmitter reuptake; MAOIs block transmitter breakdown; and mirtazapine promotes transmitter release.

b Produces moderate *stimulation*, not sedation.

c NAS = neonatal abstinence syndrome; PPHN = persistent pulmonary hypertension of the newborn.

d Hypertensive crisis is not a risk with low-dose oral selegiline (10 mg/day or less) or with low-dose transdermal selegiline (6 mg/day), and possibly not with higher transdermal doses.

e Amoxapine blocks *reuptake* of NE and blocks *receptors* for DA.

f Bupropion may increase sexual desire.

g Trazodone can cause priapism (persistent painful erection).

BOX 32-1 POSTPARTUM DEPRESSION

The vast majority (about 80%) of women experience depressive symptoms after giving birth. For most, the symptoms are mild and transient, reflecting a condition known as the "baby blues." For others, symptoms are severe and persistent, reflecting true postpartum depression, a condition that merits rapid medical attention.

An estimated 60% to 70% of women get the postpartum blues. Symptoms include tearfulness, sadness, nervousness, irritability, and anxiety, along with difficulty eating and sleeping. The new mom may feel overwhelmed, vulnerable, weak, and alone. She may cry for no clear reason. Her self-esteem and self-confidence may decline, and she may feel unqualified to care for her baby. Fortunately, all of these symptoms pass quickly: As a rule, they develop a few days after delivery and are gone by day 10. Because the baby blues are so common, they're considered a normal postpartum event. Treatment is neither necessary nor recommended.

True postpartum depression is a different matter. The condition is much less common than the baby blues, but much more serious. Left untreated, postpartum depression typically lasts for months, and is likely to become worse as time passes. Not only is the condition detrimental to the mother, it can adversely affect the child, preventing secure attachment and impairing cognitive, emotional, and behavioral development. Accordingly, immediate intervention is indicated.

Just what is postpartum depression? Simply put, it's an episode of major depression that starts after giving birth. Otherwise, the diagnostic criteria are the same as for all other episodes of major depression (see Table 32-1). According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edi-*

tion (DSM-IV), for a depressive episode to qualify as having postpartum onset, symptoms must begin within *4 weeks* of delivery. However, most clinicians who study the disorder use a different criterion: To them, depression is considered postpartum if it begins within *3 months* of delivery—not just within 4 weeks.

Who is likely to suffer postpartum depression? Sometimes the condition occurs in first-time mothers, and sometimes it doesn't strike until a second, third, or fourth child is born. Among first-time mothers, the incidence is between 8% and 15% (about 1 in 8). For women with a history of the disorder, the risk increases to 33% (1 in 3). In addition to a prior history of the disorder, risk factors include a history of depression unrelated to childbirth, a history of premenstrual dysphoric disorder (ie, severe premenstrual syndrome), and major stress related to family, work, or residence (eg, death of a loved one, loss of a job, moving away from a familiar town or city).

The underlying cause of postpartum depression is unknown, but several factors are thought to contribute. Heading the list is the sharp drop in estrogen and progesterone levels that occurs after delivery. (Levels of these hormones increase 10-fold during pregnancy, and then return to baseline after the placenta is expelled.) However, since hormone levels fall in all women, but only some get postpartum depression, other factors—physical, emotional, and social—must be involved. The birthing process leaves women feeling weak and fatigued. Caring for a baby, who needs round-the-clock attention and feeding, exacerbates tiredness and exhaustion. Emotional and social factors may also play a role. Feelings of loss are common: Women experience loss of freedom, loss of control, and even loss of identity. In addition, they may feel loss of attractiveness. Stress increases substantially, owing to increased workload and responsibilities, coupled with feelings of self-doubt and inadequacy, and compounded by a self-imposed (albeit highly unrealistic) expectation to be a “perfect” mom. Stress can be made even worse by financial insecurity and inadequate support from one's partner, family, and friends. Thyroid insufficiency may also contribute: Levels of thyroid hormone often decline after delivery, thereby causing symptoms that can mimic depression. Accordingly, thyroid levels should be checked and, if indicated, replacement therapy should be implemented.

Screening for postpartum depression can be accomplished with a quick test: the Edinburgh Postnatal Depression Scale. The test is administered 6 to 8 weeks after delivery and contains the following short statements:

1. I have been able to laugh and see the funny side of things.
2. I have looked forward with enjoyment to things.
3. I have blamed myself unnecessarily when things went wrong.
4. I have been anxious or worried for no good reason.
5. I have felt scared or panicky for no very good reason.
6. Things have been getting on top of me.
7. I have been so unhappy that I have had difficulty sleeping.
8. I have felt sad or miserable.
9. I have been so unhappy that I have been crying.
10. The thought of harming myself has occurred to me.

Each statement has four possible responses, such as these for statement 10: (1) yes, quite often, (2) sometimes, (3) hardly ever, and (4) never. When taking the test, the mother simply underlines the option that best reflects her feelings during the previous week. If her responses indicate she probably has postpartum depression, she should undergo clinical evaluation to establish a definitive diagnosis.

Treatment of postpartum depression is much like treatment of major depression unrelated to pregnancy. The goal is to normalize mood, and optimize maternal and social functioning. The principal treatment modalities are psychotherapy and antidepressant drugs, both of which can be effective. In addition, the woman should be encouraged to nurture herself as well as her baby: She should reduce isolation (by going out for at least a short time each day), she should ensure adequate rest (by doing only what's really needed and letting the rest go), and she should spend time alone with her partner. Other beneficial measures include joining a support group for new mothers and recruiting family members and friends to assist with household and baby-related chores.

Although antidepressants are clearly appropriate, there are few published data to guide selection. In one study of women with postpartum depression, fluoxetine [Prozac], a selective serotonin reuptake inhibitor (SSRI), was com-

pared with psychotherapy. Both treatments were equally effective, and both were superior to placebo. Efficacy has also been demonstrated for sertraline [Zoloft], venlafaxine [Effexor], and certain tricyclic antidepressants (TCAs). For initial therapy, the SSRIs are an attractive choice. Why? Because they are effective and well tolerated, and present little risk of toxicity if taken in overdose. However, if a woman has responded to an antidepressant from a different class in the past, that drug should be tried first. To minimize side effects, dosage should be low initially (50% of the usual starting dosage) and then gradually increased. To reduce the risk of relapse, treatment should continue for at least 6 months after symptoms have resolved. Unfortunately, even then the relapse rate is high: Between 50% and 85% of patients experience at least one more depressive episode. With each succeeding episode, the risk of another recurrence increases. Accordingly, long-term prophylactic therapy should be considered.

Which antidepressants can be taken safely while breastfeeding? All of these drugs can be detected in breast milk—but levels of some are much lower (safer) than levels of others. Sertraline, for example, appears very safe. Studies show that drug activity in breast-fed infants is extremely low, and no adverse reactions have been observed. The TCAs (eg, nortriptyline, desipramine) also appear safe: Levels are too low for detection in breast-fed infants, and follow-up studies have found no developmental deficits. In contrast to sertraline and the TCAs, fluoxetine appears unsafe: The drug and its metabolites reach therapeutic levels in breast-fed infants; potential consequences include colic and impaired weight gain.

Electroconvulsive therapy is a valuable tool for treating depression. This procedure is safe and effective, and benefits develop more rapidly than with drugs or psychotherapy. Accordingly, ECT is especially appropriate when speed is critical. Candidates for ECT include (1) severely depressed, suicidal patients; (2) elderly patients at risk of starving to death because of depression-induced lack of appetite; and (3) patients who have not responded to antidepressant drugs.

SUICIDE RISK WITH ANTIDEPRESSANT DRUGS

Patients with depression often think about or attempt suicide. During treatment with antidepressants, especially early on, the risk of suicide may actually *increase*. If mood deteriorates, or if thoughts of suicide intensify, the patient

should see his or her prescriber immediately. Concerns about antidepressant-induced suicide apply mainly to children, adolescents, and adults under the age of 25.

To reduce the risk of suicide, patients taking antidepressant drugs should be observed closely for suicidality, worsening mood, and unusual changes in behavior. Close observation is especially important during the first few months of therapy and whenever antidepressant dosage is changed (either increased or decreased). Ideally, the patient or caregiver should meet with the prescriber at least weekly during the first 4 weeks of treatment, then biweekly for the next 4 weeks, then once 1 month later, and periodically thereafter. Phone contact may be appropriate between visits. In addition, family members or caregivers should monitor the patient *daily,* being alert for symptoms of decline (eg, anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, hypomania, and, of course, emergence of suicidality). If these symptoms are severe or develop abruptly, the prescriber should be informed at once.

Because antidepressant drugs can be used to *commit* suicide, two precautions should be observed. First, prescriptions should be written for the smallest number of doses consistent with good patient management. Second, dosing of inpatients should be directly observed to ensure that each dose is swallowed and not "cheeked," thereby preventing the patient from accumulating multiple doses that might be taken with suicidal intent.

What should be done if suicidal thoughts emerge during drug therapy, or if depression is persistently worse while taking drugs? One option is to switch to another antidepressant. Another is to stop antidepressants entirely. However, option two is probably unwise. Why? Because the long-term risk of suicide from untreated depression is much greater than the long-term risk associated with antidepressant drugs. If the risk of suicide appears high, temporary hospitalization may be the best protection.

TRICYCLIC ANTIDEPRESSANTS (TCAs)

The TCAs are drugs of first choice for many patients with major depression. The first tricyclic agent—*imipramine*—was introduced to psychiatry in the late 1950s. Since then, the ability of TCAs to relieve depressive symptoms has been

firmly established. The most common adverse effects are sedation, orthostatic hypotension, and anticholinergic effects. The most dangerous effect is cardiac toxicity. Like all other antidepressants, TCAs may increase the risk of suicide. Because all of the TCAs have similar properties, we will discuss these drugs as a group, rather than focusing on a representative prototype.

Chemistry

The structure of imipramine, a representative TCA, is shown in Figure 32-1. As you can see, the nucleus of this drug has three rings, hence the classification *tricyclic* antidepressant.

As indicated in Figure 32-1, the three-ringed nucleus of the TCAs is very similar to the three-ringed nucleus of the phenothiazine antipsychotics. Because of this structural similarity, TCAs and phenothiazines have several actions in common. Specifically, both groups produce varying degrees of *sedation, orthostatic hypotension,* and *anticholinergic effects*.

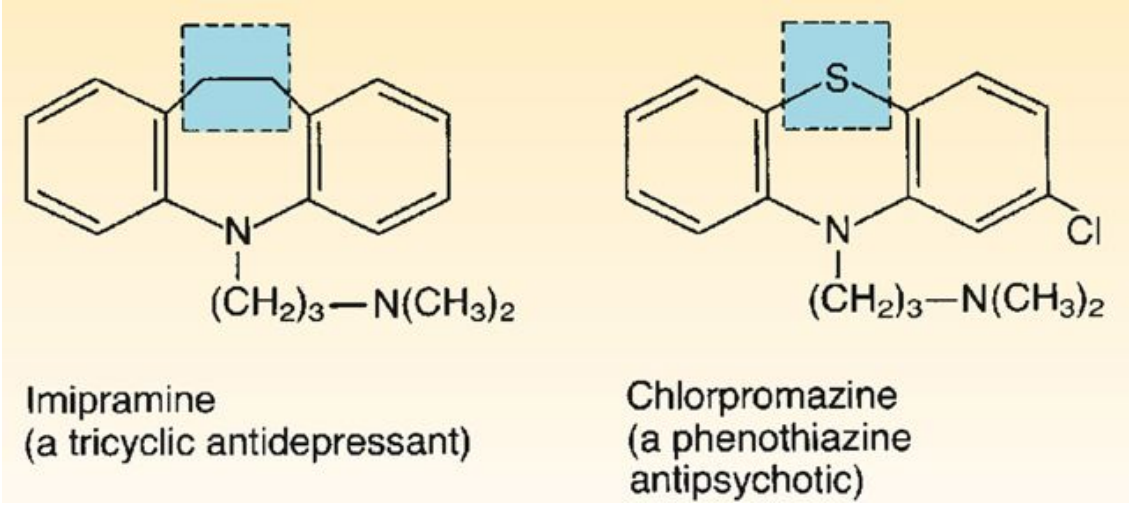


Figure 32-1 Structural similarities between tricyclic antidepressants and phenothiazine antipsychotics. Except for the areas highlighted, the phenothiazine nucleus is nearly identical to that of TCAs. Because of their structural similarities, TCAs and phenothiazines have several pharmacologic properties in common.

Mechanism of Action

The proposed mechanism of action of the TCAs is depicted in Figure 32-2. As shown, TCAs block neuronal reuptake of two monoamine transmitters: norepinephrine (NE) and serotonin (5-hydroxytryptamine, or 5-HT). By blocking reuptake of these transmitters, TCAs intensify their effects. This mechanism is consistent with the theory that depression stems from a *deficiency* in monoamine-mediated transmission—and hence should be relieved by drugs that can intensify monoamine effects. As indicated in Table 32-2, some TCAs block reuptake of NE *and* 5-HT, whereas other only block reuptake of NE.

It is important to appreciate that blockade of reuptake, by itself, cannot fully account for therapeutic effects. Why? Because clinical responses to the TCAs (relief of depressive symptoms) and biochemical effects of the TCAs (blockade of transmitter reuptake) do not occur in the same time frame. That is, whereas TCAs block transmitter uptake within hours of dosing, relief of depression takes several weeks to fully develop. Hence, it would appear that, in the interval between the onset of uptake blockade and the onset of a therapeutic response, intermediary neurochemical events must be taking place. Just what these may be is unknown.

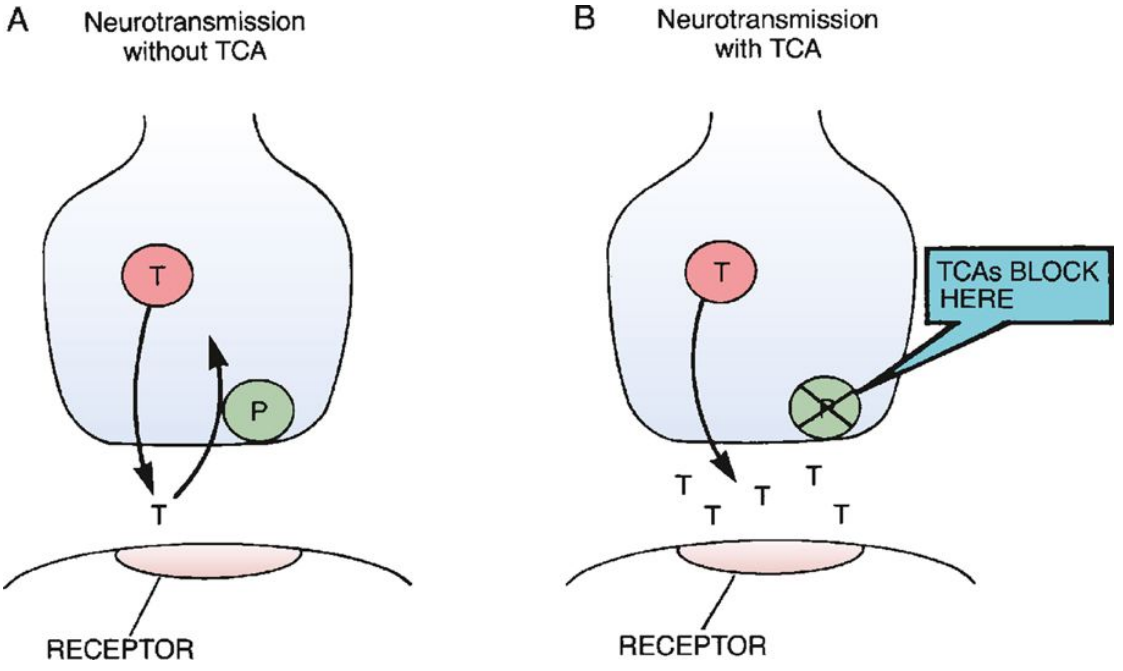


Figure 32-2 Mechanism of action of tricyclic antidepressants. A, Under drug-free conditions, the actions of norepinephrine and serotonin are terminated by active uptake of these transmitters back into the nerve terminals from which they were released. B, By inhibiting the uptake pumps for norepinephrine and serotonin, tricyclic antidepressants cause these transmitters to accumulate in the synaptic space, thereby intensifying transmission. (P = uptake pump, T = transmitter [norepinephrine or serotonin], TCA = tricyclic antidepressant, P = uptake pump.)

Pharmacokinetics

The half-lives of TCAs are long and variable. Because their half-lives are long, TCAs can usually be administered in a single daily dose. Because their half-lives are variable, TCAs require individualization of dosage.

Therapeutic Uses

Depression.

TCAs are preferred drugs for major depression. These medicines can elevate mood, increase activity and alertness, decrease morbid preoccupation, improve appetite, and normalize sleep patterns.

Like all other antidepressants, TCAs do not relieve symptoms immediately. *Initial* responses develop in 1 to 3 weeks.

Maximal responses develop over 1 to 2 months. Because therapeutic effects are delayed, TCAs cannot be used PRN. Furthermore, a therapeutic trial should not be considered a failure until medication has been administered for at least 1 month without success.

Bipolar Disorder.

Bipolar disorder (manic-depressive illness) is characterized by alternating episodes of mania and depression (see Chapter 33). TCAs can help during depressive episodes.

Other Uses.

TCAs can benefit patients with neuropathic pain (see Chapter 29), chronic insomnia (see Chapter 34), attention-deficit/hyperactivity disorder (see Chapter 36), and panic disorder or obsessive-compulsive disorder (see Chapter 35).

Adverse Effects

The most common adverse effects are orthostatic hypotension, sedation, and anticholinergic effects. The most serious adverse effect is cardiotoxicity. These effects occur because, in addition to blocking uptake of monoamine transmitters, TCAs cause direct blockade of receptors for histamine, acetylcholine, and NE. Adverse effects of individual agents are summarized in Table 32-2.

Orthostatic Hypotension.

Orthostatic hypotension is the most serious of the common adverse responses to TCAs. Hypotension is due in large part to blockade of alpha*1*adrenergic receptors on blood vessels. Patients should be informed that they can minimize orthostatic hypotension by moving slowly when assuming an upright posture. In addition, patients should be instructed to sit or lie down if symptoms (dizziness, lightheadedness) occur. For hospitalized patients, blood pressure and pulse rate should be monitored on a regular schedule (eg, 4 times a day). These measurements should be taken while the patient is lying down and again after the patient has been sitting or standing for 1 to 2 minutes. If blood pressure is low or pulse rate is high, medication should be withheld and the prescriber notified.

Anticholinergic Effects.

The TCAs block muscarinic cholinergic receptors, and can thereby cause an array of anticholinergic effects (dry mouth, blurred vision, photophobia, constipation, urinary hesitancy, and tachycardia). Patients should be informed about possible anticholinergic responses and instructed in ways to minimize discomfort. A detailed discussion of anticholinergic effects and their management is presented in Chapter 14.

Diaphoresis.

Despite their anticholinergic properties, TCAs often cause diaphoresis (sweating). The mechanism of this paradoxical effect is unknown.

Sedation.

Sedation is a common response to TCAs. The cause is blockade of histamine receptors in the central nervous system (CNS). Patients should be advised to avoid hazardous activities if sedation is prominent.

Cardiac Toxicity.

Tricyclics can adversely affect cardiac function. However, in the absence of an overdose or pre-existing cardiac impairment, serious effects are rare. The TCAs affect the heart by (1) decreasing vagal influence on the heart (secondary to muscarinic blockade) and (2) acting directly on the bundle of His to slow conduction. Both effects increase the risk of dysrhythmias. To minimize risk, all patients should undergo electrocardiographic (ECG) evaluation prior to treatment and periodically thereafter.

Seizures.

TCAs lower seizure threshold. Exercise caution in patients with epilepsy and other seizure disorders.

Hypomania.

On occasion, TCAs produce too much of a good thing, elevating mood from depression all the way to hypomania (mild mania). If hypomania develops, the patient should be evaluated to determine whether elation is drug induced or the result of bipolar disorder.

Suicide Risk.

As discussed above, TCAs and all other antidepressants may increase the risk of suicide in depressed patients, especially during the early phase of treatment. The risk of antidepressant-induced suicide is greatest among children, adolescents, and young adults.

Yawngasm.

Rarely, patients taking *clomipramine* [Anafranil] experience yawngasm. Experience *what?* A spontaneous orgasm while yawning. Honest. This unusual side effect, which affects both males and females, may be considered adverse or beneficial, depending on your view of such things. In at least one documented case, yawngasms strongly influenced adherence, as evidenced by the patient asking how long she would be "allowed" to continue treatment. Although data are scarce, one might guess that the occasional yawngasm would help relieve depression.

Drug Interactions

Monoamine Oxidase Inhibitors.

The combination of a TCA with an MAOI can lead to *severe hypertension,* owing to excessive adrenergic stimulation of the heart and blood vessels. Excessive adrenergic stimulation occurs because (1) inhibition of monoamine oxidase (MAO) causes accumulation of NE in adrenergic neurons and (2) blockade of NE reuptake by the tricyclics decreases NE inactivation. Because of the potential for hypertensive crisis, combined therapy with TCAs and MAOIs is generally avoided.

Direct-Acting Sympathomimetic Drugs.

Tricyclics *potentiate* responses to direct-acting sympathomimetics (ie, drugs such as epinephrine and dopamine that produce their effects by direct interaction with adrenergic receptors). Why are responses increased? Because TCAs block uptake of these agents into adrenergic nerve terminals, and thereby prolong their presence in the synaptic space.

Indirect-Acting Sympathomimetic Drugs.

TCAs *decrease* responses to indirect-acting sympathomimetics (ie, drugs such as ephedrine and amphetamine that promote release of transmitter from adrenergic nerves). Why? Because TCAs block uptake of these agents into adrenergic nerves, thereby preventing them from reaching their site of action within the nerve terminal.

Anticholinergic Agents.

Since TCAs have anticholinergic actions of their own, they will intensify the effects of other anticholinergic medications. Consequently, patients receiving TCAs should be advised to avoid all other drugs with anticholinergic properties, including antihistamines and certain over-the-counter sleep aids.

CNS Depressants.

CNS depression caused by TCAs will add with CNS depression caused by other drugs. Accordingly, patients should be warned against taking all other CNS depressants, including alcohol, antihistamines, opioids, and barbiturates.

Toxicity

Overdose with a TCA can be life threatening. (The lethal dose is only 8 times the average daily dose.) To minimize the risk of death by suicide, acutely depressed patients should be given no more than a 1-week supply of their TCA at a time.

Clinical Manifestations.

Symptoms result primarily from anticholinergic and cardiotoxic actions. The combination of cholinergic blockade and direct cardiotoxicity can produce *dysrhythmias,* including tachycardia, intraventricular blocks, complete atrioventricular block, ventricular tachycardia, and ventricular fibrillation. Responses to peripheral muscarinic blockade include hyperthermia, flushing, dry mouth, and dilation of the pupils. CNS symptoms are prominent. Early responses are confusion, agitation, and hallucinations. Seizures and coma may follow.

Treatment.

Absorption of ingested drug can be reduced with gastric lavage followed by ingestion of activated charcoal. Physostigmine (a cholinesterase inhibitor) is given to counteract anticholinergic actions. Propranolol, lidocaine, or phenytoin can control dysrhythmias. Dysrhythmias should not be treated with procainamide or quinidine, because these drugs cause cardiac depression.

Dosage and Routes of Administration

Dosage.

Dosages for individual TCAs are summarized in Table 32-3. General guidelines for dosing are discussed below.

Initial doses of TCAs should be low (eg, 50 mg of imipramine a day for adult outpatients). Low initial doses minimize adverse reactions and thereby help promote adherence. High initial doses are both undesirable and unnecessary. High doses are undesirable in that they pose an increased risk of adverse reactions. They are unnecessary in that onset of therapeutic effects is delayed regardless of dosage, and hence aggressive initial dosing offers no benefit.

Because of interpatient variability in TCA metabolism, dosing is highly individualized. As a rule, dosage is adjusted on the basis of clinical response. However, if there is no observable response, plasma drug levels can be used as a guide. For example, levels of imipramine must be above 225 ng/mL to be effective. If a patient has not responded to imipramine, measurements should be made to ensure that the plasma level is adequate. If the level is below 225 ng/mL, dosage should be increased.

Once an effective dosage has been established, most patients can take their entire daily dose at bedtime; the long half-lives of the TCAs make divided daily doses unnecessary. Once-a-day dosing at bedtime has three advantages: (1) it's easy, and hence facilitates adherence; (2) it promotes sleep by causing maximal sedation at night; and (3) it reduces the intensity of side effects during the day. If bedtime dosing causes residual sedation in the morning, dosing earlier in the evening can help. Although once-a-day dosing is generally desirable, not all patients can use this schedule. The elderly, for example, can be especially sensitive to the cardiotoxic actions of the tricyclics. As a result, if the entire daily dose were taken at one time, effects on the heart might be intolerable.

Once remission has been produced, therapy should continue for 6 months to a year. Failure to take medication for this period is likely to result in relapse. Patients should be encouraged to continue drug therapy even if they are symptom free and hence feel that further medication is unnecessary.

Generic Name	Trade Name	Initial Dose*,† (mg/day)	Dose after 4–8 Wk* (mg/day)	Maximum Dose‡ (mg/day)
Tricyclic Antidepressants (TCAs)				
Amitriptyline	generic only	50	100–200	300
Clomipramine	Anafranil	25	100–200	250
Desipramine	Norpramin	50	100–200	300
Doxepin	Sinequan	50	75–150	300
Imipramine	Tofranil	50	75–150	300
Maprotiline	generic only	50	100–150	225
Nortriptyline	Aventyl, Pamelor	20	75–100	125
Protriptyline	Vivactil	10	15–40	60
Trimipramine	Surmontil	50	100–200	300
Selective Serotonin Reuptake Inhibitors (SSRIs)				
Citalopram	Celexa	20	20–60	60
Escitalopram	Lexapro	10	10	20
Fluoxetine	Prozac	20	20–80	80
Fluvoxamine	Luvox	50	50–300	300
Paroxetine	Paxil, Pexeva	10	20–50	50
Sertraline	Zoloft	50	50–150	200
Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)				
Venlafaxine	Effexor	37.5	75–225	375
Desvenlafaxine	Pristiq	50	50	100
Duloxetine	Cymbalta	40–60	40–60	60
Monoamine Oxidase Inhibitors (MAOIs)				
Isocarboxazid	Marplan	20	20–60	80

TABLE 32-3 Adult Dosages for Antidepressants

* Doses listed are *total daily doses*. Depending on the drug and the patient, the total dose may be given in a single dose or in divided doses.

† Initial doses are employed for 4 to 8 weeks, the time required for most symptoms to respond. Dosage is gradually increased as required.

‡ Doses higher than these may be needed for some patients with severe depression.

Routes of Administration.

All TCAs can be administered by mouth, and they usually are. One agent—*imipramine*—may be given IM. Since effects take weeks to develop, there is no benefit to IV administration, and hence, this route is not used.

Preparations and Drug Selection

Preparations.

In the United States, nine TCAs are available (see Tables 32-2 and 32-3). All nine are equally effective. Principal differences among these drugs concern side effects (see Table 32-2).

Drug Selection.

Selection among TCAs is based on side effects. For example, if the patient is experiencing insomnia, a drug with prominent sedative properties (eg, doxepin) might be selected. Conversely, if daytime sedation is undesirable, a less sedating agent (eg, desipramine) might be preferred. Elderly patients with glaucoma or constipation and males with prostatic hypertrophy can be especially sensitive to anticholinergic effects. Hence, for these patients, a drug with weak anticholinergic properties (eg, nortriptyline) would be appropriate

Drug	Therapeutic Use*†							
	Major Depression	OCD	Panic Disorder	Social Phobia	GAD	PTSD	PMDD	Bulimia Nervosa
Citalopram [Celexa]	A	U	U	U	U	U	U	
Escitalopram [Lexapro]	A	A	U					
Fluoxetine [Prozac]	A	A	A	U	U	U	A	
Fluvoxamine [Luvox]	U	A	U	A	U	U	U	U
Paroxetine [Paxil]	A	A	A	A	A	A	A	
Sertraline [Zoloft]	A	A	A	A	U	A	A	

TABLE 32-4 Therapeutic Uses of Selective Serotonin Reuptake Inhibitors

* A = approved use, U = unlabeled use.

† GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; PTSD = post-traumatic stress disorder.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

The SSRIs were introduced in 1987 and have since become our most commonly prescribed antidepressants, accounting for over $3 billion in annual sales. These drugs are as effective as the TCAs, but do not cause hypotension, sedation, or anticholinergic effects. Moreover, overdose does not cause cardiotoxicity. Death by overdose is extremely rare. Characteristic side effects are nausea, agitation/insomnia, and sexual dysfunction (especially anorgasmia). SSRIs can interact adversely with MAOIs and other serotonergic drugs, and hence these combinations must be avoided. In addition, when used late in pregnancy, they can lead to a withdrawal syndrome and persistent pulmonary hy-

pertension in the infant. Like all other antidepressants, SSRIs may increase the risk of suicide. The SSRIs are used to treat major depression and a variety of other psychologic disorders (Table 32-4). Fluoxetine, the first SSRI available, will serve as our prototype for the group.

Fluoxetine

Fluoxetine [Prozac, Sarafem] is the most widely prescribed antidepressant in the United States. The drug is as effective as the TCAs, causes fewer side effects, and is less dangerous when taken in overdose. Combined use with MAOIs and other serotonergic drugs can cause serious adverse effects, and therefore must be avoided.

Mechanism of Action

Fluoxetine produces selective inhibition of 5-HT reuptake, and thereby intensifies transmission at serotonergic synapses. As with TCAs, blockade of transmitter uptake occurs quickly, whereas therapeutic effects develop slowly. This delay suggests that therapeutic effects are the result of adaptive cellular changes that take place in response to prolonged uptake blockade. Fluoxetine does not block uptake of dopamine or NE. In contrast to the TCAs, fluoxetine does not block cholinergic, histaminergic, or alpha*1*-adrenergic receptors. Furthermore, fluoxetine produces CNS excitation rather than sedation.

Therapeutic Uses

Fluoxetine is used primarily for major depression. Antidepressant effects begin in 1 to 3 weeks and are equivalent to those produced by TCAs. Fluoxetine is also approved for bipolar disorder (Chapter 33), obsessive-compulsive disorder (Chapter 35), panic disorder (Chapter 35), bulimia nervosa, and premenstrual dysphoric disorder (Chapter 60). Unlabeled uses include post-traumatic stress disorder, social phobia, alcoholism, attention-deficit/hyperactivity disorder, migraine, Tourette's syndrome, and obesity.

Pharmacokinetics

Fluoxetine is well absorbed following oral administration, even in the presence of food. The drug is widely distributed and highly bound (94%) to plasma proteins. Fluoxetine undergoes extensive hepatic conversion to norfluoxetine,

an active metabolite. Norfluoxetine is eventually converted to inactive metabolites that are excreted in the urine. The half-life of fluoxetine is 2 days and the half-life of norfluoxetine is 7 days. Because the effective half-life is prolonged, about 4 weeks are required to produce steady-state plasma drug levels—and about 4 weeks are required for washout after dosing stops.

Adverse Effects

Fluoxetine is safer and better tolerated than TCAs and MAOIs. Death from overdose with fluoxetine alone has not been reported. In contrast to TCAs, fluoxetine does not block receptors for histamine, NE, or acetylcholine, and hence does not cause sedation, orthostatic hypotension, anticholinergic effects, or cardiotoxicity. The most common side effects are sexual dysfunction (70%), nausea (21%), headache (20%), and manifestations of CNS stimulation, including nervousness (15%), insomnia (14%), and anxiety (10%). Weight gain can also occur. Fluoxetine and most other SSRIs appear safe for use during pregnancy.

Sexual Dysfunction.

Fluoxetine causes sexual problems (impotence, delayed or absent orgasm, delayed or absent ejaculation, decreased sexual interest) in nearly 70% of men and women. The underlying mechanism is unknown.

Sexual dysfunction can be managed in several ways. In some cases, reducing the dosage or taking "drug holidays" (eg, discontinuing medication on Fridays and Saturdays) can help. Another solution is to add a drug that can overcome the problem. Among these are yohimbine, buspirone [BuSpar], and three atypical antidepressants: bupropion [Wellbutrin, others], nefazodone, and mirtazapine [Remeron]. Sildenafil [Viagra] can also help: In *men,* the drug improves erectile dysfunction, as well as arousal, ejaculation, orgasm, and overall satisfaction; in women, the drug can improve delayed orgasm. If all of these measures fail, the patient can try a different antidepressant. Agents that cause the least sexual dysfunction are the same three atypical antidepressants named above.

Sexual problems often go unreported, either because patients are uncomfortable discussing them or because patients don't realize their medicine is the

cause. Accordingly, patients should be informed about the high probability of sexual dysfunction and told to report any problems so they can be addressed.

Weight Gain.

Like many other antidepressants, fluoxetine and other SSRIs cause weight gain. When these drugs were first introduced, we thought they caused weight *loss*. Why? Because during the first few weeks of therapy patients do lose weight, perhaps because of drug-induced nausea and vomiting. However, with long-term treatment, the lost weight is regained. Furthermore, about one-third of patients continue putting on weight—up to 20 pounds or more. Although the reason for weight gain is unknown, a good possibility is decreased sensitivity of 5-HT receptors that regulate appetite.

Serotonin Syndrome.

By increasing serotonergic transmission in the brainstem and spinal cord, fluoxetine and other SSRIs can cause serotonin syndrome. This syndrome usually begins 2 to 72 hours after initiation of treatment. Signs and symptoms include altered mental status (agitation, confusion, disorientation, anxiety, hallucinations, poor concentration) as well as incoordination, myoclonus, hyperreflexia, excessive sweating, tremor, and fever. Deaths have occurred. The syndrome resolves spontaneously after discontinuing the drug. The risk of serotonin syndrome is increased by concurrent use of MAOIs and other serotonergic drugs (see Table 32-5), and by use of ritonavir [Norvir, Kaletra] and other drugs that can increase fluoxetine levels.

Drug	Impact on Serotonin
Selective Serotonin Reuptake Inhibitors (SSRIs)	
Citalopram [Celexa]	Block 5-HT reuptake and thereby increase 5-HT in the synapse
Escitalopram [Lexapro]	
Fluoxetine [Prozac]	
Fluvoxamine [Luvox]	
Paroxetine [Paxil]	
Sertraline [Zoloft]	
Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)	
Desvenlafaxine [Pristiq]	Same as SSRIs
Duloxetine [Cymbalta]	
Venlafaxine [Effexor]	
Tricyclic Antidepressants (TCAs)	
Amitriptyline	Same as SSRIs
Clomipramine [Anafranil]	
Doxepin [Sinequan]	
Imipramine [Tofranil]	
Trimipramine [Surmontil]	
Monoamine Oxidase Inhibitors (MAOIs)	
Desipramine [Norpramin]	Inhibit neuronal breakdown of 5-HT, by MAO, and thereby increase stores of 5-HT available for release
Isocarboxazid [Marplan]	
Phenelzine [Nardil]	
Selegiline [Emsam]	
Atypical Antidepressants	
Mirtazapine [Remeron]	Promotes release of 5-HT
Nefazodone	Same as SSRIs

TABLE 32-5 Drugs That Can Increase Serotonin Activity at CNS Synapses

Withdrawal Syndrome.

Abrupt discontinuation of SSRIs can cause a withdrawal syndrome. Symptoms include dizziness, headache, nausea, sensory disturbances, tremor, anxiety, and dysphoria. These begin within days to weeks of the last dose, and then persist for 1 to 3 weeks. Resumption of drug use will make symptoms subside. The withdrawal syndrome can be minimized by tapering the dosage slowly. Of the SSRIs in use today, fluoxetine is least likely to cause a withdrawal reaction. Why? Because fluoxetine has a prolonged half-life; hence, when dosing is stopped, plasma levels decline slowly. When SSRIs are discontinued, it is important to distinguish between symptoms of withdrawal and return of depression.

Neonatal Effects from Use in Pregnancy.

Use of fluoxetine and others SSRIs late in pregnancy poses a small risk of two adverse effects in the newborn: (1) *neonatal abstinence syndrome* (NAS) and (2) *persistent pulmonary hypertension of the newborn* (PPHN). NAS is characterized by irritability, abnormal crying, tremor, respiratory distress, and possibly seizures. The syndrome can be managed with supportive care and generally abates within a few days. PPHN, which compromises tissue oxygenation, carries a significant risk of death, and, among survivors, a risk of cognitive delay, hearing loss, and neurologic abnormalities. Treatment measures include providing ventilatory support, giving oxygen and nitric oxide (to dilate pulmonary blood vessels), and giving IV sodium bicarbonate (to maintain alkalosis) and dopamine or dobutamine (to increase cardiac output, and thereby maintain pulmonary perfusion). Infants exposed to SSRIs late in gestation should be monitored closely for NAS and PPHN.

Teratogenesis.

Do fluoxetine and other SSRIs cause birth defects? Probably not. And if they do, the risk appears to be very low. Two SSRIs—*paroxetine* and *fluoxetine*—may cause heart defects. But even with these agents, the absolute risk is very low.

Suicide Risk.

As discussed above, antidepressants may increase the risk of suicide in depressed patients, especially during the early phase of treatment. The risk of antidepressant-induced suicide is greatest among children, adolescents, and young adults.

Extrapyramidal Side Effects.

SSRIs cause extrapyramidal symptoms (EPS) in about 0.1% of patients. This is much less frequent than among patients taking antipsychotic medications (see Chapter 31). Among patients taking SSRIs, the most common of the EPS is akathisia, characterized by restlessness and agitation. However, parkinsonism, dystonic reactions, and tardive dyskinesia can also occur. EPS typically develop during the first month of treatment. The risk is increased by concurrent use of an antipsychotic drug. The underlying cause of SSRI-induced EPS may be alteration of serotonergic transmission within the extrapyramidal system. For a detailed discussion of EPS, refer to Chapter 31.

Bruxism.

SSRIs may cause bruxism (clenching and grinding of teeth). However, since bruxism usually occurs during sleep, the condition often goes unrecognized. Sequelae of bruxism include headache, jaw pain, and dental problems (eg, cracked fillings).

How do SSRIs cause bruxism? One theory is that they inhibit release of dopamine, a neurotransmitter that suppresses activity in certain muscles, including those of the jaw. By decreasing dopamine availability, SSRIs could release these muscles from inhibition, and excessive activity could result. This same mechanism may be responsible for SSRI-induced EPS.

How can bruxism be managed? One option is to reduce the SSRI dosage. However, this may cause depression to return. Other options include switching to a different class of antidepressant, use of a mouth guard, and treatment with low-dose buspirone (5 to 10 mg 1 to 3 times a day).

Bleeding Disorders.

Fluoxetine and other SSRIs can increase the risk of bleeding in the GI tract and at other sites. How? By impeding platelet aggregation: Platelets require 5-HT for aggregation, but can't make it themselves, and hence must take 5-HT up from the blood; by blocking 5-HT uptake, SSRIs suppress aggregation. The SSRIs cause a threefold increase in the risk of GI bleeding. However, the *absolute* risk is still low (about 1 case for every 8000 prescriptions). Caution is advised in patients with ulcers or a history of GI bleeding, in patients older than 60, and in patients taking nonsteroidal anti-inflammatory drugs or anticoagulants.

Hyponatremia.

Fluoxetine can cause hyponatremia (serum sodium below 135 mEq/L), probably by increasing secretion of antidiuretic hormone. Most cases involve older patients taking thiazide diuretics. Accordingly, when fluoxetine is used in older patients, sodium should be measured at baseline and periodically thereafter.

Other Adverse Effects.

Fluoxetine can cause *dizziness* and *fatigue;* patients should be warned against driving and other hazardous activities. *Skin rash,* which can be severe, has occurred in 4% of patients; in most cases, rashes readily respond to drug therapy (antihistamines, glucocorticoids) or to withdrawal of fluoxetine. Other common reactions include *diarrhea* (12%) and *excessive sweating* (8%).

Drug Interactions

MAOIs and Other Serotonergic Drugs.

Fluoxetine should not be combined with MAOIs and other serotonergic drugs (see Table 32-5) owing to a risk of serotonin syndrome. Because MAOIs cause irreversible MAO inhibition (see below), their effects persist long after dosing stops. Accordingly, these drugs should be withdrawn at least 14 days before starting fluoxetine. When fluoxetine is discontinued, at least 5 weeks should elapse before giving an MAOI.

Warfarin.

Because fluoxetine is highly bound to plasma proteins, it can displace other highly bound drugs. Displacement of warfarin (an anticoagulant) is of particular concern. Monitor responses to warfarin closely.

Tricyclic Antidepressants and Lithium.

Fluoxetine can elevate plasma levels of TCAs and lithium. Exercise caution if fluoxetine is combined with these agents.

Preparations, Dosage, and Administration

Preparations.

Fluoxetine is available in several oral formulations and is sold under three trade names: Prozac, Prozac Weekly, and Sarafem. Products available under each trade name are as follows:

- *Prozac*—tablets (10 mg), pulvules (10 and 20 mg), oral solution (20 mg/5 mL)
- *Prozac Weekly*—delayed-release, enteric-coated capsules (90 mg)
- *Sarafem*—pulvules (10 and 20 mg)

In addition to these single-ingredient products, fluoxetine is available in a fixed-dose combination with olanzapine (an antipsychotic), sold as *Symbyax,* for the treatment of bipolar disorder (see Chapter 33).

Dosage for Depression

Daily Dosing.

The recommended initial dosage is 20 mg/day, taken with or without food. If needed, dosage may be increased gradually to a maximum of 80 mg/day. However, doses greater than 20 mg/day may increase adverse effects without increasing benefits. If daily doses above 20 mg are used, they should be divided. For elderly patients and patients with impaired liver function, the dosage should be low initially and then cautiously increased if needed. Since fluoxetine often impairs sleep, evening dosing should generally be avoided.

Weekly Dosing.

Patients who have been treated successfully with 20 mg of fluoxetine daily for at least 13 weeks can be switched to once-weekly dosing (using 90-mg delayed-release capsules) for maintenance. Weekly dosing is initiated 7 days after the last 20-mg dose of daily fluoxetine.

Withdrawal.

When discontinuing the drug, dosage should be reduced gradually.

Other SSRIs

In addition to fluoxetine, five other SSRIs are available: citalopram [Celexa], escitalopram [Lexapro], fluvoxamine [Luvox], paroxetine [Paxil, Pexeva], and sertraline [Zoloft]. All five are similar to fluoxetine. Antidepressant effects equal those of TCAs. Like fluoxetine, the newer SSRIs do not cause hypotension or anticholinergic effects, and, with the exception of fluvoxamine, do not cause sedation. When taken in overdose, these drugs do not cause cardiotoxicity. Characteristic side effects are nausea, insomnia, headache, nervousness, weight gain, sexual dysfunction, hyponatremia, GI bleeding, and NAS and PPHN (in infants who were exposed to these drugs late in gestation). Serotonin syndrome is a potential complication with all SSRIs, especially if these agents are combined with MAOIs or other serotonergic drugs. The principal differences among the SSRIs relate to duration of action. Patients who experience intolerable adverse effects with one SSRI may find a different SSRI more acceptable. As with fluoxetine, withdrawal should be done slowly. Therapeutic uses for individual agents are summarized in Table 32-4.

Sertraline

Sertraline [Zoloft] is much like fluoxetine: both drugs block uptake of 5-HT, both relieve symptoms of major depression, both cause CNS stimulation rather than sedation, and both have minimal effects on seizure threshold and the ECG. Sertraline is indicated for major depression, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder (social phobia). The drug is used off-label to treat generalized anxiety disorder.

Sertraline is slowly absorbed following oral administration. Food increases the extent of absorption. In the blood, the drug is highly bound (99%) to

plasma proteins. Sertraline undergoes extensive hepatic metabolism followed by elimination in the urine and feces. The plasma half-life is approximately 1 day.

Common side effects include headache, tremor, insomnia, agitation, nervousness, nausea, diarrhea, weight gain, and sexual dysfunction. Treatment may also increase the risk of suicide. Because of the risk of serotonin syndrome, sertraline must not be combined with MAOIs and other serotonergic drugs (see Table 32-5). MAOIs should be withdrawn at least 14 days before starting sertraline, and sertraline should be withdrawn at least 14 days before starting an MAOI. Because of a risk of pimozide-induced dysrhythmias, sertraline (which raises pimozide levels) and pimozide should not be combined. Like fluoxetine and other SSRIs, sertraline poses a risk of hyponatremia, GI bleeding, and NAS and PPHN when used late in pregnancy.

Sertraline is available in tablets (25, 50, and 100 mg) and a concentrated oral solution (20 mg/mL). For treatment of depression, the initial adult daily dosage is 50 mg, administered in the morning or evening. After 4 to 8 weeks, the dosage may be increased by 50-mg increments to a maximum of 200 mg/day. When discontinuing the drug, dosage should be reduced gradually.

Fluvoxamine

Like other SSRIs, fluvoxamine [Luvox] produces powerful and selective inhibition of 5-HT reuptake. The drug is approved for obsessive-compulsive disorder and social anxiety disorder. Unlabeled uses include major depression, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, and bulimia nervosa.

Fluvoxamine is rapidly absorbed from the GI tract, both in the presence and absence of food. The drug undergoes extensive hepatic metabolism followed by excretion in the urine. The half-life is about 15 hours.

Common side effects include nausea, vomiting, dry mouth, headache, constipation, weight gain, and sexual dysfunction. In contrast to other SSRIs, fluvoxamine has moderate sedative effects, although it nonetheless can cause insomnia. Some patients have developed abnormal liver function tests. Accordingly, liver function should be assessed prior to treatment and weekly during the first month of therapy. Like other SSRIs, fluvoxamine interacts adversely with

MAOIs and other serotonergic drugs, and hence these combinations must be avoided. As with other SSRIs, fluvoxamine poses a risk of hyponatremia, GI bleeding, and NAS and PPHN in infants exposed to the drug *in utero*.

Fluvoxamine is available in immediate-release tablets (25-, 50-, and 100-mg), sold as *Luvox,* and controlled-release capsules (100 and 150 mg), sold as *Luvox CR*. With the immediate-release formulation, dosing begins at 50 mg once a day at bedtime, and can be gradually increased to a maximum of 300 mg/day, given in two divided doses when the daily total exceeds 100 mg. With the controlled-release capsules, dosing begins at 100 mg once daily, and can be gradually increased to 300 mg once daily. With either formulation, drug withdrawal should be done gradually.

Paroxetine

Like other SSRIs, paroxetine [Paxil, Paxil CR, Pexeva] produces powerful and selective inhibition of 5-HT uptake. The drug is indicated for major depression, obsessive-compulsive disorder, social anxiety disorder, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, and premenstrual dysphoric disorder. Paroxetine is used off-label to treat bipolar disorder and postmenopausal hot flushes.

Paroxetine is well absorbed following oral administration, even in the presence of food. The drug is widely distributed and highly bound (95%) to plasma proteins. Concentrations in breast milk equal those in plasma. The drug undergoes hepatic metabolism followed by renal excretion. The half-life is about 20 hours.

Side effects are dose dependent and generally mild. Early reactions include nausea, somnolence, sweating, tremor, and fatigue. These tend to diminish over time. After 5 to 6 weeks, the major complaints are headache, weight gain, and sexual dysfunction. Like fluoxetine, paroxetine causes signs of CNS stimulation (increased awakenings, reduced time in rapid-eye-movement sleep, insomnia). In contrast to TCAs, paroxetine has no effect on heart rate, blood pressure, or the ECG—but does have some antimuscarinic effects. Like other SSRIs, paroxetine interacts adversely with MAOIs and other serotonergic drugs, and hence these combinations must be avoided. Also, like other SSRIs, paroxetine can increase the risk of GI bleeding, and can cause hyponatremia

(especially in elderly patients taking thiazide diuretics). As with other SSRIs, use late in pregnancy can result in NAS and PPHN. In addition, paroxetine, but not other SSRIs, poses a small risk of cardiovascular birth defects, primarily ventral septal defects. Because of this risk, the drug is now classified in FDA Pregnancy Risk Category D. Like all other antidepressants, paroxetine may increase the risk of suicide, especially in children and young adults.

Paroxetine is available as two salts: paroxetine *hydrochloride* and paroxetine *mesylate*. Although the two preparations have not been compared directly, effects are likely to be identical. The hydrochloride salt is available in immediate-release (IR) tablets (10, 20, 30, and 40 mg) and an oral suspension (2 mg/mL) as *Paxil,* and controlled-release (CR) tablets (12.5, 25, and 37.5 mg) as *Paxil CR*. Please note that the CR tablets are *not* longer acting than the IR tablets. Rather, the CR tablets are designed to dissolve in the lower intestine, and hence may cause less GI disturbance than the IR tablets. The mesylate salt [Pexeva] is available only in tablets (10, 20, 30, and 40 mg).

The initial dosage for depression is 20 mg/day. The entire daily dose is administered in the morning (to minimize sleep disturbance) and with food (to minimize GI upset). Dosage may be increased gradually (every 3 to 4 weeks) to a maximum of 50 mg/day. When discontinuing the drug, dosage should be reduced gradually.

Citalopram

Citalopram [Celexa] is very similar to fluoxetine and the other SSRIs. Benefits derive from selective blockade of 5-HT uptake. The drug does not block receptors for 5-HT, acetylcholine, NE, or histamine. Its only approved indication is major depression. Unlabeled uses include panic disorder, social anxiety disorder, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and premenstrual dysphoric disorder.

Citalopram is rapidly absorbed from the GI tract, both in the presence and absence of food. Plasma levels peak about 4 hours after administration. The drug undergoes hepatic metabolism followed by excretion in the urine and feces. The half-life is about 35 hours.

The most common adverse effects are nausea, somnolence, dry mouth, and sexual dysfunction. Additional side effects include weight gain, tachycardia,

postural hypotension, headache, paresthesias, hyponatremia, and increased risk of GI bleeding. Large doses are teratogenic in animals. Citalopram enters breast milk in amounts sufficient to cause somnolence, reduced feeding, and weight loss in the infant. Use late in pregnancy can result in NAS and PPHN in the infant. Like all other antidepressants, citalopram may increase the risk of suicide, especially in children and young adults.

Because of the risk of serotonin syndrome, citalopram should not be combined with MAOIs or other serotonergic drugs. Allow at least 14 days to pass between stopping an MAOI and starting citalopram, or vice versa.

Citalopram is available in tablets (10, 20, and 40 mg) and an oral solution (2 mg/mL). The drug may be taken in the morning or evening, with or without food. The initial dosage for depression is 20 mg once a day. Dosage may be increased slowly to a maximum of 60 mg/day. Dosage should remain low in elderly patients and those with liver impairment. When discontinuing the drug, dosage should be reduced gradually.

Escitalopram

Escitalopram [Lexapro] is the *S*-isomer of citalopram [Celexa], which is a 50:50 mixture of *S*- and *R*-isomers. The *S*-isomer (escitalopram) is responsible for antidepressant effects. The *R*-isomer has no antidepressant actions, but does contribute to side effects. Accordingly, escitalopram retains the therapeutic benefits of citalopram, but may be better tolerated. Otherwise, the pharmacology of the two drugs is largely the same. Escitalopram is approved for major depression and generalized anxiety disorder, and has been used off-label for panic disorder.

Like citalopram and other SSRIs, escitalopram is generally well tolerated. In clinical trials, the most common side effects were nausea (15%), insomnia (9%), somnolence (6%), sweating (5%), and fatigue (5%). In addition, 9% of males reported ejaculatory disorders. However, the true incidence of sexual dysfunction may be higher. Why? Because, with other SSRIs, the incidence of sexual problems reported during clinical trials was considerably lower than the incidence seen in actual practice. As with other SSRIs, combined use with MAOIs and other serotonergic drugs increases the risk of serotonin syndrome. At least 14 days should separate use of MAOIs and escitalopram. Like

citalopram and other SSRIs, escitalopram increases the risk of hyponatremia and GI bleeding, and, when used late in pregnancy, may cause NAS or PPHN in the newborn. Like all other antidepressants, this drug can increase the risk of suicide, especially in children and young adults.

Escitalopram is available in tablets (5, 10, and 20 mg) and an oral solution (1 mg/mL). The recommended initial dosage is 10 mg/day, taken in the morning or evening, with or without food. In clinical trials, dosages above 10 mg/day did not increase antidepressant effects, but did intensify side effects. There is no need to reduce the dosage in elderly patients or in patients with either hepatic impairment or mild to moderate renal impairment. However, in patients with severe renal impairment, a dosage reduction may be required. When discontinuing the drug, dosage should be reduced gradually.

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

Three drugs—venlafaxine, desvenlafaxine, and duloxetine—block neuronal reuptake of serotonin *and* norepinephrine, with minimal effects on other transmitters or receptors. Pharmacologic effects are similar to those of the SSRIs, although the SSRIs may be better tolerated.

Venlafaxine

Venlafaxine [Effexor, Effexor XR], the first SNRI available, is indicated for major depression, generalized anxiety disorder, and social anxiety disorder (social phobia). The drug produces powerful blockade of NE and 5-HT uptake and weak blockade of dopamine uptake. The relationship of these actions to therapeutic effects is uncertain. Venlafaxine does not block cholinergic, histaminergic, or alpha*1*-adrenergic receptors. Despite impressions that venlafaxine may be superior to SSRIs, when compared directly in clinical trials, the drugs were about equally effective—and SSRIs are probably safer.

Venlafaxine is well absorbed following oral administration, both in the presence and absence of food. In the liver, much of each dose is converted to desvenlafaxine, an active metabolite. The half-life is 5 hours for the parent drug and 11 hours for the active metabolite.

Venlafaxine can cause a variety of adverse effects. The most common is nausea (37%), followed by headache, anorexia, nervousness, sweating, somnolence, and insomnia. Dose-dependent weight loss may occur secondary to anorexia. Venlafaxine can also cause dose-related sustained diastolic hypertension; blood pressure should be monitored. Sexual dysfunction (eg, impotence, anorgasmia) may occur too. Like the SSRIs, venlafaxine can cause hyponatremia, especially in elderly patients taking diuretics. Like all other antidepressants, venlafaxine may increase the risk of suicide, especially in children and young adults.

Abrupt discontinuation can cause an intense withdrawal syndrome. Symptoms include anxiety, agitation, tremors, headache, vertigo, nausea, tachycardia, and tinnitus. Worsening of pretreatment symptoms may also occur. Withdrawal symptoms can be minimized by tapering the dosage over 2 to 4 weeks. Warn patients not to stop venlafaxine abruptly.

As with the SSRIs, use of venlafaxine late in pregnancy can result in a neonatal withdrawal syndrome, characterized by irritability, abnormal crying, tremor, respiratory distress, and possibly seizures. Symptoms, which can be managed with supportive care, generally abate within a few days.

Combined use of venlafaxine with MAOIs and other serotonergic drugs (see Table 32-5) increases the risk of serotonin syndrome, a potentially fatal reaction. If the clinical situation demands, venlafaxine may be cautiously combined with an SSRI or another SNRI. However, combined use with an MAOI is *contraindicated*. Accordingly, MAOIs should be withdrawn at least 14 days before starting venlafaxine. When switching from venlafaxine to an MAOI, venlafaxine should be discontinued 7 days before starting the MAOI.

Venlafaxine is available in immediate-release tablets (25, 37.5, 50, 75, and 100 mg) sold as Effexor, and extended-release capsules (37.5, 75, and 150 mg) sold as Effexor XR. The recommended initial dosage for depression is 75 mg/day (in two or three divided doses) taken with food. If needed, the dosage may be gradually increased. The usual maximum dosage is 225 mg/day. However, dosages as large as 375 mg/day have been used for severely depressed patients. Dosage should be reduced in patients with liver disease, and possibly in those with kidney disease.

Desvenlafaxine

Desvenlafaxine [Pristiq], approved in 2008, is the major active metabolite of venlafaxine. Accordingly, the actions and adverse effects of both drugs are similar. Like venlafaxine, desvenlafaxine is a strong inhibitor of 5-HT and NE reuptake, and does not block cholinergic, histaminergic, or alpha*1*-adrenergic receptors. At this time, desvenlafaxine is approved only for major depression, in contrast to venlafaxine, which is approved for major depression, generalized anxiety disorder, and social phobia.

Desvenlafaxine is well absorbed following oral administration, both in the presence and absence of food. Plasma levels peak about 7.5 hours after dosing. The drug undergoes some hepatic metabolism, and is excreted in the urine as metabolites and parent drug. The elimination half-life is 1 hour.

Adverse effects are like those of venlafaxine. The most common reactions are nausea (22%), headache (20%), dizziness (13%), insomnia (9%), diarrhea (11%), dry mouth (11%), sweating (10%), and constipation (9%). Sexual effects include erectile dysfunction (3%) and decreased libido (4%). Like all other antidepressants, desvenlafaxine may increase the risk of suicide in children and young adults. Some neonates exposed to the drug *in utero* have required prolonged hospitalization, respiratory support, and tube feeding. Additional concerns include hyponatremia, sustained hypertension, serotonin syndrome, bleeding, seizures, and withdrawal symptoms if the drug is discontinued abruptly.

As with venlafaxine, combining desvenlafaxine with another serotonergic drug increases the risk of serotonin syndrome. Combined use with an SSRI or another SNRI may be done cautiously. In contrast, combined use with an MAOI is *contraindicated*. Accordingly, MAOIs should be withdrawn at least 14 days before starting desvenlafaxine, and desvenlafaxine should be withdrawn at least 7 days before starting an MAOI.

Desvenlafaxine [Pristiq] is available in 50- and 100-mg extended-release tablets, which should be swallowed whole with fluid, and not be crushed, chewed, or dissolved. The recommended dosage is 50 mg once daily, taken with or without food, about the same time each day. Increasing the dose to 100 mg/day offers no benefit, but does increase the risk of side effects. In patients with severe renal impairment (creatinine clearance less than 30 mL/min), the dosage should be reduced to 50 mg every other day. There is no need to reduce

the dosage in patients with moderate renal impairment or in those with liver impairment of any degree. To minimize withdrawal reactions, the drug should be discontinued slowly (by gradually increasing the dosing interval).

Duloxetine

Mechanism of Action and Therapeutic Use.

Duloxetine [Cymbalta] was the second SNRI approved for major depression. The drug is a powerful inhibitor of 5-HT and NE reuptake, and a much weaker inhibitor of dopamine reuptake. Duloxetine does not bind with receptors for NE, serotonin, dopamine, acetylcholine, or histamine, and does not inhibit MAO.

Data on the antidepressant effects of duloxetine are limited. Clinical trials have shown that duloxetine is clearly superior to *placebo:* Treatment reduces depressive symptoms and may also reduce physical pain associated with depression (eg, backache). Furthermore, benefits may develop quickly, in some cases within 2 weeks of starting treatment. Unfortunately, there have been no trials comparing duloxetine directly with other antidepressants, such as venlafaxine or the SSRIs. Also, there is little information on the drug's long-term efficacy or safety. As a result, there is no basis for choosing this newer drug over older ones.

In addition to its use in depression, duloxetine is approved for *fibromyalgia, generalized anxiety disorder,* and *pain of diabetic peripheral neuropathy,* and is being studied for treatment of *stress* urinary incontinence (in contrast to *urge* urinary incontinence).

Pharmacokinetics.

Duloxetine is well absorbed following oral administration. Food reduces the rate of absorption but not the extent. In the blood, duloxetine is highly (90%) bound to albumin. The drug undergoes extensive hepatic metabolism, primarily by the CYP2D6 and CYP1A2 isozymes of cytochrome P450. Metabolites are excreted in the urine (70%) and feces (20%). The elimination half-life is 12 hours. In patients with severe renal impairment, levels of duloxetine and its metabolites are greatly increased, and in those with severe hepatic impair-

ment, the half-life is greatly prolonged. Accordingly, duloxetine is not recommended for patients with severe renal or hepatic dysfunction.

Adverse Effects.

Duloxetine is generally well tolerated. In clinical trials, the most common adverse effects were nausea (20% vs. 7% with placebo), dry mouth (15% vs. 6%), insomnia (11% vs. 6%), somnolence (7% vs. 3%), constipation (11% vs. 4%), reduced appetite (8% vs. 2%), fatigue (8% vs. 4%), increased sweating (6% vs. 2%), and blurred vision (4% vs. 1%). Duloxetine can cause a small increase in blood pressure, and hence blood pressure should be measured at baseline and periodically thereafter. Some males experience sexual dysfunction (loss of libido, impotence). Duloxetine promotes mydriasis, and hence should not be used by patients with uncontrolled narrow-angle glaucoma. Weight gain has not been observed.

Liver toxicity is a concern. Elevation of serum transaminases, indicating liver damage, occurs in about 1% of patients. There have been reports of hepatitis, hepatomegaly, cholestatic jaundice, and elevation of transaminases to more than 20 times the upper limit of normal. To reduce risk, duloxetine should not be given to patients with pre-existing liver disease or to those who drink alcohol heavily.

As with venlafaxine, abrupt cessation of treatment can cause a withdrawal syndrome. Symptoms include nausea, vomiting, dizziness, headache, nightmares, and paresthesias. To minimize risk, duloxetine should be withdrawn slowly. Use of duloxetine late in pregnancy can lead to a withdrawal syndrome in the infant.

Like all other antidepressants, duloxetine may increase the risk of suicide, especially in children and young adults.

Effects in Pregnancy and Lactation.

Animal studies indicate that duloxetine interferes with fetal and postnatal development, causing reduced fetal weight, decreased postnatal survival, and neurologic disturbances. The drug is excreted in the milk of lactating rats. Studies in pregnant or lactating women have not been conducted. Until hu-

man data are available, use of duloxetine during pregnancy and lactation is not recommended.

Drug Interactions.

The combination of duloxetine with heavy alcohol consumption greatly increases the risk of liver damage. Accordingly, duloxetine should not be prescribed to heavy drinkers.

Like venlafaxine and other drugs that block 5-HT reuptake, duloxetine can cause serotonin syndrome if combined with an MAOI or any other serotonergic drug. MAOIs should be withdrawn at least 14 days before starting duloxetine, and duloxetine should be withdrawn at least 5 days before starting an MAOI.

Drugs that inhibit CYP1A2 or CYP2D6 (the P450 isozymes that metabolize duloxetine) can increase duloxetine levels, and may thereby cause toxicity. Inhibitors of CYP1A2 include cimetidine [Tagamet], fluvoxamine [Luvox], and ciprofloxacin [Cipro]. Inhibitors of CYP2D6 include fluoxetine [Prozac], paroxetine [Paxil], and quinidine [Quinidex].

Duloxetine is a moderate inhibitor of CYP2D6, and hence may raise levels of drugs that are extensively metabolized by this enzyme. Among these are certain TCAs (eg, amitriptyline, nortriptyline), type IC antidysrhythmics (propafenone [Rythmol] and flecainide [Tambocor]), and phenothiazines, including thioridazine [Mellaril]. Interaction with thioridazine is of special concern owing to a risk of serious ventricular dysrhythmias. Accordingly, the two drugs should not be combined.

Preparations, Dosage, and Administration.

Duloxetine is available in capsules (20, 30, and 60 mg) that should be swallowed whole, with or without food. The dosage range is 40 mg/day (given as 20 mg twice a day) to 60 mg/day (given as 60 mg once a day or 30 mg twice a day). When treatment is discontinued, dosage should be tapered slowly.

MONOAMINE OXIDASE INHIBITORS (MAOIs)

The MAOIs are second or third-choice antidepressants for most patients. Although these drugs are as effective as the tricyclics and SSRIs, they are more

dangerous. Of particular concern is the risk of triggering a hypertensive crisis by eating foods rich in tyramine. At this time, MAOIs are drugs of choice only for atypical depression. Three MAOIs—isocarboxazid [Marplan], phenelzine [Nardil], and tranylcypromine [Parnate]—are administered orally, and one MAOI—selegiline [Emsam]—is administered by transdermal patch.

Oral MAOIs

Mechanism of Action

Before discussing the MAOIs, we need to discuss MAO itself. MAO is an enzyme found in the liver, the intestinal wall, and terminals of monoamine-containing neurons. The function of MAO in neurons is to convert monoamine neurotransmitters—NE, 5-HT, and dopamine—into inactive products. In the liver and intestine, MAO serves to inactivate tyramine and other biogenic amines in food. In addition, these enzymes inactivate biogenic amines administered as drugs.

The body has two forms of MAO, named MAO-A and MAO-B. In the brain, MAO-A inactivates NE and 5-HT, whereas MAO-B inactivates dopamine. In the intestine and liver, MAO-A acts on dietary tyramine and other compounds. All of the MAOIs used for depression are *nonselective*. That is, at *therapeutic* doses, they inhibit both MAO-A and MAO-B. One agent—selegiline (used for depression *and* Parkinson's disease)—is selective for MAO-B at the low doses used for Parkinson's disease, but is nonselective at the higher doses used for depression.

Antidepressant effects of the MAOIs result from inhibiting MAO-A in nerve terminals (Fig. 32-3). By inhibiting intraneuronal MAO-A, these drugs increase the amount of NE and 5-HT available for release, and thereby intensify transmission at noradrenergic and serotonergic junctions.

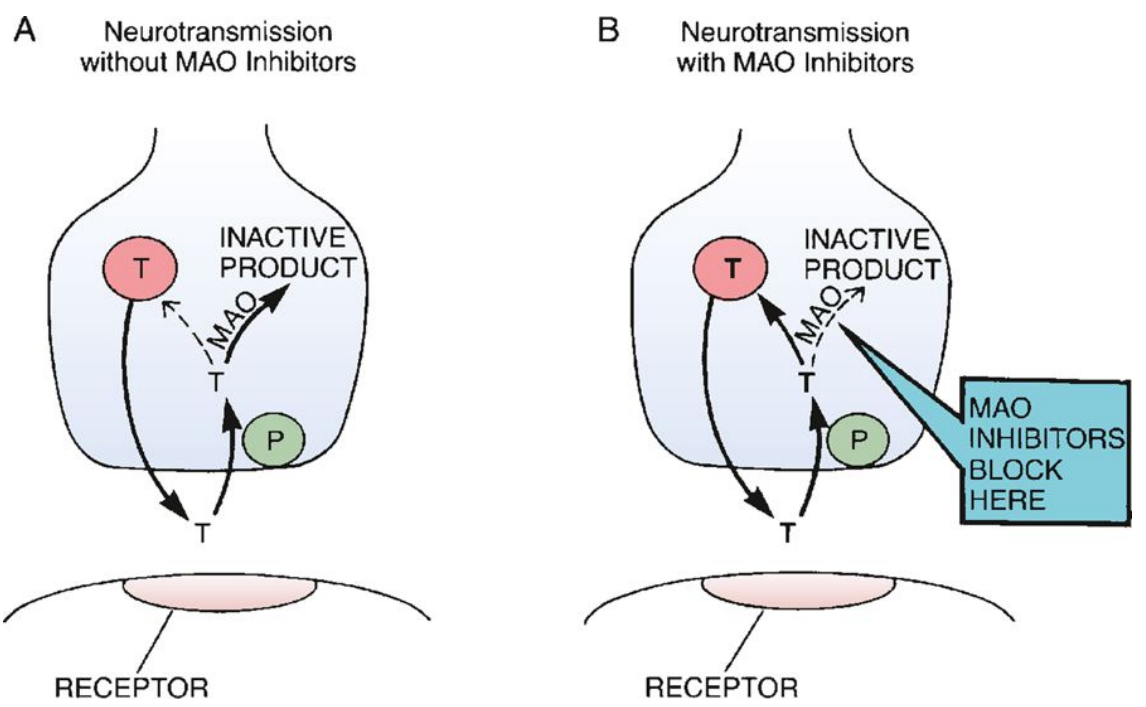


Figure 32-3 Mechanism of action of monoamine oxidase inhibitors. A, Under drug-free conditions, much of the norepinephrine or serotonin that undergoes reuptake into nerve terminals becomes inactivated by MAO. Inactivation helps maintain an appropriate concentration of transmitter within the terminal. B, MAO inhibitors prevent inactivation of norepinephrine and serotonin, thereby increasing the amount of transmitter available for release. Release of supranormal amounts of transmitter intensifies transmission. (MAO = monoamine oxidase, P = uptake pump, T = transmitter [norepinephrine or serotonin].)

Please note that antidepressant effects of the MAOIs cannot be fully explained by MAO inhibition alone. Why? Because the biochemical action of MAOIs (inhibition of MAO) takes place rapidly, whereas the clinical response to MAOIs (relief of depression) develops slowly. In the interval between initial inhibition of MAO and relief of depression, secondary neurochemical events must be taking place. It is these as-yet unknown events that are ultimately responsible for the beneficial response to treatment.

The MAOIs can act on MAO in two ways: reversibly and irreversibly. All of the MAOIs in current use cause *irreversible* inhibition. Since recovery from irreversible inhibition requires synthesis of new MAO molecules, effects of the irreversible inhibitors persist for about 2 weeks after drug withdrawal. In contrast, recovery from reversible inhibition is more rapid, occurring in 3 to 5 days.

Therapeutic Uses

Depression.

MAOIs are as effective as TCAs and SSRIs for relieving depression. However, because they can be hazardous, MAOIs are generally reserved for patients who have not responded to TCAs, SSRIs, and other safer drugs. Nonetheless, there *is* one group of patients—those with *atypical depression*—for whom MAOIs are the treatment of choice. As with other antidepressants, beneficial effects do not reach their peak for several weeks.

Other Psychiatric Uses.

MAOIs have been used with some success to treat *bulimia nervosa* and *obsessive-compulsive disorder*. Like TCAs and SSRIs, MAOIs can reduce *panic attacks* in patients with panic disorder.

Adverse Effects

CNS Stimulation.

In contrast to TCAs, MAOIs cause direct CNS stimulation (in addition to exerting antidepressant effects). Excessive stimulation can produce anxiety, insomnia, agitation, hypomania, and even mania.

Orthostatic Hypotension.

Despite their ability to increase the NE content of peripheral sympathetic neurons, the MAOIs *reduce blood pressure* when administered in usual therapeutic doses. Patients should be informed about signs of hypotension (dizziness, lightheadedness) and advised to sit or lie down if these occur. Also, they should be informed that hypotension can be minimized by moving slowly

when assuming an erect posture. For the hospitalized patient, blood pressure and pulse rate should be monitored on a regular schedule (eg, 4 times daily). These measurements should be taken while the patient is lying down and again after the patient has been sitting or standing for 1 to 2 minutes.

MAOIs lower blood pressure through actions in the CNS. The following sequence has been proposed: (1) Inhibition of MAO increases the NE content of neurons within the vasomotor center. (2) When NE is released, it binds to postsynaptic alpha receptors on neurons within the vasomotor center, thereby decreasing the firing rate of sympathetic nerves that control vascular tone. (3) This reduction in sympathetic activity results in vasodilation, causing blood pressure to fall.

Hypertensive Crisis from Dietary Tyramine.

Although the MAOIs normally produce *hypotension,* they can be the cause of severe *hypertension* if the patient eats food that is rich in *tyramine,* a substance that promotes the release of NE from sympathetic neurons. Hypertensive crisis is characterized by headache, tachycardia, hypertension, nausea, and vomiting.

Before considering the mechanism by which hypertensive crisis is produced, let's consider the effect of dietary tyramine under drug-free conditions. In the absence of MAO inhibition, dietary tyramine is not a threat. Much of the tyramine in food is metabolized by MAO in the intestinal wall. Furthermore, as shown in Figure 32-4A, any dietary tyramine that gets through the intestinal wall intact passes directly to the liver via the hepatic portal circulation. Once in the liver, tyramine is immediately inactivated by MAO there. Hence, as long as intestinal and hepatic MAO are functioning, dietary tyramine is prevented from reaching the general circulation, and therefore is devoid of adverse effects.

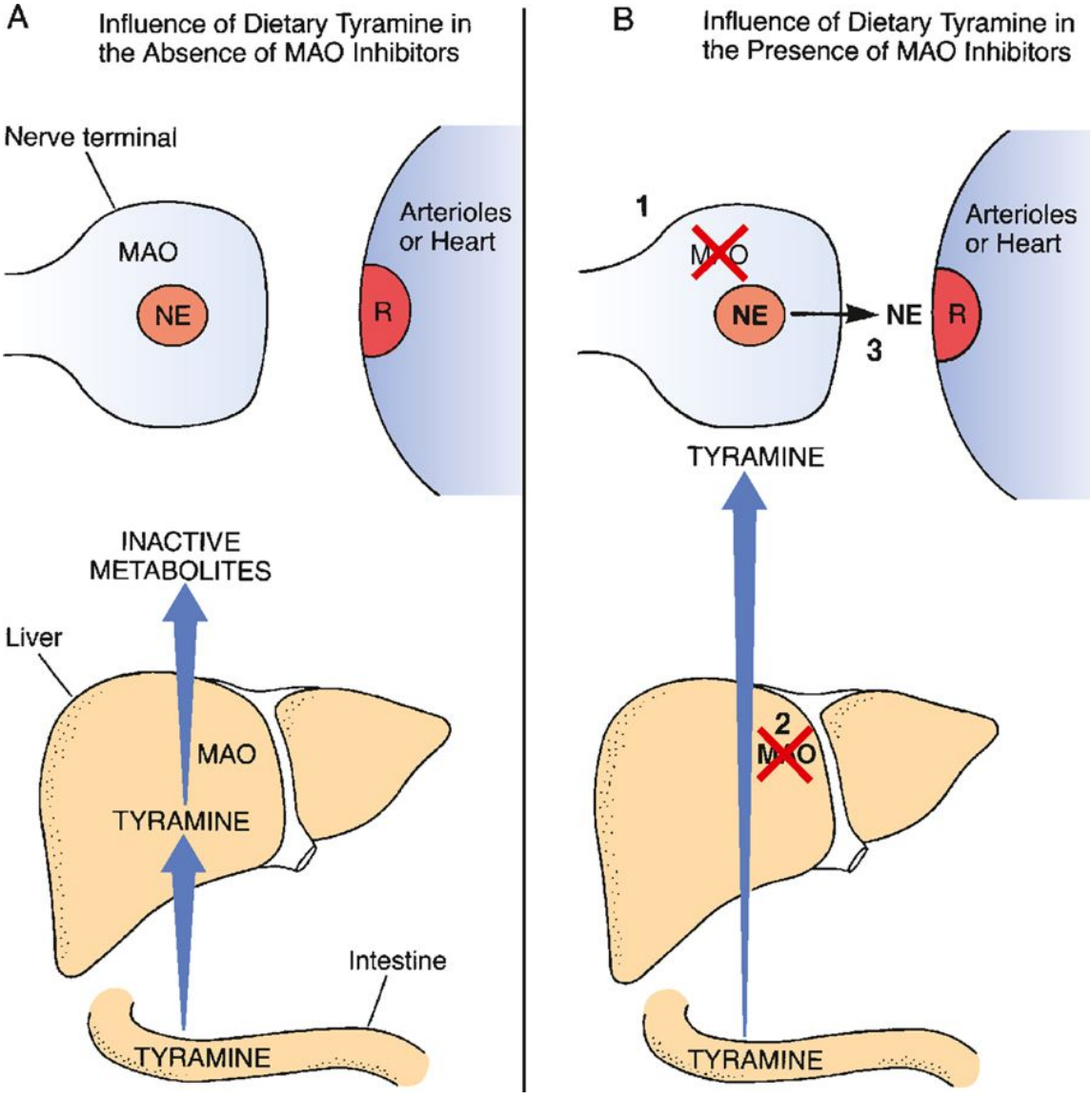


Figure 32-4 Interaction between dietary tyramine and MAOIs. A, In the absence of MAOIs, much of ingested tyramine is inactivated by MAO in the intestinal wall (not shown in the figure). Any dietary tyramine that is not metabolized in the intestinal wall is transported directly to the liver, where it undergoes immediate inactivation by hepatic MAO. No tyramine reaches the general circulation. B, Three events occur in the presence of MAOIs:

(1) Inhibition of neuronal MAO raises levels of norepinephrine in sympathetic nerve terminals. (2) Inhibition of intestinal and hepatic MAO allows dietary tyramine to pass through the intestinal wall and liver to enter the systemic circulation intact. (3) Upon reaching peripheral sympathetic nerve terminals, tyramine promotes the release of accumulated norepinephrine stores, thereby causing massive vasoconstriction and excessive stimulation of the heart. (MAO = monoamine oxidase, NE = norepinephrine, R = receptor for norepinephrine.)

In the presence of MAOIs, the picture is very different: dietary tyramine can produce a life-threatening hypertensive crisis. Three steps are involved (Fig. 32-4*B*). First, inhibition of *neuronal* MAO augments NE levels within the terminals of sympathetic neurons that regulate cardiac function and vascular tone. Second, inhibition of *intestinal* and *hepatic* MAO allows dietary tyramine to pass directly through the intestinal wall and liver, and then enter the systemic circulation intact. Third, upon reaching peripheral sympathetic nerves, tyramine stimulates the release of the accumulated NE, thereby causing massive vasoconstriction and excessive stimulation of the heart. Hypertensive crisis results. To reduce the risk of tyramine-induced hypertensive crisis, the following precautions must be taken:

- MAOIs must not be dispensed to patients considered incapable of rigid adherence to dietary restrictions.
- Before an MAOI is dispensed, the patient must be fully informed about the hazard of ingesting tyramine-rich foods.
- The patient must be given a detailed list of foods and beverages to avoid. These foods—which include yeast extracts, most cheeses, fermented sausages (eg, salami, pepperoni, bologna), and aged fish or meat—are listed in Table 32-6.

Foods That Contain Tyramine

Category	Unsafe Foods (High Tyramine Content)	Safe Foods (Little or No Tyramine)
Vegetables	Avocados, especially if overripe; fermented bean curd; fermented soybean; soybean paste	Most vegetables
Fruits	Figs, especially if overripe; bananas, in large amounts	Most fruits
Meats	Meats that are fermented, smoked, or otherwise aged; spoiled meats; liver, unless *very* fresh	Meats that are known to be fresh (exercise caution in restaurants; meat may not be fresh)
Sausages	Fermented varieties: bologna, pepperoni, salami, others	Nonfermented varieties
Fish	Dried or cured fish; fish that is fermented, smoked, or otherwise aged; spoiled fish	Fish that is known to be fresh; vacuum-packed fish, if eaten promptly or refrigerated only briefly after opening
Milk, milk products	Practically all cheeses	Milk, yogurt, cottage cheese, cream cheese
Foods with yeast	Yeast extract (eg, Marmite, Bovril)	Baked goods that contain yeast
Beer, wine	Some imported beers, Chianti wine	Major domestic brands of beer, most wines
Other foods	Protein dietary supplements; soups (may contain protein extract), shrimp paste; soy sauce	

Foods That Contain Nontyramine Vasopressors

Food	Comments

TABLE 32-6 Foods That Can Interact with MAO Inhibitors

- The patient should be instructed to avoid all drugs not specifically approved by the prescriber.

The patient should be educated about the symptoms of hypertensive crisis (headache, tachycardia, palpitations, nausea, vomiting) and instructed to seek immediate medical attention if these develop. In the event of hypertensive crisis, blood pressure can be lowered with IV *phentolamine,* a short-acting alpha-adrenergic antagonist; blood pressure declines because of vasodilation secondary to blockade of alpha***1*** receptors on blood vessels. Sublingual *nifedipine,* a calcium channel blocker, is an alternative; like IV phentolamine, sublingual nifedipine acts rapidly to promote vasodilation. Some authorities recommend that patients carry a 10-mg nifedipine capsule for use in emergencies.

In addition to tyramine, several other dietary constituents (eg, caffeine, phenylethylamine) can precipitate hypertension in patients taking MAOIs. Foods that contain these compounds are listed in Table 32-6. The patient should be instructed to avoid them.

Drug Interactions

The MAOIs can interact with many drugs to cause potentially disastrous results. Accordingly, patients should be instructed to avoid all medications—prescription agents and over-the-counter drugs—that have not been specifically approved by the prescriber.

Indirect-Acting Sympathomimetic Agents.

Indirect-acting sympathomimetics (eg, ephedrine, amphetamine) are drugs that promote the release of NE from sympathetic nerves. In patients taking MAOIs, these drugs can produce *hypertensive crisis*. The mechanism is the same as that described for tyramine. Patients should be instructed to avoid all sympathomimetic drugs, including ephedrine, methylphenidate, amphetamines, and cocaine. Sympathomimetic agents may be present in cold remedies, nasal decongestants, and asthma medications; all of these should be avoided unless approved by the prescriber.

Interactions Secondary to Inhibition of Hepatic MAO.

Inhibition of MAO in the liver can decrease the metabolism of several drugs, including epinephrine, NE, and dopamine. These drugs must be used with caution because their effects will be intensified and prolonged.

Tricyclic Antidepressants.

The combination of a TCA with an MAOI may produce hypertensive episodes or hypertensive crisis. As a result, this combination of antidepressants is not employed routinely. However, although potentially dangerous, the combination can benefit certain patients. If this combination is employed, caution must be exercised.

Serotonergic Drugs.

Combining MAOIs with SSRIs and other serotonergic drugs (see Table 32-5) poses a risk of serotonin syndrome. Accordingly, these combinations should be avoided.

Antihypertensive Drugs.

Combined use of MAOIs and antihypertensive agents may result in excessive lowering of blood pressure. This response should be no surprise considering that MAOIs, by themselves, can cause hypotension.

Meperidine.

Meperidine [Demerol] can cause hyperpyrexia (excessive elevation of temperature) in patients receiving MAOIs. Accordingly, if a strong analgesic is required, an agent other than meperidine should be chosen. Furthermore, the analgesic should be administered in its lowest effective dosage.

Preparations, Dosage, and Administration

Three oral MAOIs are available. Formulations are as follows: isocarboxazid [Marplan], 10-mg tablets; phenelzine [Nardil], 15-mg tablets; and tranylcypromine [Parnate], 10-mg tablets. Dosages are presented in Table 32-3.

Transdermal MAOI: Selegiline

Transdermal selegiline [Emsam], approved in 2006, is the first transdermal treatment for major depression. An oral formulation, available for decades, is

approved for Parkinson's disease (see Chapter 21). At the blood levels achieved during oral therapy of Parkinson's disease, selegiline produces selective inhibition of MAO-B. However, at the blood levels achieved with transdermal therapy of depression, this selectivity is lost, and hence the drug inhibits MAO-A as well as MAO-B. Like other MAOIs, selegiline should be reserved for patients who have not responded to preferred antidepressant drugs.

The pharmacology of transdermal selegiline is much like that of the oral MAOIs, but with one important difference: The risk of hypertensive crisis from dietary tyramine is much lower with transdermal dosing than with oral dosing. Why? Because with transdermal dosing, selegiline enters the systemic circulation without first passing through the GI tract. As a result, it can achieve therapeutic levels in the CNS while preserving activity of MAO-A in the intestinal wall and liver. Therefore, dietary tyramine will be destroyed before it can promote NE release in the periphery. Clinical trials have shown that restricting dietary tyramine is unnecessary with low-dose selegiline (24 mg/24 hr). However, owing to a lack of data, tyramine restriction *is* recommended at higher selegiline doses. Furthermore, with *all* doses of selegiline, sympathomimetic drugs (eg, phenylephrine, ephedrine, pseudoephedrine, amphetamines) are still be able to promote NE release, and hence must be avoided, just as they must be with *oral* MAOIs.

Two drugs—carbamazepine [Tegretol] and oxcarbazepine [Trileptal]—can significantly raise levels of selegiline. Accordingly, these drugs are contraindicated during selegiline therapy.

The most common adverse reaction is localized rash, which develops in about one-third of patients. Rash can be managed with topical glucocorticoids.

Selegiline transdermal patches are available in three strengths, delivering 6, 9, and 12 mg over 24 hours. Application is done every 24 hours to intact, dry skin of the upper torso, upper thigh, or outer surface of the upper arm. The recommended starting dose is 6 mg/24 hr. If necessary, dosage may be increased to 9 mg/24 hr, and then to 12 mg/24 hr after a minimum of 2 weeks at the lower dose.

ATYPICAL ANTIDEPRESSANTS

Bupropion

Actions and Uses.

Bupropion [Wellbutrin, Aplenzin, Budeprion] is a unique antidepressant similar in structure to amphetamine. Like amphetamine, bupropion has stimulant actions and suppresses appetite. Antidepressant effects begin in 1 to 3 weeks and equal those of amitriptyline (a TCA). The mechanism by which depression is relieved is unclear, but may be related to blockade of dopamine uptake. The drug does not affect serotonergic, cholinergic, or histaminergic transmission. In contrast to SSRIs, bupropion does not cause weight gain or sexual dysfunction. In fact, it appears to *increase* sexual desire and pleasure—hence bupropion has been used to (1) counteract sexual dysfunction in patients taking SSRIs, and (2) heighten sexual interest in women with hypoactive sexual desire disorder. Because of its efficacy and side effect profile, bupropion is a good alternative to SSRIs for patients who cannot tolerate SSRI side effects. The most serious adverse effect is seizures, which can occur when dosage is too high. Bupropion has two antidepressant indications: (1) major depressive disorder and (2) *prevention* of seasonal affective disorder (SAD). In addition to its use in depression, bupropion is approved as an aid to quit smoking (see Chapter 39). Unlabeled uses include relief of neuropathic pain and management of attention-deficit/hyperactivity disorder.

Adverse Effects.

Bupropion is generally well tolerated, but can cause seizures. The most common adverse effects are agitation (31%), headache (27%), dry mouth (27%), constipation (26%), weight loss (23%), GI upset (22%), dizziness (21%), tremor (21%), insomnia (19%), blurred vision (15%), and tachycardia (11%). Like other antidepressants, bupropion may increase the risk of suicide in children, adolescents, and young adults.

At doses greater than 450 mg/day, bupropion produces seizures in about 0.4% of patients. The risk is greatly increased in patients with predisposing factors, such as head trauma, pre-existing seizure disorder, CNS tumor, and use of other drugs that lower seizure threshold. Careful dosing reduces seizure risk.

Drug Interactions.

MAOIs can increase the risk of bupropion toxicity. Accordingly, patients should discontinue MAOIs at least 2 weeks before starting bupropion.

Preparations, Dosage, and Administration.

Preparations for Depression.

For treatment of depression, bupropion is available as two salts: bupropion hydrochloride and bupropion hydrobromide. Bupropion *hydrochloride* is available in immediate-release tablets (75 and 100 mg) as *Wellbutrin,* sustained-release tablets (100, 150, and 200 mg) as *Wellbutrin SR,* and extended-release tablets (150 and 300 mg) as *Wellbutrin XL* and *Budeprion XL.** Bupropion *hydrobromide* is available in extended-release alcohol-resistant tablets (174, 348, and 522 mg) as *Aplenzin.*

* Some patients who have switched from Wellbutrin XL to the generic Budeprion XL have reported worsening of side effects and relapse of previously controlled depressive symptoms. Whether these experiences are due to differences in the formulations or are just a coincidence has not been established.

Preparations for Smoking Cessation.

Bupropion hydrochloride marketed for smoking cessation is available in 150-mg sustained-release tablets sold as *Zyban.* Dosages are presented in Chapter 39.

Dosage for Major Depression.

Dosing must be done carefully to minimize the risk of seizures. Dosage escalation should be done slowly. The dosing schedule depends on the formulation being used. With the immediate-release tablets, the initial dosage is 75 mg twice a day. After 4 days, the dosage can be increased to 100 mg 3 times a day. If necessary, the dosage can be increased to a maximum of 150 mg 3 times a day. For maintenance therapy, once-daily dosing with Wellbutrin XL, Budeprion XL, or Aplenzin are attractive options.

Dosage for Seasonal Affective Disorder.

To prevent SAD, dosing should begin in the fall—using Wellbutrin XL—and taper off in the spring. The dosage is 150 mg/day initially, and can later increase to 300 mg/day, if needed.

Other Atypical Antidepressants

Nefazodone

Nefazodone, formerly available as *Serzone,* is a novel drug indicated only for depression. Neuropharmacologic actions include blockade of 5-HT2 receptors and alpha1-adrenergic receptors, and weak inhibition of NE and 5-HT reuptake. The contribution of these actions to therapeutic effects is unknown. Life-threatening liver failure is the adverse effect of greatest concern.

Nefazodone is rapidly and completely absorbed following oral administration. Food delays absorption and decreases bioavailability by 20%. Plasma drug levels peak about 1 hour after oral dosing. In the liver, nefazodone undergoes conversion to three active metabolites. The effective half-life of the parent drug and metabolites is 11 to 24 hours.

Nefazodone is generally well tolerated. The most common side effects are sedation, headache, somnolence, dry mouth, nausea, dizziness, blurred vision, and other visual disturbances. Weight gain and sexual dysfunction are minimal.

Nefazodone can cause life-threatening liver failure. However, the incidence is extremely low: only 1 case leading to death or liver transplantation for every 250,000 to 300,000 patient-years. As a rule, nefazodone should not be given to patients with pre-existing liver disease. Patients who develop signs of liver injury (eg, nausea, anorexia, abdominal pain, malaise, jaundice) should seek immediate medical attention. If laboratory tests confirm hepatocellular injury, nefazodone should be withdrawn.

Drugs that block uptake of 5-HT, NE, or both can cause serious reactions if combined with an MAOI. Accordingly, nefazodone and MAOIs must not be combined. If the patient has been taking an MAOI, it should be discontinued at least 2 weeks before starting nefazodone. Conversely, when switching from nefazodone to an MAOI, nefazodone should be discontinued at least 7 days before starting the MAOI.

Nefazodone inhibits hepatic drug-metabolizing enzymes, and can thereby raise levels of other drugs. When present at high levels, terfenadine or astemizole (two nonsedating antihistamines no longer available in the United States) can cause fatal ventricular dysrhythmias. Accordingly, since nefazodone can raise levels of these drugs, it must not be combined with either one.

Nefazodone is available in tablets (50, 100, 150, 200, and 250 mg) for oral use. Dosing is begun at 100 mg twice daily. If needed, the dosage can be gradually increased to between 150 and 300 mg twice daily. For elderly patients, dosing is begun at 50 mg twice daily; the usual effective range is 50 to 200 mg twice daily.

Mirtazapine

Mirtazapine [Remeron] is the first representative of a new class of antidepressants. Benefits appear to result from increased *release* of 5-HT and NE. The mechanism is blockade of presynaptic alpha***2***-adrenergic receptors that serve to inhibit release. In addition to promoting transmitter release, mirtazapine is a powerful blocker of two serotonin receptor subtypes: 5-HT***2*** and 5-HT***3***. The contribution of this effect is unclear. Mirtazapine blocks histamine receptors, and thereby promotes sedation and weight gain. Antidepressant effects equal those of SSRIs and may develop faster.

Mirtazapine is well absorbed following oral administration and reaches peak plasma levels in 2 hours. The drug undergoes extensive hepatic metabolism followed by excretion in the urine (75%) and feces (25%). The elimination half-life is 20 to 40 hours.

Mirtazapine is generally well tolerated. Somnolence is the most prominent adverse effect, occurring in 54% of patients. Weight gain, increased appetite, and elevated cholesterol are also common. Sexual dysfunction is minimal. Reversible agranulocytosis and neutropenia occur rarely. Blockade of muscarinic receptors is moderate, and hence anticholinergic effects are mild. Mirtazapine-induced somnolence can be exacerbated by alcohol, benzodiazepines, and other CNS depressants. Accordingly, these agents should be avoided. Mirtazapine should not be combined with MAOIs.

Mirtazapine is available in standard tablets (7.5, 15, 30, and 45 mg) under the trade name *Remeron,* and in orally disintegrating tablets (15, 30, and 45 mg) under the trade name *Remeron SolTab*. The initial dosage is 15 mg once a day at bedtime. Dosage may be gradually increased to a maximum of 45 mg/day.

Amoxapine

Amoxapine, formerly available as *Asendin,* is chemically related to the antipsychotic agent loxapine, and has both antidepressant and neuroleptic properties. Antidepressant effects are equivalent to those of the TCAs. Because it can cause serious side effects, amoxapine should be reserved for patients with psychotic depression.

Amoxapine is generally well tolerated. Anticholinergic and sedative effects are moderate. Following overdose, the risk of seizures is greater than with TCAs. Exercise caution in patients with epilepsy.

Like loxapine and the other antipsychotics, amoxapine can block receptors for dopamine. As a result, the drug can cause extrapyramidal side effects (eg, parkinsonism, akathisia). Because of the risk of tardive dyskinesia (an extrapyramidal effect that develops with prolonged use of dopamine antagonists), long-term use of amoxapine should generally be avoided.

Amoxapine is available in tablets (25, 50, 100, and 200 mg). The usual dosage for depression is 200 to 300 mg/day.

Reboxetine

Reboxetine [Vestra] is the first representative of a new class of antidepressants: the *selective norepinephrine reuptake inhibitors*. The drug is not related chemically to TCAs, MAOIs, SSRIs, or SNRIs. Biochemical effects are limited almost entirely to enhancing transmission at receptors for NE. The drug has little or no impact on receptors for 5-HT, dopamine, acetylcholine, or histamine. Reboxetine is available in 50 countries, but not in the United States.

In clinical trials, antidepressant effects were comparable to those of TCAs and fluoxetine [Prozac], an SSRI. With short-term use, reboxetine induced remission and, with long-term use, prevented relapse. Because reboxetine is a new drug, its therapeutic niche has not been established. However, available data

suggest that it may be especially good for patients with severe depression and for those in whom social functioning is severely impaired.

Reboxetine is rapidly absorbed following oral administration. Plasma levels peak within 2 hours. High-fat meals reduce the rate of absorption, but not the extent. Reboxetine undergoes extensive hepatic metabolism followed by excretion in the urine. The drug's half-life is 12 to 16 hours, but may be prolonged in patients with liver dysfunction.

Reboxetine is generally well tolerated. The most common side effects are dry mouth, hypotension, constipation, urinary hesitancy or retention, and decreased libido. Other effects include dizziness, headache, nausea, insomnia, tremor, diaphoresis, and tachycardia. Reboxetine does not cause sedation or weight gain, and has minimal effects on psychomotor or cognitive function.

Combining reboxetine with an MAOI may pose a risk of hypertensive crisis. Accordingly, MAOIs should be withdrawn at least 14 days before giving reboxetine.

The recommended starting dosage is 4 mg twice daily. In patients with liver dysfunction, the initial dosage should be reduced to 2 mg twice daily. In clinical trials, dosages ranged between 4 and 12 mg/day.

Trazodone

Trazodone, formerly available as *Desyrel,* is a second-line agent for depression. The drug is not very effective when used alone, but, because of its pronounced sedative effects, can be a helpful adjunct for patients with antidepressant-induced insomnia. Trazodone produces selective (but moderate) blockade of 5-HT reuptake. Antidepressant effects take several weeks to develop.

Common side effects are sedation, orthostatic hypotension, and nausea. In contrast to the tricyclic agents, trazodone has minimal anticholinergic actions and is not cardiotoxic. Accordingly, trazodone may be useful for elderly patients and other individuals for whom the cardiac and anticholinergic effects of the tricyclics may be intolerable.

Trazodone can cause priapism (prolonged, painful erection). In some cases, surgical intervention has been required. Priapism itself or the procedures required for relief can result in permanent impotence. Patients should be in-

structed to notify their prescriber or to go to an emergency department if persistent erection occurs. Prolonged clitoral erection can also occur, but the incidence is extremely low (0.016%).

Overdose with trazodone is considered safer than with TCAs or MAOIs. Death from overdose with trazodone alone has not been reported (although death has occurred following overdose with trazodone in combination with another CNS depressant).

Drugs that inhibit CYP3A4 (the 3A4 isozyme of cytochrome P450) can decrease metabolism of trazodone, and thereby increase its concentration. Toxicity may result. Accordingly, if trazodone is combined with a strong CYP3A4 inhibitor (eg, ketoconazole, ritonavir), dosage of trazodone should be reduced.

Trazodone is available in tablets (50, 100, 150, and 300 mg). The initial dosage is 150 mg/day in divided doses. Dosage may be gradually increased to a maximum of 400 mg/day (for outpatients) and 600 mg/day (for hospitalized patients).

NONDRUG THERAPY OF DEPRESSION

Electroconvulsive Therapy

Although outside the realm of pharmacology, ECT is a valuable treatment for depression and deserves our consideration. Success requires a series of treatments, typically three per week for 2 to 4 weeks. Since ECT as practiced today does not cause convulsions, a more appropriate name might be *electroshock therapy*.

ECT has two characteristics that are especially desirable: *effectiveness* and *rapid onset* (relative to antidepressant drugs). Because of these properties, ECT is indicated primarily for two types of patients: (1) those who have failed to respond to pharmacologic treatment for depression (50% to 60% will respond to ECT), and (2) severely depressed, suicidal patients who need rapid relief of symptoms.

Thanks to the adjunctive use of drugs, ECT is much less dramatic and traumatic than in the past. Prior to the delivery of electroshock, patients are treated with a combination of *thiopental* and *succinylcholine*. Thiopental is an injectable, ultrashort-acting anesthetic that prevents conscious awareness of the

ECT procedure (without interfering with beneficial actions). Succinylcholine is a short-acting neuromuscular blocker that prevents shock-induced convulsive movements, which are both hazardous and unnecessary for a therapeutic response.

ECT can terminate an ongoing depression episode, but a single series of treatments cannot prevent recurrence. Accordingly, some patients are now given "maintenance" treatments, at weekly or monthly intervals. In one study, the relapse rate at 6 months in the absence of maintenance was 73%, compared with only 8% when maintenance ECT was used. Maintenance with antidepressant drugs (eg, lithium plus amitriptyline) is another option, but appears significantly less effective than maintenance with ECT.

The principal adverse effect of ECT is some loss of memory for events immediately surrounding treatment. Patients do not lose other memories. There is also transient impairment of cognitive function. Minor adverse effects, which occur immediately after treatment, include nausea, headache, confusion, and muscle discomfort.

Vagus Nerve Stimulation

In 2005, the Food and Drug Administration (FDA) approved the Vagus Nerve Stimulation (VNS) Therapy System for adjunctive, long-term therapy of patients with "treatment-resistant depression" (TRD), which the manufacturer defines as major depression that has not responded to at least four different antidepressant drugs. The VNS Therapy System—an implanted device that delivers electrical pulses to the vagus nerve—was first developed to treat drug-resistant epilepsy. In the course of that research, mood elevation was observed in some patients. A trial was then conducted in patients with TRD. However, the results were equivocal, and led the FDA review team to request more data. The data never came, but the device was approved anyway—thanks to the intervention of Daniel Schultz, director of the FDA's Center for Devices and Radiological Health, who overruled his own team of reviewers. So, depending on who you believe, the device works, or it doesn't. Nonetheless, it's still available for use. The mechanism by which VNS alleviates depression (if it really does) is unknown. The principal side effects of VNS are hoarseness, voice alteration, cough, and dyspnea, all of which tend to diminish over time. The cost of the VNS system along with surgical implantation and calibration is about $25,000.

The VNS Therapy System and its use in epilepsy are discussed further in Box 24-1 (Nondrug Therapies for Epilepsy).

KEY POINTS

- The principal symptoms of major depression are depressed mood and loss of pleasure or interest in one's usual activities and pastimes.
- Patients with mild depression can be treated equally well with antidepressant drugs or psychotherapy. Patients with severe depression respond better to a combination of drugs plus psychotherapy than to either intervention alone.
- Patients with depression often think about or attempt suicide. During treatment with antidepressants, especially initially, the risk of suicide may *increase*. To reduce the risk of suicide, patients should be followed closely by family members, caregivers, and the prescriber. Suicide risk is greatest in children and young adults.
- Therapeutic responses to antidepressants develop slowly. Initial responses develop in 1 to 3 weeks. Maximal responses develop in 1 to 2 months.
- Antidepressant therapy should continue for 6 months to 1 year after symptoms have abated.
- CAs block reuptake of NE and 5-HT, and thereby intensify transmission at noradrenergic and serotonergic synapses. Over time, this induces adaptive cellular responses that are ultimately responsible for relieving depression.
- The most common adverse effects of TCAs are sedation, orthostatic hypotension, and anticholinergic effects (eg, dry mouth, constipation).
- The most serious adverse effect of TCAs is cardiotoxicity, which can be lethal if an overdose is taken.

•TCAs can cause a hypertensive crisis if combined with an MAOI. Accordingly, the combination is generally avoided.

- CAs intensify responses to direct-acting sympathomimetics (eg, epinephrine) and diminish responses to indirect-acting sympathomimetics (eg, amphetamine).
- SSRIs block reuptake of serotonin, and thereby intensify transmission at serotonergic synapses. Over time, this induces adaptive cellular responses that are ultimately responsible for relieving depression.
- SSRIs have two major advantages over TCAs: they cause fewer side effects and are safer when taken in overdose.
- Most SSRIs have stimulant properties, and hence can cause insomnia and agitation. This contrasts with TCAs, which cause sedation.
- Like most other antidepressants, SSRIs can cause weight gain.
- Sexual dysfunction (eg, impotence, anorgasmia) is more common with SSRIs than with most other antidepressants.
- SSRIs can cause serotonin syndrome, especially when combined with MAOIs and other serotonergic drugs. Symptoms include agitation, confusion, hallucinations, hyperreflexia, tremor, and fever.
- MAOIs increase neuronal stores of NE and 5-HT, and thereby intensify transmission at noradrenergic and serotonergic synapses. Over time, this induces adaptive cellular responses that are ultimately responsible for relieving depression.
- MAOIs are as effective as TCAs and SSRIs, but are much more dangerous.
- MAOIs are first-choice drugs only for patients with atypical depression.
- Like SSRIs (and unlike TCAs), MAOIs cause direct CNS stimulation.
- Like TCAs (and unlike SSRIs), MAOIs cause orthostatic hypotension.
- Patients taking MAOIs must not eat tyramine-rich foods because hypertensive crisis can result.
- MAOIs must not be combined with indirect-acting sympathomimetics (eg, ephedrine, amphetamine) because hypertensive crisis can result.
- MAOIs must not be combined with SSRIs and other serotonergic drugs because serotonin syndrome could result.

- ECT relieves depression faster than antidepressant drugs, and often helps when antidepressants have failed.
- ECT as practiced today is safer and less traumatic than in the past, owing to adjunctive use of thiopental (which produces unconsciousness) and succinylcholine (which prevents convulsions).

Summary of Major Nursing Implications*

IMPLICATIONS THAT APPLY TO ALL ANTIDEPRESSANTS

Psychologic Assessment

Observe and record the patient's behavior. Factors to assess include affect, thought content, interest in the environment, appetite, sleep patterns, and appearance.

Reducing the Risk of Suicide

Depression carries a risk of suicide, which may increase during the initial phase of antidepressant therapy or when antidepressant dosage is changed. The risk is greatest among children and young adults. **Advise family members and caregivers to monitor for symptoms of clinical decline (eg, anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, hypomania, and emergence of suicidal thoughts), and to immediately report symptoms that are severe or develop abruptly.** To help reduce suicide risk, the patient or caregiver should meet with the prescriber at least weekly during the first 4 weeks of treatment, then biweekly for the next 4 weeks, then once 1 month later, and periodically thereafter.

Patients who are so depressed that they are a risk to themselves and others should be hospitalized until symptoms are under control. Suicide potential should be evaluated carefully. To prevent patients from accumulating a potentially lethal supply of medication, ensure that each dose is swallowed and not cheeked. Provide outpatients with no more than a 1-week supply of medication at a time. For patients considered at high risk of suicide, TCAs and MAOIs should be avoided; SSRIs are much safer.

Promoting Adherence

Inform the patient that antidepressant effects usually develop slowly, over 1 to 3 weeks. This knowledge will make expectations more realistic, which should help promote adherence.

Premature discontinuation of therapy can result in relapse. **Educate patients about the importance of taking their medication as prescribed, even though they may be symptom free and therefore feel "cured."** In general, treatment should continue for 6 months to a year after symptoms have subsided.

Nondrug Therapy

For patients with severe depression, treatment with drugs alone is not optimal. Emotional support and psychotherapy can complement and reinforce responses to antidepressants. ECT may be indicated for suicidal patients and for patients who fail to respond to antidepressant drugs and psychotherapy. As a last resort, vagus nerve stimulation can be tried.

Evaluating Therapeutic Effects

Assess patients for improvement in symptoms, especially depressed mood and loss of interest or pleasure in usual activities.

TRICYCLIC ANTIDEPRESSANTS

Amitriptyline

Clomipramine

Desipramine

Doxepin

Imipramine

Maprotiline

Nortriptyline

Protriptyline

Trimipramine

In addition to the implications summarized below, see *Implications That Apply to All Antidepressants* above.

Preadministration Assessment

Therapeutic Goal

Alleviation of symptoms of major depression.

Baseline Data

Assess psychologic status. Arrange for an ECG, especially for patients with cardiac disease and those over 40.

Identifying High-Risk Patients

TCAs are generally *contraindicated* for patients taking MAOIs.

Use TCAs with *caution* in patients with cardiac disorders (eg, coronary heart disease, progressive heart failure, paroxysmal tachycardia), elevated intraocular pressure, urinary retention, hyperthyroidism, seizure disorders, and liver or kidney dysfunction.

Doxepin is *contraindicated* for patients with glaucoma or a tendency to urinary retention.

Maprotiline is *contraindicated* for patients with seizure disorders.

Implementation: Administration

Routes

Oral (usual); IM (occasional).

Administration

Instruct patients to take medication daily as prescribed and not PRN. Warn patients not to discontinue treatment once mood has improved, since doing so may result in relapse. Once an effective dosage has been established, the entire daily dose can usually be taken at bedtime.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Suicide Risk.

See *Implications That Apply to All Antidepressants*.

Orthostatic Hypotension.

Inform patients about symptoms of hypotension (dizziness, lightheadedness), and advise them to sit or lie down if these occur. Inform patients that hypotension can be minimized by moving slowly when assuming an erect posture. For hospitalized patients, monitor blood pressure and pulse rate on a regular schedule; take measurements while the patient is lying down and again after the patient has been sitting or standing for 1 to 2 minutes. If blood pressure is low or pulse rate is high, withhold medication and inform the prescriber.

Anticholinergic Effects.

Inform patients about possible anticholinergic effects (dry mouth, blurred vision, photophobia, urinary hesitancy, constipation, tachycardia), and advise them to notify the prescriber if these are troublesome. A detailed summary of nursing implications for anticholinergic drugs is presented in Chapter 14.

Diaphoresis.

TCAs promote sweating (despite their anticholinergic properties). Excessive sweating may necessitate frequent changes of bedding and clothing.

Sedation.

Sedation is most intense during the first weeks of therapy and declines with continued drug use. **Advise patients to avoid hazardous activities (eg, driving, operating dangerous machinery) if sedation is significant.** Giving TCAs at bedtime minimizes daytime sedation and promotes sleep.

Cardiotoxicity.

TCAs can disrupt cardiac function, but usually only when taken in excessive doses or by patients with heart disease. All patients should receive an ECG prior to treatment and periodically thereafter.

Seizures.

TCAs decrease seizure threshold. Exercise caution in patients with seizure disorders.

Hypomania.

TCAs may shift mood from depression up to hypomania. If hypomania develops, the patient must be evaluated to determine if elation is drug induced or indicates bipolar disorder.

Minimizing Adverse Interactions

MAO Inhibitors.

Rarely, the combination of a TCA and an MAOI has produced hypertensive episodes and hypertensive crisis. Exercise caution if this combination is employed.

Sympathomimetic Agents.

TCAs decrease the effects of indirect-acting sympathomimetics (eg, ephedrine, amphetamine), but potentiate the actions of direct-acting sympathomimetics (eg, epinephrine, dopamine). If sympathomimetics are to be used, these effects must be accounted for.

Anticholinergic Agents.

Drugs capable of blocking muscarinic receptors will enhance the anticholinergic effects of TCAs. **Warn patients against concurrent use of other anticholinergic drugs (eg, scopolamine, antihistamines, phenothiazines).**

CNS Depressants.

These will enhance the depressant effects of TCAs. **Warn patients against using alcohol and all other drugs with CNS-depressant properties (eg, opioids, antihistamines, barbiturates, benzodiazepines).**

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Citalopram

Escitalopram

Fluoxetine

Fluvoxamine

Paroxetine

Sertraline

In addition to the implications summarized below, see *Implications That Apply to All Antidepressants* above.

Preadministration Assessment

Therapeutic Goal

Alleviation of Symptoms of Major Depression.

All SSRIs except fluvoxamine are approved for treating depression.

Other Goals.

SSRIs are used to relieve symptoms of many psychologic disorders, including obsessive-compulsive disorder, panic disorder, social phobia, generalized anxiety disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, and bulimia nervosa (see Table 32-4).

Identifying High-Risk Patients

SSRIs are *contraindicated* for patients taking MAOIs, and should be used with *caution* in patients taking other serotonergic drugs. Use with *caution* in patients with liver disease and in the elderly and in women who are pregnant or breast-feeding.

Implementation: Administration

Route

Oral.

Administration

All SSRIs may be administered with food. Administration in the morning minimizes sleep disruption.

Warn patients not to discontinue treatment once mood has improved, since doing so could lead to relapse.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Suicide Risk.

See *Implications That Apply to All Antidepressants*.

CNS Stimulation.

Citalopram, *escitalopram, fluoxetine, paroxetine,* and *sertraline* can cause nervousness, insomnia, and anxiety. These reactions may respond to a decrease in dosage. (Fluvoxamine causes mild sedation.)

Serotonin Syndrome.

Symptoms of this potentially fatal syndrome include agitation, confusion, disorientation, anxiety, hallucinations, poor concentration, incoordination, myoclonus, hyperreflexia, excessive sweating, tremor, and fever. The risk is reduced by avoiding concurrent use of MAOIs and other serotonergic drugs (see Table 32-5). Serotonin syndrome resolves spontaneously after discontinuing the SSRI.

Sexual Dysfunction.

Inform patients about possible sexual dysfunction (anorgasmia, impotence, decreased libido), and encourage them to report problems. Management strategies include dosage reduction, drug holidays, adding a drug to counteract sexual dysfunction (eg, sildenafil, buspirone), and switching to an antidepressant that causes less sexual dysfunction (eg, bupropion, nefazodone, mirtazapine).

Dizziness and Fatigue.

Inform patients about possible dizziness and fatigue, and advise them to exercise caution while performing hazardous tasks (eg, driving).

Rash.

Fluoxetine may cause rash. **Inform patients about the risk of rash and instruct them to notify the prescriber if one develops.** Treatment consists of drug therapy (antihistamines, glucocorticoids) or withdrawal of fluoxetine.

Weight Gain.

Long-term therapy can result in significant weight gain. **Advise patients to restrict caloric intake and to get appropriate exercise.**

Neonatal Abstinence Syndrome (NAH) and Persistent Pulmonary Hypertension of the Newborn (PPHN).

Use of SSRIs late in pregnancy poses a small risk of NAS and PPHN. Newborns exposed to SSRIs *in utero* should be monitored for both disorders. If NAS occurs, it can be managed with supportive care, and generally abates within a few days. Treatment measures for PPHN include providing mechanical ventilatory support, giving inhaled nitric oxide and oxygen, and giving IV sodium bicarbonate and dopamine.

Teratogenesis.

One SSRI—*paroxetine*—poses a small risk of birth defects, especially ventral septal defects and other cardiovascular anomalies. Other SSRIs are preferred during pregnancy.

GI Bleeding.

SSRIs impair platelet aggregation, and can thereby increase the risk of GI bleeding. Exercise caution in elderly patients, patients with ulcers or a history of GI bleeding, and patients taking nonsteroidal anti-inflammatory drugs or anticoagulants.

Hyponatremia.

SSRIs can cause hyponatremia, primarily in older patients taking diuretics. When SSRIs and diuretics are used in older patients, serum sodium should be measured at baseline and periodically thereafter.

Bruxism.

SSRIs can cause bruxism (clenching and grinding of teeth), usually during sleep. **Alert patients to the sequelae of bruxism (headache, jaw pain, and dental problems, such as cracked fillings).** If these develop, investigate whether an SSRI is the cause. Bruxism can be managed by (1) a reduction in SSRI dosage (but then depression may return), (2) switching to a different class of antidepressants, (3) use of a mouth guard, and (4) treatment with low-dose buspirone.

Minimizing Adverse Interactions

Serotonergic Drugs.

Combining SSRIs with MAOIs and other serotonergic drugs increases the risk of serotonin syndrome. Withdraw MAOIs at least 14 days before starting an SSRI. Withdraw fluoxetine 5 weeks before starting an MAOI; withdraw other SSRIs at least 2 weeks before starting an MAOI.

TCAs and Lithium.

Fluoxetine can increase levels of these drugs. Exercise caution.

Nonsteroidal Anti-inflammatory Drugs and Anticoagulants.

These drugs increase the risk of GI bleeding. Exercise caution.

MONOAMINE OXIDASE INHIBITORS

Isocarboxazid

Phenelzine

Selegiline

Tranylcypromine

Preadministration Assessment

In addition to the implications summarized below, see *Implications That Apply to All Antidepressants* above.

Therapeutic Goal

Alleviation of symptoms of major depression, especially atypical depression.

Identifying High-Risk Patients

MAOIs are *contraindicated* for patients taking SSRIs; for patients with pheochromocytoma, heart failure, liver disease, severe renal impairment, cerebrovascular defect (known or suspected), cardiovascular disease, and hypertension; and for patients over the age of 60 (because of possible cerebral sclerosis associated with vessel damage).

Use with *caution* in patients taking serotonergic drugs.

Implementation: Administration

Route

Oral.

Isocarboxazid, phenelzine, tranylcypromine.

Transdermal.

Selegiline.

Administration

All MAOIs.

Instruct patients to take MAOIs every day as prescribed—not PRN. Warn patients not to discontinue treatment once mood has improved, since doing so may result in relapse.

Transdermal Selegiline.

Instruct patients to apply the Emsam patch to intact, dry skin of the upper torso, upper thigh, or outer surface of the upper arm once every 24 hours.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Suicide Risk.

See *Implications That Apply to All Antidepressants*.

Hypertensive Crisis.

Dietary tyramine, certain other dietary constituents (see Table 32-6), and indirect-acting sympathomimetics (eg, amphetamine, methylphenidate, ephedrine, cocaine) can precipitate a hypertensive crisis in patients taking MAOIs.

Inform patients about symptoms of hypertensive crisis (headache, palpitations, tachycardia, nausea, vomiting), and instruct them to seek immediate medical attention if these develop.

To reduce the risk of hypertensive crisis, the following precautions must be observed:

- Do not give MAOIs to patients who are suicidal or who are considered incapable of rigid adherence to dietary constraints.
- **Forewarn patients about the hazard of hypertensive crisis and the need to avoid tyramine-rich foods and sympathomimetic drugs.** (Patients on low-dose transdermal selegiline needn't avoid tyramine containing foods, but do need to avoid sympathomimetic drugs.)
- **Provide patients with a list of specific foods to avoid (see** Table 32-6).
- **Instruct them to avoid all drugs not approved by the prescriber.**

If hypertensive crisis develops, blood pressure can be lowered with IV phentolamine or sublingual nifedipine.

Orthostatic Hypotension.

Inform patients about signs of hypotension (dizziness, lightheadedness), and advise them to sit or lie down if these occur. Inform patients that hypotension can be minimized by moving slowly when assuming an erect posture. For the hospitalized patient, monitor blood pressure and pulse rate

on a regular schedule. Take these measurements while the patient is lying down and again after the patient has been sitting or standing for 1 to 2 minutes. If blood pressure is low, withhold medication and inform the prescriber.

Skin Rash.

Application-site rash is common with transdermal selegiline, and can be managed with a topical glucocorticoid.

Minimizing Adverse Interactions

All Drugs.

MAOIs can interact adversely with many other drugs. **Instruct the patient to avoid all medications—prescription and nonprescription—that have not been specifically approved by the prescriber.**

Indirect-Acting Sympathomimetics.

Concurrent use with MAOIs can precipitate a hypertensive crisis. **Warn patients against use of any indirect-acting sympathomimetics (eg, ephedrine, methylphenidate, amphetamines, cocaine).**

Tricyclic Antidepressants.

Concurrent use with MAOIs can produce hypertensive episodes and hypertensive crisis. Use this combination with caution.

Serotonergic Drugs.

Combining MAOIs with other serotonergic drugs (see Table 32-5) poses a risk of serotonin syndrome. Accordingly, these combinations should generally be avoided.

Antihypertensive Drugs.

These drugs will potentiate the hypotensive effects of MAOIs. If these agents are combined, monitor blood pressure periodically.

Meperidine.

Meperidine can produce hyperthermia in patients taking MAOIs and hence should be avoided.

33 Drugs for Bipolar Disorder

Our topic for this chapter is bipolar disorder (BPD), formerly known as *manic-depressive illness*. The disease afflicts an estimated 3.7% of the adult population—more than 6.7 million Americans. The mainstays of therapy are lithium and valproic acid, drugs with the ability to stabilize mood. Many patients also receive an antipsychotic, and some may require an antidepressant. Bipolar disorder is a chronic condition that requires treatment lifelong.

CHARACTERISTICS OF BIPOLAR DISORDER

Bipolar disorder is a severe biologic illness characterized by recurrent fluctuations in mood. Typically, patients experience alternating episodes in which mood is abnormally elevated or abnormally depressed—separated by periods in which mood is relatively normal. Symptoms usually begin in adolescence or early adulthood, but can occur before adolescence or as late as the fifth decade of life. In the absence of treatment, episodes of mania or depression generally persist for several months. As time passes, manic and depressive episodes tend to recur more frequently. Although the precise etiology of BPD is unknown, it is clear that symptoms are caused by altered brain physiology—not by a character flaw or an unstable personality.

Types of Mood Episodes Seen in BPD

Patients with BPD may experience four types of mood episodes. These are described below.

Pure Manic Episode (Euphoric Mania).

Manic episodes are characterized by persistently heightened, expansive, or irritable mood—typically associated with hyperactivity, excessive enthusiasm, and flight of ideas. Manic individuals display overactivity at work and at play and have a reduced need for sleep. Mania produces excessive sociability and talkativeness. Extreme self-confidence, grandiose ideas, and delusions of self-importance are common. Manic individuals often indulge in high-risk activities (eg, questionable business deals, reckless driving, gambling, sexual indiscretions), giving no forethought to the consequences. In severe cases, symptoms

may resemble those of paranoid schizophrenia (hallucinations, delusions, bizarre behavior). Specific diagnostic criteria for a manic episode, as described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* are summarized in Table 33-1.

Hypomanic Episode (Hypomania).

Hypomania can be viewed as a mild form of mania. As in mania, mood is persistently elevated, expansive, or irritable. However, symptoms are not severe enough to cause marked impairment in social or occupational functioning, or to require hospitalization. Psychotic symptoms are absent.

Major Depressive Episode (Depression).

A major depressive episode is characterized by depressed mood and loss of pleasure or interest in all or nearly all of one's usual activities and pastimes. Associated symptoms include disruption of sleeping and eating patterns; difficulty concentrating; feelings of guilt, worthlessness, and helplessness; and thoughts of death and suicide. The characteristics of major depression are discussed further in Chapter 32.

Mixed Episode.

In a true mixed episode, patients experience symptoms of mania and depression simultaneously. Patients may be agitated and irritable (as in mania), but may also feel worthless and depressed. The combination of high energy and depression puts them at significant risk of suicide.

Patterns of Mood Episodes

Among people with BPD, mood episodes can occur in a variety of patterns. Contrary to popular belief, not all patients alternate repeatedly between mania and depression. Some experience repeated episodes of mania, and some experience repeated episodes of depression (with an occasional episode of mania). Mood may be normal between episodes of mania and depression, or it may be slightly elevated (hypomania) or slightly depressed (dysphoria).

Mood episodes can vary greatly with respect to duration and how often they occur. A single episode may last for days, weeks, months, or more than a year. In the absence of treatment, episodes of mania or hypomania typically last

a few months, whereas episodes of major depression typically last at least 6 months. On average, people with BPD experience only 4 episodes during the first 10 years of their illness. However, some people cycle much more rapidly, experiencing many episodes every year.

TABLE 33-1 DSM-IV-TR Criteria for a Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

- Inflated self-esteem or grandiosity
- Decreased need for sleep (eg, feels rested after only 3 hours of sleep)
- More talkative than usual or pressure to keep talking
- Flight of ideas or subjective experience that thoughts are racing
- Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli)
- Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
- Excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The symptoms are not due to the direct physiologic effects of a substance (eg, a drug of abuse, a medication, or other treatment) or a general medical condition (eg, hyperthyroidism).*

Modified from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Press, 2000, with permission. Copyright © 2000 American Psychiatric Association.

* Manic-like episodes that are clearly caused by somatic antidepressant treatment (eg, medication, electro-convulsive therapy, light therapy) should not count toward a diagnosis of bipolar disorder.

On the basis of mood episode type and frequency, BPD can be subdivided into three major categories:

- *Bipolar I Disorder*—Patients experience manic or mixed episodes, and usually depressive episodes too.
- *Bipolar II Disorder*—Patients experience hypomanic or depressive episodes, but not manic or mixed episodes.
- *Rapid-Cycling Bipolar Disorder*—Patients experience four or more episodes of any sort (manic, hypomanic, depressive, mixed) each year.

Etiology

Theories regarding the etiology of BPD continue to evolve. In the past, there was general agreement that BPD was due primarily to an imbalance in neurotransmitters. Today, researchers suspect the real cause may be disruption of neuronal growth and survival. Why? First, neuroimaging studies have shown an association between prolonged mood disorders and atrophy of specific brain regions—especially the subgenual prefrontal cortex, an area involved in emotionality. Second, mood-stabilizing drugs can prevent or reverse neuronal atrophy in patients with BPD, apparently by influencing signaling pathways that regulate neuronal growth and survival.

TREATMENT OF BIPOLAR DISORDER

Drug Therapy

Types of Drugs Employed

Bipolar disorder is treated with three major groups of drugs: mood stabilizers, antipsychotics, and antidepressants. In addition, benzodiazepines are frequently used for sedation.

Mood Stabilizers.

Mood stabilizers are drugs that (1) relieve symptoms during manic and depressive episodes, (2) prevent recurrence of manic and depressive episodes,

and (3) do not worsen symptoms of mania or depression, or accelerate the rate of cycling. The principal mood stabilizers are *lithium* and two drugs originally developed for epilepsy: *valproic acid* (and its derivatives), and *carbamazepine*. These drugs are the mainstays of treatment. The pharmacology of lithium and the antiepileptic drugs is discussed below.

Antipsychotics.

In patients with BPD, antipsychotic drugs are given to help control symptoms during severe manic episodes, even if psychotic symptoms are absent. Although antipsychotics can be used alone, they are usually employed in combination with a mood stabilizer. For reasons discussed below, the atypical antipsychotics (eg, olanzapine, risperidone) are preferred to traditional antipsychotics (eg, haloperidol).

Antidepressants.

Antidepressants may be needed during a depressive episode. However, in patients with BPD, antidepressants are *always* combined with a mood stabilizer. Why? Because of the long-held belief that, when used alone, antidepressants may elevate mood so much that a hypomanic or manic episode will result. However, data published in 2007 indicate that the risk of inducing mania may be much lower than previously thought. Nonetheless, until the issue is fully resolved, it would seem prudent to continue the traditional practice of using an antidepressant only if a mood stabilizer is being used as well.

Although antidepressants have been studied extensively in patients with major depression, very little research has been done in patients with BPD. As a result, we lack reliable information on which to base drug selection. Even so, experts do have their preferences. Among clinicians with extensive experience in BPD, the following are considered antidepressants of choice: *bupropion* [Wellbutrin], *venlafaxine* [Effexor], and the *selective serotonin reuptake inhibitors* (SSRIs), such as fluoxetine [Prozac] and sertraline [Zoloft]. The pharmacology of these drugs is discussed in Chapter 32.

Drug Selection

Acute Therapy: Manic Episodes.

Two mood stabilizers—lithium and valproic acid—are preferred drugs for acute management of manic episodes. The choice between them is based on clinical presentation (eg, euphoric mania, mania with psychosis, rapid-cycling BPD). As shown in Table 33-2, valproic acid is preferred to lithium in most cases. In fact, the only exception is euphoric mania, for which lithium is the drug of choice. If the patient does not respond adequately to lithium or valproic acid alone, the drugs may be used together. Responses to mood stabilizers develop slowly, taking 2 or more weeks to become maximal.

		Preferred Drugs*	
Clinical Presentation	**Preferred Strategy**	**Mood Stabilizers**	**Antipsychotics**
Euphoric mania	Mood stabilizer alone	Valproic acid or **lithium**	
Dysphoric mania or true mixed mania	Mood stabilizer alone	**Valproic acid** or lithium	
Mania with psychosis	Mood stabilizer plus an antipsychotic	**Valproic acid** or lithium	Olanzapine or risperidone
Rapid cycling (currently manic)	Mood stabilizer alone	**Valproic acid**	

TABLE 33-2 Initial Treatment of First Manic Episode

* Drugs of choice, if established, are presented in **bold type.**

If needed, an antipsychotic agent or a benzodiazepine may be added to the regimen. These adjuvants can help relieve symptoms (eg, insomnia, anxiety, agitation) until the mood stabilizer takes full effect. For patients with mild mania, a benzodiazepine (eg, lorazepam [Ativan]) may be adequate. For patients with severe mania or with symptoms of psychosis, an antipsychotic is preferred; olanzapine or risperidone would be a good choice.

Acute Therapy: Depressive Episodes.

Depressive episodes may be treated with a mood stabilizer alone, or with a mood stabilizer *plus* an antidepressant—but *never* with an antidepressant alone (because hypomania or mania might result). If depression is mild, monotherapy with a mood stabilizer (lithium or valproic acid) may be sufficient. If the mood stabilizer is inadequate, an antidepressant can be added. However, recent data suggest that the benefits may be limited. Preferred agents are bupropion, venlafaxine, and the SSRIs.

Long-Term Preventive Treatment.

The purpose of long-term therapy is to prevent recurrence of both mania and depression. As a rule, one or more mood stabilizers are employed. Drug selection is based on what worked acutely. For example, if the patient responded to acute therapy with lithium alone, then lithium alone should be used long term. Other long-term options include valproic acid alone, and valproic acid plus lithium. More recently, antipsychotic agents have been employed for long-term maintenance, either as monotherapy or in combination with a mood stabilizer.

Promoting Adherence

Poor patient adherence can frustrate attempts to treat manic episodes. Patients may resist treatment because they fail to see anything wrong with their thinking or behavior. Furthermore, the experience is not necessarily unpleasant. In fact, individuals going through a manic episode may well enjoy it. As a result, in order to ensure adherence, short-term hospitalization may be required. To achieve this, collaboration with the patient's family may be needed. Since hospitalization per se won't guarantee success, lithium administration should be observed to ensure that each dose is actually taken.

After an acute manic episode has been controlled, long-term prophylactic therapy is indicated, making adherence an ongoing issue. To promote adherence, the patient and family should be educated about the nature of BPD and the importance of taking medication as prescribed. Family members can help ensure adherence by overseeing medication use, and by urging the patient to visit his or her prescriber or a psychiatric clinic if a pattern of nonadherence develops.

Nondrug Therapy

Education and Psychotherapy

Ideally, BPD should be treated with a combination of drugs and adjunctive psychotherapy (individual, group, or family); drug therapy alone is not optimal. Bipolar disorder is a chronic illness that requires supportive therapy and education for the patient and family. Counseling can help patients cope with the sequelae of manic episodes, such as strained relationships, reduced self-confidence, and a sense of shame regarding uncontrolled behavior. Certain life stresses (eg, moving, job loss, bereavement, childbirth) can precipitate a mood change. Therapy can help reduce the destabilizing impact of these events. Patients should be taught to recognize early symptoms of mood change, and encouraged to contact their primary clinician immediately if these develop. Additional measures by which patients can help themselves include

- Maintaining a stable sleep pattern
- Maintaining a regular pattern of activity
- Avoiding alcohol and psychoactive street drugs
- Enlisting the support of family and friends
- Taking steps to reduce stress at work
- Keeping a mood chart to monitor progress

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is an effective intervention that can be lifesaving in patients with severe mania or depression. However, ECT is not a treatment of first choice. Rather, it should be reserved for patients who have not responded adequately to drugs. Candidates for ECT include patients with psychotic depression, severe nonpsychotic depression, severe mania, and rapid-cycling BPD. Details of ECT are discussed in Chapter 32.

MOOD-STABILIZING DRUGS

As noted, mood stabilizers are drugs that can relieve an acute manic or depressive episode, and can prevent symptoms from recurring—all without ag-

gravating mania or depression, and without accelerating cycling. The agents used most often are lithium, valproic acid, and carbamazepine.

BOX 33-1 OMEGA-3 FATTY ACIDS FOR BIPOLAR DISORDER: A FISH STORY WITH A HAPPY ENDING

In 1999, researchers from Harvard University made an exciting discovery: Fish oil can stabilize mood in people with bipolar disorder. Their results were so striking, in fact, that the experiment was stopped after 4 months so that control patients could switch to the fish-oil regimen. All subjects in the study had diagnosed bipolar disorder. Some took 9.6 gm of fish oil daily, and some took olive oil as a control. All continued on their usual medications. Among the group that ate fish oil, 11 of 15 improved after 4 months—and only 2 suffered eventual relapse. Among the group that ate olive oil, only 6 of 20 improved after 4 months—and 11 experienced relapse. Patients taking the fish oil had longer periods of remission, and, when symptoms did appear, they were less severe. Several patients were able to discontinue their medications and remain symptom free on fish oil alone. Side effects of the fish oil were minor—nausea, belching, fishy taste, loose stools—and easily controlled. At this time, the long-term benefits or detriments of fish oil are unknown. This study is of special interest in that it suggests that dietary therapy for a major illness can be as effective as drugs.

How does fish oil work? No one knows. Fish oil is composed of omega-3 fatty acids*—specifically, eicosapentaenoic acid and docosahexaenoic acid. In humans, the highest concentrations of omega-3s are found in the eyes and brain, where they are present in cell membranes. It may be that eating fish oil increases the concentration of omega-3s in neuronal membranes, and thereby slows nerve signaling, which in turn may stabilize mood. There is some evidence that omega-6 fatty acids—the kind found in vegetable oils, margarine, and mayonnaise—may negate the beneficial effects of omega-3s. Accordingly, patients taking fish oil for bipolar disorder should probably decrease intake of omega-6s.

* Omega-3 fatty acids are long-chain polyunsaturated fats that have a double bond located three carbons from the methyl terminus of the chain.

Lithium

Lithium [Lithobid, Lithonate, Lithotabs] can stabilize mood in patients with BPD. Beneficial effects were first described in 1949 by John Cade, an Australian psychiatrist. Because of concerns about toxicity, lithium was not approved for use in the United States until 1970. Lithium has a low therapeutic index. As a result, toxicity can occur at blood levels only slightly greater than therapeutic levels. Accordingly, monitoring lithium levels is mandatory.

Chemistry

Lithium is a simple inorganic ion that carries a single positive charge. In the periodic table of elements, lithium is in the same group as potassium and sodium. Not surprisingly, lithium has properties in common with both elements. Lithium is found naturally in animal tissues but has no known physiologic function.

Therapeutic Uses

Bipolar Disorder.

Lithium is a drug of choice for controlling acute manic episodes in patients with BPD and for long-term prophylaxis against recurrence of mania or depression. In manic patients, lithium reduces euphoria, hyperactivity, and other symptoms but does not cause sedation. Antimanic effects begin 5 to 7 days after treatment onset—but full benefits may not develop for 2 to 3 weeks. In the past, lithium was considered the drug of choice for all patients experiencing an acute manic episode, regardless of clinical presentation. Today, however, lithium is reserved primarily for patients with classic (euphoric) mania; valproic acid is generally preferred for all other patients (see Table 33-2). However, recent data show that lithium is superior to valproate at preventing suicide in patients with BPD, and hence use of lithium is likely to increase.

Other Uses.

Although approved only for treatment of BPD, lithium has been used with varying degrees of success in other psychiatric disorders, including *alcoholism, bulimia, schizophrenia,* and *glucocorticoid-induced psychosis*. Nonpsychiatric uses include *hyperthyroidism, cluster headache, migraine,* and *syndrome of inappropriate*

secretion of antidiuretic hormone. In addition, lithium can *raise neutrophil counts* in children with chronic neutropenia and in patients receiving anticancer drugs or zidovudine (AZT).

Mechanism of Action

Although lithium has been studied extensively, the precise mechanism by which it stabilizes mood is unknown. In the past, research focused on three aspects of brain neurochemistry: (1) altered distribution of certain ions (calcium, sodium, magnesium) that are critical to neuronal function; (2) altered synthesis and release of norepinephrine, serotonin, and dopamine; and (3) effects on second messengers (eg, cyclic AMP, phosphatidyl inositol), which mediate intracellular responses to neurotransmitters. Unfortunately, this research has failed to provide a definitive explanation of how lithium works. Current neurochemical research suggests that lithium may work by (1) altering glutamate uptake and release, (2) blocking the binding of serotonin to its receptors, and/or (3) inhibiting glycogen synthase kinase-3 beta.

Recently, there has been growing interest in the neurotrophic and neuroprotective actions of lithium. As noted above, there is evidence that symptoms of BPD may result from neuronal atrophy in certain brain areas. In animal studies, "therapeutic" doses of lithium doubled the level of neurotrophic Bcl-2 proteins. In addition, lithium has been shown to facilitate regeneration of damaged optic nerves. In patients with BPD taking lithium long term, volume of the subgenual prefrontal cortex is greater than in untreated patients. Furthermore, lithium can increase total gray matter in regions known to atrophy in BPD, including the prefrontal cortex, hippocampus, and caudate nucleus. All of these studies suggest that the benefits of lithium may result at least in part from an ability to protect against neuronal atrophy and/or promote neuronal growth.

Pharmacokinetics

Absorption and Distribution.

Lithium is well absorbed following oral administration. The drug distributes evenly to all tissues and body fluids.

Excretion.

Lithium has a short half-life owing to rapid renal excretion. Because of its short half-life (and high toxicity), the drug must be administered in divided daily doses. Large, single daily doses cannot be used, even when a slow-release preparation is prescribed. Because lithium is excreted by the kidneys, it must be employed with great care in patients with renal impairment.

Renal excretion of lithium is affected by blood levels of sodium. Specifically, lithium excretion is *reduced* when levels of sodium are *low*. Why? Because the kidney processes lithium and sodium in the same way. Hence, when the kidney senses that sodium levels are inadequate, it retains lithium in an attempt to compensate. Because of this relationship, in the presence of low sodium, lithium can accumulate to toxic levels. Accordingly, it is important that sodium levels remain normal. Patients should be instructed to maintain normal sodium intake. Obviously, a sodium-free diet cannot be used. Since diuretics promote sodium loss, these agents must be employed with caution. Sodium loss secondary to diarrhea can be sufficient to cause lithium accumulation. The patient should be told about this possibility.

Dehydration will cause lithium retention by the kidneys, posing the risk of accumulation to dangerous levels. Potential causes of dehydration include hot weather and diarrhea. Counsel patients to maintain adequate hydration.

Monitoring Plasma Lithium Levels.

Measurement of plasma lithium levels is an essential component of treatment. *Lithium levels must be kept below 1.5 mEq/L; levels greater than this can produce significant toxicity*. For *initial* therapy of a manic episode, lithium levels should range from 0.8 to 1.4 mEq/L. Once the desired therapeutic effect has been achieved, the dosage should be reduced to produce *maintenance* levels of 0.4 to 1.0 mEq/L. Blood for lithium determinations should be drawn in the morning, 12 hours after the evening dose.

Adverse Effects

The adverse effects of lithium can be divided into two categories: (1) effects that occur at excessive lithium levels and (2) effects that occur at therapeutic lithium levels. In the discussion below, adverse effects produced at excessive

lithium levels are considered as a group. Effects produced at therapeutic levels are considered individually.

Adverse Effects That Occur When Lithium Levels Are Excessive.

Certain toxicities are closely correlated with the concentration of lithium in blood. As indicated in Table 33-3, mild responses (eg, fine hand tremor, GI upset, thirst, muscle weakness) can develop at lithium levels that are still within the therapeutic range (ie, below 1.5 mEq/L). When plasma levels exceed 1.5 mEq/L, more serious toxicities appear. At drug levels above 2.5 mEq/L, death can occur. Patients should be informed about early signs of toxicity and instructed to interrupt lithium dosing if these appear. In adherent patients, the most common cause of lithium accumulation is sodium depletion.

To keep lithium levels within the therapeutic range, plasma drug levels should be monitored routinely. Levels should be measured every 2 to 3 days at the beginning of treatment and every 1 to 3 months during maintenance therapy.

Treatment of acute overdose is primarily supportive; there is no specific antidote. The severely intoxicated patient should be hospitalized. Hemodialysis is an effective means of lithium removal and should be considered whenever drug levels exceed 2.5 mEq/L.

Plasma Lithium Level (mEq/L)	Signs of Toxicity
Below 1.5	Nausea, vomiting, diarrhea, thirst, polyuria, lethargy, slurred speech, muscle weakness, fine hand tremor
1.5–2	Persistent GI upset, coarse hand tremor, confusion, hyperirritability of muscles, ECG changes, sedation, incoordination
2–2.5	Ataxia, giddiness, high output of dilute urine, serious ECG changes, fasciculations, tinnitus, blurred vision, clonic movements, seizures, stupor, severe hypotension, coma, death (usually secondary to pulmonary complications)
Above 2.5	Symptoms may progress rapidly to generalized convulsions, oliguria, and death

ECG = electrocardiogram.

TABLE 33-3 Toxicities Associated with Excessive Plasma Level of Lithium

Adverse Effects That Occur at Therapeutic Levels of Lithium.

Early Adverse Effects.

Several responses occur early in treatment and then usually subside. *Gastrointestinal effects* (eg, nausea, diarrhea, abdominal bloating, anorexia) are common but transient. About 30% of patients experience *transient fatigue, muscle weakness, headache, confusion,* and *memory impairment. Polyuria* and *thirst* occur in 30% to 50% of patients and may persist.

Tremor.

Patients may develop a fine hand tremor, especially in the fingers, that can interfere with writing and other motor skills. Lithium-induced tremor can be augmented by stress, fatigue, and certain drugs (antidepressants, antipsychotics, caffeine). Tremor can be reduced with a beta blocker (eg, propranolol) and by measures that reduce peak levels of lithium (ie, dosage reduction, use of divided doses, or use of a sustained-release formulation).

Polyuria.

Polyuria occurs in 50% to 70% of patients taking lithium chronically. In some patients, daily urine output may exceed 3 L. Lithium promotes polyuria by antagonizing the effects of antidiuretic hormone. To maintain adequate hydration, patients should be instructed to drink 8 to 12 glasses of fluids daily. Polyuria, nocturia, and excessive thirst can discourage patients from adhering to the regimen.

Lithium-induced polyuria can be reduced with *amiloride* [Midamor], a potassium-sparing diuretic. Amiloride appears to help by reducing the entry of lithium into epithelial cells of the renal tubule. Polyuria can also be reduced with a thiazide diuretic. However, because thiazides can lower levels of sodium (see Chapter 40), and would thereby increase lithium retention, amiloride is preferred.

Renal Toxicity.

Chronic lithium use has been associated with degenerative changes in the kidney. The risk of renal injury can be reduced by keeping the dosage low and, when possible, avoiding long-term lithium therapy. Kidney function should be assessed prior to treatment and once a year thereafter.

Goiter and Hypothyroidism.

Lithium can reduce incorporation of iodine into thyroid hormone, and can inhibit thyroid hormone secretion. With long-term use, the drug can cause *goiter* (enlargement of the thyroid gland). Although usually benign, lithium-induced goiter is sometimes associated with *hypothyroidism*. Treatment with thyroid hormone (levothyroxine) or withdrawal of lithium will reverse both goiter and hypothyroidism. Levels of thyroid hormones—triiodothyronine (T_3) and thyroxine (T_4)—and levels of thyroid-stimulating hormone (TSH) should be measured prior to giving lithium and annually thereafter.

Teratogenesis.

Lithium may—or may not—be a teratogen. In older studies, lithium appeared to have significant teratogenic effects: drug use during the first trimester of pregnancy was associated with an 11% incidence of birth defects (usually mal-

formations of the heart). However, in more recent studies, lithium showed little or no teratogenic potential. Nonetheless, lithium is still classified in Food and Drug Administration (FDA) Pregnancy Risk Category D. To minimize any potential fetal risk, *lithium should be avoided during the first trimester of pregnancy* and, unless the benefits of therapy clearly outweigh the risks, it should be avoided during the remainder of pregnancy as well. Women of child-bearing age should be counseled to avoid pregnancy while taking lithium. Also, pregnancy should be ruled out before initiating lithium therapy.

Use in Lactation.

Lithium readily enters breast milk and can achieve concentrations that are potentially harmful to the nursing infant. Consequently, breast-feeding during lithium therapy should be discouraged.

Other Effects.

Lithium can cause mild, reversible *leukocytosis* (10,000 to 18,000 white blood cells/mm***3***); complete blood counts with a differential should be obtained prior to treatment and annually thereafter. Possible *dermatologic reactions* include psoriasis, acne, folliculitis, and alopecia.

Drug Interactions

Diuretics.

Diuretics promote sodium loss, and can thereby increase the risk of lithium toxicity. Toxicity can occur because, in the presence of low sodium, renal excretion of lithium is reduced, causing lithium levels to rise.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs).

NSAIDs can increase lithium levels by as much as 60%. How? By suppressing synthesis of prostaglandins in the kidney, NSAIDs disrupt (increase) renal reabsorption of lithium (and also sodium), thereby causing lithium levels to rise. NSAIDs known to increase lithium levels include ibuprofen [Motrin, others], naproxen [Naprosyn], piroxicam [Feldene], indomethacin [Indocin], and celecoxib [Celebrex]. Interestingly, aspirin (the prototype NSAID) and sulindac

[Clinoril] do *not* increase lithium levels. Accordingly, if a mild analgesic is needed, aspirin or sulindac would be a good choice.

Anticholinergic Drugs.

Anticholinergics can cause urinary hesitancy. Coupled with lithium-induced polyuria, this can result in considerable discomfort. Accordingly, patients should avoid drugs with prominent anticholinergic actions (eg, antihistamines, phenothiazine antipsychotics, tricyclic antidepressants).

Preparations, Dosage, and Administration

Preparations and Administration.

Lithium is available as two salts: *lithium carbonate* and *lithium citrate*. With either salt, administration is oral. Lithium carbonate is supplied in capsules, standard tablets, and slow-release tablets. Lithium citrate is supplied in a syrup. Lithium formulations and trade names are summarized in Table 33-4.

Lithium can cause gastric upset. This can be reduced by administering lithium with meals or milk.

Lithium Salt	Formulation	Lithium Content*	Trade Name
Lithium carbonate (Li_2CO_3)	Capsules	4.06 mEq lithium (150 mg Li_2CO_3)	(generic only)
		8.12 mEq lithium (300 mg Li_2CO_3)	Lithonate
		16.24 mEq lithium (600 mg Li_2CO_3)	(generic only)
	Tablets: standard	8.12 mEq lithium (300 mg Li_2CO_3)	Lithotabs
	Tablets: slow-release	8.12 mEq lithium (300 mg Li_2CO_3)	Lithobid
Lithium citrate	Syrup	8 mEq lithium/5 mL (equivalent to 300 mg Li_2CO_3)	

TABLE 33-4 Lithium Preparations

* Lithium content is expressed in two ways: (1) milliequivalents (mEq) of lithium ion and (2) milligrams (mg) of the particular lithium salt of which the preparation is composed.

Dosing.

Lithium dosing is highly individualized. Dosage adjustments are based on plasma drug levels and clinical response.

Plasma levels should be kept within the therapeutic range. Levels between 0.8 and 1.4 mEq/L are generally appropriate for *acute therapy* of manic episodes. For *maintenance therapy,* lithium levels should range from 0.4 to 1.0 mEq/L. (Levels of 0.6 to 0.8 mEq/L are effective for most patients.) To avoid serious toxicity, *lithium levels should not exceed 1.5 mEq/L*.

Knowledge of plasma drug levels is not the only guide to lithium dosing; the clinical response is at least as important. Accordingly, when evaluating lithium dosage, we must not forget to look at the patient. Laboratory tests are all well and good, but they are not a substitute for clinical assessment. For example, if blood levels of lithium appear proper but clinical evaluation indicates toxicity, there is no question as to what should be done: Reduce

the dosage—despite the apparent acceptability of the dosage as reflected by plasma lithium levels.

Because of its short half-life and low therapeutic index, *lithium cannot be administered in a single daily dose:* With once-a-day dosing, peak levels would be excessive. Hence, a typical dosage is 300 mg (of lithium carbonate) taken 3 or 4 times a day. A dosage of 600 mg twice a day is acceptable, provided a slow-release formulation is employed. However, even these preparations cannot be given once daily.

Antiepileptic Drugs

Certain antiepileptic drugs (eg, valproic acid, carbamazepine) can suppress mania and stabilize mood in patients with BPD. The efficacy of these agents is firmly established. In fact, one drug—valproic acid—is so effective that it has replaced lithium as the drug of choice for many patients. The basic pharmacology of the antiepileptic drugs and their use in seizure disorders is discussed in Chapter 24. Discussion here focuses on their use in BPD.

Valproic Acid

Valproic acid* [Depakene, Depakote, Depacon, Stavzor] was the first antiseizure agent approved for BPD. The drug can control symptoms in acute manic episodes and can provide prophylaxis against recurrent episodes of mania and depression. As with lithium, benefits appear to result at least in part from neurotrophic and neuroprotective effects. In patients with BPD, valproic acid compares favorably with lithium: both drugs are highly effective, and valproate works faster and has a higher therapeutic index and a more desirable side effect profile. However, lithium *is* superior in one important respect: the ability to decrease suicide. Nonetheless, because of its rapid onset, efficacy, and safety, valproic acid has become a first-line treatment for BPD. The starting dosage for acute mania in adults is 250 mg 3 times a day or 500 mg once daily at bedtime. Typical maintenance dosages range from 1000 to 2500 mg/day. The target trough plasma level is 50 to 120 mcg/mL.

Although valproic acid has a higher therapeutic index than lithium and is generally better tolerated, it *can* cause serious toxicity. Of greatest concern are rare cases of thrombocytopenia, pancreatitis, and liver failure—all of which

require immediate drug withdrawal. In addition, valproic acid is a teratogen, and hence should not be used during pregnancy. Gastrointestinal disturbances (nausea, vomiting, diarrhea, dyspepsia, indigestion) are common. These can be minimized by using Depakote, an enteric-coated formulation of divalproex sodium (a form of valproic acid). Despite causing GI distress, valproic acid frequently causes weight gain, a serious and chronic complication of treatment.

* As discussed in Chapter 24, valproic acid is available in three closely related forms: (1) valproic acid itself [Depakene, Depacon, Stavzor]; (2) the sodium salt of valproic acid [Depakene]; and (3) divalproex sodium [Depakote], a mixture of valproic acid and its sodium salt. All three forms have identical actions. In this chapter, the term *valproic acid* refers to all three.

Carbamazepine

Carbamazepine was the first drug to be widely studied as an alternative to lithium for patients with BPD. However, it wasn't approved for BPD until 2005. Like lithium, carbamazepine reduces symptoms during manic and depressive episodes. In addition, when taken for maintenance, it can protect against recurrence of mania and depression. Like valproic acid, carbamazepine is preferred to lithium for patients with mixed mania or rapid-cycling BPD. For treatment of acute manic episodes, the dosage should be low initially (100 or 200 mg twice daily) and then gradually increased. The maximum dosage is 1600 mg/day. The target trough plasma level is 4 to 12 mcg/mL. Neurologic side effects (visual disturbances, ataxia, vertigo, unsteadiness, headache) are common early in treatment, but generally resolve despite continued drug use. Hematologic effects (leukopenia, anemia, thrombocytopenia, aplastic anemia) are relatively uncommon, but can be severe. Accordingly, complete blood counts including platelets should be obtained at baseline and periodically thereafter. Carbamazepine induces cytochrome P450 enzymes, and can thereby accelerate its own metabolism and the metabolism of other drugs (eg, oral contraceptives, warfarin, valproic acid, tricyclic antidepressants). To maintain efficacy, dosages of carbamazepine and these other drugs should be increased as needed.

Drug products containing carbamazepine are available under four trade names: *Carbatrol, Equetro, Epitol,* and *Tegretol*. Carbamazepine formulations with any of these names can be used for BPD. However, only one

product—Equetro—is actually *approved* for BPD. Equetro is an extended-release formulation, manufactured by Shire Pharmaceuticals, that is *identical* to Carbatrol, a product approved for seizure control, also manufactured by Shire. Why use two trade names for the same formulation made by the same company? To facilitate marketing, of course. This name game is another good example of why your author wants trade names to be outlawed (see discussion of drug names in Chapter 3).

Lamotrigine

In 2003, lamotrigine [Lamictal] became a third antiepileptic agent approved for BPD. The drug is indicated for long-term maintenance therapy, with the objective of delaying or preventing affective relapses. Lamotrigine may be used alone or in combination with other mood-stabilizing agents. Side effects include headache, dizziness, double vision, and, rarely, life-threatening rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis). To minimize the risk of serious rash, dosage should be low initially (25 to 50 mg/day) and then gradually increased. The target maintenance dosage is 200 mg/day (if used alone), 100 mg/day (if combined with valproate), or 400 mg/day (if combined with carbamazepine or some other inducer of P450).

ANTIPSYCHOTIC DRUGS

In patients with BPD, antipsychotic drugs are used *acutely* to control symptoms during manic episodes, and *long term* to help stabilize mood. These drugs benefit patients with or without psychotic symptoms. Although antipsychotics can be used alone, they are usually employed in combination with a mood stabilizer, typically lithium or valproic acid.

Which antipsychotics are preferred? As discussed in Chapter 31, the antipsychotic drugs fall into two major groups: conventional agents (eg, haloperidol) and atypical agents (eg, olanzapine). Compared with the conventional agents, the atypical agents carry a lower risk of extrapyramidal side effects, including tardive dyskinesia. Accordingly, the atypical agents are preferred.

Six atypical antipsychotics are available, and five—*olanzapine* [Zyprexa], *quetiapine* [Seroquel], *risperidone* [Risperdal], *aripiprazole* [Abilify], and *zi-*

prasidone [Geodon]—are now approved for BPD. (The sixth agent—*clozapine* [Clozaril]—although highly effective in BPD, is not used owing to a risk of agranulocytosis.) All of these drugs are effective against acute mania, when used alone or combined with lithium or valproate. Currently, only one atypical agent—olanzapine—is approved for long-term maintenance therapy to prevent recurrence of mood episodes. However, the other atypical agents are probably just as effective. Dosages for patients with BPD are summarized in Table 33-5.

The pharmacology of the antipsychotics is presented in Chapter 31.

Drug	Dosage
Olanzapine [Zyprexa]	*Acute Mania:* Start with 10–15 mg once daily. Increase or decrease, in 5-mg/day increments, as indicated. The effective range is 5–20 mg once daily. *Maintenance Therapy:* The effective range is 5–20 mg once daily.
Olanzapine/Fluoxetine [Symbyax]	*Depressive Episodes:* Start with 6 mg olanzapine/25 mg fluoxetine once daily in the evening. The effective range for antidepressant effects is olanzapine 6–12 mg and fluoxetine 25–50 mg.
Risperidone [Risperdal]	*Acute Mania:* Start with 2–3 mg once daily; increase to a maximum of 6 mg once daily; if needed.
Quetiapine [Seroquel]	*Acute Mania (with normal liver function):* Give 100 mg (in two divided doses) on day 1, 200 mg on day 2, 300 mg on day 3, and 400 mg on day 4. If needed, increase to 600 mg on day 5 and 800 mg on day 6. *Acute Mania (with liver impairment):* Give 25 mg on day 1, then increase by 25–50 mg/day until symptoms are controlled or side effects are intolerable, whichever comes first. *Depressive Episodes:* Give once-daily doses at bedtime as follows: 50 mg on day 1, 100 mg on day 2, 200 mg on day 3, and 300 mg on day 4; if needed, increase to 400 mg on day 5, and 600 mg on day 8.
Aripiprazole [Abilify]	*Acute Mania:* Start with 30 mg once daily and do not exceed this dose. Decrease to 15 mg once daily if needed.
Ziprasidone [Geodon]	*Acute Mania:* On day 1, give 80 mg (in two divided doses with food). On day 2, increase to 60 or 80 mg twice daily. Based on tolerability and efficacy, adjust dosage within the range of 40–80 mg twice daily.

TABLE 33-5 Adult Oral Dosages for Atypical Antipsychotics Used in Bipolar Disorder

KEY POINTS

- Bipolar disorder is treated with three kinds of drugs: mood stabilizers, antipsychotic drugs, and antidepressants.
- Mood stabilizers are drugs that (1) relieve symptoms during manic and depressive episodes; (2) prevent recurrence of manic and depressive episodes; and (3) do not worsen symptoms of mania or depression, and do not accelerate the rate of cycling.
- Antipsychotic drugs are used acutely to treat manic episodes, and long term to help stabilize mood. Benefits occur in patients with and without psychotic symptoms.
- In patients with bipolar depression, using an antidepressant alone may induce mania—although the risk appears lower than previously believed. Nonetheless, to minimize any risk of mania, antidepressants should not be used alone; rather, they should be combined with a mood-stabilizing drug.
- Lithium and valproic acid are the preferred mood stabilizers for BPD.
- To minimize the risk of toxicity, lithium levels must be monitored. The trough level, measured 12 hours after the evening dose, should be less than 1.5 mEq/L.
- Common side effects that occur at therapeutic lithium levels include tremor, goiter, and polyuria.
- Lithium may be teratogenic, and hence should be avoided during the first trimester of pregnancy. Also, unless the benefits outweigh the risks, lithium should be avoided during the second and third trimesters too.
- A reduction in sodium levels will reduce lithium excretion, causing lithium to accumulate—possibly to toxic levels. Patients must maintain normal sodium intake and levels.

- Lithium levels can be increased by diuretics (especially thiazides) and by several nonsteroidal anti-inflammatory drugs.

Summary of Major Nursing Implications*

LITHIUM

Preadministration Assessment

Therapeutic Goal

Control of acute manic episodes in patients with BPD, and prophylaxis against recurrent mania and depression in patients with BPD.

Baseline Data

Make baseline determinations of cardiac status (electrocardiogram, blood pressure, pulse), hematologic status (complete blood counts with differential), serum electrolytes, renal function (serum creatinine, creatinine clearance, urinalysis), and thyroid function (T_3, T_4, and TSH).

Identifying High-Risk Patients

Lithium should be *avoided* during the first trimester of pregnancy, and used with *caution* during the remainder of pregnancy and in the presence of renal disease, cardiovascular disease, dehydration, sodium depletion, and concurrent therapy with diuretics.

Implementation: Administration

Route

Oral.

Administration

Advise patients to administer lithium with meals or milk to decrease gastric upset. Instruct patients to swallow slow-release tablets intact, without crushing or chewing.

Promoting Adherence

Rigid adherence to the prescribed regimen is important. Deviations in dosage size and timing can cause toxicity. Inadequate dosing may cause relapse.

To promote adherence, educate patients and families about the nature of BPD and the importance of taking lithium as prescribed. Encourage family members to oversee lithium use, and advise them to urge the patient to visit the prescriber or a psychiatric clinic if a pattern of nonadherence develops.

When medicating inpatients, make certain each lithium dose is ingested.

Ongoing Evaluation and Interventions

Monitoring Summary

Lithium Levels.

Monitor lithium levels to ensure that they remain within the therapeutic range (0.8 to 1.4 mEq/L for initial therapy and 0.4 to 1 mEq/L for maintenance). Levels should be measured every 2 to 3 days during initial therapy, and every 1 to 3 months during maintenance. Blood for lithium determination should be drawn in the morning, 12 hours after the evening dose.

Other Parameters to Monitor.

Evaluate the patient at least once a year for hematologic status (complete blood count with differential), serum electrolytes, renal function (serum creatinine, creatinine clearance, urinalysis), and thyroid function (T_3, T_4, and TSH).

Evaluating Therapeutic Effects

Evaluate the patient for abatement of manic symptoms (eg, flight of ideas, pressured speech, hyperactivity) and for mood stabilization.

Minimizing Adverse Effects

Effects Caused by Excessive Drug Levels.

Excessive lithium levels can result in serious adverse effects (see Table 33-3). Lithium levels must be monitored (see *Monitoring Summary* above) and dosage adjusted accordingly.

Teach patients about signs of toxicity, and instruct them to withhold medication and notify the prescriber if they develop.

Renal impairment can cause lithium accumulation. Kidney function should be assessed prior to treatment and once yearly thereafter.

Sodium deficiency can cause lithium to accumulate. **Instruct patients to maintain normal sodium intake. Inform patients that diarrhea can cause significant sodium loss.** Diuretics promote sodium excretion and must be used with caution.

In the event of severe toxicity, hospitalization may be required. If lithium levels exceed 2.5 mEq/L, hemodialysis should be considered.

Tremor.

Lithium can cause fine hand tremor that can interfere with motor skills. Tremor can be reduced with a beta blocker (eg, propranolol) and by measures that reduce peak lithium levels (dosage reduction; use of divided doses or a sustained-release formulation).

Hypothyroidism and Goiter.

Lithium can promote goiter (thyroid enlargement) and frank hypothyroidism. Plasma levels of T***3***, T***4***, and TSH should be measured prior to treatment and yearly thereafter. Treat hypothyroidism with levothyroxine.

Renal Toxicity.

Lithium can cause renal damage. Kidney function should be assessed prior to treatment and once a year thereafter. If renal impairment develops, lithium dosage must be reduced.

Polyuria.

Lithium increases urine output. Polyuria can be suppressed with amiloride (a potassium-sparing diuretic). **Instruct patients to drink 8 to 12 glasses of fluid daily to maintain hydration.**

Use in Pregnancy and Lactation.

Lithium may cause birth defects. The drug should be avoided during pregnancy, especially in the first trimester. **Counsel women of child-bearing age about the importance of avoiding pregnancy.** Rule out pregnancy before initiating therapy.

Lithium enters breast milk. **Advise patients to avoid breast-feeding.**

Minimizing Adverse Interactions

Diuretics.

By promoting sodium loss, diuretics can reduce lithium excretion, thereby causing lithium levels to rise. Monitor closely for signs of toxicity.

Anticholinergic Drugs.

By causing urinary hesitancy, drugs with anticholinergic actions (eg, antihistamines, phenothiazine antipsychotics, tricyclic antidepressants) can intensify discomfort associated with lithium-induced diuresis.

Nonsteroidal Anti-inflammatory Drugs.

Several NSAIDs (eg, ibuprofen, naproxen, celecoxib), but *not* aspirin or sulindac, can increase renal reabsorption of lithium, thereby causing lithium levels to rise. If a mild analgesic is needed, aspirin or sulindac would be a good choice.

34 Sedative-Hypnotic Drugs

The sedative-hypnotics are drugs that depress central nervous system (CNS) function. With some of these drugs, CNS depression is more generalized than with others. The sedative-hypnotics are used primarily to treat anxiety and insomnia. Because both disorders are common, the sedative-hypnotics are widely used. Agents given to relieve anxiety are known as *antianxiety agents* or *anxiolytics;* an older term is *tranquilizers*. Agents given to promote sleep are known as *hypnotics*. The distinction between antianxiety effects and hypnotic effects is often a matter of dosage: typically, sedative-hypnotics relieve anxiety in low doses and induce sleep in higher doses. Hence, a single drug may be considered both an antianxiety agent and a hypnotic agent, depending upon the reason for its use and the dosage employed.

There are three major groups of sedative-hypnotics: barbiturates (eg, secobarbital), benzodiazepines (eg, diazepam), and benzodiazepine-like drugs (eg, zolpidem). The barbiturates were introduced in the early 1900s, the benzodiazepines in the 1950s, and the benzodiazepine-like drugs in the 1990s. Although barbiturates were widely used as sedative-hypnotics in the past, they are rarely used for this purpose today, having been replaced by the newer drugs.

Before the benzodiazepines became available, anxiety and insomnia were treated with barbiturates and other *general* CNS depressants—drugs with multiple undesirable qualities: (1) These drugs are powerful respiratory depressants that can readily prove fatal in overdose. As a result, they are "drugs of choice" for suicide. (2) Because they produce subjective effects that many individuals find desirable, most general CNS depressants have a high potential for abuse. (3) With prolonged use, most of these drugs produce significant tolerance and physical dependence. (4) Barbiturates and some other CNS depressants induce synthesis of hepatic drug-metabolizing enzymes, and can thereby decrease responses to other drugs. Because the benzodiazepines are just as effective as the general CNS depressants, but do not share their undesirable properties, the benzodiazepines are clearly preferred to the general CNS depressants for treating anxiety and insomnia.

We begin the chapter by discussing the basic pharmacology of the sedative-hypnotics, and end by discussing their use in insomnia. Use of these drugs for anxiety is discussed in Chapter 35.

BENZODIAZEPINES

Benzodiazepines are drugs of first choice for anxiety and insomnia. In addition, these drugs are used to induce general anesthesia and to manage seizure disorders, muscle spasm, panic disorder, and withdrawal from alcohol.

Benzodiazepines were introduced in the late 1950s and remain important today. Perhaps the most familiar member of the family is diazepam [Valium]. The most frequently prescribed members are lorazepam [Ativan] and alprazolam [Xanax, Niravam].

The popularity of the benzodiazepines as sedatives and hypnotics stems from their clear superiority over the alternatives: barbiturates and other general CNS depressants. The benzodiazepines are safer than the general CNS depressants and have a lower potential for abuse. In addition, benzodiazepines produce less tolerance and physical dependence and are subject to fewer drug interactions. Contrasts between the benzodiazepines and barbiturates are summarized in Table 34-1.

Since all of the benzodiazepines produce nearly identical effects, we will consider the family as a group, rather than selecting a representative member as a prototype.

Area of Comparison	Benzodiazepines	Barbiturates
Relative safety	High	Low
Maximal ability to depress CNS function	Low	High
Respiratory depressant ability	Low	High
Suicide potential	Low	High
Ability to cause physical dependence	Low*	High
Ability to cause tolerance	Low	High
Abuse potential	Low	High
Ability to induce hepatic drug metabolism	Low	High

TABLE 34-1 Contrasts Between Benzodiazepines and Barbiturates

* Although dependence is low in most patients, significant dependence *can* develop with long-term, high-dose use.

Overview of Pharmacologic Effects

Practically all responses to benzodiazepines result from actions in the CNS. Benzodiazepines have few direct actions outside the CNS. All of the benzodiazepines produce a similar spectrum of responses. However, because of pharmacokinetic differences, individual benzodiazepines may differ in clinical applications.

Central Nervous System.

All beneficial effects of benzodiazepines and most adverse effects result from depressant actions in the CNS. With increasing dosage, effects progress from sedation to hypnosis to stupor.

Benzodiazepines depress neuronal function at multiple sites in the CNS. They *reduce anxiety* through effects on the limbic system, a neuronal network associated with emotionality. They *promote sleep* through effects on cortical areas and on the sleep-wakefulness "clock." They *induce muscle relaxation* through effects on supraspinal motor areas, including the cerebellum. Two important

side effects—*confusion* and *anterograde amnesia*—result from effects on the hippocampus and cerebral cortex.

Cardiovascular System.

When taken *orally,* benzodiazepines have almost no effect on the heart and blood vessels. In contrast, when administered *intravenously,* even in therapeutic doses, benzodiazepines can produce profound hypotension and cardiac arrest.

Respiratory System.

In contrast to the barbiturates, the benzodiazepines are weak respiratory depressants. When taken alone in therapeutic doses, benzodiazepines produce little or no depression of respiration—and with toxic doses, respiratory depression is moderate at most. With oral therapy, clinically significant respiratory depression occurs only when benzodiazepines are combined with other CNS depressants (eg, opioids, barbiturates, alcohol).

Although benzodiazepines generally have minimal effects on respiration, they can be a problem for patients with respiratory disorders. In patients with chronic obstructive pulmonary disease, benzodiazepines may worsen hypoventilation and hypoxemia. In patients with obstructive sleep apnea (OSA), benzodiazepines may exacerbate apneic episodes. In patients who snore, benzodiazepines may convert partial airway obstruction into OSA.

Molecular Mechanism of Action

Benzodiazepines *potentiate the actions of gamma-aminobutyric acid* (GABA), an inhibitory neurotransmitter found throughout the CNS. These drugs enhance the actions of GABA by binding to specific receptors in a supramolecular structure known as the GABA receptor–chloride channel complex (Fig. 34-1). Please note that benzodiazepines act only by intensifying the effects of GABA; they do not act as direct GABA agonists.

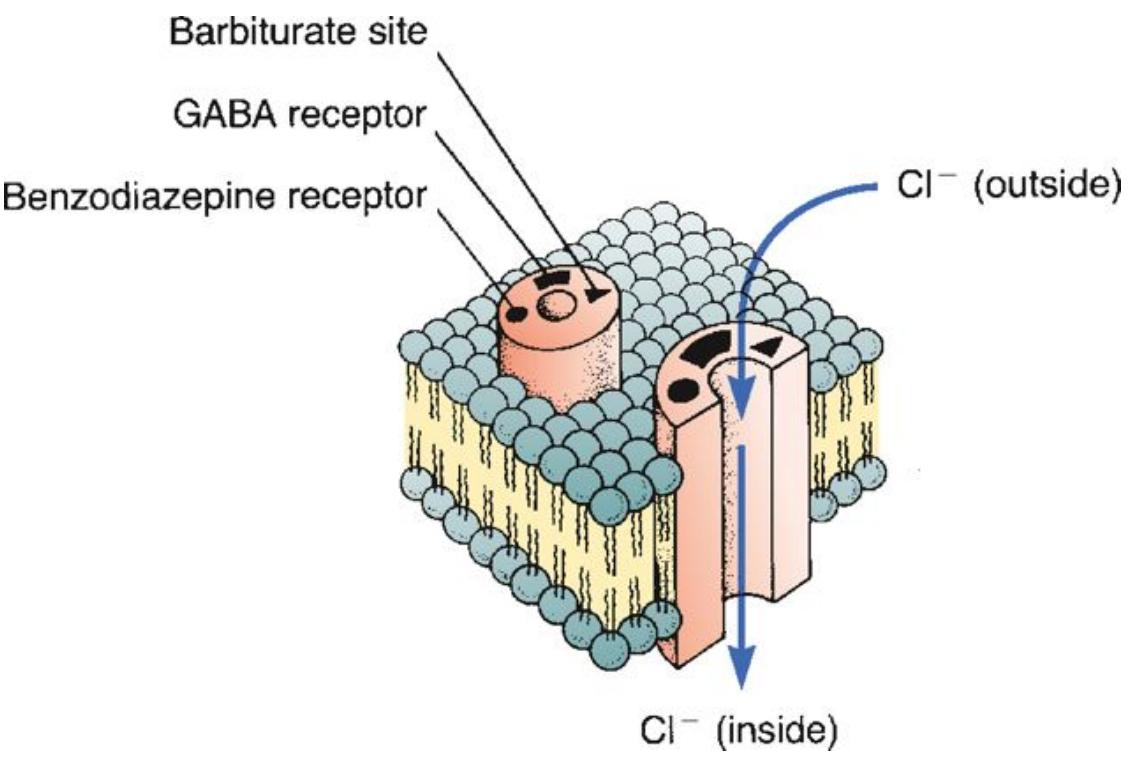


Figure 34-1 Schematic model of the GABA receptor–chloride channel complex showing binding sites for benzodiazepines and barbiturates. The GABA receptor–chloride channel complex, which spans the neuronal cell membrane, can exist in an open or closed configuration. Binding of GABA to its receptor on the complex causes the chloride channel to open. The resulting inward flow of chloride ions hyperpolarizes the neuron (makes the cell highly negative inside) and thereby decreases its ability to fire. Hence GABA is an inhibitory neurotransmitter. Binding of a benzodiazepine to its receptor on the complex increases the frequency of channel opening, thereby increasing chloride influx. Hence, benzodiazepines enhance the inhibitory effects of GABA. In the absence of GABA, benzodiazepines have no effect on channel opening. The benzodiazepine-like drugs (zolpidem, zaleplon, and eszopiclone) have actions much like those of the benzodiazepines. Effects of barbiturates on the chloride channel are dose dependent: at low doses, barbiturates enhance the ac-

tions of GABA (by prolonging the duration of channel opening); at high doses, barbiturates directly mimic the actions of GABA.

Because benzodiazepines act by amplifying the actions of endogenous GABA, rather than by directly mimicking GABA, there is a limit to how much CNS depression benzodiazepines can produce. This explains why benzodiazepines are so much safer than the barbiturates—drugs that can directly mimic GABA. Since benzodiazepines simply potentiate the inhibitory effects of endogenous GABA, and since the amount of GABA in the CNS is finite, there is a built-in limit to the depth of CNS depression the benzodiazepines can produce. In contrast, since the barbiturates are direct-acting CNS depressants, maximal effects are limited only by the amount of barbiturate administered.

Pharmacokinetics

Absorption and Distribution.

Most benzodiazepines are well absorbed following oral administration. Because of their high lipid solubility, benzodiazepines readily cross the blood-brain barrier to reach sites in the CNS.

Metabolism.

Most benzodiazepines undergo extensive metabolic alterations. With few exceptions, the *metabolites are pharmacologically active*. As a result, responses produced by administering a particular benzodiazepine often persist long after the parent drug has disappeared. Hence, there may be a poor correlation between the plasma half-life of the parent drug and duration of pharmacologic effects. Flurazepam, for example, whose plasma half-life is only 2 to 3 hours, is converted into an active metabolite with a half-life of 50 hours. Hence, giving flurazepam produces long-lasting effects, even though flurazepam itself is gone from the plasma in 8 to 12 hours.

In patients with liver disease, metabolism of benzodiazepines can decline, thereby prolonging and intensifying responses. Because certain benzodiazepines (oxazepam, temazepam, and lorazepam) undergo very little metabolic alteration, they may be preferred for patients with hepatic impairment.

Time Course of Action.

Benzodiazepines differ significantly from one another with respect to time course. Specifically, they differ in onset and duration of action, and tendency to accumulate with repeated dosing.

Because all benzodiazepines have essentially equivalent pharmacologic actions, selection among them is based largely on differences in time course. For example, if a patient needs medication to accelerate falling asleep, a benzodiazepine with a rapid onset (eg, triazolam) would be indicated. However, if medication is needed to prevent waking later in the night, a benzodiazepine with a slower onset (eg, estazolam) would be preferred. For treatment of anxiety, a drug with an intermediate duration is desirable. For treatment of any benzodiazepine-responsive condition in the elderly, a drug such as lorazepam, which is not likely to accumulate with repeated dosing, is generally preferred.

Therapeutic Uses

The benzodiazepines have three principal indications: (1) anxiety, (2) insomnia, and (3) seizure disorders. In addition, they are used as preoperative medications and to treat muscle spasm, panic disorder, and withdrawal from alcohol. Although all benzodiazepines share the same pharmacologic properties, and therefore might be equally effective for all applications, not every benzodiazepine is actually employed for all potential uses. The principal factors that determine the actual applications of a particular benzodiazepine are (1) the pharmacokinetic properties of the drug itself and (2) research and marketing decisions of pharmaceutical companies. Specific applications of individual benzodiazepines are summarized in Table 34-2.

Generic Name [Trade Name]	Approved Applications						
	GAD*	Insomnia	Seizures	Muscle Spasm, Spasticity	Alcohol Withdrawal	Anesthesia Induction or Preanesthesia	Panic Disorder
Alprazolam [Xanax, Niravam]	✓						✓
Chlordiazepoxide [Librium]	✓				✓		
Clonazepam [Klonopin]			✓				✓
Clorazepate [Tranxene]	✓		✓		✓		
Diazepam [Valium, Diastat AcuDial]	✓		✓	✓	✓	✓	
Estazolam (generic only)		✓					
Flurazepam (generic only)		✓					
Lorazepam [Ativan]	✓		✓		✓	✓	✓
Midazolam [Versed]						✓†	
Oxazepam [Serax]	✓				✓		
Quazepam [Doral]		✓					
Temazepam [Restoril]		✓					
Triazolam [Halcion]		✓					

TABLE 34-2 Applications of the Benzodiazepines

* GAD = generalized anxiety disorder.

† Midazolam, in conjunction with an opioid analgesic, is also used to produce *conscious sedation,* a semiconscious state suitable for minor surgeries and endoscopic procedures.

Anxiety.

Benzodiazepines are drugs of first choice for anxiety. Although all benzodiazepines have anxiolytic actions, only six are marketed for this indication (see Table 34-2). Anxiolytic effects result from depressing neurotransmission in the limbic system and cortical areas. Use of benzodiazepines to treat anxiety is discussed in Chapter 35.

Insomnia.

Benzodiazepines are drugs of first choice for insomnia. These drugs decrease latency time to falling asleep, reduce awakenings, and increase total sleeping time. The role of benzodiazepines in managing insomnia is discussed in depth later.

Seizure Disorders.

Four benzodiazepines—diazepam, clonazepam, lorazepam, and clorazepate—are employed for seizure disorders. Antiseizure applications are discussed in Chapter 24.

Muscle Spasm.

One benzodiazepine—diazepam—is used to relieve muscle spasm and spasticity (see Chapter 25). Effects on muscle tone are secondary to actions in the CNS. Diazepam cannot relieve spasm without causing sedation.

Alcohol Withdrawal.

Diazepam and other benzodiazepines may be administered to facilitate withdrawal from alcohol (see Chapter 38). Benefits derive from cross-dependence with alcohol, which enables benzodiazepines to suppress symptoms brought on by alcohol abstinence.

Panic Disorder.

Alprazolam [Xanax, Niravam], clonazepam [Klonopin], and lorazepam [Ativan] can help patients with panic disorder, although certain antidepressants (eg, fluoxetine [Prozac]) are preferred. Drugs for panic disorder are discussed in Chapter 35.

Perioperative Applications.

Three benzodiazepines—diazepam [Valium], lorazepam [Ativan], and midazolam [Versed]—are given IV for *induction of anesthesia*. In addition, midazolam (in combination with an opioid analgesic) can be used to produce *conscious sedation*—a semiconscious state suitable for endoscopic procedures and minor surgeries. Benzodiazepines are also used for *preoperative sedation*. All of these applications are discussed in Chapter 27.

Adverse Effects

Benzodiazepines are generally well tolerated, and serious adverse reactions are rare. In contrast to barbiturates and other general CNS depressants, benzodiazepines are remarkably safe.

CNS Depression.

When taken to promote sleep, benzodiazepines cause drowsiness, lightheadedness, incoordination, and difficulty concentrating. When these effects occur at bedtime, they are generally inconsequential. However, if sedation and other manifestations of CNS depression persist beyond waking, interference with daytime activities can result.

Anterograde Amnesia.

Benzodiazepines can cause anterograde amnesia (impaired recall of events that take place after dosing). Anterograde amnesia has been especially troublesome with *triazolam* [Halcion]. If patients complain of forgetfulness, the possibility of drug-induced amnesia should be evaluated.

Sleep Driving and Other Complex Sleep-Related Behaviors.

Patients taking benzodiazepines in sleep-inducing doses may carry out complex behaviors, and then have no memory of their actions. Reported behaviors include sleep driving, preparing and eating meals, making phone calls, and

having sexual intercourse. Although these events can occur with normal doses, they are more likely when doses are excessive, and when benzodiazepines are combined with alcohol and other CNS depressants. Because of the potential for harm, benzodiazepines should be withdrawn if sleep driving is reported. To minimize withdrawal symptoms, dosing should be tapered slowly, rather than discontinued abruptly.

Paradoxical Effects.

When employed to treat anxiety, benzodiazepines sometimes cause paradoxical responses, including insomnia, excitation, euphoria, heightened anxiety, and rage. If these occur, the benzodiazepine should be withdrawn.

Respiratory Depression.

Benzodiazepines are weak respiratory depressants. Death from overdose with oral benzodiazepines alone has never been documented. Hence, in contrast to the barbiturates, benzodiazepines present little risk as vehicles for suicide. It must be emphasized, however, that although respiratory depression with *oral* therapy is rare, benzodiazepines can cause severe respiratory depression when administered *intravenously*. In addition, substantial respiratory depression can result from combining oral benzodiazepines with other CNS depressants (eg, alcohol, barbiturates, opioids).

Abuse.

Benzodiazepines have a lower abuse potential than barbiturates and most other general CNS depressants. The behavior pattern that constitutes "addiction" is uncommon among people who take benzodiazepines for therapeutic purposes. When asked about their drug use, individuals who regularly abuse drugs rarely express a preference for benzodiazepines over barbiturates. Because their potential for abuse is low, the benzodiazepines are classified under Schedule IV of the Controlled Substances Act. This contrasts with the barbiturates, most of which are classified under Schedule II or III.

Use in Pregnancy and Lactation.

Benzodiazepines are highly lipid soluble and can readily cross the placental barrier. Use of benzodiazepines during the first trimester of pregnancy is as-

sociated with an increased risk of congenital malformations, such as cleft lip, inguinal hernia, and cardiac anomalies. Use near term can cause CNS depression in the neonate. Because they may represent a risk to the fetus, most benzodiazepines are classified in Food and Drug Administration (FDA) Pregnancy Risk Category D. Five of these drugs—estazolam, flurazepam, quazepam, temazepam, and triazolam—are in Category X. Women of child-bearing age should be warned about the potential for fetal harm and instructed to discontinue benzodiazepines if pregnancy occurs.

Benzodiazepines enter breast milk with ease and may accumulate to toxic levels in the breast-fed infant. Accordingly, these drugs should be avoided by nursing mothers.

Other Adverse Effects.

Occasional reactions include weakness, headache, blurred vision, vertigo, nausea, vomiting, epigastric distress, and diarrhea. Neutropenia and jaundice occur rarely. Rarely, benzodiazepines may cause severe allergic reactions, including angioedema and anaphylaxis.

Drug Interactions

Benzodiazepines undergo very few important interactions with other drugs. Unlike barbiturates, benzodiazepines do not induce hepatic drug-metabolizing enzymes. Hence, benzodiazepines do not accelerate the metabolism of other drugs.

CNS Depressants.

The CNS-depressant actions of benzodiazepines add with those of other CNS depressants (eg, alcohol, barbiturates, opioids). Hence, although benzodiazepines are very safe when used alone, they can be extremely hazardous in combination with other depressants. Combined overdose with a benzodiazepine plus another CNS depressant can cause profound respiratory depression, coma, and death. Patients should be warned against use of alcohol and all other CNS depressants.

Tolerance and Physical Dependence

Tolerance.

With prolonged use of benzodiazepines, tolerance develops to some effects but not others. No tolerance develops to anxiolytic effects, and tolerance to hypnotic effects is generally low. In contrast, significant tolerance develops to antiseizure effects. Patients tolerant to barbiturates, alcohol, and other general CNS depressants show some cross-tolerance to benzodiazepines.

Physical Dependence.

Benzodiazepines can cause physical dependence—but the incidence of *substantial* dependence is low. When benzodiazepines are discontinued following short-term use at therapeutic doses, the resulting withdrawal syndrome is generally mild and often goes unrecognized. Symptoms include anxiety, insomnia, sweating, tremors, and dizziness. Withdrawal from long-term, high-dose therapy can elicit more serious reactions, such as panic, paranoia, delirium, hypertension, muscle twitches, and outright convulsions. Symptoms of withdrawal are usually more intense with benzodiazepines that have a short duration of action. With one agent—*alprazolam* [Xanax, Niravam]—dependence may be a greater problem than with other benzodiazepines. Because the benzodiazepine withdrawal syndrome can resemble an anxiety disorder, it is important to differentiate withdrawal symptoms from the return of original anxiety symptoms.

The intensity of withdrawal symptoms can be minimized by discontinuing treatment gradually. Doses should be slowly tapered over several weeks or months. Substituting a benzodiazepine with a long half-life for one with a short half-life is also helpful. Patients should be warned against abrupt cessation of treatment. Following discontinuation of treatment, patients should be monitored for 3 weeks for indications of withdrawal or recurrence of original symptoms.

Acute Toxicity

Oral Overdose.

When administered in excessive dosage by mouth, benzodiazepines rarely cause serious toxicity. Symptoms include drowsiness, lethargy, and confusion. Significant cardiovascular and respiratory effects are uncommon. If an indi-

vidual known to have taken an overdose of benzodiazepines does exhibit signs of serious toxicity, it is probable that another drug was taken too.

Intravenous Toxicity.

When injected IV, even in therapeutic doses, benzodiazepines can cause severe adverse effects. Life-threatening reactions (eg, profound hypotension, respiratory arrest, cardiac arrest) occur in about 2% of patients.

General Treatment Measures.

Benzodiazepine-induced toxicity is managed the same as toxicity from barbiturates and other general CNS depressants. Oral benzodiazepines can be removed from the body with gastric lavage followed by ingestion of activated charcoal and a saline cathartic; dialysis may be helpful if symptoms are especially severe. Respiration should be monitored and the airway kept patent. Support of blood pressure with IV fluids and norepinephrine may be required.

Treatment with Flumazenil.

Flumazenil [Romazicon] is a competitive benzodiazepine receptor antagonist. The drug can reverse the sedative effects of benzodiazepines but may not reverse respiratory depression. Flumazenil is approved for benzodiazepine overdose and for reversing the effects of benzodiazepines following general anesthesia. The principal adverse effect is precipitation of convulsions. This is most likely in patients taking benzodiazepines to treat epilepsy and in patients who are physically dependent on benzodiazepines. Flumazenil is administered IV. Doses are injected slowly (over 30 seconds) and may be repeated every minute as needed. The first dose is 0.2 mg, the second is 0.3 mg, and all subsequent doses are 0.5 mg. Effects of flumazenil fade in about 1 hour, hence additional dosing may be required.

Preparations, Dosage, and Administration

Preparations and Dosage.

Preparations and dosages for *insomnia* are presented later in the chapter. Preparations and dosages of benzodiazepines used for other disorders are presented in Chapter 24 (Drugs for Epilepsy), Chapter 25 (Drugs for Muscle Spasm

and Spasticity), Chapter 27 (General Anesthetics), and Chapter 35 (Management of Anxiety Disorders).

Routes.

All benzodiazepines can be administered orally. In addition, three agents—diazepam, chlordiazepoxide, and lorazepam—may be administered parenterally (IM and IV). When used for sedation or induction of sleep, benzodiazepines are almost always administered by mouth. Parenteral administration is reserved for emergencies, including acute alcohol withdrawal, severe anxiety, and status epilepticus.

Oral.

Patients should be advised to take oral benzodiazepines with food if gastric upset occurs. Also, they should be instructed to swallow sustained-release formulations intact, without crushing or chewing. Patients should be warned not to increase the dosage or discontinue therapy without consulting the prescriber.

For treatment of insomnia, benzodiazepines should be given on an intermittent schedule (eg, 3 or 4 days a week) in the lowest effective dosage for the shortest duration required. This will minimize physical dependence and associated drug-dependency insomnia.

Intravenous.

Intravenous administration is hazardous and must be performed with care. Life-threatening reactions (severe hypotension, respiratory arrest, cardiac arrest) have occurred. In addition, IV administration carries a risk of venous thrombosis, phlebitis, and vascular impairment.

To reduce complications, the following precautions should be taken: (1) inject the drug slowly; (2) take care to avoid intra-arterial injection and extravasation; (3) if direct venous injection is impossible, make the injection into infusion tubing as close to the vein as possible; (4) follow the manufacturer's instructions regarding suitable diluents for preparing solutions; and (5) have facilities for resuscitation available.

Intramuscular.

If IM administration is needed, *lorazepam* is the preferred benzodiazepine to use, owing to consistent absorption from IM sites. Absorption of IM diazepam is erratic and may be delayed. Accordingly, IM diazepam should be avoided.

BENZODIAZEPINE-LIKE DRUGS

Three benzodiazepine-like drugs are available: zolpidem, zaleplon, and eszopiclone. All three are preferred agents for treating insomnia. They are not indicated for anxiety. These drugs are structurally different from benzodiazepines, but nonetheless share the same mechanism of action: They all act as *agonists at the benzodiazepine receptor site* on the GABA receptor–chloride channel complex. These drugs are highly effective hypnotics, and have a low potential for tolerance, dependence, or abuse.

Zolpidem

Zolpidem [Ambien, Ambien CR, ZolpiMist], our most widely used hypnotic, is approved only for short-term management of insomnia. However, although approval is limited to short-term use, many patients have taken the drug long term with no apparent tolerance or increase in adverse effects. All zolpidem formulations have a rapid onset, and hence can help people who have difficulty falling asleep. In addition, the extended-release formulation—Ambien CR—can help people who have difficulty maintaining sleep.

Although structurally unrelated to the benzodiazepines, zolpidem binds to the benzodiazepine receptor site on the GABA receptor–chloride channel complex and shares some properties of the benzodiazepines. Like the benzodiazepines, zolpidem can reduce sleep latency and awakenings and can prolong sleep duration. The drug does not significantly reduce time in rapid-eye-movement (REM) sleep and causes little or no rebound insomnia when therapy is discontinued. In contrast to the benzodiazepines, zolpidem lacks anxiolytic, muscle relaxant, and anticonvulsant actions. Why? Because zolpidem doesn't bind with all benzodiazepine receptors. Rather, binding is limited to the benzodiazepine***1*** subtype of benzodiazepine receptors.

Zolpidem is rapidly absorbed following oral administration. Plasma levels peak in 2 hours. The drug is widely distributed, although levels in the brain

remain low. Zolpidem is extensively metabolized to inactive compounds that are excreted in the bile, urine, and feces. The elimination half-life is 2.4 hours.

Zolpidem has a side effect profile like that of the benzodiazepines. *Daytime drowsiness and dizziness* are most common, and these occur in only 1% to 2% of patients. Like the benzodiazepines, zolpidem has been associated with *sleep driving* and other *sleep-related complex behaviors*. At therapeutic doses, zolpidem causes little or no respiratory depression. Safety in pregnancy has not been established. According to the FDA, zolpidem may pose a small risk of anaphylaxis and angioedema.

Short-term treatment is not associated with significant tolerance or physical dependence. Withdrawal symptoms are minimal or absent. Similarly, the abuse liability of zolpidem is low. Accordingly, the drug is classified under Schedule IV of the Controlled Substances Act.

Like other sedative-hypnotics, zolpidem can intensify the effects of other CNS depressants. Accordingly, patients should be warned against combining zolpidem with alcohol and all other drugs that depress CNS function.

Zolpidem is available in immediate-release tablets (5 and 10 mg) as *Ambien,* extended-release tablets (6.25 and 12.5 mg) as *Ambien CR,* and an oral spray (5 and 10 mg) as *ZolpiMist*. With the immediate-release tablets and oral spray, the usual dose is 10 mg. The initial dose should be reduced to 5 mg for elderly and debilitated patients and for those with hepatic insufficiency. With the extended-release tablets, the usual dose is 12.5 mg (or 6.25 mg for elderly or debilitated patients). All formulations have a rapid onset, and hence should be taken just before bedtime. This timing will promote sleep while minimizing daytime sedation.

Zaleplon

Zaleplon [Sonata] is the first representative of a new class of hypnotics, the pyrazolopyrimidines. The drug is approved only for short-term management of insomnia, but prolonged use does not appear to cause tolerance. Like zolpidem, zaleplon binds to the benzodiazepine***1*** receptor site on the GABA receptor–chloride channel complex, and thereby enhances the depressant actions of endogenous GABA. In contrast to zolpidem, zaleplon has a very rapid

onset and short duration of action, and hence is good for helping patients fall asleep, but not for maintaining sleep.

Zaleplon is rapidly and completely absorbed from the GI tract. However, because of extensive first-pass metabolism, bioavailability is only 30%. A large or high-fat meal can delay absorption substantially. Plasma levels peak about 1 hour after administration and then rapidly decline, returning to baseline in 4 to 5 hours. Zaleplon is metabolized by hepatic aldehyde oxidase prior to excretion in the urine. Its half-life is just 1 hour.

Because of its kinetic profile, zaleplon is well suited for people who have trouble falling asleep, but not for people who can't maintain sleep. The drug can also help people who need a sedative in the middle of the night: Because of its short duration, zaleplon can be taken at 3:00 AM without causing hangover when the alarm goes off at 7:00 AM.

Zaleplon is well tolerated. The most common side effects are headache, nausea, drowsiness, dizziness, myalgia, and abdominal pain. Like the benzodiazepines, zaleplon has been associated with rare cases of sleep driving and other complex sleep-related behaviors. Respiratory depression has not been observed. Physical dependence is minimal, the only sign being mild rebound insomnia the first night after drug withdrawal. Next-day sedation and hangover have not been reported. Like the benzodiazepines, zaleplon has a low potential for abuse, and hence is classified as a Schedule IV drug.

Cimetidine (a drug for peptic ulcer disease) inhibits hepatic aldehyde oxidase, and can thereby greatly increase levels of zaleplon. Accordingly, dosage of zaleplon must be reduced if these drugs are used concurrently.

Zaleplon is available in 5- and 10-mg capsules. The usual dose is 10 mg. The dose should be reduced to 5 mg for (1) the elderly, (2) small individuals, (3) patients with liver impairment, and (4) patients taking cimetidine. The maximum dose is 20 mg. Dosing is usually done just before retiring. However, dosing may also be done after going to bed on nights when sleep fails to come.

Eszopiclone

Eszopiclone [Lunesta], approved in 2005, is the *S*-isomer of zopiclone, a drug used for years in Canada and Europe. Like zaleplon and zolpidem, eszopiclone binds selectively with the benzodiazepine***1*** receptor on the GABA recept-

or–chloride channel complex, and thereby enhances the depressant actions of endogenous GABA.

Eszopiclone is approved for treating insomnia, with no limitation on how long it can be used. This contrasts with zaleplon and zolpidem, which are approved for short-term use only. Does this mean that eszopiclone is safer than the other two drugs, or less likely to promote tolerance? Not necessarily. It only means that the manufacturer of eszopiclone conducted a prolonged (6-month) study, whereas the manufacturers of the other two drugs did not. In that prolonged study, eszopiclone reduced sleep latency and nighttime awakening, increased total sleep time and sleep quality, had no significant effect on sleep architecture, and showed no indication of tolerance.

Eszopiclone is rapidly absorbed after oral dosing, reaching peak blood levels in 1 to 2 hours. The drug undergoes extensive hepatic metabolism, primarily by CYP3A4 (the 3A4 isozyme of cytochrome P450). The resulting inactive (or weakly active) metabolites are excreted in the urine. The elimination half-life is 6 hours.

Eszopiclone is generally well tolerated. The most common adverse effect is a bitter aftertaste, reported by 17% of patients dosed with 2 mg and 34% of those dosed with 3 mg. Other common effects are headache, somnolence, dizziness, and dry mouth. Rebound insomnia may occur on the first night after discontinuing the drug. Like the benzodiazepines and the other benzodiazepine-like drugs, eszopiclone has been associated with cases of sleep driving and other sleep-related complex behaviors. Rarely, eszopiclone may cause anaphylaxis or angioedema. Eszopiclone has a low potential for abuse and hence is classified as a Schedule IV drug.

Eszopiclone [Lunesta] is available in 1-, 2-, and 3-mg tablets. For nonelderly adults, the recommended starting dose is 2 mg, taken just before bedtime. The dose can be raised to 3 mg if needed. For patients with severe hepatic impairment, and for those taking inhibitors of CYP3A4 (eg, ketoconazole), the starting dose is 1 mg. For elderly patients, the starting dose is 1 mg (for those who can't fall asleep) or 2 mg (for those who can't stay asleep).

RAMELTEON: A MELATONIN AGONIST

Ramelteon [Rozerem] is a relatively new hypnotic with a unique mechanism of action: activation of receptors for melatonin. The drug is approved for treating chronic insomnia characterized by difficulty with sleep onset. Long-term use is permitted. Of the major drugs for insomnia, ramelteon is the only one not regulated as a controlled substance.

Therapeutic Use.

Ramelteon has a rapid onset (about 30 minutes) and short duration, and hence is good for inducing sleep but not for maintaining sleep. There are no significant residual effects on the day after dosing. Nor is there any rebound insomnia when treatment is stopped after 35 consecutive nights of use. When approving the drug, the FDA put no limit on how long it may be used.

Mechanism of Action.

Ramelteon activates receptors for melatonin—specifically the MT***1*** and MT***2*** subtypes, which are key mediators of the normal sleep-wakefulness cycle. Sleep promotion derives primarily from activating MT***1*** receptors. (Under physiologic conditions, activation of MT***1*** receptors by endogenous melatonin induces sleepiness.) Ramelteon does not activate MT***3*** receptors, which help regulate numerous systems unrelated to sleep. Selectivity for MT***1*** and MT***2*** receptors explains why ramelteon is superior to melatonin itself for treating insomnia (see Box 34-1). Ramelteon does not bind with the GABA receptor–chloride channel complex, or with receptors for neuropeptides, benzodiazepines, dopamine, serotonin, norepinephrine, acetylcholine, or opioids.

BOX 34-1 MELATONIN: HYPNOTIC OR HYPE?

Melatonin has been the subject of at least four popular books and has received prominent coverage in the media. Proponents claim melatonin can treat insomnia and jet lag, protect against cancer and pregnancy, and prolong life and youthfulness. However, despite the publicity, very little is actually known about melatonin's efficacy or safety. Why? Because only a few clinical trials have been performed—and these were short, poorly designed, and involved just a few subjects. What follows is a summary of what we do know.

Melatonin is a hormone produced by the pineal gland, which is located at the base of the brain. Secretion is suppressed by environmental light and stimulated by darkness. Normally, secretion is low during the day, begins to rise around 9:00 PM, reaches a peak between 2:00 AM and 4:00 AM, and returns to baseline by morning. Signals that control secretion travel along a multineuron pathway that connects the retina to the pineal gland. Nocturnal secretion is greatest in children and declines with age. In blind people, melatonin secretion has no predictable pattern. Melatonin levels are low in insomniacs.

Although melatonin is a hormone, it is marketed as a dietary supplement—not as a drug. As a result, melatonin is not regulated by the FDA and has not been reviewed for safety and efficacy. Because melatonin is not regulated, commercial preparations may contain impurities and may not have the exact amount of melatonin advertised on the label (typically 0.3, 1.5, or 3 mg). Melatonin is the only hormone that can be purchased without a prescription. It is available in health-food stores, vitamin shops, and even airport newsstands.

Several small, short-term trials suggest that melatonin can promote sleep. For example, doses of 0.3 to 1 mg taken 1 to 2 hours before bedtime hastened onset of sleep and the time to REM sleep, without reducing total time in REM sleep. At a slightly higher dose (2 mg of a controlled-release formulation 2 hours before bedtime), melatonin hastened sleep onset by 14 minutes and decreased total time awake during the night by 24 minutes. When taken in huge doses (80 to 100 mg) at noon, melatonin can cause daytime fatigue. In blind insomniacs, taking melatonin for 3 weeks normalized the melatonin production cycle and relieved insomnia. Because small doses may fail to elevate melatonin levels throughout the night, maintenance of sleep may be best with larger doses or with sustained-release formulations.

Benefits of melatonin in jet lag are in doubt. Two older studies suggest that melatonin can help. In one, the severity and duration of jet lag were reduced by taking 5 mg of melatonin once daily for 3 days before the flight and for 3 days after. In the other, subjective feelings of fatigue were reduced by taking 8 mg at 10:00 PM on the evening of the flight and for 3 days after. However, these results were not supported by a large, double-blind trial reported in 1999. This trial involved 257 Norwegian physicians flying home from New York. They were randomly assigned to one of four regimens: placebo, 0.5 mg

of melatonin at bedtime, 5 mg at bedtime, or 0.5 mg taken at bedtime on the first night and then progressively earlier each day after. Dosing started on the day of their flight and continued for 5 days after. The result? Melatonin had no effect: Symptoms of jet lag in all three treatment groups were the same as those in the placebo group.

When used short term in low doses (eg, under 2 mg), melatonin has not caused observable adverse effects. In contrast, short-term use of large doses has caused hangover, headache, nightmares, hypothermia, and transient depression. In one case, reversible psychosis occurred with a huge daytime dose. Possible adverse effects of long-term use are unknown.

In conclusion, melatonin is the miracle that awaits definitive proof. Although benefits in jet lag seem unlikely, small studies on insomnia *have* been encouraging. However, large-scale, long-term, carefully controlled trials are needed to prove that melatonin is truly safe and effective for insomnia, and to establish optimal dosages and dosing schedules.

Pharmacokinetics.

Absorption is rapid and nearly complete, although food can reduce both the rate and extent of absorption. Despite generally good absorption, the absolute bioavailability of ramelteon is very low—only 1.8%, owing to extensive first-pass metabolism, primarily by hepatic CYP1A2 (the 1A2 isozyme of cytochrome P450). Much of each dose is converted to an active metabolite, designated M-II, that contributes to therapeutic effects. The half-lives of the parent drug and active metabolite average 2 to 5 hours. In patients with hepatic impairment, elimination is delayed and drug levels can rise. Renal impairment does not affect drug levels.

Adverse Effects.

Ramelteon is very well tolerated. In clinical trials, the incidence of adverse effects was nearly identical to that of placebo. The most common side effects are somnolence (5% vs. 3% with placebo), dizziness (5% vs. 3%), and fatigue (4% vs. 2%). According to the FDA, ramelteon may share the ability of benzodiazepines to cause sleep driving and other sleep-related complex behaviors.

Ramelteon can increase levels of prolactin and reduce levels of testosterone. As a result, the drug has the potential to cause amenorrhea, galactorrhea, reduced libido, and fertility problems. If these occur, the prescriber should be consulted.

Physical Dependence and Abuse.

There is no evidence that taking ramelteon leads to physical dependence or abuse. As a result, ramelteon is the first FDA-approved sleep remedy that is not regulated under the Controlled Substances Act.

Drug Interactions.

Fluvoxamine [Luvox], a strong inhibitor of CYP1A2, can increase levels of ramelteon more than 50-fold. Accordingly, the combination should be avoided. Weaker inhibitors of CYP1A2 should be used with caution. Alcohol can intensify sedation, and hence should be avoided.

Precautions.

Ramelteon should be used with caution by patients with moderate hepatic impairment, and should be avoided by those with severe impairment. Because ramelteon promotes sedation, patients should be advised to avoid dangerous activities, such as operating a motor vehicle or heavy machinery.

Use in Pregnancy and Breast-Feeding.

Very high doses (197 times the human dose) are teratogenic in rats. Effects during human pregnancy have not been studied. Until more is known, prudence dictates avoiding the drug during pregnancy (or at least using it with caution). Ramelteon is not recommended for use by nursing mothers.

Preparations, Dosage, and Administration.

Ramelteon [Rozerem] is available in 8-mg tablets. The usual dosage is 8 mg taken 30 minutes before bedtime. Because food reduces absorption, ramelteon should not be taken with or immediately after a high-fat meal.

BARBITURATES

The barbiturates have been available for more than 100 years. These drugs cause relatively nonselective depression of CNS function and are the prototypes of the general CNS depressants. Because they depress multiple aspects of CNS function, barbiturates can be used for daytime sedation, induction of sleep, suppression of seizures, and general anesthesia. Barbiturates cause tolerance and dependence, have a high abuse potential, and are subject to multiple drug interactions. Moreover, barbiturates are powerful respiratory depressants that can be fatal in overdose. Because of these undesirable properties, barbiturates are used much less than in the past, having been replaced by newer and safer drugs—primarily the benzodiazepines and benzodiazepine-like drugs (eg, zolpidem). However, although their use has declined greatly, barbiturates still have important applications in seizure control and anesthesia. Moreover, barbiturates are valuable from an instructional point of view: By understanding these prototypic agents, we gain an understanding of the general CNS depressants as a group, along with an appreciation of why barbiturates are no longer used for anxiety and insomnia.

Classification

The barbiturates can be grouped into three classes based on duration of action: (1) ultrashort-acting agents, (2) short to intermediate-acting agents, and (3) long-acting agents. As indicated in Table 34-3, the duration of action of these drugs is inversely related to their lipid solubility. Barbiturates with the highest lipid solubility have the shortest duration of action. Conversely, barbiturates with the lowest lipid solubility have the longest duration.

Duration of action influences the clinical applications of barbiturates. The ultrashort-acting agents (eg, thiopental) are used for induction of anesthesia. The short to intermediate-acting agents (eg, secobarbital) are used as sedatives and hypnotics. The long-acting agents (eg, phenobarbital) are used primarily as antiseizure drugs.

Barbiturate Subgroups	Representative Drug	Lipid Solubility	Time Course		Applications
			Onset (min)	Duration (hr)	
Ultrashort-acting	Thiopental	High	0.5	0.2	Induction of anesthesia; treatment of seizures
Short- to intermediate-acting	Secobarbital	Moderate	10–15	3–4	Treatment of insomnia
Long-acting	Phenobarbital	Low	60 or less	10–12	Treatment of seizures

TABLE 34-3 Characteristics of Barbiturate Subgroups

Mechanism of Action

Like benzodiazepines, barbiturates bind to the GABA receptor–chloride channel complex (see Fig. 34-1). By doing so, these drugs can (1) enhance the inhibitory actions of GABA and (2) directly mimic the actions of GABA.

Since barbiturates can directly mimic GABA, there is no ceiling to the degree of CNS depression they can produce. Hence, in contrast to the benzodiazepines, these drugs can readily cause death by overdose. Although barbiturates can cause general depression of the CNS, they show some selectivity for depressing the *reticular activating system* (RAS), a neuronal network that helps regulate the sleep-wakefulness cycle. By depressing the RAS, barbiturates produce sedation and sleep.

Pharmacologic Effects

CNS Depression.

Most effects of barbiturates—both therapeutic and adverse—result from generalized depression of CNS function. With increasing dosage, responses progress from sedation to sleep to general anesthesia.

Most barbiturates can be considered nonselective CNS depressants. The main exception is phenobarbital, a drug used to control seizures. Seizure control is achieved at doses that have minimal effects on other aspects of CNS function.

Cardiovascular Effects.

At hypnotic doses, barbiturates produce modest reductions in blood pressure and heart rate. In contrast, toxic doses can cause profound hypotension and shock. How? At high doses, barbiturates depress the myocardium and vascular smooth muscle—as well as all other electrically excitable tissues.

Induction of Hepatic Drug-Metabolizing Enzymes.

Barbiturates stimulate synthesis of hepatic microsomal enzymes, the principal drug-metabolizing enzymes of the liver. As a result, barbiturates can accelerate their own metabolism and the metabolism of many other drugs.

Barbiturates stimulate drug metabolism by promoting the synthesis of porphyrin (Fig. 34-2). Porphyrin is then converted into heme, which in turn is incorporated into cytochrome P450, a key component of the hepatic drug-metabolizing system.

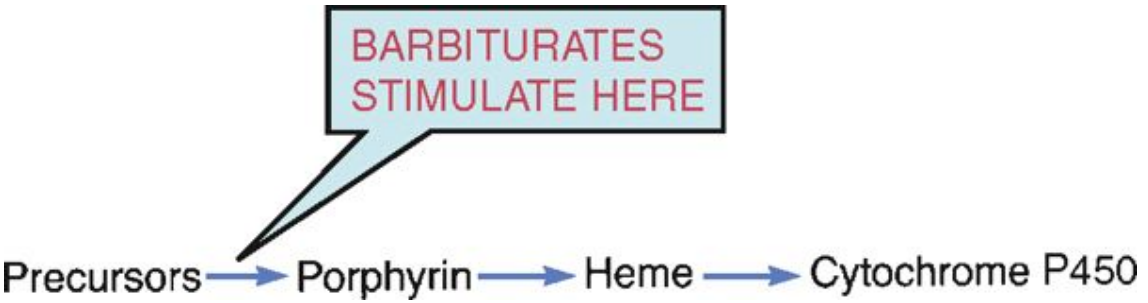


Figure 34-2 Induction of hepatic microsomal enzymes by barbiturates. By increasing synthesis of porphyrin, barbiturates increase production of cytochrome P450, a key component of the hepatic drug-metabolizing system.

Tolerance and Physical Dependence

Tolerance.

Tolerance is defined as reduced drug responsiveness that develops over the course of repeated drug use. When barbiturates are taken regularly, tolerance develops to many—but not all—of their CNS effects. Specifically, tolerance develops to sedative and hypnotic effects and to other effects that underlie barbiturate abuse. However, even with chronic use, *very little tolerance develops to toxic effects*.

In the tolerant user, doses must be increased to produce the same intensity of response that could formerly be achieved with smaller doses. Hence, individuals who take barbiturates for prolonged periods—be it for therapy or recreation—require steadily increasing doses to achieve the effects they desire.

It is important to note that *very little tolerance develops to respiratory depression*. Because tolerance to respiratory depression is minimal, and because tolerance does develop to therapeutic effects, with continued treatment, the lethal (respiratory-depressant) dose remains relatively constant while the therapeutic dose climbs higher and higher (Fig. 34-3). As tolerance to therapeutic effects increases, the therapeutic dose grows steadily closer to the lethal dose—a situation that is clearly hazardous.

As a rule, tolerance to one general CNS depressant bestows tolerance to all other general CNS depressants. Hence, there is cross-tolerance among barbiturates, alcohol, benzodiazepines, general anesthetics, chloral hydrate, and a number of other agents. Tolerance to barbiturates and the other general CNS depressants does *not* produce significant cross-tolerance with opioids (eg, morphine).

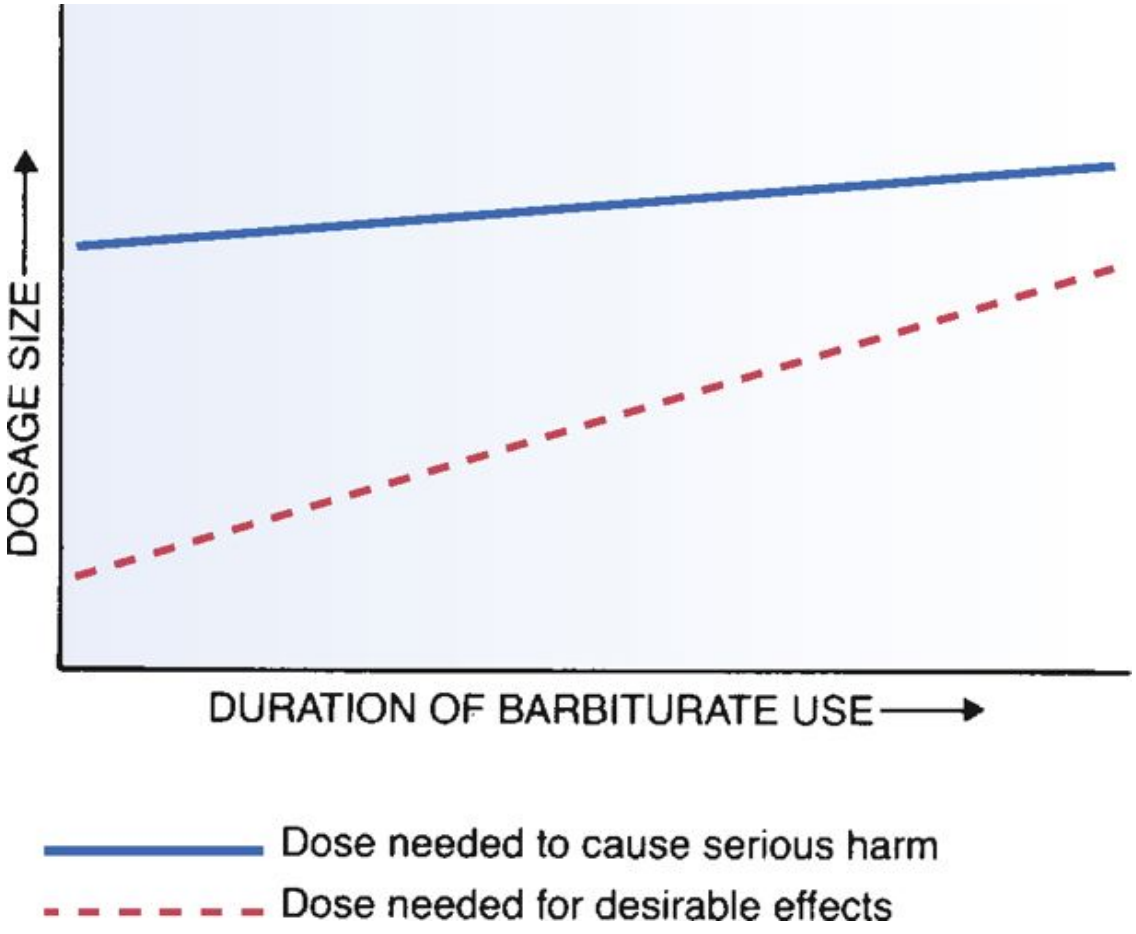


Figure 34-3 Development of tolerance to the toxic and subjective effects of barbiturates. With prolonged barbiturate use, tolerance develops. However, less tolerance develops to toxic effects than to desired effects. Consequently, as duration of use increases, the difference between the dose producing desirable effects and the dose producing toxicity becomes progressively smaller, thereby increasing the risk of serious harm.

Physical Dependence.

Prolonged use of barbiturates results in physical dependence, a state in which continued use is required to avoid an abstinence syndrome. Physical dependence results from adaptive neurochemical changes that occur in response to chronic drug exposure.

Individuals who are physically dependent on barbiturates exhibit cross-dependence with other general CNS depressants. Because of cross-dependence, a person physically dependent on barbiturates can prevent withdrawal symptoms by taking any other general CNS depressant (eg, alcohol, benzodiazepines). As a rule, cross-dependence exists among all of the general CNS depressants. However, there is no significant cross-dependence with opioids.

The general CNS depressant abstinence syndrome can be severe. Contrary to popular understanding, abrupt withdrawal from general CNS depressants is more dangerous than withdrawal from opioids. Although withdrawal from opioids is certainly unpleasant, the risk of serious injury is low. In contrast, the abstinence syndrome associated with general CNS depressants can be fatal.

The following description illustrates how dangerous withdrawal from general CNS depressants can be. Early reactions include weakness, restlessness, insomnia, hyperthermia, orthostatic hypotension, confusion, and disorientation. By the third day, major convulsive episodes may develop. Approximately 75% of patients experience psychotic delirium (a state similar to alcoholic delirium tremens). In extreme cases, these symptoms may be followed by exhaustion, cardiovascular collapse, and death. The entire abstinence syndrome evolves over approximately 8 days. The intensity of symptoms can be greatly reduced by withdrawing general CNS depressants slowly.

A long-acting barbiturate (eg, phenobarbital) may be administered to facilitate the withdrawal process. Because of cross-dependence, phenobarbital can substitute for other CNS depressants, and can thereby suppress symptoms of withdrawal. Because phenobarbital leaves the body slowly, treatment permits a gradual transition from a drug-dependent state to a drug-free state. When phenobarbital is given to aid withdrawal, its dosage should be reduced gradually over 10 days to 3 weeks.

It is important to note that physical dependence should not be equated with addiction. Addiction is defined as a behavior pattern characterized by continued drug use despite physical, psychologic, or social harm. Although physical dependence can contribute to this behavior pattern, physical dependence, by itself, will neither cause nor sustain addictive behavior. The distinction

between addiction and physical dependence is discussed further in Chapter 37 (Drug Abuse I: Basic Considerations).

Pharmacokinetics

Lipid solubility has a significant impact on the pharmacokinetic properties of individual barbiturates. As noted, barbiturates of high lipid solubility have a rapid onset and brief duration. Onset is rapid because lipid solubility allows these drugs to penetrate the blood-brain barrier with ease, thereby reaching sites of action quickly. As they undergo uptake by tissues other than the brain, levels in plasma fall, creating a concentration gradient favoring movement from the brain back into the blood. As a result, highly lipid-soluble barbiturates undergo rapid redistribution from the brain back into the blood and then into other tissues. This redistribution terminates CNS effects.

In comparison to the highly lipid-soluble agents, barbiturates of lower lipid solubility have effects of relatively slow onset but prolonged duration. Onset is delayed because low lipid solubility impedes passage across the blood-brain barrier. Effects are prolonged because termination is dependent on renal excretion and hepatic metabolism—processes that are slower than simple redistribution from the brain to other tissues.

With the exception of the highly lipid-soluble agents, all of the barbiturates have long half-lives. These half-lives are so long, in fact, that significant amounts remain in plasma more than 24 hours after giving a single dose. This persistence has two clinical consequences: First, when barbiturates are taken at night to promote sleep, residual drug may cause sedation the following day. Second, since barbiturates are not eliminated entirely in 24 hours, daily administration produces accumulation. As a result, the brain undergoes continuous exposure to progressively higher levels of drug—a phenomenon that promotes tolerance.

Therapeutic Uses

Seizure Disorders.

Two barbiturates—phenobarbital and mephobarbital—are employed to treat seizure disorders (see Chapter 24). These drugs suppress seizures at doses that are essentially nonsedative.

Induction of Anesthesia.

Thiopental and other highly lipid-soluble barbiturates are given to induce general anesthesia (see Chapter 27). Unconsciousness develops within seconds of IV injection.

Insomnia.

By depressing the CNS, barbiturates can promote sleep. However, because they can cause multiple undesired effects, barbiturates have been replaced by benzodiazepines and related drugs as treatments of choice for insomnia.

Other Uses.

Barbiturates have been used to treat acute manic states and delirium. In children, they can decrease restlessness secondary to colic, pylorospasm, and whooping cough. In addition, they can help reduce anxiety in children prior to minor dental and medical procedures. Excessive excitation from overdose with CNS stimulants (eg, amphetamine, theophylline, ephedrine) can be decreased with barbiturates. They can also be employed for emergency treatment of convulsions caused by tetanus, eclampsia, and epilepsy. When administered in anesthetic doses, barbiturates can help reduce mortality from head injury; deep anesthesia reduces the brain's requirements for oxygen and glucose and thereby helps preserve CNS function. However, until anesthetic levels are achieved, barbiturates *increase* sensitivity to pain, and hence should not be used until pain is under control.

Adverse Effects

Respiratory Depression.

Barbiturates reduce ventilation by two mechanisms: (1) depression of brainstem neurogenic respiratory drive and (2) depression of chemoreceptive mechanisms that control respiratory drive. Doses only 3 times greater than those needed to induce sleep can cause complete suppression of the neurogenic respiratory drive. With severe overdose, barbiturates can cause apnea and death.

For most patients, the degree of respiratory depression produced at therapeutic doses is not significant. However, in elderly patients and those with respiratory disease, therapeutic doses can compromise respiration substantially. Combining a barbiturate with another CNS depressant intensifies respiratory depression.

Suicide.

Barbiturates have a low therapeutic index. Accordingly, overdose can readily cause death. Because of their toxicity, the barbiturates are frequently employed as vehicles for suicide, and hence should not be dispensed to patients with suicidal tendencies.

Abuse.

Barbiturates produce subjective effects that many individuals find desirable. As a result, they are popular drugs of abuse. The barbiturates that are most prone to abuse are those in the short to intermediate-acting group (eg, secobarbital). Individual barbiturates within the group are classified under Schedule II or III of the Controlled Substances Act, reflecting their high potential for abuse. Although barbiturates are frequently abused in nonmedical settings, they are rarely abused during medical use.

Use in Pregnancy.

Barbiturates readily cross the placenta and can injure the developing fetus. Women of child-bearing age should be informed about the potential for fetal harm and warned against becoming pregnant. Use of barbiturates during the third trimester may cause drug dependence in the infant.

Exacerbation of Intermittent Porphyria.

Barbiturates can intensify attacks of acute intermittent porphyria, a condition brought on by excessive synthesis of porphyrin. Symptoms include nausea, vomiting, abdominal colic, neuromuscular disturbances, and disturbed behavior. Barbiturates exacerbate porphyria by stimulating porphyrin synthesis (see Fig. 34-2). Because they intensify porphyria, barbiturates are absolutely contraindicated for individuals with a history of the disorder.

Hangover.

Barbiturates have long half-lives, and therefore can produce residual effects (hangover) when taken for insomnia. Hangover can manifest as sedation, impaired judgment, and reduced motor skills. Patients should be forewarned that their ability to perform complex tasks, both manual and intellectual, may be significantly decreased the day after taking a barbiturate to induce sleep.

Paradoxical Excitement.

In some patients, especially the elderly and debilitated, barbiturates may cause excitation. The mechanism of this paradoxical response is unknown.

Hyperalgesia.

Barbiturates can intensify sensitivity to pain. In addition, they may cause pain directly. These drugs have caused muscle pain, joint pain, and pain along nerves.

Drug Interactions

CNS Depressants.

Drugs with CNS-depressant properties (eg, barbiturates, benzodiazepines, alcohol, opioids, antihistamines) intensify each other's effects. If these agents are combined, fatal CNS depression can result. Accordingly, patients should be warned emphatically against combining barbiturates with alcohol and other drugs that can depress CNS function.

Interactions Resulting from Induction of Drug-Metabolizing Enzymes.

As discussed above, barbiturates stimulate synthesis of hepatic drug-metabolizing enzymes, thereby accelerating metabolism of other drugs. Increased metabolism is of particular concern with *warfarin* (an anticoagulant), *oral contraceptives,* and *phenytoin* (an antiseizure agent). When these drugs are taken concurrently with a barbiturate, their dosages should be increased.

Following barbiturate withdrawal, rates of drug metabolism gradually decline to baseline values. Several weeks are required for this to occur. Drug dosages

that had been increased to account for augmented metabolism must now be reduced to their prebarbiturate amount.

Acute Toxicity

Acute intoxication with barbiturates is a medical emergency; left untreated, overdose can be fatal. Poisoning is often the result of attempted suicide, although it can also occur by accident (usually in children and drug abusers). Since acute toxicity from barbiturates and other general CNS depressants is very similar, the discussion below applies to all of these drugs.

Symptoms.

Acute overdose produces a classic triad of symptoms: *respiratory depression, coma,* and *pinpoint pupils*. (Pupils may later dilate as hypoxia caused by respiratory depression sets in.) The three classic symptoms are frequently accompanied by *hypotension* and *hypothermia*. Death is likely to be the result of pulmonary complications and renal failure.

Treatment.

Proper management requires an intensive care unit. With vigorous treatment, most patients recover fully.

Treatment has two main objectives: (1) removal of barbiturate from the body and (2) maintenance of an adequate oxygen supply to the brain. Oxygenation can be maintained by keeping the airway patent and giving oxygen.

Several measures can promote barbiturate removal. Unabsorbed drug can be removed from the stomach (using gastric lavage) and from the intestine (using a saline cathartic). Drug that has already been absorbed can be removed with hemodialysis. For phenobarbital and other barbiturates that are excreted intact in the urine, forced diuresis and alkalinization of urine may facilitate their renal excretion.

Steps should be taken to prevent hypotension and loss of body heat. Blood pressure can be supported with fluid replacement and dopamine. Body heat can be maintained with blankets and warming devices.

Barbiturate poisoning has no specific antidote. CNS stimulants should definitely *not* be employed. Not only are stimulants ineffective, they are dangerous:

Their use in barbiturate poisoning has been associated with a significant increase in mortality. Naloxone, a drug that can reverse poisoning by opioids, is *not* effective against poisoning by barbiturates.

Administration

Oral.

Oral administration is employed for daytime sedation and to treat insomnia. Patients should be warned not to increase their dosage or discontinue treatment without consulting the prescriber. Dosages should be reduced for elderly patients. When terminating therapy, the dosage should be gradually tapered.

Intravenous.

Intravenous administration is reserved for general anesthesia and emergency treatment of convulsions. Injections should be made slowly to minimize respiratory depression and hypotension. Blood pressure, pulses, and respiration should be monitored, and facilities for resuscitation should be available. The patient should be under continuous observation. Extravasation may result in local necrosis, hence care must be taken to ensure that extravasation does not occur. Solutions that are cloudy or contain a precipitate should not be used. Intra-arterial injection should be avoided, owing to a risk of gangrene secondary to prolonged arteriospasm.

Intramuscular.

Barbiturate solutions are highly alkaline and can cause pain and necrosis when injected IM. Consequently, IM injection is generally avoided. Injection in the vicinity of peripheral nerves can cause irreversible neurologic injury.

MISCELLANEOUS SEDATIVE-HYPNOTICS

Basic Pharmacologic Profile

The three drugs discussed in this section are nonselective CNS depressants, with actions much like those of the barbiturates. At therapeutic doses, they can cause substantial drowsiness, and hence patients should avoid driving and other hazardous activities. Combining these drugs with other CNS depress-

ants (eg, alcohol, barbiturates, benzodiazepines, opioids, antihistamines) can produce profound depression of CNS function, and hence must be avoided. Prolonged use can produce tolerance and physical dependence. Consequently, these agents should be reserved for short-term therapy. In patients who have been treated long term, termination should be done gradually to minimize the withdrawal reaction. The nonselective CNS depressants can produce subjective effects that individuals prone to drug abuse consider desirable. As a result, the agents discussed here are classified under Schedule IV of the Controlled Substances Act.

In general, acute overdose resembles poisoning with barbiturates. Characteristic signs are respiratory depression, coma, miosis, and hypotension. Management is the same as with barbiturate poisoning. Because overdose can cause potentially fatal respiratory depression, these drugs should not be given to patients suspected of suicidal tendencies.

Nonselective CNS depressants should be avoided during pregnancy and lactation. Some of these agents may cause birth defects, especially if taken during the first trimester. In addition, if these drugs are taken late in pregnancy, the infant may be born drug dependent. These drugs can achieve concentrations in breast milk that are sufficient to cause lethargy in the infant. Accordingly, nursing mothers should not use them.

Chloral Hydrate

Chloral hydrate [Aquachloral Supprettes, Somnote] is a general CNS depressant with properties similar to those of the barbiturates. This agent is a prodrug that undergoes rapid conversion to its active form in the liver. The drug's principal application is induction of sleep. However, tolerance to hypnotic effects develops quickly, and withdrawal is associated with sleep disruption and nightmares.

Chloral hydrate is supplied in capsules (500 mg), a syrup (50 and 100 mg/mL), and suppositories (324 and 648 mg). Patients should be instructed to swallow the capsules intact, without crushing or chewing. The syrup should be diluted with water, fruit juice, or ginger ale. With oral administration, epigastric distress, nausea, and flatulence are common.

The recommended dosage is 0.5 to 1 gm 30 minutes before bedtime. However, doses in this range are frequently too low to induce sleep. To elicit an adequate response, as much as 2 gm may be needed.

Chloral hydrate is subject to abuse and is classified as a Schedule IV drug. Abuse is similar to that seen in alcoholism. Prolonged consumption of chloral hydrate results in substantial tolerance and physical dependence. As a result, chloral hydrate addicts may ingest extremely large amounts of the drug. Abrupt withdrawal can cause delirium and seizures. Left untreated, the abstinence syndrome can be fatal.

Meprobamate

Meprobamate [Miltown] has pharmacologic properties that lie between those of barbiturates and benzodiazepines. As a CNS depressant, meprobamate is more selective than barbiturates but less selective than benzodiazepines. Meprobamate induces hepatic drug-metabolizing enzymes and can exacerbate intermittent porphyria. Its only indication is short-term management of anxiety. However, it is rarely used today. Meprobamate is available in 200- and 400-mg tablets. The usual adult dosage is 1.2 to 1.6 gm/day in three or four divided doses. Meprobamate is a Schedule IV drug.

Paraldehyde

Paraldehyde [Paral] is a general CNS depressant indicated for insomnia and management of alcoholic delirium tremens. The drug is employed almost exclusively in hospitals and institutions. Use by outpatients is rare.

Poisoning with paraldehyde is different from poisoning with other CNS depressants. In addition to causing respiratory depression and hypotension, paraldehyde causes prominent metabolic acidosis. Symptoms of toxicity include rapid, labored breathing; bleeding gastritis; toxic hepatitis; nephrosis; pulmonary hemorrhage; and edema. An oral dose of 25 mL can be fatal.

Solutions of paraldehyde decompose rapidly to acetic acid. Preparations that smell strongly of acetic acid (ie, that smell like vinegar) should be discarded. Since decomposition occurs rapidly, containers that have been open for more than 24 hours should not be used.

Administration may be oral or rectal (as a retention enema). Oral paraldehyde has an unpleasant taste and irritates the throat and stomach. The usual oral dosage for adults is 4 to 8 mL diluted in milk or iced fruit juice to improve palatability. Paraldehyde is a Schedule IV drug.

MANAGEMENT OF TRANSIENT INSOMNIA

Insomnia can be defined as an inability to sleep well. Some people have difficulty falling asleep, some have difficulty maintaining sleep, some are troubled by early morning awakening, and some have sleep that is not refreshing. Insomnia is transient for some people and chronic for others. In any given year, about 30% of Americans experience short-term insomnia, and about 10% experience chronic insomnia. In the United States, the direct costs of insomnia total about $13.9 billion a year—a figure that includes the costs of testing, prescriber visits, and hypnotic drugs.

As a result of sleep loss, insomniacs experience daytime drowsiness along with impairment of mood, memory, coordination, and the ability to concentrate and make decisions. Chronic insomnia is major risk factor for automotive and industrial accidents, marital and social problems, major depression, coronary heart disease, and metabolic and endocrine dysregulation.

Loss of sleep is often the result of a medical condition. Psychiatric disorders often disturb sleep, and pain can keep anyone awake. Sleep is frequently lost owing to concern regarding impending surgery and other procedures.

At one time or another, nearly everyone suffers from situational insomnia. Worry about exams may keep students awake. Job-related pressures may deprive workers of sleep. Deadlines may keep authors awake. Unfamiliar surroundings may keep travelers awake. Major life stressors (bereavement, divorce, loss of job) frequently disrupt sleep. Other factors, such as uncomfortable bedding, excessive noise, and bright light, can deprive us of sound sleep.

Sleep Phases

The sleeping state has two primary phases: *rapid-eye-movement* (REM) sleep and *non–rapid-eye-movement* (NREM) sleep. NREM sleep is further divided into four stages, labeled I, II, III, and IV. Sleep is relatively light in stages I and II, and deep in stages III and IV. REM sleep is the phase when most recallable

dreams occur. In a typical night, we go through four to six REM periods. Males often experience penile erection during REM sleep, a curious phenomenon unrelated to dream content. The percentage of time spent in each sleep phase is as follows:

- Stage I: 5%
- Stage II: 50%–60%
- Stages III and IV: 10%–20%
- REM: 20%–25%

Basic Principles of Management

Cause-Specific Therapy

Treatment is highly dependent on the cause of insomnia. Accordingly, if therapy is to succeed, the underlying reason for sleep loss must be determined. To make this assessment, a thorough history is required.

When the cause of insomnia is a known medical disorder, primary therapy should be directed at the underlying illness; hypnotics should be employed only as adjuncts. For example, if pain is the reason for lack of sleep, analgesics should be prescribed. If insomnia is secondary to major depression, antidepressants are the appropriate treatment. If anxiety is the cause of insomnia, the patient should be given an anxiolytic.

Nondrug Therapy

For many insomniacs, nondrug measures may be all that is needed to promote sleep. For some individuals, avoidance of naps and adherence to a regular sleep schedule is sufficient. For others, decreased consumption of caffeine-containing beverages (eg, coffee, tea, cola drinks) may fix the problem. Still others may benefit from restful activity as bedtime nears. If environmental factors are responsible for lack of sleep, the patient should be taught how to correct them or compensate for them. All patients should be counseled about sleep fitness (also known as sleep hygiene). Rules for sleep fitness are summarized in Table 34-4.

A recent study found that *cognitive behavioral therapy* is *superior* to drug therapy (with zopiclone) for short-term and long-term management of chronic insomnia in older adults. The cognitive and behavioral interventions employed were sleep restriction, control of bedroom environment, cognitive therapy, progressive relaxation, and education about sleep hygiene.

Therapy with Hypnotic Drugs

Hypnotics should be used only when insomnia cannot be managed by other means. Hence, before resorting to drugs, we should implement nondrug measures, and we should treat any pathology that may underlie inadequate sleep.

Drug therapy of transient insomnia should be short term (just 2 to 3 weeks). The patient should be reassessed on a regular basis to determine if drug therapy is still needed.

Escalation of dosage should be avoided. A need for increased dosage suggests development of tolerance. If hypnotic effects are lost in the course of treatment, it is preferable to interrupt therapy rather than elevate dosage. Interruption will allow tolerance to decline, thereby restoring responsiveness to treatment.

TABLE 34-4 Rules for Sleep Fitness

- Establish a regular time to go to bed and a regular time to rise. This will help reset your biologic clock.
- Sleep only as long as needed to feel refreshed. Too much time in bed causes fragmented and shallow sleep. In contrast, restricting time in bed helps consolidate and deepen sleep.
- Insulate your bedroom against light and sounds that disturb your sleep (eg, install carpeting and insulated curtains).
- Keep your bedroom temperature moderate. High temperature may disturb sleep.
- Exercise daily, but not later than 7:00 PM. Regular exercise helps deepen sleep.
- Avoid daytime naps. Staying awake during the day helps you sleep at night.
- Avoid caffeine, especially in the evening.

- Avoid consuming too much fluid in the evening so as to minimize nighttime trips to the bathroom.
- Avoid alcohol in the evening. Although alcohol can help you fall asleep, it causes sleep to be fragmented.
- Avoid tobacco; it disturbs sleep (and shortens your life, too).
- Try having a light snack near bedtime, since hunger can disturb sleep—but don't eat heavily.
- Relax before bedtime with soft music, mild stretching, yoga, or pleasurable reading.
- Leave your problems outside the bedroom. Reserve time earlier in the evening to work on problems and to plan tomorrow's activities.
- Reserve your bedroom for sleeping (and sex). This will help condition your brain to see the bedroom as a place where sleep happens. Don't eat, read, or watch TV in bed.
- If you don't fall asleep within 20 minutes or so, get up and do something relaxing (eg, read, listen to music, watch TV), and then return to bed when you feel drowsy. Repeat as often as required.
- Don't look at the clock if you wake up during the night. If necessary, turn its face away from the bed.

In certain patients, hypnotics must be employed with special caution. Patients who snore heavily and those with respiratory disorders have reduced respiratory reserve, which can be further compromised by the respiratory-depressant actions of hypnotics. Hypnotic agents are generally contraindicated for use during pregnancy; these drugs have the potential to cause fetal harm, and their use is never an absolute necessity.

Patients taking hypnotics should be forewarned that residual CNS depression may persist the next day. Although CNS depression may not be pronounced, it may still compromise intellectual or physical performance.

When hypnotics are employed, care must be taken to prevent *drug-dependency insomnia,* a condition that can lead to inappropriate prolongation of therapy. Drug-dependency insomnia is a particular problem with older hypnotics (eg, barbiturates), and develops as follows: (1) Insomnia motivates treatment with

hypnotics. (2) With continuous drug use, low-level physical dependence develops. (3) Upon cessation of treatment, a mild withdrawal syndrome occurs and disrupts sleep. (4) Failing to recognize that the inability to sleep is a manifestation of drug withdrawal, the patient becomes convinced that insomnia has returned and resumes drug use. (5) Continued drug use leads to heightened physical dependence, making it even more difficult to withdraw medication without producing another episode of drug dependency insomnia. To minimize drug-dependency insomnia, hypnotics should be employed judiciously. That is, they should be used in the lowest effective dosage for the shortest time required.

Major Drugs Used for Treatment

Transient insomnia can be treated with prescription drugs, nonprescription drugs, and alternative medicines. Among the prescription drugs, benzodiazepines and the benzodiazepine-like drugs (zolpidem, zaleplon, and eszopiclone) are drugs of first choice. Older sedative-hypnotics, such as barbiturates and chloral hydrate, are rarely used today. Nonprescription drugs and alternative medicines are much less effective than the first-choice drugs, and hence should be reserved for people whose insomnia is mild.

Drug	Time Course: Onset (min)	Time Course: Duration	Use in Insomnia*: DFA	Use in Insomnia*: DMS	Bedtime Dosage (mg): Nonelderly	Bedtime Dosage (mg): Elderly
Benzodiazepines						
Triazolam [Halcion]	15–30	Short	✓		0.125–0.25	0.13
Flurazepam† (generic only)	30–60	Long	✓	✓	30	7.5
Quazepam† [Doral]	20–45	Long	✓	✓	15	7.5
Estazolam (generic only)	15–60	Intermediate		✓	1–2	0.5–1
Temazepam [Restoril]	45–60	Intermediate		✓	15–30	7.5–15
Benzodiazepine-like Drugs						
Eszopiclone [Lunesta]	30	Intermediate	✓	✓	2–3	1–2
Zolpidem						
Immediate release [Ambien]	30	Short	✓		10	5
Extended release [Ambien CR]	30	Intermediate	✓	✓	12.5	6.25
Zaleplon [Sonata]	15–30	Ultrashort	✓		10–20	5
Melatonin Receptor Agonist						
Ramelteon [Rozerem]	30	Short	✓		8	

TABLE 34-5 Major Drugs for Insomnia

* DFA = difficulty falling asleep, DMS = difficulty maintaining sleep.

† Because of its long duration, this drug is not generally recommended.

As shown in Table 34-5, hypnotic drugs differ with respect to onset and duration of action, and hence differ in their applications. Drugs with a rapid onset (eg, zolpidem) are good for patients who have difficulty falling asleep, whereas drugs with a long duration (eg, estazolam) are good for patients who have

difficulty maintaining sleep. Drugs like flurazepam, which have both a rapid onset and long duration, are good for patients with both types of sleep problems.

Benzodiazepines

Benzodiazepines are drugs of first choice for short-term treatment of insomnia. These agents are safe and effective and lack the undesirable properties that typify barbiturates and other older hypnotics. Benzodiazepines have a low abuse potential, cause minimal tolerance and physical dependence, present a minimal risk of suicide, and undergo few interactions with other drugs. Only five benzodiazepines are marketed specifically for use as hypnotics (see Table 34-5). However, any benzodiazepine with a short to intermediate onset could be employed.

Benzodiazepines have multiple desirable effects on sleep: they decrease the latency to sleep onset, decrease the number of awakenings, and increase total sleeping time. In addition, they impart a sense of deep and refreshing sleep. With most benzodiazepines, tolerance to hypnotic actions develops slowly, allowing them to be used nightly for several weeks without a noticeable loss in hypnotic effects. Furthermore, with most benzodiazepines, treatment does not significantly reduce the amount of time spent in REM sleep, and withdrawal is not associated with significant rebound insomnia.

Two agents—*triazolam* [Halcion] and *flurazepam* [Dalmane]—can be considered prototypes of the benzodiazepines used to promote sleep. Triazolam has a rapid onset and short duration, making it a good choice for patients who have difficulty falling asleep (as compared with difficulty maintaining sleep). Flurazepam has a delayed onset and more prolonged duration, making it an effective agent for patients who have difficulty maintaining sleep. However, because flurazepam has a relatively long half-life, the drug is likely to cause daytime drowsiness, and hence is not used widely today. Triazolam has a much shorter half-life than flurazepam, which is both good news and bad news. The good news is that, because it leaves the body rapidly, triazolam does not cause daytime sedation. The bad news is that, because triazolam is rapidly cleared, treatment is associated with two problems: (1) tolerance to hypnotic effects can develop quickly—in 11 to 18 days, which is much faster than with other

benzodiazepines; and (2) triazolam causes more rebound insomnia than other benzodiazepines.

Benzodiazepine-like Drugs: Zolpidem, Zaleplon, and Eszopiclone

Zolpidem [Ambien], zaleplon [Sonata], and eszopiclone [Lunesta] are drugs of first choice for insomnia. In fact, one of these drugs—zolpidem—is prescribed more often than any other hypnotic. All three drugs have the same mechanism as the benzodiazepines—and all three are as effective as the benzodiazepines, and may be safer for long-term use. Furthermore, whereas benzodiazepines are contraindicated during pregnancy, the benzodiazepine-like drugs are not (although use during pregnancy should be discouraged). All three drugs have a rapid onset, and hence can help people with difficulty *falling* asleep. Also, with zolpidem and eszopiclone, effects persist long enough to help people who have difficulty *staying* asleep. In contrast, effects of zaleplon fade too rapidly to help people with trouble staying asleep. However, zaleplon is great for people who wake up in the middle of the night. Why? Owing to its ultrashort duration, zaleplon can be taken a few hours before arising and still not cause drowsiness during the day. Of the three drugs, only eszopiclone has been *proved* effective for long-term use. However, even though long-term studies for zaleplon and zolpidem are lacking, it seems likely that they too would retain efficacy when taken long term.

Ramelteon

Ramelteon [Rozerem] is a melatonin agonist approved for long-term therapy of insomnia. The drug has a rapid onset and short duration, and hence is good for inducing sleep, but not maintaining sleep. Ramelteon does not cause tolerance or dependence, and is not regulated as a controlled substance.

Other Hypnotics

Trazodone

Trazodone [Desyrel] is an atypical antidepressant with strong sedative actions. The drug can decrease sleep latency and prolong sleep duration, and does not cause tolerance or physical dependence. Trazodone is especially use-

ful for treating insomnia resulting from use of antidepressants that cause significant CNS stimulation (eg, fluoxetine [Prozac], bupropion [Wellbutrin]). Principal adverse effects are daytime grogginess and postural hypotension. (Hypotension results from alpha-adrenergic blockade.) The basic pharmacology of trazodone is presented in Chapter 32.

Antihistamines

Two antihistamines—diphenhydramine [Nytol, Sominex, others] and doxylamine [Unisom]—are FDA-approved for use as "sleep aids," and can be purchased without a prescription. These drugs are less effective than benzodiazepines and benzodiazepine-like drugs, and tolerance develops quickly (in 1 to 2 weeks). Daytime drowsiness and anticholinergic effects (eg, dry mouth, blurred vision, urinary hesitancy, constipation) are common.

Alternative Medicines

Of the alternative medicines employed to promote sleep, only two—valerian root *(Valeriana officinalis)* and melatonin—appear moderately effective. Several others—chamomile, passionflower, lemon balm, and lavender—have very mild sedative effects, and proof of benefits in insomnia is lacking. Valerian can help people fall asleep, but does not help them maintain sleep. Furthermore, hypnotic effects take a week or more to develop, and hence valerian is no good for acute therapy. Valerian root is discussed further in Chapter 107 (Dietary Supplements).

KEY POINTS

- Drugs used to treat anxiety are called antianxiety agents, anxiolytics, or tranquilizers.
- Drugs that promote sleep are called hypnotics.
- Barbiturates and other general CNS depressants are undesirable in that they can cause fatal respiratory depression, have a high potential for abuse, cause significant tolerance and physical dependence, and often induce hepatic drug-metabolizing enzymes.

- Benzodiazepines are preferred to barbiturates and other general CNS depressants because they are much safer, have a low abuse potential, cause less tolerance and dependence, and don't induce drug-metabolizing enzymes.
- Although benzodiazepines can cause physical dependence, the withdrawal syndrome is usually mild (except in patients who have undergone prolonged, high-dose therapy).
- To minimize withdrawal symptoms, benzodiazepines should be discontinued gradually, over several weeks or even months.
- Benzodiazepines cause minimal respiratory depression when used alone, but can cause profound respiratory depression when combined with other CNS depressants (eg, opioids, barbiturates, alcohol).
- Benzodiazepines produce their effects by enhancing the actions of GABA, the principal inhibitory neurotransmitter in the CNS.
- Although benzodiazepines undergo extensive metabolism, in most cases the metabolites are pharmacologically active. As a result, responses produced by administering a particular benzodiazepine often persist long after the parent drug has disappeared from the blood.
- All of the benzodiazepines have essentially equivalent pharmacologic actions; hence, selection among them is based in large part on differences in time course.
- The principal indications for benzodiazepines are anxiety, insomnia, and seizure disorders.
- The principal adverse effects of benzodiazepines are daytime sedation and anterograde amnesia.
- Rarely, patients taking benzodiazepines to promote sleep carry out sleep driving and other complex behaviors, and then have no memory of their actions.
- Flumazenil, a benzodiazepine receptor antagonist, can be used to treat benzodiazepine overdose.
- Like the benzodiazepines, the benzodiazepine-like drugs—zaleplon [Sonata], eszopiclone [Lunesta], and zolpidem [Ambien, Tovalt]—produce their effects by enhancing the actions of GABA.

- When insomnia has a treatable cause (eg, pain, depression, schizophrenia), primary therapy should be directed at the underlying illness; hypnotics should be used only as adjuncts.
- Benzodiazepines and the benzodiazepine-like drugs (zolpidem, zaleplon, eszopiclone) are drugs of choice for insomnia.
- When benzodiazepines are used for transient insomnia, treatment should last only 2 to 3 weeks.

Summary of Major Nursing Implications*

BENZODIAZEPINES

Alprazolam

Chlordiazepoxide

Clorazepate

Diazepam

Estazolam

Flurazepam

Lorazepam

Oxazepam

Quazepam

Temazepam

Triazolam

The nursing implications summarized here apply to the sedative-hypnotic benzodiazepines and their use in insomnia.

Preadministration Assessment

Therapeutic Goal

Benzodiazepines are used to promote sleep, relieve symptoms of anxiety (see Chapter 35), suppress seizure disorders (see Chapter 24), relax muscle spasm

(see Chapter 25), and ease withdrawal from alcohol (see Chapter 38). They are also used for preanesthetic medication and to induce general anesthesia (see Chapter 27).

Baseline Data

Determine the nature of the sleep disturbance (prolonged latency, frequent awakenings, early morning awakening) and how long it has lasted. Assess for a possible underlying cause (eg, medical illness, psychiatric illness, use of caffeine and other stimulants, poor sleep hygiene, major life stressor).

Identifying High-Risk Patients

Benzodiazepines are *contraindicated* during pregnancy and for patients who experience sleep apnea. Use with *caution* in patients with suicidal tendencies or a history of substance abuse.

Implementation: Administration

Routes

Oral.

All benzodiazepines.

IM and IV.

Diazepam, chlordiazepoxide, and lorazepam.

Rectal.

Diazepam.

Administration

Oral.

Advise patients to administer benzodiazepines with food if gastric upset occurs. Instruct patients to swallow sustained-release formulations intact, without crushing or chewing.

Warn patients not to increase the dosage or discontinue treatment without consulting the prescriber.

To minimize physical dependence when treating insomnia, administer intermittently (three or four nights a week) and use the lowest effective dosage for the shortest duration required.

To minimize abstinence symptoms, taper the dosage gradually (over several weeks or even months).

Intravenous.

Perform IV injections with care. Life-threatening reactions (severe hypotension, respiratory arrest, cardiac arrest) have occurred, along with less serious reactions (venous thrombosis, phlebitis, vascular impairment). To reduce complications, follow these guidelines: (1) make injections slowly; (2) take care to avoid intra-arterial injection and extravasation; (3) if direct venous injection is impossible, inject into infusion tubing as close to the vein as possible; (4) follow the manufacturer's instructions regarding suitable diluents for preparing solutions; and (5) have facilities for resuscitation available.

Implementation: Measures to Enhance Therapeutic Effects

Educate patients about sleep fitness (see Table 34-4**). Reassure patients with situational insomnia that sleep patterns will normalize once the precipitating stressor has been eliminated.** Ensure that correctable underlying causes of insomnia (psychiatric or medical illness, use of stimulant drugs) are being managed.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Insomnia is usually self-limiting. Consequently, drug therapy is usually short term. Benzodiazepines should be discontinued periodically to determine if they are still required. If insomnia is long term, make a special effort to identify possible underlying causes (eg, psychiatric illness, medical illness, use of caffeine and other stimulants).

Minimizing Adverse Effects

CNS Depression.

Drowsiness may be present the next day when benzodiazepines are used for insomnia. **Warn patients about possible residual CNS depression and advise them to avoid hazardous activities (eg, driving) if daytime sedation is significant.**

Sleep Driving and Other Complex Sleep-Related Behaviors.

Rarely, patients taking benzodiazepines to promote sleep may carry out complex behaviors (eg, sleep driving, eating, making phone calls), and then have no memory of the event. To reduce the risk of these events, dosage should be as low as possible, and alcohol and other CNS depressants should be avoided. **Inform patients about the possibility of complex sleep-related behaviors and instruct them to notify the prescriber if they occur.** If the patient reports driving while asleep, the benzodiazepine should be withdrawn (albeit slowly).

Paradoxical Effects.

Inform patients about possible paradoxical reactions (rage, excitement, heightened anxiety), and instruct them to notify the prescriber if these occur. If the reaction is verified, benzodiazepines should be withdrawn.

Physical Dependence.

With most benzodiazepines, significant physical dependence is rare. However, with one agent—alprazolam [Xanax, Niravam]—substantial dependence has been reported. With all benzodiazepines, development of dependence can be minimized by using the lowest effective dosage for the shortest time necessary and by using intermittent dosing when treating insomnia.

When dependence is mild, withdrawal can elicit insomnia and other symptoms that resemble anxiety. These must be distinguished from a return of the patient's original sleep disorder. **Warn patients about possible drug-dependency insomnia during or after benzodiazepine withdrawal.**

When dependence is severe, withdrawal reactions may be serious (panic, paranoia, delirium, hypertension, convulsions). To minimize symptoms, withdraw benzodiazepines slowly (over several weeks or months). **Warn patients**

against abrupt discontinuation of treatment. After drug cessation, patients should be monitored for 3 weeks for signs of withdrawal or recurrence of original symptoms.

Abuse.

The abuse potential of the benzodiazepines is low. However, some individuals do abuse them. Be alert to requests for increased dosage, since this may reflect an attempt at abuse. Benzodiazepines are classified under Schedule IV of the Controlled Substances Act and must be dispensed accordingly.

Use in Pregnancy and Lactation.

Benzodiazepines may injure the developing fetus, especially during the first trimester. **Inform women of child-bearing age about the potential for fetal harm and warn them against becoming pregnant.** If pregnancy occurs, benzodiazepines should be withdrawn.

Benzodiazepines readily enter breast milk and may accumulate to toxic levels in the infant. **Warn mothers against breast-feeding.**

Minimizing Adverse Interactions

CNS Depressants.

Combined overdose with a benzodiazepine plus another CNS depressant can cause profound respiratory depression, coma, and death. **Warn patients against use of alcohol and all other CNS depressants (eg, opioids, barbiturates, antihistamines).**

35 Management of Anxiety Disorders

Anxiety is an uncomfortable state that has both psychologic and physical components. The psychologic component can be characterized with terms such as *fear, apprehension, dread,* and *uneasiness*. The physical component manifests as tachycardia, palpitations, trembling, dry mouth, sweating, weakness, fatigue, and shortness of breath.

Anxiety is a nearly universal experience that often serves an adaptive function. When anxiety is moderate and situationally appropriate, therapy may not be needed or even desirable. In contrast, when anxiety is persistent and disabling, intervention is clearly indicated.

In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), primary anxiety disorders are divided into six major classes: generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, phobic disorders, post-traumatic stress disorder, and acute stress disorder. Although each class is distinct, they all have one element in common: an unhealthy level of anxiety. In addition, with all classes, depression is frequently comorbid.

Anxiety disorders are among the most common psychiatric illnesses. In the United States, about 25% of people develop pathologic anxiety at some time in their lives. As a rule, the incidence is higher in women than in men.

Fortunately, anxiety disorders often respond well to treatment—either psychotherapy, drug therapy, or both. As indicated in Table 35-1, two classes of drugs are used most: *benzodiazepines* and *selective serotonin reuptake inhibitors* (SSRIs). Benzodiazepines are used primarily for one condition: generalized anxiety disorder (GAD). In contrast, the SSRIs are now used for *all* anxiety disorders. It should be noted that, although SSRIs were developed as antidepressants, they are highly effective against anxiety—whether or not depression is present.

Anxiety Disorder	Benzodiazepines	SSRIs	Others
Generalized Anxiety Disorder	Alprazolam	Paroxetine	Buspirone
	Chlordiazepoxide	Escitalopram	Venlafaxine
	Clorazepate		Duloxetine
	Diazepam		
	Lorazepam		
	Oxazepam		
Panic Disorder		Fluoxetine	
		Paroxetine	
		Sertraline	
Obsessive-Compulsive Disorder		Citalopram	
		Escitalopram	
		Paroxetine	
		Fluoxetine	
		Fluvoxamine	
		Sertraline	
Social Anxiety Disorder		Fluvoxamine	Venlafaxine
		Paroxetine	
		Sertraline	
Post-traumatic Stress Disorder		Paroxetine*	
		Sertraline*	

SSRIs = selective serotonin reuptake inhibitors.

TABLE 35-1 First-Line Drugs for Anxiety Disorders

* According to the Institute of Medicine of the National Academies, these drugs are not effective in PTSD, even though they are approved by the Food and Drug Administration for this disorder.

GENERALIZED ANXIETY DISORDER

Characteristics

Generalized anxiety disorder is a chronic condition characterized by uncontrollable worrying. Of all anxiety disorders, GAD is the least likely to remit. Most patients with GAD also have another psychiatric disorder, usually depression. GAD should not be confused with *situational anxiety,* which is a normal response to a stressful situation (eg, family problems, exams, financial difficulties); symptoms may be intense, but they are temporary.

The hallmark of GAD is unrealistic or excessive anxiety about several events or activities (eg, work or school performance) that lasts 6 months or longer. Other psychologic manifestations include vigilance, tension, apprehension, poor concentration, and difficulty falling or staying asleep. Somatic manifestations include trembling, muscle tension, restlessness, and signs of autonomic hyperactivity, such as palpitations, tachycardia, sweating, and cold clammy hands. Diagnostic criteria for GAD, as described in DSM-IV, are shown in Table 35-2.

Treatment

GAD can be managed with nondrug therapy and with drugs. Nondrug approaches include supportive therapy, cognitive behavioral therapy, biofeedback, and relaxation training. These can help relieve symptoms and improve coping skills in anxiety-provoking situations. When symptoms are mild, nondrug therapy may be all that is needed. However, if symptoms are intensely uncomfortable or disabling, drugs are indicated. Current first-line choices are the benzodiazepines, buspirone, and four antidepressants: venlafaxine, paroxetine, escitalopram, and duloxetine. With the benzodiazepines, onset of relief is rapid. In contrast, with buspirone and the antidepressants, onset is delayed. Accordingly, benzodiazepines are preferred drugs for immediate stabilization, especially when anxiety is severe. However, for long-term management, buspirone and the antidepressants are preferred. Because GAD is a chronic disorder, ini-

tial drug therapy should be prolonged, lasting at least 2 to 6 months. Unfortunately, even after extended treatment, drug withdrawal frequently results in relapse. Hence, for many patients, drug therapy must continue indefinitely.

TABLE 35-2 DSM-IV-TR Diagnostic Criteria for GAD

A. Excessive anxiety and worry about several events or activities (such as work or school performance) that occur more days than not for at least 6 months.

B. The person finds the worry difficult to control.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). *Note:* only one item is required in children.

- Restlessness or feeling keyed up or on edge
- Being easily fatigued
- Difficulty concentrating or mind going blank
- Irritability
- Muscle tension
- Sleep disturbance (difficulty falling asleep or staying asleep, or restlessness, unsatisfying sleep)

D. The focus of the anxiety and worry is not related to another psychiatric disorder.

E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

F. The disturbance is not due to the direct physiologic effects of a substance (eg, drug of abuse, medication) or a general medical condition (eg, hyperthyroidism) and does not occur exclusively during a mood disorder, psychotic disorder, or pervasive developmental disorder.

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Benzodiazepines

Benzodiazepines are first-choice drugs for anxiety. As discussed in Chapter 34, benefits derive from enhancing responses to gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. Onset of effects is immediate, and the margin of safety is high. Principal side effects are sedation and psychomotor slowing. Patients should be warned about these effects and informed they will subside in 7 to 10 days. Because of their abuse potential, benzodiazepines should be used with caution in patients known to abuse alcohol or other psychoactive substances.

Long-term use of benzodiazepines carries a risk of physical dependence. Withdrawal symptoms include panic, paranoia, and delirium. These can be especially troubling for patients with GAD. Furthermore, they can be confused with a return of pretreatment symptoms. Accordingly, clinicians must differentiate between a withdrawal reaction and relapse. To minimize withdrawal symptoms, benzodiazepines should be tapered gradually—over a period of several months. If relapse occurs, treatment should resume.

Of the 14 benzodiazepines available, 6 are approved for anxiety. The agents prescribed most often are alprazolam [Xanax, Xanax XR, Niravam] and lorazepam [Ativan]. However, there is no proof that any one benzodiazepine is clearly superior to the others. Hence, selection among them is largely a matter of prescriber preference. Dosages for anxiety are summarized in Table 35-3.

The basic pharmacology of the benzodiazepines is discussed in Chapter 34.

Generic Name	Trade Name	Dosage	
		Initial	Usual Range (mg/day)
Alprazolam	Xanax, Niravam	0.25–0.5 mg 3 times/day	0.5–6
	Xanax XR	0.5–1 mg once/day	3–6
Chlordiazepoxide	Librium	—	15–100
Clorazepate	Tranxene	—	15–60
Diazepam	Valium	—	4–40
Lorazepam	Ativan	0.5–1 mg 3 times/day	2–6
Oxazepam	Serax	—	30–120

TABLE 35-3 Dosages of Benzodiazepines Approved for Anxiety

Buspirone

Actions and Therapeutic Use.

Buspirone [BuSpar] is an anxiolytic drug that differs significantly from the benzodiazepines. Most notably, buspirone is *not* a central nervous system (CNS) depressant. For treatment of anxiety, buspirone is as effective as the benzodiazepines and has three distinct advantages: It does not cause sedation, has no abuse potential, and does not intensify the effects of CNS depressants (benzodiazepines, alcohol, barbiturates, and related drugs). Its major disadvantage is that anxiolytic effects develop *slowly:* initial responses take a week to appear, and several more weeks must pass before responses peak. Because therapeutic effects are delayed, buspirone is not suitable for PRN use or for patients who need immediate relief. Since buspirone has no abuse potential, it may be especially appropriate for patients known to abuse alcohol and other drugs. Because it lacks depressant properties, buspirone is an attractive alternative to benzodiazepines in patients who require long-term therapy

but cannot tolerate benzodiazepine-induced sedation and psychomotor slowing. Buspirone is labeled only for *short-term* treatment of anxiety. However, the drug has been taken for as long as a year with no reduction in benefit. Buspirone does not display cross-dependence with benzodiazepines. Hence, when patients are switched from a benzodiazepine to buspirone, the benzodiazepine must be tapered slowly. Furthermore, since the effects of buspirone are delayed, buspirone should be initiated 2 to 4 weeks before beginning benzodiazepine withdrawal. In contrast to benzodiazepines, buspirone lacks sedative, muscle relaxant, and anticonvulsant actions—and hence cannot be used for insomnia, muscle spasm, or epilepsy.

The mechanism by which buspirone relieves anxiety has not been established. The drug binds with high affinity to receptors for serotonin and with lower affinity to receptors for dopamine. Buspirone does not bind to receptors for GABA or benzodiazepines.

Pharmacokinetics.

Buspirone is well absorbed following oral administration but undergoes extensive metabolism on its first pass through the liver. Administration with food delays absorption but enhances bioavailability (by reducing first-pass metabolism). The drug is excreted in part by the kidneys, primarily as metabolites.

Adverse Effects.

Buspirone is generally well tolerated. The most common reactions are *dizziness, nausea, headache, nervousness, lightheadedness,* and *excitement*. The drug is nonsedating and does not interfere with daytime activities. Furthermore, it poses little or no risk of suicide; huge doses (375 mg/day) have been given to healthy volunteers with only moderate adverse effects (nausea, vomiting, dizziness, drowsiness, miosis).

Drug and Food Interactions.

Levels of buspirone can be greatly increased (5- to 13-fold) by *erythromycin* and *ketoconazole*. Levels can also be increased by *grapefruit juice*. Elevated levels may cause drowsiness and subjective effects (dysphoria, feeling “spacey”).

Buspirone does not enhance the depressant effects of alcohol, barbiturates, and other general CNS depressants.

Tolerance, Dependence, and Abuse.

Buspirone has been used for up to a year without evidence of tolerance, physical dependence, or psychologic dependence. No withdrawal symptoms have been observed upon termination. There is no cross-tolerance or cross-dependence between buspirone and the sedative-hypnotics (eg, benzodiazepines, barbiturates). Buspirone appears to have no potential for abuse, and hence is not regulated under the Controlled Substances Act.

Preparations, Dosage, and Administration.

Buspirone tablets [BuSpar] are available in five strengths: 5, 7.5, 10, 15, and 30 mg. The initial dosage is 5 mg 3 times a day. Dosage may be increased to a maximum of 60 mg/day.

Antidepressants: Venlafaxine, Paroxetine, Escitalopram, and Duloxetine

At this time, only four antidepressants—venlafaxine [Effexor XR], paroxetine [Paxil], escitalopram [Lexapro], and duloxetine [Cymbalta]—are approved for GAD. Venlafaxine is an atypical antidepressant; paroxetine and escitalopram are SSRIs, and duloxetine is a serotonin/norepinephrine reuptake inhibitor (SNRI). All four drugs are especially well suited for patients who have depression in addition to GAD. However, they are also effective even when depression is absent. As with buspirone, anxiolytic effects develop slowly: Initial responses can be seen in a week, but optimal responses require several more weeks to develop. Because relief is delayed, the antidepressants cannot be used PRN. Compared with benzodiazepines, the antidepressants do a better job of decreasing cognitive and psychic symptoms of anxiety, but are not as good at decreasing somatic symptoms. In contrast to the benzodiazepines, antidepressants have no potential for abuse. However, abrupt discontinuation *can* produce withdrawal symptoms.

Venlafaxine was the first antidepressant approved for GAD. The drug has been proved effective for both short-term and long-term use. The most common side effect is nausea, which develops in 37% of patients. Fortunately, nausea

subsides despite continued treatment. Other common reactions include headache, anorexia, nervousness, sweating, daytime somnolence, and insomnia. In addition, venlafaxine can cause hypertension, although this is unlikely at the doses used in GAD. Combining venlafaxine with a monoamine oxidase inhibitor can result in serious toxicity, and hence must be avoided. Venlafaxine is available in two formulations: standard tablets [Effexor] and extended-release capsules [Effexor XR]. Only the extended-release formulation is approved for GAD. The initial dosage is 37.5 mg once a day, and the maintenance range is 75 to 225 mg once a day.

Paroxetine and *escitalopram* are the only SSRIs approved for GAD. These drugs are as effective as the benzodiazepines, but less well tolerated. For paroxetine, the initial dosage is 20 mg once a day in the morning. Dosage can be gradually increased to a maintenance range of 20 to 50 mg/day. For escitalopram, dosing begins at 10 mg once daily and can be increased to 20 mg once daily after a week. Treatment beyond 8 weeks has not been studied.

Duloxetine is the only SNRI approved for GAD. The usual dosage, both initial and maintenance, is 60 mg once a day.

The basic pharmacology of venlafaxine, paroxetine, escitalopram, and duloxetine is discussed in Chapter 32.

PANIC DISORDER

Characteristics

Panic disorder is characterized by recurrent, intensely uncomfortable episodes known as *panic attacks*. As defined in DSM-IV, panic attacks have a sudden onset, reach peak intensity within 10 minutes, and have four or more of the following symptoms:

- Palpitations, pounding heart, racing heartbeat
- Chest pain or discomfort
- Sensation of shortness of breath or smothering
- Feeling of choking
- Dizziness, lightheadedness
- Nausea or abdominal discomfort

- Derealization (feelings of unreality) or depersonalization (feeling detached from oneself)
- Fear of losing control or going crazy
- Fear of dying
- Tingling or numbness in the hands
- Flushes or chills

Symptoms typically dissipate within 30 minutes. Many patients go to an emergency department because they think they are having a heart attack. Some patients experience panic attacks daily; others have only one or two a month. Panic disorder is a common condition that affects 1.6% of Americans at some time in their lives. The incidence in women is 2 to 3 times the incidence in men. Onset of panic disorder usually occurs in the late teens or early 20s.

Perhaps 50% of patients who get panic disorder also experience *agoraphobia,* a condition characterized by anxiety about being in places or situations from which escape might be difficult or embarrassing, or in which help might be unavailable in the event that a panic attack should occur. Agoraphobia leads to avoidance of certain places (eg, elevators, bridges, tunnels, movie theaters) and situations (eg, being outside the home alone; being in a crowd; standing on line; driving in traffic; traveling by bus, train, or plane). In extreme cases, agoraphobics may never set foot outside the home. Because of avoidance behavior, agoraphobia can severely limit occupational and social options.

What's the underlying cause of panic attacks? We don't know. However, malfunction of the brain's "alarm system" is suspected. This malfunction may result from abnormalities in noradrenergic systems, serotonergic systems, and/or benzodiazepine receptors. Genetic vulnerability also may play a role.

Treatment

Between 70% and 90% of patients with panic disorder respond well to treatment. Two modalities may be employed: drug therapy and cognitive behavioral therapy (CBT). Combining drug therapy with CBT is more effective than either modality alone. As a rule, patients experience rapid and significant improvement. Drug therapy helps suppress panic attacks, while CBT helps patients become more comfortable with situations and places they've been

avoiding. Additional benefit can be derived from avoiding caffeine and sympathomimetics (which can trigger panic attacks), avoiding sleep deprivation (which can predispose to panic attacks), and doing regular aerobic exercise (which can reduce anxiety).

Drug therapy should continue at least 6 to 9 months. Stopping sooner is associated with a high rate of relapse.

Antidepressants

Panic disorder responds well to all three major classes of antidepressants: SSRIs, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). With all three, full benefits take 6 to 12 weeks to develop. Owing to better tolerability, SSRIs are preferred to TCAs and MAOIs. The basic pharmacology of the antidepressants is discussed in Chapter 32.

Selective Serotonin Reuptake Inhibitors.

The SSRIs are first-line drugs for panic disorder. At this time, only three SSRIs—fluoxetine [Prozac], paroxetine [Paxil], and sertraline [Zoloft]—are approved for this condition. However, the other SSRIs appear just as effective. The SSRIs decrease the frequency and intensity of attacks, anticipatory anxiety, and avoidance behavior. Furthermore, they decrease panic attacks regardless of whether the patient is actually depressed. However, if the patient does have coexisting depression, antidepressants will benefit the depression and panic disorder simultaneously. Common side effects include nausea, headache, insomnia, and sexual dysfunction. Weight gain is also a problem. In addition, SSRIs can *increase* anxiety early in treatment. To minimize exacerbation of anxiety, dosage should be low initially and then gradually increased. For paroxetine, the initial dosage is 10 mg/day, and the target range is 20 to 40 mg/day. For fluoxetine, the initial dosage is 10 mg/day, and the usual maintenance dosage is 20 mg/day. For sertraline, the initial dosage is 25 mg/day, and the target range is 50 to 200 mg/day.

Tricyclic Antidepressants.

The TCAs (eg, imipramine [Tofranil], clomipramine [Anafranil]) are second-line drugs for panic disorder. They should be used only after a trial with at least one SSRI has failed. Although TCAs are as effective as SSRIs, they are

not as well tolerated. The most common side effects are sedation, orthostatic hypotension, and anticholinergic effects: dry mouth, blurred vision, urinary retention, constipation, and tachycardia. Of greater concern, TCAs can cause fatal dysrhythmias if taken in overdose. As with the SSRIs, dosage should be low initially and then gradually increased. For clomipramine, the initial dosage is 25 mg/day, and the target range is 50 to 200 mg/day. For imipramine, the initial dosage is 10 mg/day, and the target range is 100 to 300 mg/day.

Monoamine Oxidase Inhibitors.

Although MAOIs (eg, phenelzine) are very effective in panic disorder, they are difficult to use. MAOIs can cause significant side effects, including orthostatic hypotension, weight gain, and sexual dysfunction. In addition, they can cause hypertensive crisis if the patient takes certain drugs or consumes foods rich in tyramine. Because of these drawbacks, MAOIs are considered last-line drugs for panic disorder.

Benzodiazepines.

Although benzodiazepines are effective in panic disorder, they are now considered second-line drugs. Why? Because, unlike the SSRIs, benzodiazepines pose a risk of abuse, dependence, and rapid re-emergence of symptoms after discontinuation. Of the available benzodiazepines, the agents used most often are alprazolam [Xanax, Xanax XR, Niravam], clonazepam [Klonopin], and lorazepam [Ativan]. All three provide rapid and effective protection against panic attacks. These drugs also reduce anticipatory anxiety and phobic avoidance. In contrast to antidepressants, which take weeks or even months to work, benzodiazepines often provide relief with the first few doses. Accordingly, benzodiazepines can be especially useful as initial therapy while responses to antidepressants are developing. The principal side effect of the benzodiazepines is sedation, but some tolerance develops in 7 to 10 days. As noted, benzodiazepines can cause physical dependence, which can make withdrawal extremely hard for some patients. The difficulty is that withdrawal produces intense anxiety, which people with panic disorder may find intolerable. To minimize withdrawal symptoms, benzodiazepines should be withdrawn very slowly—over a period of several months. In addition, withdraw-

al symptoms can be reduced by concurrent treatment with an SSRI. The basic pharmacology of the benzodiazepines is discussed in Chapter 34.

OBSESSIVE-COMPULSIVE DISORDER

Characteristics

Obsessive-compulsive disorder (OCD) is a potentially disabling condition characterized by persistent obsessions and compulsions that cause marked distress, consume at least 1 hour a day, and significantly interfere with daily living. An *obsession* is defined as a recurrent, persistent thought, impulse, or mental image that is unwanted and distressing, and comes involuntarily to mind despite attempts to ignore or suppress it. Common obsessions include fear of contamination (eg, acquiring a disease by touching another person), aggressive impulses (eg, harming a family member), a need for orderliness or symmetry (eg, personal bathroom items must be arranged in a precise way), and repeated doubts (eg, did I unplug the iron?). A *compulsion* is a ritualized behavior or mental act that the patient is driven to perform in response to his or her obsessions. In the patient's mind, carrying out the compulsion is essential to prevent some horrible event from occurring (eg, death of a loved one). If performing the compulsion is suppressed or postponed, the patient experiences increased anxiety. Common compulsions include hand washing, mental counting, arranging objects symmetrically, and hoarding. Patients usually understand that their compulsive behavior is excessive and senseless, but nonetheless are unable to stop. Diagnostic criteria for OCD, as described in DSM-IV, are presented in Table 35-4.

Treatment

Patients with OCD respond to drugs and behavioral therapy. Optimal treatment consists of both.

Behavioral therapy is probably more important in OCD than in any other psychiatric disorder. In the technique employed, patients are exposed to sources of their fears, while being encouraged to refrain from acting out their compulsive rituals. When no dire consequences come to pass, despite the absence of “protective” rituals, patients are able to gradually give up their compulsive

behavior. Although this form of therapy causes great anxiety, the success rate is high.

Five drugs are approved for OCD: four SSRIs and one TCA (clomipramine). All five enhance serotonergic transmission. The SSRIs are better tolerated than clomipramine, and hence are preferred.

Selective Serotonin Reuptake Inhibitors

The SSRIs are first-line drugs for OCD. Only four SSRIs—fluoxetine [Prozac], fluvoxamine [Luvox], sertraline [Zoloft], and paroxetine [Paxil]—are approved for OCD. However, the remaining two—citalopram [Celexa] and escitalopram [Lexapro]—are also effective. All six reduce symptoms by enhancing serotonergic transmission. They all are equally effective, although individual patients may respond better to one than to another. With all six, beneficial effects develop slowly, taking several months to become maximal. Common side effects include nausea, headache, insomnia, and sexual dysfunction. Weight gain can also occur. Despite this array of side effects, SSRIs are safer than clomipramine and better tolerated. Dosages are as follows:

- *Citalopram*—20 mg once daily initially, increased to a maximum of 60 mg/day
- *Escitalopram*—10 mg once daily initially; a maximum dosage has not been established
- *Fluoxetine*—20 mg in the morning initially, increased to a maximum of 80 mg/day

TABLE 35-4 DSM-IV-TR Diagnostic Criteria for Obsessive-Compulsive Disorder

A. The presence of either obsessions or compulsions:

Obsessions

1. Recurrent and persistent thoughts, impulses, or images that are experienced at some time during the disturbance as intrusive and senseless and that cause marked anxiety and distress.
2. The thoughts, impulses, or images are not simply excessive worries about real-life problems.

3. The person attempts to ignore or suppress the thoughts, impulses, or images, or to neutralize them with some other thought or action.

4. The person recognizes that the obsessions are a product of his or her own mind.

Compulsions

1. Repetitive behaviors (eg, hand washing, putting objects in order) or mental acts (eg, praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession or according to rigid rules.

2. The behaviors or mental acts are performed to prevent or reduce distress or to prevent some dreaded event; however, these behaviors or mental acts either have no realistic connection with what they are designed to neutralize or prevent, or are clearly excessive.

B. At some time during the disorder, the person recognizes that the obsessions or compulsions are excessive or unreasonable. (This does not apply to children.)

C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with normal routines, occupational or academic functioning, or usual social activities or relationships.

D. The symptoms are not related to another psychiatric disorder, and are not caused by a substance, medication, or general medical illness.

- *Fluvoxamine*—50 mg at bedtime initially, increased to a maximum of 300 mg/day
- *Paroxetine*—20 mg in the morning initially, increased to a maximum of 60 mg/day
- *Sertraline*—50 mg once a day initially, increased to a maximum of 300 mg/day

How long should treatment last? Therapy of an initial episode should continue for at least 1 year, after which discontinuation can be tried. Withdrawal should be done slowly, reducing the dosage by 25% every 1 to 2 months. Unfortunately, relapse is common; estimates range from 23% to as high as 90%. If relapse continues to occur after three or four attempts at withdrawal, lifelong treatment may be indicated.

Clomipramine

For patients with OCD, clomipramine [Anafranil] is as effective as SSRIs, but less well tolerated. Accordingly, clomipramine is considered a second-line drug for this disorder, and hence should be used only after treatment with one or more SSRIs has failed.

Clomipramine is the only TCA shown effective in OCD. About 70% of patients experience a significant improvement. Initial effects take 4 weeks to develop; maximal effects are seen in 12 weeks.

Clomipramine affects several neurotransmitter systems. As with the SSRIs, benefits in OCD derive from blocking uptake of serotonin. (Among the TCAs, clomipramine is the most effective inhibitor of serotonin uptake.) However, in contrast to SSRIs, which block reuptake of serotonin only, clomipramine blocks reuptake of norepinephrine as well. Like other TCAs, clomipramine also blocks *receptors* for norepinephrine, acetylcholine, and histamine.

Clomipramine can cause a variety of side effects. Sedation, dry mouth, dizziness, and tremor occur in over 50% of patients. Other common effects include weight gain, constipation, blurred vision, insomnia, headache, and nausea. Of greatest concern, clomipramine can induce *seizures*. Because of seizure risk, the drug should be avoided in patients with a history of seizures or head injury. Clomipramine greatly increases the risk of hypertensive crisis from MAOIs, and therefore is contraindicated for patients taking these drugs.

Doses should be low initially (20 to 25 mg/day) and then gradually increased. Side effects can be minimized by dividing the early doses and taking them with meals. Maintenance doses of 150 to 250 mg/day are achieved in 2 to 4 weeks.

The basic pharmacology of clomipramine and other TCAs is discussed in Chapter 32.

SOCIAL ANXIETY DISORDER (SOCIAL PHOBIA)

Characteristics

Social anxiety disorder, formerly known as social phobia, is characterized by an intense, irrational fear of situations in which one might be scrutinized by others, or might do something that is embarrassing or humiliating. Exposure to the feared situation almost always elicits anxiety. As a result, the person

avoids the situation or, if it can't be avoided, endures it with intense anxiety (manifestations include blushing, stuttering, sweating, palpitations, dry throat, and muscle tension and twitches). Diagnostic criteria for social anxiety disorder, as defined in DSM-IV, are listed in Table 35-5.

Social anxiety disorder has two forms: generalized and nongeneralized. In the generalized form, the person fears nearly all social and performance situations. In the nongeneralized form, fear is limited to a specific type of situation, such as public speaking.

Social anxiety disorder can be very debilitating. In younger people, it can retard social development, inhibit participation in social activities, impair acquisition of friends, and make dating difficult or even impossible. It can also preclude pursuit of higher education. In older people, it can severely limit social and occupational options.

TABLE 35-5 DSM-IV-TR Diagnostic Criteria for Social Anxiety Disorder (Social Phobia)

A. A marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way that will be embarrassing or humiliating, or will show anxiety symptoms that will be embarrassing or humiliating.

B. Exposure to the feared situation almost always provokes anxiety.

C. The person recognizes that the fear is excessive or unreasonable (not required in children).

D. The feared situation is avoided, or endured with intense anxiety.

E. The avoidance or anxious anticipation causes marked distress or interferes significantly with the person's relationships, normal routine, social activities, or performance at work or at school.

F. For persons under age 18, the fear has lasted at least 6 months.

G. The fear or avoidance is not caused by a substance, medication, or general medical illness, and cannot be better accounted for by another psychiatric illness.

Social anxiety disorder is one of the most common psychiatric disorders, and *the* most common anxiety disorder. In the United States, 13% to 14% of the population is affected at some time in their lives. The disorder typically begins during the teenage years and, left untreated, is likely to continue lifelong.

Treatment

Social anxiety disorder can be treated with psychotherapy, drug therapy, or both. Studies indicate that psychotherapy—both cognitive and behavioral—can be as effective as drugs. A combination of psychotherapy and drugs may be more effective than either modality alone.

The SSRIs are considered first-line drugs for most patients. These drugs are especially well suited for patients who fear multiple situations and are obliged to face those situations on a regular basis. Currently, only three SSRIs—fluvoxamine [Luvox], paroxetine [Paxil], and sertraline [Zoloft]—are approved for social anxiety disorder. However, available data indicate that the other SSRIs are effective too. Initial effects take about 4 weeks to develop; optimal effects are seen in 8 to 12 weeks. Patients should be informed that benefits will be delayed. For paroxetine, the initial dosage is 20 mg once a day in the morning. The usual maintenance range is 20 to 40 mg/day. Treatment should continue for at least 1 year, after which gradual withdrawal can be tried. Unfortunately, withdrawal frequently results in relapse.

Benzodiazepines (eg, clonazepam [Klonopin], alprazolam [Xanax]) are an option for some patients. These drugs are well tolerated and their benefits are immediate, unlike those of the SSRIs. As a result, benzodiazepines can provide rapid relief and can be used PRN. Accordingly, these drugs are well suited for people whose fear is limited to specific situations, and who must face those situations only occasionally. The usual dosage is 1 to 3 mg/day for clonazepam, and 1 to 6 mg/day for alprazolam.

Propranolol [Inderal] and other beta blockers can benefit patients with performance anxiety, a form of nongeneralized social anxiety disorder. When taken 1 to 2 hours before a scheduled performance, these drugs can reduce symptoms caused by autonomic hyperactivity (eg, tremors, sweating, tachycardia, palpitations). Doses are relatively small—only 10 to 80 mg for propranolol.

POST-TRAUMATIC STRESS DISORDER

Characteristics

As described in DSM-IV (see Table 35-6), post-traumatic stress disorder (PTSD) develops following a *traumatic event* that elicited an immediate reaction of *fear, helplessness,* or *horror*. PTSD has three core symptoms: *re-experiencing* the event, *avoiding reminders* of the event (coupled with generalized emotional numbing), and a persistent state of *hyperarousal*. According to DSM-IV, a traumatic event is one that involves a threat of injury or death, or a threat to one's physical integrity. Many events meet this criterion. Among these are physical or sexual assault, rape, torture, combat, industrial explosions, serious accidents, natural disasters, being taken hostage, displacement as a refugee, and terrorist attacks, such as the ones that took place against the World Trade Center and the Pentagon on September 11, 2001. It should be noted that PTSD can affect persons who were only *witnesses* to a traumatic event—not just those who were directly involved.

The epidemiology of PTSD is revealing. In the United States, more than 5 million Americans have PTSD in any given year, making PTSD the fourth most common psychiatric disorder. PTSD develops in 5% to 6% of men at some time in their lives, and in 10% to 14% of women. Traumatic events that involve interpersonal violence (eg, assault, rape, torture) are more likely to cause PTSD than are traumatic events that do not (eg, car accidents, natural disasters). For example, among rape victims, the incidence of PTSD is 45.9% for women and 65% for men. In contrast, among natural disaster survivors, the incidence is only 5.4% for women and 3.7% for men. Combat carries a high risk of PTSD: the disorder develops in 40% of soldiers who go to war.

Treatment

Optimal treatment for PTSD—be it psychotherapy and/or drugs—has not been established. In 2007, the Institute of Medicine (IOM) of the National Academies issued a report—*Treatment of PTSD: An Assessment of the Evidence*—that concluded that, for most PTSD treatments, evidence of efficacy is insufficient to recommend their use. This does not meant that most treatments don't work. Rather, it means we lack conclusive proof that they *do* work.

The IOM evaluated research on five kinds of psychotherapy: exposure therapy, group therapy, cognitive restructuring, coping skills training, and eye-movement desensitization and reprocessing. Of the treatments, only one—*exposure therapy*—had sufficient proof of efficacy to recommend its use. In this technique, patients repeatedly reimagine traumatic events as a way to make those events lose their power.

TABLE 35-6 DSM-IV-TR Diagnostic Criteria for Post-traumatic Stress Disorder

A. The person participated in (or witnessed) a *traumatic event,* and reacted with a sense of intense fear, helplessness, or horror. The event could involve serious physical injury, actual or threatened death, or a threat to physical integrity.

B. The traumatic event is *persistently re-experienced,* either through flashbacks, hallucinations, distressing dreams, or recurrent thoughts, or through intense psychologic or physiologic reactions triggered by exposure to cues associated with the event.

C. Persistent *avoidance* of reminders of the event stimuli along with *generalized emotional numbing,* as indicated by three or more of the following:

- Efforts to avoid thoughts, feelings, or conversations associated with the trauma
- Efforts to avoid activities, places, or people that arouse recollections of the trauma
- Inability to recall an important aspect of the trauma
- Markedly diminished interest or participation in significant activities
- Feeling detached or estranged from others
- Restricted range of affect (eg, unable to have loving feelings)
- Sense of foreshortened future (eg, does not expect to have a career, marriage, children, or a normal life span)

D. Persistent symptoms of increased arousal, as indicated by two or more of the following:

- Difficulty falling or staying asleep

- Irritability or outbursts of anger
- Difficulty concentrating
- Hypervigilance
- Exaggerated startle response

E. The symptoms (B, C, and D) have lasted more than 1 month.

F. The symptoms cause significant distress, or disrupt relationships, job performance, or some other important facet of life.

Regarding drugs used for PTSD, the IOM report found no proof that *any* of them help, including *paroxetine* [Paxil] and *sertraline* [Zoloft], the only agents approved for PTSD by the Food and Drug Administration (FDA). Other drugs lacking proof of efficacy include benzodiazepines, anticonvulsants, prazosin (an alpha-adrenergic blocker), phenelzine (an MAOI), olanzapine and risperidone (atypical antipsychotics), and all antidepressants, including all SSRIs.

KEY POINTS

- Anxiety is an uncomfortable state that has psychologic manifestations (fear, apprehension, dread, uneasiness) and physical manifestations (tachycardia, palpitations, trembling, dry mouth, sweating, weakness, fatigue, shortness of breath).
- When anxiety is persistent and disabling, intervention is indicated.
- As a rule, optimal therapy of anxiety disorders consists of psychotherapy combined with drug therapy.
- The drugs used most often for anxiety disorders are benzodiazepines and selective serotonin reuptake inhibitors (SSRIs).
- Benzodiazepines are used primarily for panic disorder and generalized anxiety disorder (GAD), whereas SSRIs are used for *all* anxiety disorders.
- GAD is a chronic condition characterized by uncontrollable worrying.
- First-line drugs for GAD are benzodiazepines, buspirone, and four antidepressants: venlafaxine, paroxetine, escitalopram, and duloxetine.

- Benzodiazepines suppress symptoms of GAD immediately. Accordingly, these drugs are preferred agents for rapid stabilization, especially when anxiety is severe.
- With buspirone, venlafaxine, paroxetine, escitalopram, and duloxetine, anxiolytic effects are delayed. Accordingly, these drugs are best suited for long-term management—not rapid relief.
- Benzodiazepines are CNS depressants and hence can cause sedation and psychomotor slowing. In addition, they can intensify CNS depression caused by other drugs.
- Benzodiazepines have some potential for abuse, and hence should be used with caution in patients known to abuse alcohol or other psychoactive drugs.
- When taken long term, benzodiazepines can cause physical dependence. To minimize withdrawal symptoms, dosage should be tapered off gradually—over a period of several months.
- Buspirone has three advantages over benzodiazepines: It does not cause CNS depression, has no abuse potential, and does not intensify the effects of CNS depressants.
- Buspirone levels can be increased by erythromycin, ketoconazole, and grapefruit juice.
- Venlafaxine, paroxetine, escitalopram, and duloxetine are especially well suited for treating patients who have depression in addition to GAD. However, they are also effective even when even depression is absent.
- Patients with panic disorder experience recurrent panic attacks, characterized by palpitations, pounding heart, chest pain, derealization or depersonalization, and fear of dying or going crazy.
- Many patients with panic disorder also experience agoraphobia, a condition characterized by anxiety about being in places or situations from which escape might be difficult or embarrassing, or in which help might be unavailable if a panic attack should occur.
- SSRIs are first-line drugs for panic disorder.

- SSRIs decrease the frequency and intensity of panic attacks, anticipatory anxiety, and avoidance behavior, and they work regardless of whether the patient has depression.
- Obsessive-compulsive disorder (OCD) is characterized by persistent obsessions and compulsions that cause marked distress, consume at least 1 hour a day, and significantly interfere with daily living.
- SSRIs are first-line drugs for OCD.
- Social anxiety disorder, formerly known as social phobia, is characterized by an intense, irrational fear of being scrutinized by others, or of doing something that is embarrassing or humiliating.
- The SSRIs are first-line drugs for most patients with social anxiety disorder.
- When social anxiety disorder is limited to fear of specific situations, and when those situations arise infrequently, PRN treatment with benzodiazepines may be preferred to long-term treatment with SSRIs.
- Post-traumatic stress disorder (PTSD) develops following a traumatic event that elicited an immediate reaction of fear, helplessness, or horror.
- PTSD has three core symptoms: re-experiencing, avoidance/emotional numbing, and hyperarousal.
- Events that can precipitate PTSD include physical or sexual assault, rape, torture, combat, industrial explosions, serious accidents, natural disasters, being taken hostage, displacement as a refugee, and terrorist attacks.
- According to the IOM, exposure therapy is the only treatment for PTSD with good proof of efficacy.
- According to the IOM, there is no good proof that any drugs are effective in PTSD, even though two SSRIs—paroxetine and sertraline—are approved by the FDA for this indication.

36 Central Nervous System Stimulants and Attention-Deficit/Hyperactivity Disorder

Central nervous system (CNS) stimulants increase the activity of CNS neurons. Most stimulants act by enhancing neuronal excitation. A few act by suppressing neuronal inhibition. In sufficient doses, all stimulants can cause convulsions.

Clinical applications of the CNS stimulants are limited. Currently these drugs have two principal indications: attention-deficit/hyperactivity disorder (ADHD) and narcolepsy. In the past, stimulants were used to treat obesity and counteract poisoning by CNS depressants, but these uses are no longer recommended.

Please note that CNS stimulants are not the same as antidepressants. The antidepressants act selectively to elevate mood, and hence can relieve depression without affecting other CNS functions. In contrast, CNS stimulants cannot elevate mood without producing generalized excitation. Accordingly, the role of stimulants in treating depression is minor.

Our principal focus is on *amphetamines, methylphenidate* [Ritalin, others], and *methylxanthines* (eg, caffeine). These agents are by far the most widely used stimulant drugs.

AMPHETAMINES

The amphetamine family consists of amphetamine, dextroamphetamine, methamphetamine, and lisdexamfetamine. All are powerful CNS stimulants. In addition to their CNS actions, amphetamines have significant actions in the periphery—actions that can cause cardiac stimulation and vasoconstriction. The amphetamines have a high potential for abuse.

Chemistry

Dextroamphetamine and Levoamphetamine.

The amphetamines are molecules that contain an asymmetric carbon atom. As a result, amphetamines can exist as mirror images of each other. Such compounds are termed *optical isomers* or *enantiomers*. Dextroamphetamine and

levoamphetamine, whose structures are shown in Figure 36-1, illustrate the mirror-image concept. As we can see, dextroamphetamine and levoamphetamine both contain the same atomic components, but those components are arranged differently around the asymmetric carbon. Because of this structural difference, these compounds have somewhat different properties. For example, dextroamphetamine is more selective than levoamphetamine for causing stimulation of the CNS, and hence produces fewer peripheral side effects.

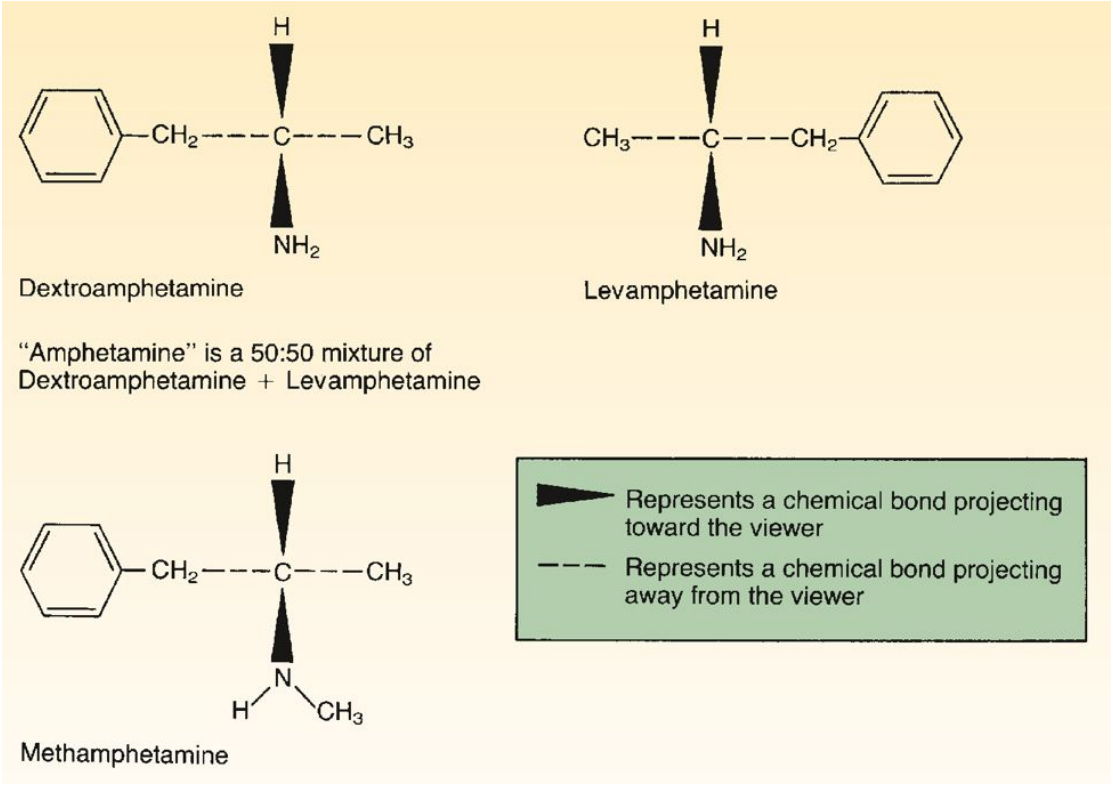


Figure 36-1 Structural formulas of the amphetamines. "Amphetamine" is a 50:50 mixture of dextroamphetamine and levoamphetamine. Note that dextroamphetamine and levoamphetamine are simply mirror images of each other. Both compounds contain the same atomic components.

Amphetamine.

The term *amphetamine* refers not to a single compound but rather to a 50:50 mixture of dextroamphetamine and levoamphetamine. (In chemistry, we refer to such equimolar mixtures of enantiomers as racemic.)

Lisdexamfetamine.

Lisdexamfetamine [Vyvanse], introduced in 2007, is a prodrug composed of dextroamphetamine covalently linked to L-lysine. Following oral dosing, the drug undergoes rapid hydrolysis by enzymes in the intestine and liver to yield lysine and dextroamphetamine, the active form of the drug. If lisdexamfetamine is inhaled or injected, hydrolysis will not take place, and hence the drug is not effective by these routes. Accordingly, it may have a lower abuse potential than other forms of amphetamine.

Methamphetamine.

Methamphetamine is simply dextroamphetamine with an extra methyl group (see Fig. 36-1).

Mechanism of Action

The amphetamines act primarily by promoting release of norepinephrine (NE) and dopamine (DA), and partly by inhibiting reuptake of both transmitters. These actions take place in the CNS and in peripheral nerves. Most effects result from release of NE.

Pharmacologic Effects

Central Nervous System.

The amphetamines have prominent effects on mood and arousal. At usual doses, they increase wakefulness and alertness, reduce fatigue, elevate mood, and augment self-confidence and initiative. Euphoria, talkativeness, and increased motor activity are likely. Task performance that had been reduced by fatigue or boredom improves.

Amphetamines can stimulate respiration, and suppress appetite and perception of pain. Stimulation of the medullary respiratory center increases respiration. Effects on the hypothalamic feeding center depress appetite. By a mech-

anism that is not understood, amphetamines can enhance the analgesic effects of morphine and other opioids.

Cardiovascular System.

Cardiovascular effects occur secondary to release of NE from sympathetic neurons. Norepinephrine acts in the heart to increase heart rate, atrioventricular (AV) conduction, and force of contraction. Excessive cardiac stimulation can cause dysrhythmias. In blood vessels, NE promotes constriction. Excessive vasoconstriction can cause hypertension.

Tolerance

With regular amphetamine use, tolerance develops to elevation of mood, suppression of appetite, and stimulation of the heart and blood vessels. In highly tolerant users, doses up to 1000 mg (IV) every few *hours* may be required to maintain *euphoric* effects. This compares with *daily* doses of 5 to 30 mg for nontolerant individuals.

Physical Dependence

Chronic amphetamine use produces physical dependence. If amphetamines are abruptly withdrawn from a dependent person, an abstinence syndrome will ensue. Symptoms include exhaustion, depression, prolonged sleep, excessive eating, and a craving for more amphetamine. Sleep patterns may take months to normalize.

Abuse

Because amphetamines can produce euphoria (extreme mood elevation), they have a high potential for abuse. Psychologic dependence can occur. (Users familiar with CNS stimulants find the psychologic effects of amphetamines nearly identical to those of cocaine.) Because of their abuse potential, all amphetamines, including lisdexamfetamine, are classified under Schedule II of the Controlled Substances Act and must be dispensed accordingly. Whenever amphetamines are used therapeutically, their potential for abuse must be weighed against their potential benefits.

Adverse Effects

CNS Stimulation.

Stimulation of the CNS can cause insomnia, restlessness, and extreme loquaciousness. These effects can occur at therapeutic doses.

Weight Loss.

By suppressing appetite, amphetamines can cause weight loss. For people who are lean to start with, weight loss is considered an adverse effect. Conversely, for people who are obese, weight loss is desirable.

Cardiovascular Effects.

Stimulation of the heart and blood vessels can result in dysrhythmias, anginal pain, and hypertension. Accordingly, amphetamines must be employed with extreme caution in patients with cardiovascular disease.

Do amphetamines increase the risk of *sudden death?* Probably not. And should children *routinely* receive an electrocardiogram (ECG) before using these drugs? Probably not—despite a 2008 statement from the American Heart Association (AHA) saying it would be reasonable to consider obtaining an ECG in children being evaluated for stimulant therapy of ADHD. Why is the AHA concerned? Because 14 children, 5 with heart defects, died suddenly while using Adderall, a mixture of amphetamine and dextroamphetamine. However, given that millions of children have used the drug, the death rate is no greater than would be expected for a group this size, whether or not Adderall was being used. The bottom line? First, there are no data showing that stimulants increase the risk of sudden death, even in children with heart disease. Second, there are no data showing that limiting the use of stimulants in children with heart defects will protect them from sudden death. And third, there are no data showing that screening for heart disease with an ECG before starting stimulants will be of any benefit. Therefore, it would seem that routine ECGs are unnecessary before starting a child on stimulant therapy, especially if there is no evidence of heart disease. If there *is* evidence of heart disease, an ECG might be helpful, but certainly is not required.

Psychosis.

Excessive amphetamine use produces a state of paranoid psychosis, characterized by hallucinations and paranoid delusions (suspiciousness, feelings of being watched). Amphetamine-induced psychosis looks very much like schizophrenia. Symptoms are thought to result from release of DA. Consistent with this hypothesis is the observation that symptoms can be alleviated with a DA receptor blocking agent (eg, haloperidol). Following amphetamine withdrawal, psychosis usually resolves spontaneously within a week.

In some individuals, amphetamines can unmask latent schizophrenia. For these people, symptoms of psychosis do not clear spontaneously, and hence psychiatric care is needed.

Acute Toxicity

Symptoms.

Overdose produces dizziness, confusion, hallucinations, paranoid delusions, palpitations, dysrhythmias, and hypertension. Death is rare. Fatal overdose is associated with convulsions, coma, and cerebral hemorrhage.

Treatment.

Hallucinations can be controlled with chlorpromazine, an antipsychotic drug. An alpha-adrenergic blocker (eg, phentolamine) can reduce hypertension (by promoting vasodilation). Because of its ability to block alpha receptors, chlorpromazine helps lower blood pressure. Seizures can be managed with diazepam. Acidifying the urine can accelerate amphetamine excretion.

Therapeutic Uses

Attention-Deficit/Hyperactivity Disorder.

The role of amphetamines in ADHD is discussed later.

Narcolepsy.

Narcolepsy is a disorder characterized by daytime somnolence and uncontrollable attacks of sleep. By stimulating the CNS, amphetamines can promote arousal and thereby alleviate symptoms.

Obesity.

Because they suppress appetite, amphetamines have been employed in programs for weight loss. However, because of their high potential for abuse, and because they offer no advantages over less dangerous drugs, amphetamines are not recommended for weight reduction.

Preparations, Dosage, and Administration

Four members of the amphetamine family are used clinically: dextroamphetamine sulfate, an amphetamine/dextroamphetamine mixture, lisdexamfetamine, and methamphetamine. A fifth agent—amphetamine sulfate (racemic amphetamine)—has been discontinued. In clinical practice, amphetamines are given *orally*. (These drugs are not approved for IV administration. Amphetamines for IV use are available only through illegal sources.) All amphetamines are regulated under Schedule II of the Controlled Substances Act and must be dispensed accordingly.

Dextroamphetamine Sulfate.

Dextroamphetamine is available in short-duration (SD) and long-duration (LD) formulations. Both are indicated for ADHD.

Short Duration.

SD dextroamphetamine [DextroStat] is available in 5- and 10-mg tablets. Effects begin rapidly and last 4 to 6 hours. The usual dosage for ADHD is 5 mg at 8:00 AM, noon, and 4:00 PM.

Long Duration.

LD dextroamphetamine [Dexedrine Spansules] is available in 5-, 10-, and 15-mg capsules. Effects begin rapidly and last 6 to 10 hours. The usual dosage for ADHD is 10 mg once daily in the morning.

Amphetamine/Dextroamphetamine Mixture.

Amphetamine mixture is available in SD and LD formulations. Both are used for ADHD.

Short Duration.

The SD formulation [Adderall] is available in immediate-release tablets (5, 7.5, 10, 12.5, 15, 20, and 30 mg). Effects begin rapidly and last 4 to 6 hours. The usual dosage for ADHD is 5 mg twice daily, taken 5 hours apart.

Long Duration.

The LD formulation [Adderall-XR] is available in 5-, 10-, 15-, 20-, 25-, and 30-mg capsules. Half the dose is released immediately, and the remainder 4 hours later. As a result, effects begin rapidly and last 10 to 12 hours. The usual dosage is 20 mg once daily in the morning. This is equivalent to taking 10 mg of SD Adderall at 8:00 AM and again around noon.

Lisdexamfetamine.

Lisdexamfetamine [Vyvanse] is available in capsules (20, 30, 40, 50, 60, and 70 mg). Effects begin rapidly and persist 10 to 12 hours. Dosing is done once daily in the morning without regard to meals. The capsules may be swallowed intact, or their contents may be dissolved in water and swallowed immediately. The usual daily dosage for ADHD is 30 mg.

Methamphetamine.

Methamphetamine [Desoxyn] is indicated for ADHD and obesity, although it is not a preferred treatment for either condition. The drug is available in 5-mg SD tablets. The usual regimen for ADHD is 20 to 25 mg/day, administered in two divided doses.

METHYLPHENIDATE AND DEXMETHYLPHENIDATE

Methylphenidate and dexmethylphenidate are nearly identical in structure and pharmacologic actions. Furthermore, the pharmacology of both drugs is nearly identical to that of the amphetamines.

Methylphenidate

Although methylphenidate [Ritalin, Metadate, Methylin, Concerta, Daytrana] is structurally dissimilar from the amphetamines, the pharmacologic actions of these drugs are essentially the same. Consequently, methylphenidate can

be considered an amphetamine in all but structure and name. Methylphenidate and amphetamine share the same mechanism of action (promotion of NE and DA release, and inhibition of NE and DA reuptake), adverse effects (insomnia, reduced appetite, emotional lability), and abuse liability (Schedule II). Like amphetamine, methylphenidate is not a single compound, but rather a 50:50 mixture of dextro and levo isomers. The dextro isomer is highly active; the levo isomer is not. Methylphenidate has two indications: ADHD and narcolepsy.

Preparations, Dosage, and Administration

Methylphenidate is available in three types of formulations: short duration (SD), intermediate duration (ID), and long duration (LD). All three are indicated for ADHD. As a rule, the SD and ID formulations must be taken 2 or 3 times a day, whereas the LD formulations can be taken just once a day.

Short Duration.

SD methylphenidate [Ritalin, Methylin] is available in standard tablets (5, 10, and 20 mg), chewable tablets (2.5, 5, and 10 mg), and an oral solution (5 and 10 mg/5 mL). Effects begin rapidly and last 3 to 5 hours. Because effects are brief, dosing must be done 2 or 3 times a day. The usual pediatric dosage for ADHD is 10 mg at 8:00 AM and noon, and 5 mg at 4:00 PM.

Intermediate Duration.

ID methylphenidate [Ritalin SR, Metadate ER, Methylin ER] is available in 10- and 20-mg tablets. Effects are delayed and last 6 to 8 hours. Dosing is done once or twice daily. For children with ADHD, the usual dosage is 20 to 40 mg in the morning, supplemented with 20 mg in the early afternoon if needed.

Long Duration.

Four LD products are available. Their trade names are Concerta, Metadate CD, Ritalin LA, and Daytrana. With all four, dosing is done once daily in the morning; no afternoon dose is needed.

Concerta.

Concerta tablets—formulated as an osmotic-release oral system (OROS)—consist of an outer coating of immediate-release methylphenidate and a special inner core that releases the remainder of each dose gradually. As a result, effects begin rapidly and last up to 14 hours. Because of their special architecture, Concerta tablets must be swallowed whole, not crushed or chewed. The tablet shell may not dissolve fully in the GI tract. Accordingly, patients should be informed they may see tablet "ghosts" in the stool. Concerta tablets are available in four strengths: 18, 27, 36, and 54 mg.

Dosage depends on whether the patient is already taking methylphenidate (SD or ID). For children *not* already taking methylphenidate, the initial dosage is 18 mg once daily in the morning. Dosage can be increased to a maximum of 72 mg once daily. For children who *are* taking methylphenidate (SD or ID), the initial dosage of Concerta is as follows:

- For those taking 5 mg (2 or 3 times a day) of SD methylphenidate or 20 mg once daily of ID methylphenidate, start with 18 mg of Concerta.
- For those taking 10 mg (2 or 3 times a day) of SD or 40 mg once daily of ID, start with 36 mg of Concerta.
- For those taking 15 mg (2 or 3 times a day) of SD or 60 mg once daily of ID, start with 54 mg of Concerta.

Metadate CD.

Metadate CD is available in 20-mg capsules that contain immediate-release and delayed-release beads. The beads release 30% of the dose rapidly, and the remaining 70% four hours later. As a result, plasma levels peak twice—at 1.5 and 4.5 hours. This is the same pattern produced by taking SD methylphenidate twice daily. For ADHD patients *not* already taking methylphenidate, the initial dosage is 20 mg once daily in the morning. This can be gradually increased to a maximum of 60 mg once daily. For patients who *are* already taking methylphenidate, start with 20 mg of Metadate once daily (for those taking 10 mg of SD methylphenidate twice daily), or with 40 mg of Metadate once daily (for those taking 20 mg of SD methylphenidate twice daily). If needed, Metadate CD capsules can be opened and sprinkled on a small amount of soft food (eg, applesauce) just prior to ingestion.

Ritalin LA.

Ritalin LA is formulated as extended-release capsules (10, 20, 30, and 40 mg). The product is much like Metadate CD in that some of the dose is released immediately and the rest 4 hours later. Dosing is done *once daily in the morning*. As with Metadate CD and Concerta, dosage depends on whether the patient is already taking methylphenidate (SD or ID). For children *not* already taking methylphenidate, the initial dosage is 20 mg. Dosage can be gradually increased to a maximum of 60 mg. For children who *are* taking methylphenidate (SD or ID), the initial dosage is as follows:

- For those taking 10 mg twice daily of SD methylphenidate or 20 mg once daily of ID methylphenidate, start with 20 mg of Ritalin LA.
- For those taking 15 mg twice daily of SD, start with 30 mg of Ritalin LA.
- For those taking 20 mg twice daily of SD or 40 mg once daily of ID, start with 40 mg of Ritalin LA.
- For those taking 30 mg twice daily of SD or 60 mg once daily of ID, start with 60 mg of Ritalin LA.

Daytrana.

Daytrana—a *transdermal methylphenidate patch*—is the first nonoral treatment for ADHD. Following patch application, blood levels of methylphenidate rise slowly and peak in about 9 hours, after which the patch should be removed. Because of the slow rise, effects are delayed about 2 hours. Furthermore, effects will persist for about 3 hours after patch removal. Daytrana patches are available in four sizes—12.5, 18.75, 25, and 37.5 cm^2—that deliver 10, 15, 20, and 30 mg/9 hours, respectively. Treatment should begin with the smallest patch, even in patients already taking methylphenidate PO. If needed, larger patches can be tried at weekly intervals. Patients should apply the patch to the hip in the morning—alternating hips each day—and remove it no more than 9 hours later. (They can remove it sooner to terminate effects early). Application to inflamed skin or applying heat will accelerate drug absorption, and hence should be avoided. Patients should be informed that bathing, showering, and swimming will not dislodge the patch.

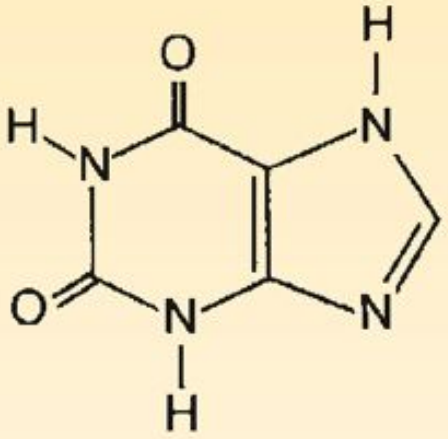
Side effects of the patch are like those of oral methylphenidate, with two exceptions. First, users may experience erythema and pruritus at the application site. Second, exposing the skin to methylphenidate can cause a *hypersensitivity reaction*. If hypersensitivity develops, the patient may be unable to use *any* methylphenidate formulation—transdermal or oral—ever again.

Dexmethylphenidate

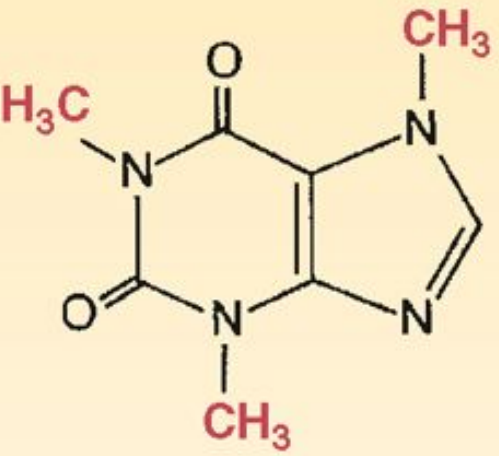
Dexmethylphenidate [Focalin, Focalin XR], a drug for ADHD, is simply the dextro isomer of methylphenidate. As noted, the dextro isomer accounts for most of the pharmacologic activity of methylphenidate, a 50:50 mixture of dextro and levo isomers. Accordingly, the pharmacology of dexmethylphenidate is nearly identical to that of methylphenidate. The only difference is that the dosage of dexmethylphenidate is one-half the dosage of methylphenidate. Dexmethylphenidate is available in SD tablets (2.5, 5, and 10 mg) marketed as *Focalin,* and in LD capsules (5, 10, 15, and 20 mg) marketed as *Focalin XR*. Both formulations may be administered with or without food. For children currently treated with methylphenidate, the initial dosage of dexmethylphenidate is one-half the methylphenidate dosage. For children who are *not* currently being treated, the initial dosage is 2.5 mg twice daily (using Focalin), or 5 mg once daily (using Focalin XR). The maximum dosage is 10 mg twice daily (for Focalin) and 20 mg once daily (for Focalin XR). Dexmethylphenidate is a Schedule II drug and must be dispensed accordingly.

METHYLXANTHINES

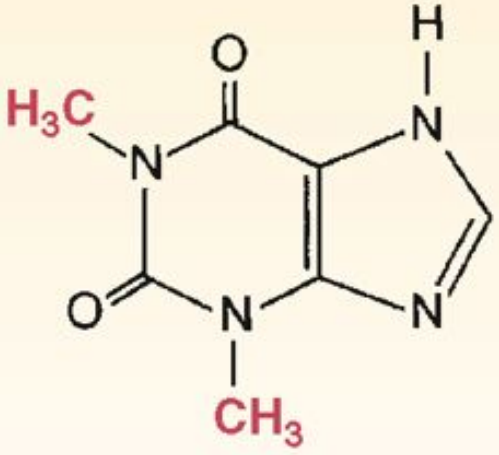
The methylxanthines are derivatives of xanthine, hence the family name. As shown in Figure 36-2, these compounds consist of a xanthine nucleus to which one or more methyl groups is attached. Caffeine, the most familiar member of the family, will serve as our prototype.



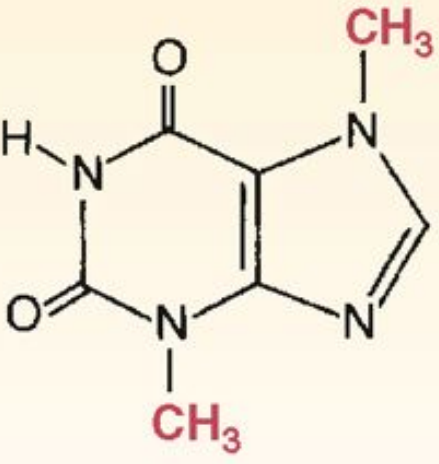
XANTHINE



CAFFEINE



THEOPHYLLINE



THEOBROMINE

Figure 36-2 Structural formulas of the methylxanthines.

Caffeine

Caffeine is consumed worldwide for its stimulant effects. In the United States, per capita consumption is about 200 mg/day, mostly in the form of coffee. Although clinical applications of caffeine are few, caffeine remains of interest because of its widespread ingestion for nonmedical purposes.

Dietary Sources

Caffeine can be found in chocolates, desserts, soft drinks, and beverages prepared from various natural products. Common dietary sources are coffee, tea, and cola drinks. The caffeine in cola drinks derives partly from the cola nut and partly from caffeine added by the manufacturer. Caffeine is also present in many noncola soft drinks. The caffeine content of some common foods and beverages is shown in Table 36-1.

Product	Amount	Caffeine (mg)
Coffee		
Brewed (typical)	8 oz	60–180
Brewed (Starbucks café latte)	16 oz	150
Instant	8 oz	30–120
Espresso (Starbucks)	1 oz	89
Decaffeinated	8 oz	1–5
Tea		
Brewed (Lipton)	8 oz	35–40
Snapple ice tea	16 oz	48
Celestial Seasonings Herbal Tea, all varieties	8 oz	0
Lipton Natural Brew Iced Tea Mix, decaffeinated	8 oz	<5
Soda		
Jolt	12 oz	71
Red Bull Cola	12 oz	45
Mountain Dew	12 oz	55
Diet Coke	12 oz	47
Coca-Cola	12 oz	45
Dr. Pepper	12 oz	41
Orange soda, Sunkist	12 oz	40
Pepsi-Cola	12 oz	37
7-UP	12 oz	0
Sprite	12 oz	0
Caffeinated Water		
Java Water	16.9 oz	125

TABLE 36-1 Dietary Caffeine

Mechanism of Action

Several mechanisms of action have been proposed. These include (1) reversible blockade of adenosine receptors, (2) enhancement of calcium permeability in the sarcoplasmic reticulum, and (3) inhibition of cyclic nucleotide phosphodiesterase, resulting in accumulation of cyclic adenosine monophosphate (cyclic AMP). Blockade of adenosine receptors appears responsible for most effects.

Pharmacologic Effects

Central Nervous System.

In low doses, caffeine decreases drowsiness and fatigue and increases the capacity for prolonged intellectual exertion. With increasing dosage, caffeine produces nervousness, insomnia, and tremors. When administered in very large amounts, the drug can cause convulsions. Despite popular belief, there is little evidence that caffeine can restore mental function during intoxication with alcohol, although it might delay passing out.

Heart.

High doses of caffeine stimulate the heart. When caffeinated beverages are consumed in excessive amounts, dysrhythmias may result.

Blood Vessels.

Caffeine affects blood vessels in the periphery differently from those in the CNS. In the periphery, caffeine promotes *vasodilation,* whereas in the CNS, caffeine promotes *vasoconstriction*. Constriction of cerebral blood vessels is thought to underlie the drug's ability to relieve headache.

Bronchi.

Caffeine and other methylxanthines cause relaxation of bronchial smooth muscle, and thereby promote bronchodilation. Theophylline is an especially effective bronchodilator, and hence can be used to treat asthma (see Chapter 75).

Kidney.

Caffeine is a diuretic. The mechanism underlying increased urine formation is not fully understood.

Reproduction: Birth Defects and Miscarriage.

Caffeine readily crosses the placenta and may pose a risk of birth defects. When applied to cells in culture, caffeine can cause chromosomal damage and mutations. However, the concentrations required are much greater than can be achieved by drinking caffeinated beverages. Also, although there is clear proof that caffeine can cause birth defects in animals, studies have failed to document birth defects in humans.

A study published in 2008 showed that caffeine carries a dose-dependent risk of miscarriage. Consuming less than 200 mg/day poses little risk. In contrast, consuming 200 mg/day or more appears to double the risk. Accordingly, in order to reduce the risk of miscarriage, pregnant women should consume no more than 200 mg of caffeine a day—and preferably less.

Pharmacokinetics

Caffeine is readily absorbed from the GI tract, and achieves peak plasma levels within 1 hour. Plasma half-life ranges from 3 to 7 hours. Elimination is by hepatic metabolism.

Therapeutic Uses

Neonatal Apnea.

Premature infants may experience prolonged apnea (lasting 15 seconds or more) along with bradycardia. Hypoxemia and neurologic damage may result. Caffeine and other methylxanthines can reduce the number and duration of apnea episodes and can promote a more regular pattern of breathing.

Promoting Wakefulness.

Caffeine is used commonly to aid staying awake. The drug is marketed in various over-the-counter preparations [Maximum Strength NoDoz, Vivarin, others] for this purpose. Of course, individuals desiring increased alertness needn't take a pill; they can get just as much caffeine by drinking coffee or some other caffeine-containing beverage.

Other Applications.

Intravenous caffeine can help relieve headache induced by spinal puncture. The drug is used orally to enhance analgesia induced by opioids and by nonopioid analgesics (eg, aspirin).

Acute Toxicity

Caffeine poisoning is characterized by intensification of the responses seen at low doses. Stimulation of the CNS results in excitement, restlessness, and insomnia; if the dosage is very high, convulsions may occur. Tachycardia and respiratory stimulation are likely. Sensory phenomena (ringing in the ears, flashing lights) are common. Death from caffeine overdose is rare. When fatalities have occurred, between 5 and 10 gm have been ingested.

Preparations, Dosage, and Administration

For Promoting Wakefulness.

Caffeine is available in three formulations for promoting wakefulness: 200-mg tablets, 200-mg capsules, and 75-mg lozenges. The usual dosage for promoting alertness is 100 to 200 mg every 3 to 4 hours as needed.

For Neonatal Apnea.

Caffeine citrate [Cafcit] is used for neonatal apnea. The drug is available in oral and IV solutions. Both have the same concentration: 20 mg/mL. Treatment consists of an IV loading dose (20 mg/kg) followed every 24 hours by an oral or IV maintenance dose (5 mg/kg). *Note:* The amount of caffeine *base* in a 20-mg dose of caffeine citrate is only 10 mg (ie, one-half of the total dose on a milligram basis).

Theophylline

Theophylline has pharmacologic actions much like those of caffeine. Like caffeine, theophylline is an effective CNS stimulant. However, in contrast to caffeine, theophylline is used to treat asthma; benefits derive from causing bronchodilation. Use in asthma is discussed in Chapter 75.

Theobromine

Theobromine is a methylxanthine that occurs naturally in the seeds of *Theobroma cacao,* from which cocoa and chocolate are made. The caffeine content of these seeds is relatively low. Although there are similarities between theobromine and caffeine, these compounds do differ. The most distinct difference is that caffeine is a more effective CNS stimulant. Accordingly, CNS excitation produced by ingestion of cocoa and chocolate derives primarily from their caffeine content and not from theobromine. Toxicity from theobromine in chocolate is discussed in Box 36-1.

BOX 36-1 DID KISSES KILL CALVIN?

Well...no. But they might have. Calvin, recently deceased, was a happy little Jack Russell terrier who lived with Nancy, my very significant other, on her horse farm here in central Virginia. Our country squire graciously shared his home with sundry horses and ponies, gaggles of geese, and his dearest friends: Gucci, Hannah, Sandy, and Lucy—Nancy's other four dogs. Calvin enjoyed a rich, tranquil, contented life, until being mortally wounded while defending his home and friends from a canine intruder. We loved our little man. And we miss him.

So, what's the connection between Calvin and lethal kisses? One day, when I tossed Calvin a Hershey's Chocolate Kiss, Nancy became horrified and demanded I stop. “Why?” I asked. “Because,” she said, “chocolate is poisonous to dogs. Didn't you know?” Right. Death by chocolate. Needless to say, this pharmacologist was skeptical. So I did some reading. Turns out, Nancy was correct: Chocolate really can kill dogs. What follows is for readers who, like me, didn't know that chocolate could hurt those we love.

Why is chocolate toxic? Because it contains two methylxanthines: *theobromine* and *caffeine*. Both drugs are stimulants that can cause seizures and cardiac dysrhythmias. In the absence of treatment, death can result. Although both compounds are of concern, chocolate contains much more theobromine than caffeine. Accordingly, our discussion focuses on theobromine.

Why is theobromine toxic to dogs but not us? Because dogs eliminate this compound very slowly: In dogs, the half-life of theobromine is 17.5 hours, compared with only 2 hours in humans. Because of delayed elimination, theobromine climbs to higher levels in dogs, and remains at those high levels a long time. If humans took theobromine in big enough doses, it would hurt us too.

What are the symptoms of theobromine/chocolate poisoning? Initial symptoms, which typically develop in 6 to 12 hours, include vomiting, diarrhea, restlessness, and excessive fluid intake. Later symptoms involve the CNS (hyperactivity, incoordination, disturbed balance, tremors, seizures, coma), cardiovascular system (premature ventricular contractions, tachycardia or bradycardia, hypertension or hypotension), oxygenation (rapid breathing, cyanosis), and thermoregulation (hyperthermia). Symptoms may persist for 72 hours. Death, if it occurs, is usually from dysrhythmias, hyperthermia, or respiratory failure.

How is theobromine poisoning treated? There is no specific antidote to theobromine, so treatment is directed at symptom control and poison removal. Tremors and mild seizures can be controlled with diazepam. Severe seizures may require a barbiturate. Tachydysrhythmias can be controlled with a beta blocker (eg, metoprolol), bradydysrhythmias with atropine, and refractory ventricular dysrhythmias with lidocaine. Once the victim is stabilized—or if symptoms have not yet appeared—decontamination should be implemented. Theobromine can be removed from the stomach by gastric lavage, or by inducing emesis with apomorphine. Activated charcoal can prevent further absorption from the

stomach and intestine. Inducing diuresis with fluids can accelerate excretion of theobromine in the urine.

How much chocolate is lethal? To answer this question, we need to know two things: (1) the average lethal dose (LD***50***) for theobromine in dogs and (2) the theobromine content of various types of chocolate. In dogs, the LD***50*** for theobromine is about 100 mg/kg body weight (45 mg/lb). Put another way, it takes about 450 mg of theobromine to kill a 10-pound dog. The approximate theobromine content of chocolate types is as follows:

- White chocolate—1 mg/ounce
- Milk chocolate—50 mg/ounce
- Semisweet chocolate—150 mg/ounce
- Unsweetened baker's chocolate—450 mg/ounce

These numbers indicate that, in order to get a lethal dose of theobromine (450 mg), a 10-pound dog would have to ingest the following:

- White chocolate—450 ounces (28 pounds), which is impossible.
- Milk chocolate—9 ounces (0.6 lb), which equals the chocolate in 3 average candy bars. Easy for a dog who likes candy.
- Semisweet chocolate—only 3 ounces.
- Unsweetened baker's chocolate—just one 1-ounce square.

From this information, it's clear that giving Calvin a Chocolate Kiss or two was safe, despite Nancy's alarm. However, it's also clear that it doesn't take a basket of candy to do serious harm. In fact, although the LD***50*** for theobromine is 100 mg/kg, significant reactions can develop at much lower doses. For example, at 20 mg/kg, vomiting and diarrhea can develop; at 40 to 50 mg/kg, cardiotoxicity can develop; and at doses above 60 mg/kg, seizures may develop. Accordingly, it would seem prudent to keep your entire chocolate stash in a doggy-proof place, especially if your little friend is a chocaholic.

So, Dr. Lehne, is chocolate really going to kill my dog—or better yet, my neighbor's little yapper? Probably not. Fact is, *fatal* chocolate poisoning is rare. Nonetheless, chocolate poisoning *is* the most common reason for calls to the ASPCA's *Animal Poison Control Center* (APCC), which, for a small fee, can provide professional assistance 24 hours a day, 7 days a week. So, the next time your dog

scarfs up an entire pan of brownies, you can call the APCC at 1-888-426-4435 for immediate help.

MISCELLANEOUS CNS STIMULANTS

Modafinil

Therapeutic Use.

Modafinil [Provigil], a unique nonamphetamine stimulant, is approved for promoting wakefulness in patients with excessive sleepiness associated with three disorders: narcolepsy, shift-work sleep disorder (SWSD), and obstructive sleep apnea/hypopnea syndrome (OSAHS). Investigational uses include ADHD and fatigue associated with multiple sclerosis. The military is studying the drug for use in situations that might require alertness for an extended time. And some people are using it just to stay awake so they can work or play more.

In clinical trials, modafinil has been moderately effective. In patients with narcolepsy, modafinil increased wakefulness, but only to about 50% of the level seen in normal people. In contrast, methylphenidate and dextroamphetamine increase wakefulness to about 70% of normal. In patients with SWSD and OSAHS, benefits are about the same as those seen in patients with narcolepsy.

Mechanism of Action.

How does modafinil ward off sleep? No one knows. The drug does seem to influence hypothalamic areas involved in maintaining the normal sleep-wakefulness cycle. Also, there is evidence indicating that modafinil inhibits the activity of sleep-promoting neurons (in the ventrolateral preoptic nucleus) by blocking reuptake of norepinephrine.

Pharmacokinetics.

Modafinil is rapidly absorbed from the GI tract. Plasma levels peak in 2 to 4 hours. Food decreases the rate of absorption but not the extent. Elimination is by hepatic metabolism followed by renal excretion. The half-life is about 15 hours.

Adverse Effects.

Modafinil is generally well tolerated. The most common adverse effects are headache, nausea, nervousness, diarrhea, and rhinitis. Modafinil does not disrupt nighttime sleep. In clinical trials, only 5% of patients dropped out because of undesired effects. Initially, the drug was believed devoid of cardiovascular effects. However, we now know it can increase heart rate and blood pressure, apparently by altering autonomic function. Subjective effects—euphoria; altered perception, thinking, and feeling—are like those of other CNS stimulants. However, modafinil has less abuse potential, and hence is regulated as a Schedule IV substance. Physical dependence and withdrawal have not been reported. Modafinil is embryotoxic in laboratory animals, and hence should be avoided during pregnancy.

Postmarketing reports link modafinil to rare cases of serious skin reactions, including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis. Patients should be informed about signs of these reactions—swelling or rash, especially in the presence of fever or changes in the oral mucosa—and instructed to discontinue the drug if they develop.

Drug Interactions.

Modafinil inhibits some forms of cytochrome P450 (CYP) and induces others. Induction of CYP3A4 may accelerate the metabolism of oral contraceptives, cyclosporine, and certain other drugs, thereby causing their levels to decline. Caution is needed.

Preparations, Dosage, and Administration.

Modafinil is available in 100- and 200-mg tablets. For patients with narcolepsy or OSAHS, the usual dosage is 200 mg/day, taken as a single dose in the morning. For patients with SWSD, the usual dosage is 200 mg/day, taken as a single dose 1 hour before the shift starts. For patients with severe hepatic impairment, doses should be decreased by 50%. Dosage reduction may also be needed in the elderly.

Armodafinil

Armodafinil [Nuvigil] is simply the *R*-enantiomer of modafinil, a mixture of *R*- and *S*-enantiomers. Armodafinil differs from modafinil in that the *R*-enantiomer (armodafinil) has a longer half-life than the *S*-enantiomer component

of modafinil. Otherwise, the two drugs are essentially identical. Armodafinil has the same indications as modafinil—improving wakefulness in people with narcolepsy, SWSD, and OSAHS—and has similar adverse effects, including the potential for rare but severe skin reactions. Like modafinil, armodafinil is classified as a Schedule IV substance. Armodafinil is available in 50-, 150-, and 250-mg tablets. The recommended dosage for narcolepsy and OSAHS is 150 or 250 mg, taken in the morning. The recommended dosage for SWSD is 150 mg, taken 1 hour before the work shift.

Strychnine

Strychnine was introduced in the 16th century as a rat poison. At one time the drug was also employed therapeutically. Although strychnine is no longer used as a medicine, it remains a source of accidental poisoning.

Strychnine is a powerful convulsant that stimulates the CNS at all levels. Stimulation results from blockade of receptors for glycine, an inhibitory neurotransmitter.

Strychnine Poisoning

Causes.

A common cause of strychnine poisoning is accidental ingestion of strychnine-based rodenticides. Poisoning also occurs through the use of "street drugs" to which strychnine has been added. (Since strychnine does not enhance the effects of illicit drugs, the practice of mixing this agent with street drugs is not only dangerous, it also lacks any pharmacologic rationale.) The lethal dose is about 15 mg in children, and 50 to 100 mg in adults.

Symptoms.

The first manifestation of poisoning is stiffness in the muscles of the face and neck. This is followed by a generalized increase in reflex excitability. During the early stages of poisoning, the victim is fully conscious. As poisoning progresses, convulsions occur. Strychnine-induced convulsions are characterized by tonic contraction of all voluntary muscles; contraction of the diaphragm, abdominal muscles, and thoracic muscles stops respiration. Convulsive episodes alternate with periods of depression until the victim dies or until the

poisoning is successfully treated. Few patients survive beyond the fifth convulsive episode; some are killed by the first. Death is from respiratory arrest.

Treatment.

Management is directed primarily at controlling convulsions and supporting respiration. Intravenous diazepam is the treatment of choice to suppress convulsions. If poisoning is severe, general anesthesia or neuromuscular blockade may be needed to eliminate convulsions. If anticonvulsant therapy fails to permit adequate breathing, mechanical support of respiration is indicated.

Doxapram

Doxapram [Dopram] stimulates the CNS at all levels. The drug is employed clinically to stimulate respiration. However, since the doses required are close to those that can produce generalized CNS stimulation and convulsions, doxapram must be used with great care. Furthermore, although doxapram is labeled for treatment of general CNS depressant poisoning, its use for this purpose should be discontinued: Experience has shown that respiratory depression from CNS depressant poisoning can be managed more safely and effectively with mechanical support of ventilation than with pharmacologic stimulation of respiration.

Cocaine

Cocaine is a powerful CNS stimulant with a high potential for abuse. The only clinical application of this drug—local anesthesia—is discussed in Chapter 26. The basic pharmacology of cocaine and cocaine abuse are discussed in Chapter 39.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

ADHD in Children

ADHD is the most common neuropsychiatric disorder of childhood. In the United States, over 2 million school-age children are affected—an average of one child with ADHD for every classroom. The incidence in boys is 2 to 3 times the incidence in girls. Symptoms begin between ages 3 and 7, usually persist into the teens, and often persist into adulthood. The majority (60% to 70%) of

children respond well to stimulant drugs. Methylphenidate [Ritalin, Concerta, others] is the agent employed most.

Signs and Symptoms

ADHD is characterized by *inattention, hyperactivity,* and *impulsivity*. Affected children are fidgety, unable to concentrate on schoolwork, and unable to wait their turn; switch excessively from one activity to another; call out excessively in class; and never complete tasks. For a diagnosis to be made, symptoms must appear prior to age 7 and be present for at least 6 months. Since other disorders—especially anxiety and depression—may cause similar symptoms, diagnosis must be done carefully. Specific diagnostic criteria for ADHD, as described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* are summarized in Table 36-2. Depending on the symptom profile, ADHD can be subclassified as predominately inattentive type, predominately hyperactive-impulsive type, or combined type. Former names for ADHD—*hyperkinetic syndrome* and *minimal brain dysfunction*—are misleading and have been abandoned.

Etiology

Although various theories have been proposed, the underlying pathophysiology of ADHD has not been firmly established. Neuroimaging studies indicate structural and functional abnormalities in multiple brain areas, including the frontal cortex, basal ganglia, brainstem, and cerebellum—regions involved with regulating attention, impulsive behavior, and motor activity. Several theories implicate dysregulation in neuronal pathways that employ NE and DA as transmitters. These theories would be consistent with the beneficial effects of atomoxetine (which blocks NE reuptake) and the effects of stimulant drugs (which promote release of NE and DA and, to some degree, block their reuptake). Genetic factors appear to play an important role.

TABLE 36-2 DSM-IV-TR Diagnostic Criteria for ADHD

A. Either (1) or (2)

(1) **Inattention.** Six (or more) of the following symptoms have persisted for at least 6 months:

- Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- Often has difficulty sustaining attention in tasks or play activities
- Often does not seem to listen when spoken to directly
- Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace
- Often has difficulty organizing tasks and activities
- Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (eg, schoolwork, homework)
- Often loses things necessary for tasks or activities (eg, toys, school assignments, pencils, books, tools)
- Is often easily distracted by extraneous stimuli
- Is often forgetful in daily activities

(2) **Hyperactivity-impulsivity.** Six (or more) of the following symptoms have persisted for at least 6 months:

Hyperactivity

- Often fidgets with hands or feet or squirms in seat
- Often leaves seat in classroom or in other situations in which remaining seated is expected
- Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- Often has difficulty playing or engaging in leisure activities quietly
- Is often "on the go" or often acts as if "driven by a motor"
- Often talks excessively

Impulsivity

- Often blurts out answers before questions have been completed
- Often has difficulty awaiting turn

- Often interrupts or intrudes on others (eg, butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms were present before age 7 years.

C. Symptoms are present in two or more settings (eg, at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder, and are not better accounted for by another mental disorder (eg, mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).

Modified from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Press, 2000, with permission. Copyright © 2000 American Psychiatric Association.

Management Overview

Multiple strategies may be employed to manage ADHD. In addition to drugs, the treatment program can include family therapy, parent training, and cognitive therapy for the child. In 2001, the American Academy of Pediatrics issued clinical practice guidelines emphasizing the importance of a comprehensive treatment program, involving collaboration among clinicians, families, and educators. For long-term gains, a combination of cognitive therapy and stimulant drugs appears most effective.

Drug Therapy I: CNS Stimulants

Stimulant drugs are the mainstay of therapy. Drugs with proven efficacy include *methylphenidate* [Ritalin, Concerta, others], *dexmethylphenidate* [Focalin], *dextroamphetamine* [DextroStat, others], and *amphetamine mixture* [Adderall].

The response to stimulants can be dramatic. These drugs can increase attention span and goal-oriented behavior while decreasing impulsiveness, distractibility, hyperactivity, and restlessness. Tests of cognitive function (memory, reading, arithmetic) often improve significantly. Unfortunately, al-

though benefits can be dramatic initially, they diminish after 2 to 3 years, as reported in a 2009 paper: *MTA at 8 Years: Prospective Follow-up of Children Treated for Combined-Type ADHD in a Multisite Study*. Nonetheless, stimulant therapy can still buy time to teach youngsters behavioral strategies to help them combat inattention and hyperactivity over the long-term.

Although reduction of impulsiveness and hyperactivity with a stimulant may seem paradoxical—it isn't. Stimulants don't suppress rowdy behavior directly. Rather, they improve attention and focus. Impulsiveness and hyperactivity decline because the child is now able to concentrate on the task at hand. It should be noted that stimulants do not create *positive* behavior; they only reduce *negative* behavior. Accordingly, they cannot give a child good study skills and other appropriate behaviors. Rather, these must be learned once the disruptive behavior is no longer an impediment.

Drug	Trade Name	Duration (hr)	Dosing Schedule	Usual Pediatric Dosage
STIMULANTS				
Methylphenidate				
Short Duration	Ritalin Methylin	3–5	2 or 3 times daily	10 mg at 8:00 AM and noon, and 5 mg at 4:00 PM
Intermediate Duration	Ritalin SR Metadate ER Methylin ER	6–8	Once or twice daily	20 or 40 mg in AM plus 20 mg in early PM if needed
Long Duration	Concerta	Up to 14	Once daily	36 mg in AM
	Metadate CD	6–8	Once daily	40 mg in AM
	Ritalin LA	7–9	Once daily	60 mg in AM
	Daytrana	10–12	Once daily	One 15- or 20-mg patch, applied in AM and removed 9 hr later
Dexmethylphenidate				
Short Duration	Focalin	4–5	Twice daily	10 mg in AM plus 10 mg in early PM
	Focalin XR	Up to 12	Once daily	20 mg in AM
Dextroamphetamine				
Short Duration	DextroStat	4–6	2 or 3 times daily	5 mg at 8:00 AM, noon, and 4:00 PM
Long Duration	Dexedrine	6–10	Once or twice	

TABLE 36-3 Major Drugs for Attention-Deficit/Hyperactivity Disorder

The dosing schedule employed is important, and is determined by the time course of the formulation selected. As discussed above (and shown in Table 36-3), CNS stimulants are available in short-, intermediate-, and long-duration formulations. With the SD and ID formulations, the child usually takes two or three doses a day. In contrast, the LD formulations are taken just once a day (in the morning). Not only is once-daily dosing more convenient, it spares the child any embarrassment or stigma associated with taking medicine at school. Accordingly, LD formulations (eg, Adderall-XR, Concerta, Daytrana) are generally preferred. Dosage is determined by monitoring for improvement in symptoms and appearance of side effects.

Principal adverse effects of the stimulants are *insomnia* and *growth suppression*. Insomnia results from CNS stimulation, and can be minimized by reducing the size of the afternoon dose and taking it no later than 4:00 PM. Growth suppression occurs secondary to appetite suppression. Growth reduction can be minimized by administering stimulants during or after meals (which reduces the impact of appetite suppression). In addition, some clinicians recommend taking "drug holidays" on weekends and in the summer (which creates an opportunity for growth to catch up). However, other clinicians argue against this strategy. Why? Because depriving children of medication during these unstructured times can be hard on them. When stimulants are discontinued, a rebound increase in growth will take place; as a result, adult height may not be affected. Other adverse effects include *headache* and *abdominal pain,* which have an incidence of 10%, and *lethargy* and *listlessness,* which can occur when dosage is excessive.

Drug Therapy II: Atomoxetine

Description and Therapeutic Effects.

Atomoxetine [Strattera] is a unique drug approved for ADHD in children and adults. This is the first *nonstimulant* approved for ADHD, and one of only three drugs approved for ADHD in adults (the others are amphetamine mixture [Adderall XR] and lisdexamfetamine [Vyvanse]). Older nonstimulants, such as imipramine and bupropion, although *used* for ADHD, are not actually *approved* for

ADHD. In contrast to the CNS stimulants, atomoxetine has no potential for abuse, and hence is not regulated as a controlled substance. As a result, prescriptions can be refilled over the phone, making atomoxetine more convenient than the stimulants. Like the long-acting stimulants, atomoxetine can be administered just once a day.

In clinical trials comparing atomoxetine with placebo in children or adults with ADHD, atomoxetine was clearly superior at reducing symptoms. Benefits were similar whether the drug was given once a day or in two divided doses. It should be noted that responses develop slowly: The initial response takes a few days to develop, and the maximal response takes 1 to 3 weeks. This contrasts with the CNS stimulants, whose effects are near-maximal with the first dose.

How does atomoxetine compare with stimulants for treating children with ADHD? In two older 3-week randomized trials, comparing atomoxetine with either methylphenidate [Concerta] or an amphetamine [Adderall XR], the stimulants were superior: More children responded to the stimulants, symptom reduction was greater, and benefits developed more quickly. In 2008, these results were reinforced in a large, 6-week, placebo-controlled trial, in which a stimulant—methylphenidate [Concerta]—was again clearly superior to atomoxetine.

Mechanism of Action.

Atomoxetine is a *selective inhibitor of NE reuptake,* and hence causes NE to accumulate at synapses. Although the precise relationship between this neurochemical action and symptom relief is unknown, it would appear that *adaptive changes* that occur following uptake blockade underlie benefits. Why? Because uptake blockade occurs immediately, whereas full therapeutic effects are not seen for at least a week—suggesting that, after uptake blockade occurs, additional processes must take place before benefits can be seen.

Pharmacokinetics.

Atomoxetine is rapidly and completely absorbed following oral administration. Plasma levels peak in 1 to 3 hours, depending on whether the drug was taken without or with food. Atomoxetine is metabolized in the liver, primar-

ily by CYP2D6 (the 2D6 isozyme of cytochrome P450). For most patients, the half-life is 5 hours. However, for 5% to 10% of patients, the half-life is much longer: 24 hours. Why? Because they have an atypical form of CYP2D6, which metabolizes atomoxetine slowly. Dosage should be reduced in these people.

Adverse Effects.

Like the CNS stimulants, atomoxetine is generally well tolerated. In clinical trials, the most common effects were GI reactions (dyspepsia, nausea, and vomiting), reduced appetite, dizziness, somnolence, mood swings, and trouble sleeping. Sexual dysfunction and urinary retention were seen in adults. Severe allergic reactions, including angioneurotic edema, occurred rarely. If allergy develops, patients should discontinue the drug and contact the prescriber immediately. Atomoxetine may cause a small increase in blood pressure and heart rate, and hence should be used with caution by patients with hypertension, tachycardia, and other cardiovascular disorders.

Atomoxetine may cause *suicidal thinking* in children and adolescents, but not in adults. Fortunately, the incidence is relatively low: about 4 cases per 1000 patients. Risk is greatest during the first few months of treatment. Young patients should be monitored closely for suicidal thinking and behavior, and for signs of clinical worsening (eg, agitation, irritability).

Appetite suppression may result in *weight loss and growth retardation*. Among children who took atomoxetine for 18 months or longer, mean height and weight percentiles declined. Because experience with the drug is limited, we don't know if expected adult height will be affected. Nor do we know if "drug holidays" would have an impact on growth.

Atomoxetine poses a small risk of *severe liver injury* that may progress to outright liver failure, resulting in death or the need for a liver transplant. Patients should be informed about signs of liver injury—jaundice, dark urine, abdominal tenderness, unexplained flu-like symptoms—and instructed to report these immediately. In the event of jaundice or laboratory evidence of liver injury, atomoxetine should be discontinued.

Drug Interactions.

Combining atomoxetine with a *monoamine oxidase inhibitor* (eg, isocarboxazid [Marplan], phenelzine [Nardil]) can cause hypertensive crisis, owing to accumulation of NE at synapses in the periphery. Accordingly, these drugs must not be used together or within 3 weeks of each other.

Inhibitors of CYP2D6 can increase levels of atomoxetine, and hence must be used with caution. Common examples include paroxetine [Paxil], fluoxetine [Prozac], and quinidine.

Role in ADHD Therapy.

Because atomoxetine is a relatively new drug, its role in ADHD has not been firmly established. Yes, atomoxetine appears both safe and effective, and it lacks the potential for abuse. However, we have little information on its long-term dangers, including detrimental effects on growth. Furthermore, current evidence indicates that stimulants work better. Accordingly, because CNS stimulants are more effective and have a long record of safety and efficacy, it would seem prudent to reserve atomoxetine for patients who are unresponsive to or intolerant of the stimulants. In the absence of a compelling reason, patients doing well on the stimulants shouldn't switch.

Preparations, Dosage, and Administration.

Atomoxetine [Strattera] is available in capsules (10, 18, 25, 40, 60, 80, and 100 mg) that should be swallowed whole, with or without food. Dosage is based on body weight as follows:

- Children who weigh *less than 70 kg*—Start with 0.5 mg/kg/day and then, after at least 3 days, increase to the recommended target of 1.2 mg/kg/day. The maximum dosage is 1.4 mg/kg/day or 100 mg, whichever is smaller.
- Children who weigh *more than 70 kg* and *all adults*—Start with 40 mg/day and then, after at least 3 days, increase to the recommended target of 80 mg/day. Do not exceed 100 mg/day.

Two dosing schedules may be used: patients may either (1) take the total daily dose all at once in the morning or (2) divide the dosage up, taking half in the morning and half in the late afternoon or early evening. Note that, with either schedule, dosing during school hours is unnecessary.

Dosage should be reduced in patients who are slow metabolizers, either because of hepatic insufficiency or atypical CYP2D6.

Drug Therapy III: Antidepressants

Three antidepressants—desipramine, imipramine, and bupropion—can reduce behavioral symptoms in children with ADHD. However, these antidepressants are less effective than CNS stimulants and are not approved for ADHD. Accordingly, they are generally reserved for children who have not responded to trials with at least two different stimulants.

Tricyclic Antidepressants.

Desipramine [Norpramin] and imipramine [Tofranil] can reduce symptoms in children with ADHD. These drugs decrease hyperactivity but have little effect on impulsivity and inattention. Responses develop slowly. Beneficial effects begin in 2 to 3 weeks and reach a maximum at around 6 weeks. Tolerance frequently develops within a few months. In contrast to the stimulants, which can be discontinued on weekends, antidepressants must be taken continuously. Adverse effects include sedation and anticholinergic effects (eg, dry mouth, blurred vision, urinary retention, constipation). More importantly, sudden death (from cardiotoxicity) has occurred in at least three children. Compared with stimulants, antidepressants have their benefits (no insomnia, abuse potential, or suppression of appetite and growth) as well as their drawbacks (anticholinergic effects, delayed onset, tolerance, less efficacy, risk of sudden death). Because these antidepressants are less effective and more dangerous than the stimulants, they are considered second-line drugs. Dosages for ADHD range from 2 to 5 mg/kg/day, administered in two or three divided doses. The basic pharmacology of the antidepressants is presented in Chapter 32.

Bupropion.

Bupropion [Wellbutrin] can reduce behavioral symptoms of ADHD, but is less effective than stimulants. The drug lacks the adverse effects associated with tricyclic antidepressants (eg, cardiotoxicity, anticholinergic effects), but does pose a risk of seizures. Like the tricyclic antidepressants, bupropion is con-

sidered a second-line drug for ADHD. Dosage is 100 to 150 mg twice a day. The basic pharmacology of bupropion is presented in Chapter 32.

ADHD in Adults

Contrary to traditional assumptions, we now know that, in about 60% of cases, ADHD persists into adulthood. In the United States, about 10 million adults are afflicted. Symptoms include poor concentration, stress intolerance, antisocial behavior, outbursts of anger, and inability to maintain a routine. Also, adults with ADHD experience more job loss, divorce, and driving accidents. As in childhood ADHD, stimulants are the preferred drugs for treatment. Methylphenidate is prescribed most often. About 33% of adults fail to respond to stimulants or cannot tolerate their side effects. For these patients, a trial with atomoxetine, desipramine, or bupropion may help.

KEY POINTS

- The amphetamine family consists of dextroamphetamine, amphetamine (a racemic mixture of dextroamphetamine and levoamphetamine), methamphetamine, and lisdexamfetamine.
- The amphetamines work primarily by promoting neuronal release of NE and DA, and partly by blocking NE and DA reuptake.
- Through actions in the CNS, the amphetamines can increase wakefulness and alertness, reduce fatigue, elevate mood, stimulate respiration, and suppress appetite.
- By promoting release of norepinephrine from peripheral neurons, amphetamines can cause vasoconstriction and cardiac effects (increased heart rate, increased AV conduction, and increased force of contraction).
- The most common adverse effects of amphetamines are insomnia and weight loss. Amphetamines may also cause psychosis and cardiovascular effects (dysrhythmias, angina, hypertension).
- The principal indication for amphetamines is ADHD.

- The pharmacology of methylphenidate is nearly identical to that of the amphetamines.
- Methylphenidate is the drug most frequently prescribed for ADHD.
- Methylphenidate and other CNS stimulants reduce symptoms of ADHD by enhancing the patient's ability to focus.
- Atomoxetine is the only nonstimulant approved for ADHD.
- Caffeine and other methylxanthines act primarily by blocking adenosine receptors.
- Responses to caffeine are dose dependent: low doses decrease drowsiness and fatigue; higher doses cause nervousness, insomnia, and tremors; and huge doses cause convulsions.
- Caffeine has two principal uses: treatment of apnea in premature infants and reversal of drowsiness.

Summary of Major Nursing Implications*

AMPHETAMINES, METHYLPHENIDATE, AND DEXMETHYLPHENIDATE

Preadministration Assessment

Therapeutic Goal

Reduction of symptoms in children and adults with ADHD. Reduction of sleep attacks in patients with narcolepsy.

Baseline Data

Children with ADHD.

Document the degree of inattention, impulsivity, hyperactivity, and other symptoms of ADHD. Symptoms must be present for at least 6 months to allow a diagnosis of ADHD. Obtain baseline values of height and weight.

Narcolepsy.

Document the degree of daytime sleepiness and the frequency and circumstances of sleep attacks.

Identifying High-Risk Patients

All amphetamines are *contraindicated* for patients with symptomatic cardiovascular disease, advanced atherosclerosis, hypertension, hyperthyroidism, agitated states, and a history of drug abuse, and in those who have taken monoamine oxidase inhibitors within the previous 2 weeks. *Amphetamine mixture* [Adderall XR] is *generally contraindicated* for patients with structural cardiac defects.

Implementation: Administration

Routes

Oral.

Amphetamines, methylphenidate, and dexmethylphenidate.

Transdermal.

Methylphenidate only.

Administration

Oral.

Instruct patients to swallow long-acting formulations intact, without crushing or chewing.

Children with ADHD should take the morning dose after breakfast and the last daily dose by 4:00 PM.

Transdermal.

Instruct patients using transdermal methylphenidate [Daytrana] to apply one patch to alternating hips each morning, and to remove each patch

not more than 9 hours after applying it. Instruct patients to avoid application to skin that is inflamed.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Children with ADHD.

Monitor for reductions in symptoms (impulsiveness, hyperactivity, inattention) and for improvement in cognitive function.

Minimizing Adverse Effects

Excessive CNS Stimulation.

These drugs can cause restlessness and insomnia. **Advise patients to use the smallest dose required and to avoid dosing late in the day. Advise patients to minimize or eliminate dietary caffeine (eg, coffee, tea, caffeinated soft drinks).**

Weight Loss.

Appetite suppression can cause weight loss. **Advise patients to take the morning dose after breakfast and the last daily dose early in the afternoon to minimize interference with eating.**

Cardiovascular Effects.

Warn patients about cardiovascular responses (palpitations, hypertension, angina, dysrhythmias) and instruct them to notify the prescriber if these develop.

Very rarely, children using stimulants for ADHD have experienced sudden cardiac death. In response, the AHA says it is reasonable to consider giving a child an ECG before starting stimulant therapy. However, there is no proof that stimulants actually cause sudden death, or that withholding stimulants will protect from sudden death, or that screening for cardiac defects with an ECG will be of any benefit. Therefore, it would seem that routine ECG screen-

ing is unnecessary, especially in children with no signs or symptoms of heart defects.

Psychosis.

If amphetamine-induced psychosis develops, therapy should be discontinued. For most individuals, symptoms resolve within a week. For some patients, drug-induced psychosis may represent unmasking of latent schizophrenia, indicating a need for psychiatric care.

Withdrawal Reactions.

Abrupt discontinuation can produce extreme fatigue and depression. Minimize by withdrawing amphetamines and methylphenidate gradually.

Hypersensitivity Reactions.

Transdermal methylphenidate [Daytrana] can cause hypersensitivity reactions, which may necessitate discontinuing *all* methylphenidate products, oral as well as transdermal. **Inform patients about signs of hypersensitivity—erythema, edema, papules, vesicles—and instruct them to inform the prescriber if these develop.**

Minimizing Abuse

If the medical history reveals the patient is prone to drug abuse, monitor use of these drugs closely.

Avoid routine use of amphetamines for weight loss.

CAFFEINE

General Considerations

Caffeine is usually administered to promote wakefulness. **Warn patients against habitual caffeine use to compensate for chronic lack of sleep. Advise patients to consult the prescriber if fatigue is persistent or recurrent.**

Minimizing Adverse Effects

Cardiovascular Effects.

Inform patients about cardiovascular responses to caffeine (palpitations, rapid pulse, dizziness) and instruct them to discontinue caffeine if these occur.

Excessive CNS Stimulation.

Warn patients that overdose can cause convulsions. Advise them to ingest no more caffeine than needed.

Miscarriage.

Caffeine increases the risk of miscarriage, especially at doses above 200 mg/day. **Advise pregnant women to consume no more than 200 mg/day—and preferably less.**

Drug Abuse

37 Drug Abuse I: Basic Considerations

Mind-altering drugs have intrigued human beings since the dawn of civilization. Throughout history, people have taken drugs to elevate mood, release inhibitions, distort perceptions, induce hallucinations, and modify thinking. Many of those who take mind-altering drugs restrict usage to socially approved patterns. However, many others self-administer drugs to excess. Excessive drug use is our focus in this chapter and the two that follow.

Drug abuse confronts clinicians in a variety of ways, making knowledge of abuse a necessity. Important areas in which expertise on drug abuse may be applied include (1) diagnosis and treatment of acute toxicity, (2) diagnosis and treatment of secondary medical complications of drug abuse, (3) facilitating drug withdrawal, and (4) providing education and counseling to maintain long-term abstinence.

Our discussion of drug abuse occurs in two stages. In this chapter we discuss basic concepts in drug abuse. In Chapters 38 and 39, we focus on the pharmacology of specific abused agents and methods of treatment.

DEFINITIONS

Drug Abuse

Drug abuse can be defined as *using a drug in a fashion inconsistent with medical or social norms*. Traditionally, the term also implies drug usage that is harmful to the individual or society. As we shall see, although we can give abuse a general definition, deciding whether a particular instance of drug use constitutes "abuse" is often difficult.

Whether or not drug use is considered abuse depends, in part, on the purpose for which a drug is taken. Not everyone who takes large doses of psychoactive agents is an abuser. For example, we do not consider it abuse to take opioids in large doses long term to relieve pain caused by cancer. However, we do con-

sider it abusive for an otherwise healthy individual to take those same opioids in the same doses to produce euphoria.

Abuse can have different degrees of severity. Some people, for example, use heroin only occasionally, whereas others use it habitually and compulsively. Although both patterns of drug use are socially condemned, and therefore constitute abuse, there is an obvious quantitative difference between taking heroin once or twice and taking it routinely and compulsively.

Note that, by the definition above, *drug abuse is culturally defined*. Because abuse is culturally defined, and because societies differ from one another and are changeable, there can be wide variations in what is labeled abuse. *What is defined as abuse can vary from one culture to another*. For example, in the United States, moderate consumption of alcohol is not usually considered abuse. In contrast, *any ingestion of alcohol would be considered abuse in some Muslim societies*. Furthermore, *what is defined as abuse can vary from one time to another within the same culture*. For example, when a few Americans first experimented with lysergic acid diethylamide (LSD) and other psychedelic drugs, these agents were legal and their use was not generally disapproved. However, when use of psychedelics became widespread, our societal posture changed and legislation was passed to make the manufacture, sale, and use of these drugs illegal.

Within the United States, there is divergence of opinion about what constitutes drug abuse. For example, some people would consider any use of marijuana to be abuse, whereas others would call smoking marijuana abusive only if it were done *habitually*. Similarly, although many Americans do not consider cigarette smoking abuse (even though the practice is compulsive and clearly harmful to the individual and society), others believe very firmly that cigarette smoking is a blatant form of abuse.

As we can see, distinguishing between culturally acceptable drug use and drug use that is to be called abuse is more in the realm of social science than pharmacology. Accordingly, since this is a pharmacology text and not a sociology text, we will not attempt to define just what patterns of drug use do or do not constitute abuse. Instead, we will focus on the pharmacologic properties of abused drugs—leaving distinctions about what is and is not abuse to sociologists and legislators. Fortunately, we can identify the drugs that tend to be abused

and discuss their pharmacology without having to resolve all arguments about what patterns of use should or should not be considered abusive.

As discussed later, the American Psychiatric Association has established diagnostic criteria for *substance abuse,* a specific substance use disorder. These objective criteria are largely independent of cultural bias, and should not be confused with the concept of drug abuse as just presented.

Addiction

The American Society of Addiction Medicine defines addiction as *a disease process characterized by the continued use of a specific psychoactive substance despite physical, psychologic, or social harm*. Please note that nowhere in this definition is addiction equated with physical dependence. As discussed below, although physical dependence can contribute to addictive behavior, it is neither necessary nor sufficient for addiction to occur. Addiction can be considered essentially equivalent to substance dependence as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) (see below).

Other Definitions

Tolerance results from regular drug use and can be defined as a state in which a particular dose elicits a smaller response than it did with initial use. As tolerance increases, higher and higher doses are needed to elicit desired effects.

Cross-tolerance is a state in which tolerance to one drug confers tolerance to another. Cross-tolerance generally develops among drugs within a particular class, and not between drugs in different classes. For example, tolerance to one opioid (eg, heroin) confers cross-tolerance to other opioids (eg, morphine), but not to central nervous system (CNS) depressants, psychostimulants, psychedelics, or nicotine.

Psychologic dependence can be defined as an intense subjective need for a particular psychoactive drug.

Physical dependence can be defined as a state in which an abstinence syndrome will occur if drug use is discontinued. Physical dependence is the result of neuroadaptive processes that take place in response to prolonged drug exposure.

Cross-dependence refers to the ability of one drug to support physical dependence on another drug. When cross-dependence exists between drug A and drug B, drug A will be able to prevent withdrawal in a patient physically dependent on drug B, and vice versa. As with cross-tolerance, cross-dependence generally exists among drugs in the same pharmacologic family, but not between drugs in different families.

A ***withdrawal syndrome*** is a constellation of signs and symptoms that occurs in physically dependent individuals when they discontinue drug use. Quite often, the symptoms seen during withdrawal are opposite to effects the drug produced before it was withdrawn. For example, discontinuation of a CNS depressant can cause CNS excitation.

DIAGNOSTIC CRITERIA FOR SUBSTANCE ABUSE AND SUBSTANCE DEPENDENCE

Diagnostic criteria for substance abuse and substance dependence are set forth in DSM-IV, published by the American Psychiatric Association. A summary appears in Table 37-1. As defined in DSM-IV, substance dependence, which can be equated with addiction, is a more severe disorder than substance abuse. Accordingly, individuals whose drug problem is not bad enough to meet the criteria for substance dependence might nonetheless meet the criteria for substance abuse.

As indicated in Table 37-1, tolerance and withdrawal are among the criteria for substance dependence. Please note, however, that tolerance and withdrawal, by themselves, are neither necessary nor sufficient for substance dependence (addiction) to exist. Put another way, the pattern of drug use that constitutes substance dependence can exist in persons who are not physically dependent on drugs and who have not developed tolerance. Because this distinction is extremely important, I will express it another way: *Being physically dependent on a drug is not the same as being addicted!* Many people are physically dependent but do not meet the criteria for substance dependence. These people are not considered addicts because they do not demonstrate the behavior pattern that constitutes substance dependence. Patients with terminal cancer, for example, are often physically dependent on opioids. However, since their lives are not disrupted by their medication (quite the contrary), their drug use does not meet the criteria for substance dependence (or sub-

stance abuse, for that matter). Similarly, some degree of physical dependence occurs in all patients who take phenobarbital to control epilepsy; despite their physical dependence, epileptics do not carry out stereotypic addictive behavior, and therefore are not substance dependent as defined in DSM-IV.

TABLE 37-1 DSM-IV-TR Diagnostic Criteria for Substance Abuse and Substance Dependence

Substance Abuse

Substance abuse is a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following within a 12-month period:

- Recurrent substance use that results in a failure to fulfill major role obligations at work, school, or home
- Recurrent substance use in situations in which it is physically hazardous
- Recurrent substance-related legal problems
- Continued substance use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the substance

Individuals who display tolerance, withdrawal, and other symptoms of substance dependence would be diagnosed under substance dependence, a more severe disorder, rather than under substance abuse.

Substance Dependence

Substance dependence is a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

- Tolerance to the substance
- Withdrawal, as manifested by either:
- The characteristic withdrawal syndrome for the substance, *or*
- The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
- The substance is often taken in larger amounts or over a longer time than intended

- Substance use continues despite a persistent desire or repeated efforts to cut down or control consumption
- A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
- Important social, occupational, or recreational activities are given up or reduced because of substance use
- Substance use continues despite knowledge of a persistent or recurrent physical or psychologic problem that substance use probably caused or exacerbated (eg, drinking despite knowing that alcohol made an ulcer worse)

Modified from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association, 2000, with permission. Copyright © 2000 American Psychiatric Association.

Having stressed that physical dependence and substance dependence (addiction) are different from each other, we must note that the two states are not entirely unrelated. As discussed below, although physical dependence is not the same as addiction, physical dependence often contributes to addictive behavior.

FACTORS THAT CONTRIBUTE TO DRUG ABUSE

Drug abuse is the end result of a progressive involvement with drugs. Taking psychoactive drugs is usually initiated out of curiosity. From this initial involvement, the user can progress to occasional use. Occasional use can then evolve into compulsive use. Factors that play a role in the progression from experimental use to compulsive use are discussed below.

Reinforcing Properties of Drugs

Although there are several reasons for initiating drug use (eg, curiosity, peer pressure), individuals would not continue drug use unless drugs produced desirable feelings or experiences. By making people feel "good," drugs reinforce the reasons for their use. Conversely, if drugs did not give people experiences that they found desirable, the reasons for initiating drug use would not be reinforced, and drug use would stop.

Reinforcement by drugs can occur in two ways. First, drugs can give the individual an experience that is pleasurable. Cocaine, for example, produces a state of euphoria. Second, drugs can reduce the intensity of unpleasant experience. For example, drugs can reduce anxiety and stress.

The reinforcing properties of drugs can be clearly demonstrated in experiments with animals. In the laboratory, animals will self-administer most of the drugs that are abused by humans (eg, opioids, barbiturates, alcohol, cocaine, amphetamines, phencyclidine, nicotine, caffeine). When these drugs are made freely available, animals develop patterns of drug use that are similar to those of humans. Animals will self-administer these drugs (except for nicotine and caffeine) in preference to eating, drinking, and sex. When permitted, they often die from lack of food and fluid. These observations strongly suggest that pre-existing psychopathology is not necessary for drug abuse to develop. Rather, these studies suggest that drug abuse results, in large part, from the reinforcing properties of drugs themselves.

Physical Dependence

As defined, physical dependence is a state in which an abstinence syndrome will occur if drug use is discontinued. The degree of physical dependence is determined largely by dosage and duration of drug use. Physical dependence is greatest in people who take large doses for a long time. The more physically dependent a person is, the more intense the withdrawal syndrome. Substantial physical dependence develops to the opioids (eg, morphine, heroin) and CNS depressants (eg, barbiturates, alcohol). Physical dependence tends to be less prominent with other abused drugs (eg, psychostimulants, psychedelics, marijuana).

Physical dependence can contribute to compulsive drug use. Once dependence has developed, the desire to avoid withdrawal becomes a motivator for continued dosing. Furthermore, if the drug is administered after the onset of withdrawal, its ability to alleviate the discomfort of withdrawal can reinforce its desirability. Please note, however, that although physical dependence plays a role in the abuse of drugs, physical dependence should not be viewed as the primary cause of addictive behavior. Rather, physical dependence is just one of several factors that can contribute to the development and continuation of compulsive use.

Psychologic Dependence

Psychologic dependence is defined as *an intense subjective need for a drug*. Individuals who are psychologically dependent feel very strongly that their sense of well-being is dependent upon continued drug use; a sense of "craving" is felt when the drug is unavailable. There is no question that psychologic dependence can be a major factor in addictive behavior. For example, it is psychologic dependence—and not physical dependence—that plays the principal role in causing renewed use of opioids by addicts who had previously gone through withdrawal.

Social Factors

Social factors can play an important role in the development of abuse. The desire for social status and approval is a common reason for initiating drug use. Also, since initial drug experiences are frequently unpleasant, the desire for social approval can be one of the most compelling reasons for repeating drug use after the initial exposure. For example, most people do not especially enjoy their first cigarette; were it not for peer pressure, many would quit before they smoked enough for it to be pleasurable. Similarly, initial use of heroin, with its associated nausea and vomiting, is often deemed unpleasant; peer pressure is a common reason for continuing heroin use long enough to develop tolerance to these undesirable effects.

Drug Availability

Drug availability is clearly a factor in the development and maintenance of abuse. Abuse can flourish only in environments where drugs can be readily obtained. In contrast, where procurement of drugs is difficult, abuse is minimal. The ready availability of drugs in hospitals and clinics is a major reason for the unusually high rate of addiction among pharmacists, nurses, and physicians.

Vulnerability of the Individual

Some individuals are more prone to becoming drug abusers than others. By way of illustration, let's consider three individuals from the same social setting who have equal access to the same psychoactive drug. The first person experiments with the drug briefly and never uses it again. The second person progresses from experimentation to occasional use. The third goes on to take

the drug compulsively. Since social factors, drug availability, and the properties of the drug itself are the same for all three people, these factors cannot explain the three different patterns of drug use. We must conclude, therefore, that the differences must lie in the people: one individual was not prone to drug abuse, one had only moderate tendencies toward abuse, and the third was highly vulnerable to becoming an abuser.

Several psychologic factors have been associated with tendencies toward drug abuse. Drug abusers are frequently individuals who are impulsive, have a low tolerance for frustration, and are rebellious against social norms. Other psychologic factors that seem to predispose individuals to abusing drugs include depressive disorders, anxiety disorders, and antisocial personality. It is also clear that individuals who abuse one type of drug are likely to abuse other drugs.

There is speculation that some instances of drug abuse may actually represent self-medication to relieve emotional discomfort. For example, some people may use alcohol and other depressants to control severe anxiety. Although their drug use may appear excessive, it may be no more than they need to neutralize intolerable feelings.

Genetics also contribute to drug abuse. Vulnerability to alcoholism, for example, may result from an inherited predisposition.

NEUROBIOLOGY OF ADDICTION

How does repeated use of an addictive drug contribute to the transition from voluntary drug use to compulsive use? By causing molecular changes in the brain. Each time the drug is taken, it causes changes that promote further drug use. With repeated drug exposure, these changes are reinforced, making drug use more and more difficult to control.

Where do these molecular changes occur? The most important site is the so-called *reward circuit*—a system that normally serves to reinforce behaviors essential for survival, such as eating and reproductive activities. Neurons of the reward circuit originate in the ventral tegmental area of the midbrain, and project to the nucleus accumbens. Their major transmitter is *dopamine*. Under normal circumstances, biologically critical behavior, such as sexual intercourse, activates the circuit. The resultant release of dopamine rewards

and reinforces the behavior. Like natural positive stimuli, addictive drugs can also activate the system, causing synaptic levels of dopamine to rise. Whether the system is activated by use of drugs or by behavior essential for survival, the outcome is the same: a tendency to repeat the behavior that turned the system on. With repeated activation over time, the system eventually undergoes synaptic remodeling, thereby consolidating changes in brain function, and hence in addiction-related behavior. Remodeling persists after drug use has ceased.

PRINCIPLES OF ADDICTION TREATMENT

Drug addiction is a treatable disease. With therapy, between 40% and 60% of addicts can reduce drug use. In 1999, treatment underwent a significant advance when the National Institute on Drug Abuse published *Principles of Drug Addiction Treatment,* the first science-based guide on addiction therapy. The guide centers on 13 principles of effective treatment, summarized in Table 37-2.

Ideally, the goal of treatment is *complete cessation* of drug use. However, total abstinence is not the only outcome that can be considered successful. Treatment that changes drug use from compulsive to moderate will permit increased productivity, better health, and a decrease in socially unacceptable behavior. Clearly, this outcome is beneficial both to the individual and to society—even though some degree of drug use continues. It must be noted, however, that in the treatment of some forms of abuse, nothing short of total abstinence can be considered a true success. Experience has shown that abusers of *cigarettes, alcohol,* and *opioids* are rarely capable of sustained moderation. Hence, for many of these individuals, abstinence must be complete if there is to be any hope of avoiding a return to compulsive use.

Recovery from addiction is a prolonged process that typically requires multiple treatment episodes. Why? Because addiction is a *chronic, relapsing* illness. As such, periods of treatment-induced abstinence will very likely be followed by relapse. This does not mean that treatment has failed. Rather, it simply means that at least one more treatment episode is needed. Eventually, many patients achieve stable, long-term abstinence, along with a more productive and rewarding life.

Because addiction is a complex illness that affects all aspects of life, the treatment program must be comprehensive and multifaceted. In addition to addressing drug use itself, the program should address any related medical, psychologic, social, vocational, and legal problems. Obviously, treatment must be tailored to the individual; no single approach works for all people. Multiple techniques are employed. Techniques with proven success include (1) therapy directed at resolving emotional problems that underlie drug use, (2) substitution of alternative rewards for the rewards of drug use, (3) threats and external pressure to discourage drug use, and (4) use of pharmacologic agents to modify the effects of abused drugs. The most effective treatment programs incorporate two or more of these methods.

THE CONTROLLED SUBSTANCES ACT

The *Comprehensive Drug Abuse Prevention and Control Act* of 1970, known informally as the *Controlled Substances Act* (CSA), is the principal federal legislation addressing drug abuse. One objective of the CSA is to reduce the chances that drugs originating from legitimate sources will be diverted to abusers. To accomplish this goal, the CSA sets forth regulations for the handling of controlled substances by manufacturers, distributors, pharmacists, nurses, and physicians. Enforcement of the CSA is the responsibility of the *Drug Enforcement Agency* (DEA), an arm of the U.S. Department of Justice.

Record Keeping

In order to keep track of controlled substances that originate from legitimate sources, a written record must be made of all transactions involving these agents. Every time a controlled substance is purchased or dispensed, the transfer must be recorded. Physicians, pharmacists, and hospitals must keep an inventory of all controlled substances in stock. This inventory must be reported to the DEA every 2 years. Although not specifically obliged to do so by the CSA, many hospitals require that floor stocks of controlled substances be counted at the beginning and end of each nursing shift.

TABLE 37-2 Principles of Drug-Addiction Treatment

1. **No single treatment is appropriate for all individuals.** Matching treatment settings, interventions, and services to each patient's problems and needs is critical.

2. **Treatment needs to be readily available.** Treatment applicants can be lost if treatment is not immediately available or readily accessible.
3. **Effective treatment must attend to multiple needs of the individual, not just his or her drug use.** In addition to addressing drug use, treatment must address the individual's medical, psychologic, social, vocational, and legal problems.
4. **Because needs of the individual can change, the treatment plan must be reassessed continually and modified as indicated.** At different times during treatment, a patient may develop a need for medical services, family therapy, vocational rehabilitation, and social and legal services.
5. **Remaining in treatment for an adequate time is critical for effectiveness.** The time depends on the individual's needs. For most patients, the threshold for significant improvement is reached at about 3 months. Additional treatment can produce further progress. Programs should include strategies to prevent patients from leaving prematurely.
6. **Individual and/or group counseling and other behavioral therapies are critical components of treatment.** In therapy, patients address motivation, build skills to resist drug use, replace drug-using activities with constructive and rewarding non–drug-related activities, and improve problem-solving abilities. Behavioral therapy also facilitates interpersonal relationships.
7. **Medication can be an important element of treatment, especially when combined with counseling and other behavioral therapies.** Methadone, buprenorphine, and naltrexone can help persons addicted to opiates. Nicotine replacement therapy (eg, patches, gum), bupropion, and/or varenicline can help patients addicted to nicotine.
8. **Addicted individuals who also have mental disorders should have both conditions treated in an integrated way.**
9. **Medical detoxification is only the first stage of addiction treatment and, by itself, does little to change long-term drug use.** Medical detoxification manages the acute physical symptoms of withdrawal—and can serve as a precursor to effective drug addiction treatment.

10. **Treatment needn't be voluntary to be effective.** Sanctions or enticements coming from the family, employer, or criminal justice system can significantly increase treatment entry, retention, and success.

11. **Individuals in treatment must undergo continuous monitoring for possible drug use.** Monitoring drug use (eg, through urinalysis) can help the patient withstand urges to use drugs. Monitoring also can provide early evidence of drug use, thereby allowing appropriate adjustment of the treatment program.

12. **Treatment programs should provide assessment for HIV/AIDS, hepatitis B and C, tuberculosis, and other infectious diseases, along with counseling to help patients modify behaviors that place them or others at risk.**

13. **Recovery from drug addiction is typically a long-term process, and often requires multiple treatment episodes.** As with other chronic illnesses, relapses can occur during or after successful treatment episodes. Participation in self-help support programs during and following treatment can help maintain abstinence.

HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome.

DEA Schedules

Each drug preparation regulated under the Controlled Substances Act has been assigned to one of five categories: Schedule I, II, III, IV, or V. Drugs in Schedule I have a high potential for abuse and no approved medical use in the United States. In contrast, drugs in Schedules II through V all have approved applications. Assignment to Schedules II through V is based on abuse potential and potential for causing physical or psychologic dependence. Of the drugs that have medical applications, those in Schedule II have the highest potential for abuse and dependence. Drugs in the remaining schedules have decreasing abuse and dependence liabilities. Table 37-3 lists the primary drugs that come under the five DEA Schedules.

Schedule I Drugs	Schedule II Drugs	Schedule III Drugs	Schedule IV Drugs	Schedule V Drugs
Opioids	**Opioids**	**Opioids**	**Opioids**	**Opioids**
Acetylmethadol	Alfentanil	Buprenorphine	Butorphanol	Diphenoxylate plus atropine
Heroin	Codeine	Hydrocodone	Pentazocine	
Normethadone	Fentanyl	Paregoric	Propoxyphene	
Many others	Hydromorphone	**Cannabinoids**	**Stimulants**	
Psychedelics	Levorphanol	Dronabinol (THC)	Diethylpropion	
Bufotenin	Meperidine	**Stimulants**	Fenfluramine	
Diethyltryptamine	Methadone	Benzphetamine	Mazindol	
Dimethyltryptamine	Morphine	Phendimetrazine	Pemoline	
Ibogaine	Opium tincture	**Barbiturates**	Phentermine	
d-Lysergic acid diethylamide (LSD)	Oxycodone	Aprobarbital	**Barbiturates**	
Mescaline	Oxymorphone	Butabarbital	Mephobarbital	
3,4-Methylenedioxy-methamphetamine (MDMA)	Remifentanil	Metharbital	Methohexital	
	Sufentanil	Talbutal	Phenobarbital	
Psilocin	**Psychostimulants**	Thiamylal	**Benzodiazepines**	
Psilocybin	Amphetamine	Thiopental	Alprazolam	
Cannabis Derivatives	Cocaine	**Miscellaneous Depressants**	Chlordiazepoxide	
Hashish	Dextroamphetamine	Methyprylon	Clonazepam	
Marijuana	Methamphetamine	**Anabolic Steroids**	Clorazepate	
Others	Methylphenidate	Fluoxymesterone	Diazepam	
Flunitrazepam	Phenmetrazine	Methyltestosterone	Estazolam	
Gamma-hydroxybutyrate	**Barbiturates**	Nandrolone	Flurazepam	
Methaqualone	Amobarbital	Oxandrolone	Halazepam	
Phencyclidine	Pentobarbital	Stanozolol	Lorazepam	
	Secobarbital	Testosterone	Midazolam	
	Miscellaneous Depressants	Many others	Oxazepam	
	Glutethimide	**Others**	Prazepam	
		Ketamine	Quazepam	
			Temazepam	

TABLE 37-3 Classification of Controlled Substances by the Drug Enforcement Agency

Scheduling of drugs under the Controlled Substances Act undergoes periodic re-evaluation. With increased understanding of the abuse and dependence liabilities of a drug, the DEA may choose to reassign it to a different Schedule. For example, glutethimide (a general CNS depressant) was recently switched from Schedule III to Schedule II.

Prescriptions

The Controlled Substances Act places restrictions on prescribing drugs in Schedules II through V. (Drugs in Schedule I have no approved uses, and hence are not prescribed.) Only prescribers registered with the DEA are authorized to prescribe controlled drugs. Regulations on prescribing controlled substances are summarized below.

Schedule II.

All prescriptions for Schedule II drugs must be typed or filled out in ink or indelible pencil and signed by the prescriber. Oral prescriptions may be made, but only in emergencies, and a written prescription must follow within 72 hours. Prescriptions for Schedule II drugs cannot be refilled. However, a DEA rule issued in 2007 now allows a prescriber to write multiple prescriptions on the same day—for the same patient and same drug—to be filled sequentially for up to a 90-day supply.

Schedules III and IV.

Prescriptions for drugs in Schedules III and IV may be oral or written. If authorized by the prescriber, these prescriptions may be refilled up to 5 times. Refills must be made within 6 months of the original order. If additional medication is needed beyond the amount provided for in the original prescription, a new prescription must be written.

Schedule V.

The same regulations for prescribing drugs in Schedules III and IV apply to drugs in Schedule V. In addition, Schedule V drugs may be dispensed without a prescription provided the following conditions are met: (1) the drug is dis-

pensed by a pharmacist; (2) the amount dispensed is very limited; (3) the recipient is at least 18 years old and can prove it; (4) the pharmacist writes and initials a record indicating the date, the name and amount of the drug, and the name and address of the recipient; and (5) state and local laws do not prohibit dispensing Schedule V drugs without a prescription.

Labeling

When drugs in Schedules II, III, and IV are dispensed, their containers must bear this label: *Caution—Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed*. The label must also indicate whether the drug belongs to Schedule II, III, or IV. The symbols C-II, C-III, and C-IV are used to indicate the Schedule.

State Laws

All states have their own laws regulating drugs of abuse. In many cases, state laws are more stringent than federal laws. As a rule, whenever there is a difference between state and federal laws, the more restrictive of the two takes precedence.

KEY POINTS

- Drug abuse can be defined as drug use that is inconsistent with medical or social norms.
- Drug abuse is a culturally defined term. Hence, what is considered abuse can vary from one culture to another and from one time to another within the same culture.
- Addiction can be defined as a disease process characterized by the continued use of a specific psychoactive substance despite physical, psychologic, or social harm.
- Addiction is largely equivalent to substance dependence as defined in DSM-IV.
- Tolerance is a state in which a particular drug dose elicits a smaller response than it formerly did.

- Cross-tolerance is a state in which tolerance to one drug confers tolerance to another drug.
- Psychologic dependence is defined as an intense subjective need for a particular psychoactive drug.
- Physical dependence is a state in which an abstinence syndrome will occur if drug use is discontinued. Physical dependence is *not* the same as addiction.
- Cross-dependence refers to the ability of one drug to support physical dependence on another drug.
- A withdrawal syndrome is a group of signs and symptoms that occur in physically dependent individuals when they discontinue drug use.
- As defined in DSM-IV, substance dependence is a more severe substance use disorder than substance abuse.
- Although tolerance and withdrawal are among the diagnostic criteria for substance dependence, they are neither necessary nor sufficient for a diagnosis.
- Although physical dependence is not the same as addiction (substance dependence), physical dependence can certainly contribute to addictive behavior.
- Drugs can reinforce their own use by providing pleasurable experiences, reducing the intensity of unpleasant experiences, and warding off a withdrawal syndrome.
- All addictive drugs activate the brain's dopamine reward circuit. Over time, they cause adaptive changes in the circuit that make it more and more difficult to control use.
- Some individuals, because of psychologic or genetic factors, are more prone to drug abuse than others.
- Because addiction is a chronic, relapsing illness, recovery is a prolonged process that typically requires multiple episodes of treatment.
- The ideal goal of treatment is complete abstinence. However, treatment that substantially reduces drug use can still be considered a success.

- Under the Controlled Substances Act, drugs in Schedule I have a high potential for abuse and no medically approved use in the United States. Drugs in Schedules II through V have progressively less abuse potential and are all medically approved.

38 Drug Abuse II: Alcohol

Alcohol (ethyl alcohol, ethanol) is the most commonly used and abused psychoactive agent in the United States. Although alcohol does have some therapeutic applications, the drug is of interest primarily for its nonmedical use. When consumed in moderation, alcohol prolongs life; reduces the risk of dementia and cardiovascular disorders; and, many would argue, contributes to the joy of living. Conversely, when consumed in excess, alcohol does nothing but diminish life both in quality and quantity. These dose-related contrasts between the detrimental and beneficial effects of alcohol were aptly summed up by our 16th president, Abraham Lincoln, when he noted:

"*None seemed to think the injury arose from use of a bad thing, but from the abuse of a very good thing.*"

In approaching our study of alcohol, we begin by discussing the basic pharmacology of alcohol, and then we discuss alcohol use disorders and the drugs employed for their treatment.

BASIC PHARMACOLOGY OF ALCOHOL

Central Nervous System Effects

Acute Effects.

Alcohol has two acute effects on the brain: (1) general depression of central nervous system (CNS) function (like that seen with barbiturates) and (2) activation of the reward circuit.

How does alcohol affect neuronal activity? For many years, we believed that alcohol simply dissolved into the neuronal membrane, thereby disrupting the ordered arrangement of membrane phospholipids. However, we now know that alcohol interacts with specific proteins—certain receptors, ion channels, and enzymes—that regulate neuronal excitability. Two target proteins are of particular importance, namely (1) receptors for gamma-aminobutyric acid (GABA) and (2) the 5-HT***3*** subset of receptors for serotonin (5-hydroxytryptamine, 5-HT). The *depressant* effects of alcohol result from

binding with receptors for GABA, the principal inhibitory transmitter in the CNS. When alcohol binds with GABA receptors, it enhances GABA-mediated inhibition, thereby causing widespread depression of CNS function. The *rewarding* effects of alcohol result from binding with 5-HT3 receptors in the brain's reward circuit. When these receptors are activated (by serotonin), they promote release of dopamine, the major transmitter of the reward system. When alcohol binds with these receptors, it enhances serotonin-mediated release of dopamine, and thereby intensifies the reward process.

The depressant effects of alcohol are dose dependent. When dosage is low, higher brain centers (cortical areas) are primarily affected. As dosage increases, more primitive brain areas (eg, medulla) become depressed. With depression of cortical function, thought processes and learned behaviors are altered, inhibitions are released, and self-restraint is replaced by increased sociability and expansiveness. Cortical depression also impairs motor function. As CNS depression deepens, reflexes diminish greatly and consciousness becomes impaired. At very high doses, alcohol produces a state of general anesthesia. (Alcohol can't be used for anesthesia because the doses required are close to lethal.) Table 38-1 summarizes the effects of alcohol as a function of blood alcohol level and indicates the brain areas involved.

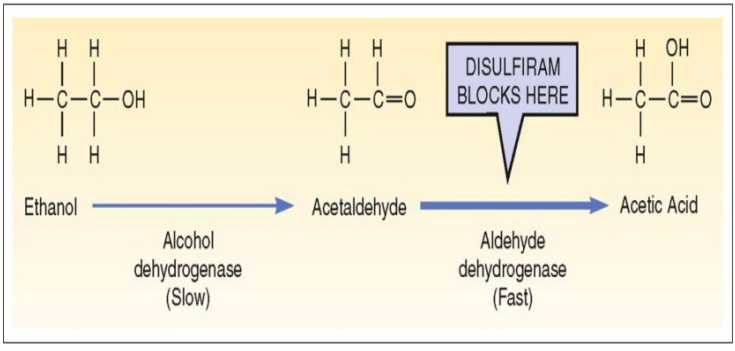


TABLE 38-1 Central Nervous System Responses at Various Blood Alcohol Levels

Chronic Effects.

When consumed chronically and in excess, alcohol can produce severe neurologic and psychiatric disorders. Injury to the CNS is caused by the direct ac-

tions of alcohol and by the nutritional deficiencies often seen in chronic heavy drinkers.

Two neuropsychiatric syndromes are common in alcoholics: *Wernicke's encephalopathy* and *Korsakoff's psychosis*. Both disorders are caused by thiamin deficiency, which results from poor diet and alcohol-induced suppression of thiamin absorption. Wernicke's encephalopathy is characterized by confusion, nystagmus, and abnormal ocular movements. This syndrome is readily reversible with thiamin. Korsakoff's psychosis is characterized by polyneuropathy, inability to convert short-term memory into long-term memory, and confabulation (unconscious filling of gaps in memory with fabricated facts and experiences). Korsakoff's psychosis is not reversible.

Perhaps the most dramatic effect of long-term excessive alcohol consumption is enlargement of the cerebral ventricles, presumably in response to atrophy of the cerebrum itself. These gross anatomic changes are associated with impairment of memory and intellectual function. With cessation of drinking, ventricular enlargement and cognitive deficits partially reverse, but only in some individuals.

Impact on Cognitive Function.

Low to moderate drinking helps preserve cognitive function in older people and may protect against development of dementia.

Effect on Sleep.

Although alcohol is commonly used as a sleep aid, it actually disrupts sleep. Drinking can alter sleep cycles, decrease total sleeping time, and reduce the quality of sleep. In addition, alcohol can intensify snoring and exacerbate obstructive sleep apnea. Having a drink with dinner won't affect sleep—but drinking late in the evening will.

Other Pharmacologic Effects

Cardiovascular System.

When alcohol is consumed acutely and in moderate doses, cardiovascular effects are minor. The most prominent effect is *dilation of cutaneous blood vessels,*

which increases blood flow to the skin. By doing so, alcohol imparts a sensation of warmth—but at the same time promotes loss of heat. Hence, despite images of Saint Bernards with little barrels of whiskey about their necks, alcohol may do more harm than good for the individual stranded in the snow with hypothermia.

Although the cardiovascular effects of moderate alcohol consumption are unremarkable, chronic and excessive consumption is clearly harmful. Abuse of alcohol results in *direct damage to the myocardium,* thereby increasing the risk of heart failure. Some investigators believe that alcohol may be the major cause of cardiomyopathy in the Western world.

In addition to damaging the heart, alcohol produces a dose-dependent *elevation of blood pressure*. The cause is vasoconstriction in vascular beds of skeletal muscle brought on by increased activity of the sympathetic nervous system. Estimates suggest that heavy drinking may be responsible for 10% of all cases of hypertension.

Not all of the cardiovascular effects of alcohol are deleterious: There is clear evidence that people who drink *moderately* (2 drinks a day or less for men, 1 drink a day or less for women) experience less ischemic stroke, coronary artery disease (CAD), myocardial infarction (MI), and heart failure than do abstainers. It is important to note, however, that with heavy drinking (5 or more drinks/day) the risk of heart disease and stroke is increased. Available data suggest that alcohol protects against heart disease largely by raising levels of high-density lipoprotein (HDL) cholesterol. As discussed in Chapter 49, HDL cholesterol protects against CAD, whereas low-density lipoprotein (LDL) cholesterol promotes CAD. In addition to raising HDL cholesterol, alcohol may confer protection through three other mechanisms: decreasing platelet aggregation, increasing levels of tissue plasminogen activator (a clot-dissolving enzyme), and suppressing the inflammatory component of atherosclerosis. The degree of cardiovascular protection is nearly equal for beer, wine, and distilled spirits. That is, protection is determined primarily by the *amount* of alcohol consumed—not by the particular beverage the alcohol is in. Red wine may confer additional protection because it contains flavonoids and polyphenols—compounds that can (1) induce endothelium-dependent vasodilation, (2) suppress synthesis of endothelin-1 (a potent vasoconstrictor), and (3) protect

LDL from oxidation (LDL must first be oxidized before it can promote atherosclerosis).

Respiration.

Like all other CNS depressants, alcohol depresses respiration. Respiratory depression from moderate drinking is negligible. However, when consumed in excess, alcohol can cause death by respiratory arrest. The respiratory depressant effects of alcohol are potentiated by other CNS depressants (eg, benzodiazepines, opioids, barbiturates).

Liver.

Alcohol-induced liver damage can progress from fatty liver to hepatitis to cirrhosis, depending on the amount consumed. Acute drinking causes reversible accumulation of fat and protein in the liver. With more chronic drinking, *hepatitis* develops in about 90% of heavy users. In 8% to 20% of chronic alcoholics, hepatitis evolves into cirrhosis—a condition characterized by proliferation of fibrous tissue and destruction of liver parenchymal cells. Although various factors other than alcohol can cause cirrhosis, alcohol abuse is unquestionably the major cause of *fatal* cirrhosis.

Stomach.

Immoderate use of alcohol can cause *erosive gastritis*. About one-third of alcoholics have this disorder. Two mechanisms are involved. First, alcohol stimulates secretion of gastric acid. Second, when present in high concentrations, alcohol can injure the gastric mucosa directly.

Kidney.

Alcohol is a diuretic. It promotes urine formation by inhibiting the release of antidiuretic hormone (ADH) from the pituitary. Since ADH acts on the kidney to promote water reabsorption, thereby decreasing urine formation, a reduction in circulating ADH will increase urine production.

Pancreas.

Approximately 35% of cases of acute pancreatitis can be attributed to alcohol, making alcohol the second most common cause of the disorder. Flare-ups typ-

ically occur after a bout of heavy drinking. Only 5% of alcoholics develop pancreatitis, and then only after years of overindulgence.

Sexual Function.

Alcohol has both psychologic and physiologic effects related to human sexual behavior. Although alcohol is not exactly an aphrodisiac, its ability to release inhibitions has been known to motivate sexual activity. Ironically, the physiologic effects of alcohol may frustrate attempts at consummating the activity that alcohol inspired: Objective measurements in males and females show that alcohol significantly decreases our physiologic capacity for sexual responsiveness. The opposing psychologic and physiologic effects of alcohol on sexual function were aptly described long ago by no less an authority than William Shakespeare. In *Macbeth* (Act II, Scene 1), Macduff inquires of a porter "What ... does drink especially provoke?" To which the porter replies,

"*Lechery, sir, it provokes, and unprovokes; it provokes the desire, but it takes away the performance*."

In males, long-term use of alcohol may induce *feminization*. Symptoms include testicular atrophy, impotence, sterility, and breast enlargement.

Cancer.

Alcohol—even in moderate amounts—is associated with an increased risk of several common cancers, including cancer of the breast, rectum, liver, esophagus, and oropharynx. Regarding cancer risk, no dose can be considered safe.

Pregnancy.

Fetal alcohol exposure can cause structural and functional abnormalities, ranging from mild neurobehavioral deficits to facial malformation and mental retardation. The term *fetal alcohol spectrum disorder* (FASD) is used in reference to the *full range* of outcomes—from mild to severe—that drinking during pregnancy can cause. In contrast, the term *fetal alcohol syndrome* (FAS) is reserved for the most severe cases of FASD, characterized by craniofacial malformations, growth restriction (including microcephaly), and neurodevelopmental abnormalities, manifesting during childhood as cognitive and social dysfunc-

tion. In addition to causing FASD and FAS, drinking during pregnancy can result in stillbirth, spontaneous abortion, and giving birth to an alcohol-dependent infant.

How much alcohol can be consumed safely during pregnancy? No one knows. What we do know is that fetal exposure from even moderate drinking can result in mood disorders, distractibility, learning problems, and memory deficits. In fact, drinking at social levels is considered the most common cause of mental retardation in the United States, and the leading cause of preventable birth defects. These observations suggest that, if there is some amount of alcohol that is safe during pregnancy, that amount must be very low. Accordingly, in the interests of fetal health, pregnant women should be advised to avoid alcohol entirely. Having said that, it is important to appreciate that a few drinks early in pregnancy are not likely to harm the fetus. Consequently, if a woman consumed a little alcohol before realizing she was pregnant, she should be reassured that the risk to her baby—if any—is extremely low.

Lactation.

The concentration of alcohol in breast milk parallels the concentration in blood. Recent data indicate that drinking while breast-feeding can adversely affect the infant's feeding and behavior.

Impact on Longevity

The effects of alcohol on life span depend on the amount consumed. *Heavy* drinkers have a higher mortality rate than the population at large. Causes of death include cirrhosis, respiratory disease, cancer, and fatal accidents. The risk of mortality associated with alcohol abuse increases markedly in individuals who consume 6 or more drinks a day.

Interestingly, people who consume *moderate* amounts of alcohol live *longer* than those who abstain—and combining regular exercise with moderate drinking prolongs life even more. Compared with nondrinkers, moderate drinkers have a 30% lower mortality rate, a 50% lower incidence of MI, and a 59% lower incidence of heart failure. According to a study by the American Medical Association, if all Americans were to give up drinking, deaths from heart disease would *increase* by 81,000 a year. Hence, for people who already

are moderate drinkers, continued moderate drinking would seem beneficial. Conversely, despite the apparent benefits of drinking—and the apparent health disadvantage of abstinence—no one is recommending that abstainers take up drinking. Furthermore, when the risks of alcohol outweigh any possible benefits—as in the examples listed in Table 38-2—then alcohol consumption should be avoided entirely.

TABLE 38-2 People Who Should Avoid Alcohol*

- Women who are pregnant or trying to conceive.
- People who plan to drive or perform other activities that require unimpaired attention or muscular coordination.
- People taking antihistamines, sedatives, or other drugs that can intensify alcohol's effects.
- Recovering alcoholics.
- People under age 21.

Caution is indicated for people with a strong family history of alcoholism and for those with diabetes, peptic ulcer disease, and other medical conditions that can be exacerbated by alcohol.

* According to the National Institute on Alcohol Abuse and Alcoholism.

How does alcohol prolong life? In large part by reducing cardiovascular disease. For people who drink red wine, a small benefit may come from *resveratrol*, although the amount present appears too small to have a significant effect.

Pharmacokinetics

Absorption.

Alcohol is absorbed from the stomach and small intestine. About 20% of ingested alcohol is absorbed from the stomach. Gastric absorption is relatively slow and is delayed even further by the presence of food. Milk is especially effective at retarding absorption. Absorption from the small intestine is rapid and largely independent of food; about 80% of ingested alcohol is absorbed from this site. Because most alcohol is absorbed from the small intestine, gastric

emptying time is a major determinant of individual variation in alcohol absorption.

Distribution.

Alcohol is distributed to all tissues and body fluids. The drug crosses the blood-brain barrier with ease, allowing alcohol in the brain to equilibrate rapidly with alcohol in the blood. Alcohol also crosses the placenta and hence can affect the developing fetus.

Metabolism.

Alcohol is metabolized in both the liver and stomach. The liver is the primary site. The pathway for alcohol metabolism is shown in Figure 38-1. As depicted, the process begins with conversion of alcohol to acetaldehyde, a reaction catalyzed by *alcohol dehydrogenase*. This reaction is slow and puts a limit on the rate at which alcohol can be inactivated. Once formed, acetaldehyde undergoes *rapid* conversion to acetic acid. Through a series of reactions, acetic acid is then used to synthesize cholesterol, fatty acids, and other compounds.

Blood Alcohol Level (%)	Pharmacologic Response	Brain Area Affected
0.50		
	Peripheral collapse	Medulla
0.45		
	Respiratory depression	
0.40	Stupor, coma	Diencephalon
0.35	Apathy, inertia	
0.30	Altered equilibrium	Cerebellum
	Double vision	Occipital lobe
0.25	Altered perception	
0.20	↓ Motor skills	Parietal lobe
	Slurred speech	
0.15	Tremors	
	Ataxia	
	↓ Attention	Frontal lobe
0.10	Loquaciousness	
	Altered judgment	
0.05	Increased confidence	
	Euphoria, ↓ inhibitions	

Figure 38-1 Ethanol metabolism and the effect of disulfiram. Conversion of ethanol into acetaldehyde takes place slowly (about 15 mL/hr). Consumption of more than 15 mL/hr will cause ethanol to accumulate. Effects of disulfiram result from accumulation of acetaldehyde secondary to inhibition of aldehyde dehydrogenase.

The kinetics of alcohol metabolism differ from those of most other drugs. With most drugs, as plasma drug levels rise, the amount of drug metabolized per unit time increases too. This is not true for alcohol: As the alcohol content of blood increases, there is almost no change in the speed of alcohol breakdown. That is, alcohol is metabolized at a relatively *constant rate*—regardless of how much alcohol is present.

The average rate at which individuals can metabolize alcohol is about *15 mL (0.5 oz) per hour*.

Because alcohol is metabolized at a slow and constant rate, there is a limit to how much alcohol one can consume without having the drug accumulate. For practical purposes, that limit is about *1 drink per hour*. Consumption of more than 1 drink per hour—be that drink beer, wine, straight whiskey, or a cocktail—will result in alcohol buildup.

	Wine	Beer	Whiskey
Usual serving	1 glass	1 can or bottle	1 shot
Serving size	150 mL (5 oz)	360 mL (12 oz)	45 mL (1.5 oz)
Alcohol concentration	12%[a]	5%[b]	40%[c]
Alcohol per serving	18 mL[d] (0.6 oz)	18 mL[e] (0.6 oz)	18 mL[f] (0.6 oz)

TABLE 38-3 Alcohol Content of Beer, Wine, and Whiskey

a The alcohol content of wine varies from 8% to 20%; typical table wines contain 12%.

b The alcohol content of beer varies: 5% alcohol is typical of American premium beers; cheaper American beers and light beers have less alcohol (2.4% to 5%); and imported beers may have more alcohol (6%). Beer sold in Europe may have 7% to 8% alcohol.

c Whiskeys and other distilled spirits (eg, rum, vodka, gin) are usually 80 proof (40% alcohol) but may also be 100 proof (50% alcohol).

d The alcohol in a 5-ounce glass of wine varies from 12 to 30 mL, depending on the alcohol concentration in the wine. Wine with 12% alcohol has 18 mL of alcohol per 5-ounce glass.

e The alcohol in a 12-ounce can of beer varies from 9 to 29 mL, depending on the alcohol concentration in the beer. Beer with 5% alcohol has 18 mL per 12-ounce can.

f The alcohol in a 1.5-ounce shot of whiskey can be either 18 or 22.5 mL, depending on the proof of the whiskey. Eighty-proof whiskey has 18 mL alcohol per 1.5-ounce serving.

The information in Table 38-3 helps explain why we can't metabolize more than 1 drink's worth of alcohol per hour. As the table indicates, beer, wine, and whiskey differ from one another with respect to alcohol concentration and usual serving size. However, despite these differences, it turns out that *the average can of beer, the average glass of wine, and the average shot of whiskey all contain the same amount of alcohol—namely, 18 mL (0.6 oz)*. Since the liver can metabolize about 15 mL of alcohol per hour, and since the average alcoholic drink contains 18 mL of alcohol, 1 drink contains just about the amount of alcohol that the liver can comfortably process each hour. Consumption of more than 1 drink per hour will overwhelm the capacity of the liver for alcohol metabolism, and therefore alcohol will accumulate.

When used on a regular basis, alcohol induces hepatic drug-metabolizing enzymes, thereby increasing the rate of its own metabolism and that of other drugs. As a result, individuals who consume alcohol routinely in high amounts can metabolize the drug faster than people who drink occasionally and moderately.

Males and females differ with respect to activity of alcohol dehydrogenase in the stomach. Specifically, women have much lower activity than men. As a result, gastric metabolism of alcohol is significantly less in women. This difference partly explains why women achieve higher blood alcohol levels than men after consuming the same number of drinks.

Blood Levels of Alcohol.

Since alcohol in the brain rapidly equilibrates with alcohol in the blood, blood levels of alcohol are predictive of CNS effects. The behavioral effects associated with specific blood levels are summarized in Table 38-1. The earliest effects (euphoria, reduced inhibitions, increased confidence) are seen when blood alcohol content is about 0.05%. As blood alcohol rises, intoxication becomes more intense. When blood alcohol exceeds 0.4%, there is a substantial

risk of respiratory depression, peripheral collapse, and death. In all states of the Union, a level of 0.08% defines intoxication.

Tolerance

Chronic consumption of alcohol produces tolerance. As a result, in order to alter consciousness, people who drink on a regular basis require larger amounts of alcohol than people who drink occasionally. Tolerance to alcohol confers cross-tolerance to general anesthetics, barbiturates, and other general CNS depressants. However, no cross-tolerance develops to opioids. Tolerance subsides within a few weeks following drinking cessation.

Although tolerance develops to many of the effects of alcohol, *very little tolerance develops to respiratory depression*. Consequently, the lethal dose of alcohol for chronic, heavy drinkers is not much bigger than the lethal dose for nondrinkers. Alcoholics may tolerate blood alcohol levels as high as 0.4% (5 times the amount defined by law as intoxicating) with no marked reduction in consciousness. However, if blood levels rise only slightly above this level, death may ensue.

Physical Dependence

Chronic use of alcohol produces physical dependence. If alcohol is withdrawn abruptly, an abstinence syndrome will result. The intensity of the abstinence syndrome is proportional to the degree of physical dependence. Individuals who are physically dependent on alcohol show cross-dependence with other general CNS depressants (eg, barbiturates, chloral hydrate, benzodiazepines) but not with opioids. The alcohol withdrawal syndrome and its management are discussed in detail below.

Drug Interactions

CNS Depressants.

The CNS effects of alcohol are additive with those of other CNS depressants (eg, barbiturates, benzodiazepines, opioids). Consumption of alcohol with other CNS depressants intensifies the psychologic and physiologic manifestations of CNS depression, and greatly increases the risk of death from respiratory depression.

Nonsteroidal Anti-inflammatory Drugs.

Like alcohol, aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs (NSAIDs) can injure the GI mucosa. The combined effects of alcohol and NSAIDs can result in significant gastric bleeding.

Acetaminophen.

The combination of acetaminophen [Tylenol, others] with alcohol poses a risk of potentially fatal liver injury. There is evidence that relatively modest alcohol consumption (2 to 4 drinks a day) can cause fatal liver damage when combined with acetaminophen taken in normal therapeutic doses. Accordingly, some authorities recommend that people who drink take no more than 2 gm of acetaminophen a day (ie, half the normal dosage). The interaction between alcohol and acetaminophen is discussed further in Chapter 70.

Disulfiram.

The combination of alcohol with disulfiram [Antabuse] can cause a variety of adverse effects, some of which are dangerous. These effects, and the use of disulfiram to maintain abstinence, are discussed later.

Antihypertensive Drugs.

Since alcohol raises blood pressure, it tends to counteract the effects of antihypertensive medications. However, elevation of blood pressure is significant only when alcohol dosage is high. Conversely, when the dosage is low, alcohol may actually help: Among hypertensive men, light to moderate alcohol consumption is associated with reduced risk for both cardiovascular mortality and all-cause mortality.

Acute Overdose

Acute overdose produces vomiting, coma, pronounced hypotension, and respiratory depression. The combination of vomiting and unconsciousness can result in aspiration, which in turn can result in pulmonary obstruction and pneumonia. Alcohol-induced hypotension results from a direct effect on peripheral blood vessels, and cannot be corrected with vasoconstrictors (eg, epinephrine). Hypotension can lead to renal failure (secondary to compromised renal blood flow) and cardiovascular shock, a common cause of alcohol-re-

lated death. Although death can also result from respiratory depression, this is not the usual cause.

Because symptoms of acute alcohol poisoning can mimic symptoms of other pathologies (eg, diabetic coma, skull fracture), a definitive diagnosis may not be possible without measuring alcohol in the blood, urine, or expired air. The smell of "alcohol" on the breath is not a reliable means of diagnosis, since the breath odors we associate with alcohol are due to impurities in alcoholic beverages—and not to alcohol itself. Hence, these odors may or may not be present.

Alcohol poisoning is treated like poisoning with all other general CNS depressants. Details of management are discussed in Chapter 34. Alcohol can be removed from the body by gastric lavage and dialysis. Stimulants (eg, caffeine, pentylenetetrazol) should not be given.

Summary of Precautions and Contraindications

Alcohol can injure the GI mucosa and should not be consumed by persons with *peptic ulcer disease*. Alcohol is harmful to the liver and should not be used by individuals with *liver disease*. Alcohol should be avoided during *pregnancy* because of the risk of FASD (including FAS), stillbirth, and spontaneous abortion.

Alcohol must be used with caution by patients with *epilepsy*. During alcohol use, the CNS is depressed. When alcohol consumption ceases, the CNS undergoes rebound excitation; seizures can result.

Alcohol increases the risk of *breast cancer*. All women—and especially those at high risk—should minimize alcohol consumption.

Consuming more than 2 drinks a day appears to increase the risk of *colorectal cancer*.

Alcohol can cause serious adverse effects if combined with *CNS depressants, NSAIDs, acetaminophen, vasodilators,* and *disulfiram*. These combinations should be avoided.

Therapeutic Uses

Although our emphasis has been on the nonmedical use of alcohol, it should be remembered that alcohol does have therapeutic applications.

Topical.

Alcohol applied to the skin can promote cooling in febrile patients. Topical alcohol is also an effective skin disinfectant. In addition, alcohol application can help prevent decubitus ulcers.

Oral.

Because of its ability to promote gastric secretion, alcohol can serve as an aid to digestion in bedridden patients. Oral alcohol is frequently used as self-medication for insomnia—although it can actually disrupt sleep.

Intravenous.

Solutions of alcohol (5% or 10%) in 5% dextrose are administered by slow IV infusion to provide calories and fluid replacement. Intravenous alcohol is also used to treat poisoning by methanol and ethylene glycol. Intravenous alcohol should not be used to manage alcohol withdrawal symptoms.

Local Injection.

Injection of alcohol in the vicinity of nerves produces nerve block. This technique can relieve pain of trigeminal neuralgia, inoperable carcinoma, and other causes.

ALCOHOL USE DISORDERS

Alcoholism is a chronic, relapsing disorder characterized by impaired control over drinking, preoccupation with alcohol consumption, use of alcohol despite awareness of adverse consequences, and distortions in thinking, especially as evidenced by denial of a drinking problem. The development and manifestations of alcoholism are influenced by genetic, psychosocial, and environmental factors. The disease is progressive and often fatal. In the United States, about 8 million adults are alcoholics.

In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), the pattern of alcohol use that constitutes alcoholism is termed *alcohol dependence* (if tolerance and withdrawal are present) or *alcohol abuse* (if tolerance and withdrawal are absent). Complete diagnostic criteria from DSM-IV for alcohol dependence and alcohol abuse are presented in Table 38-4.

TABLE 38-4 DSM-IV Diagnostic Criteria for Alcohol Dependence and Alcohol Abuse

Alcohol Dependence

Alcohol dependence is a maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

- Tolerance to alcohol
- Withdrawal from alcohol
- Consumption of alcohol in larger amounts or over longer periods than intended
- Continued alcohol use despite a persistent desire or repeated efforts to cut down or control consumption
- A great deal of time is spent drinking alcohol or recovering from its effects.
- Important social, occupational, or recreational activities are given up or reduced because of alcohol.
- Alcohol use continues despite knowledge of a persistent or recurrent physical or psychologic problem that alcohol probably caused or exacerbated (eg, drinking despite knowing that alcohol made an ulcer worse).

Alcohol Abuse

Alcohol abuse is a maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by one (or more) of the following within a 12-month period:

- Recurrent alcohol use that results in a failure to fulfill major role obligations at work, school, or home
- Recurrent alcohol use in situations in which it is physically hazardous
- Recurrent alcohol-related legal problems
- Continued alcohol use despite persistent or recurrent social or interpersonal problems caused or exacerbated by alcohol

Individuals who display tolerance, withdrawal, and other symptoms of alcohol dependence would be diagnosed under alcohol dependence rather than alcohol abuse.

Misuse of alcohol is responsible for 6 million nonfatal injuries each year, and 85,000 deaths. Causes of death range from liver disease to automobile wrecks. Fully 45% of all fatal highway crashes are alcohol related. Among teens, alcohol-related crashes are the leading cause of death. Alcohol also causes industrial accidents, and is responsible for 40% of industrial fatalities.

Alcohol abuse is a major public health problem, and its consequences are numerous. Alcoholism produces psychologic derangements, including anxiety, depression, and suicidal ideation. Malnutrition, secondary to inadequate diet and malabsorption, is common. Poor work performance and disruption of family life reflect the social deterioration suffered by alcoholics. Alcohol abuse during pregnancy can result in FASD (including FAS), stillbirth, and spontaneous abortion. Lastly, chronic alcohol abuse is harmful to the body; consequences include liver disease, cardiomyopathy, and brain damage—not to mention injury and death from accidents.

Chronic alcohol consumption produces substantial tolerance. Tolerance is both pharmacokinetic (accelerated alcohol metabolism) and pharmacodynamic. Pharmacodynamic tolerance is evidenced by an increase in the blood alcohol level required to produce intoxication. Alcoholics may tolerate blood alcohol levels of 200 to 400 mg/dL—2.5 to 5 times the level that defines legal intoxication—with no marked reduction in consciousness. It should be noted, however, that very little tolerance develops to respiratory depression. Hence, as the alcoholic consumes increasing amounts in an effort to produce desired psychologic effects, the risk of death from respiratory arrest gets increasingly high. Cross-tolerance exists with general anesthetics and other CNS depressants, but not with opioids.

Chronic use of alcohol produces physical dependence, and abrupt withdrawal produces an abstinence syndrome. When the degree of physical dependence is low, withdrawal symptoms are mild (disturbed sleep, weakness, nausea, anxiety, mild tremors) and last less than a day. In contrast, when the degree of dependence is high, withdrawal symptoms can be severe. Initial symptoms appear 12 to 72 hours after the last drink and continue 5 to 7 days. Early manifestations include cramps, vomiting, hallucinations, and intense tremors; heart rate, blood pressure, and temperature may rise, and tonic-clonic seizures may develop. As the syndrome progresses, disorientation and loss

of insight occur. A few alcoholics (less than 1%) experience *delirium tremens* (severe persecutory hallucinations). Hallucinations can be so vivid and lifelike that alcoholics often can't distinguish them from reality. In extreme cases, alcohol withdrawal can result in cardiovascular collapse and death. Drugs used to ease withdrawal are discussed below.

In 2005, the National Institute on Alcohol Abuse and Alcoholism issued a document—*Helping Patients Who Drink Too Much: A Clinician's Guide*—that contains clear and concise information on screening, counseling, and treatment of alcohol use disorders. By following this guide, clinicians can help reduce morbidity and mortality among people who drink more than is safe, defined as more than 4 drinks in a day (or 14/week) for men, or more than 3 drinks in a day (or 7/week) for women. Helping patients involves four simple steps:

- Ask about alcohol use.
- Assess for alcohol use disorders, using the Alcohol Use Disorders Identification Test (AUDIT).
- Advise and assist (brief intervention).
- At follow-up: continue support.

This process is founded in part on two lines of evidence. First, we can identify people who misuse alcohol with an easily administered questionnaire, such as AUDIT (Table 38-5). Second, for many people, alcohol consumption can be reduced through brief interventions, such as offering feedback and advice about drinking and about setting goals. Long-term follow-up studies have shown that these simple interventions can decrease hospitalization and lower mortality rates. The guide is available online at www.niaaa.nih.gov/guide.

	0	1	2	3	4	Score
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have 5 or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	

TABLE 38-5 Screening Instrument: The Alcohol Use Disorders Identification Test (AUDIT)

DRUGS FOR ALCOHOL USE DISORDERS

In the United States, about 1 million alcoholics seek treatment every year. Although the success rate is discouraging—nearly 50% relapse during the first few months—treatment should nonetheless be tried. The objective is to modify drinking patterns (ie, to reduce or completely eliminate alcohol consumption). Drugs can help in two ways. First, they can facilitate withdrawal. Second, they can help maintain abstinence after withdrawal has been accomplished.

Drugs Used to Facilitate Withdrawal

Management of withdrawal depends on the degree of dependence. When dependence is mild, withdrawal can be accomplished on an outpatient basis without drugs. However, when dependence is great, withdrawal carries a risk of death. Accordingly, hospitalization and drug therapy are indicated. The goals of management are to minimize symptoms of withdrawal, prevent seizures and delirium tremens, and facilitate transition to a program for maintaining abstinence. In theory, any drug that has cross-dependence with alcohol (ie, any of the general CNS depressants) should be effective. However, in actual practice, benzodiazepines are the drugs of choice. The benefits of benzodiazepines and other drugs used during withdrawal are summarized in Table 38-6.

Drug	Benefit During Withdrawal
Benzodiazepines	
Chlordiazepoxide	Decrease withdrawal symptoms; stabilize vital signs; prevent seizures and delirium tremens
Diazepam	
Oxazepam	
Lorazepam	
Beta-Adrenergic Blockers	
Atenolol	Improve vital signs; decrease craving; decrease autonomic component of withdrawal symptoms
Propranolol	
Central Alpha-Adrenergic Agonist	
Clonidine	Decreases autonomic component of withdrawal symptoms
Antiepileptic Drug	
Carbamazepine	Decreases withdrawal symptoms; prevents seizures

TABLE 38-6 Drugs Used to Facilitate Alcohol Withdrawal

Benzodiazepines

Of the drugs used to facilitate alcohol withdrawal, benzodiazepines are the most effective. Furthermore, they are safe. In patients with severe alcohol dependence, benzodiazepines can stabilize vital signs, reduce symptom intensity, and decrease the risk of seizures and delirium tremens. Although all benzodiazepines are effective, agents with longer half-lives are generally preferred. Why? Because they provide the greatest protection against seizures and breakthrough symptoms. The benzodiazepines employed most often are chlordiazepoxide [Librium, others], diazepam [Valium], oxazepam [Serax], and lorazepam [Ativan]. Traditionally, benzodiazepines have been administered around-the-clock on a fixed schedule. However, PRN administration

(in response to symptoms) is just as effective and permits speedier withdrawal.

Adjuncts to Benzodiazepines

Combining a benzodiazepine with another drug may improve withdrawal outcome. Agents that have been tried include carbamazepine (an antiepileptic drug), clonidine (an alpha-adrenergic blocker), and atenolol and propranolol (beta-adrenergic blockers). Carbamazepine may reduce withdrawal symptoms and the risk of seizures. Clonidine and the beta blockers reduce the autonomic component of withdrawal symptoms. In addition, the beta blockers may improve vital signs and decrease craving. It should be stressed, however, that these drugs are not very effective as monotherapy. Hence, they should be viewed only as adjuncts to benzodiazepines—not as substitutes.

Drugs Used to Maintain Abstinence

Once detoxification has been accomplished, the goal is to prevent—or at least minimize—future drinking. The ideal goal is complete abstinence. However, if drinking must resume, keeping it to a minimum is still beneficial, since doing so will reduce alcohol-related morbidity.

In trials of drugs used to maintain abstinence, several parameters are used to measure efficacy. These include

- Proportion of patients who maintain complete abstinence
- Days to relapse
- Number of drinking days
- Number of drinks per drinking day

In the United States, only three drugs—disulfiram, naltrexone, and acamprosate—are approved for maintaining abstinence. Disulfiram works by causing an unpleasant reaction if alcohol is consumed. Naltrexone blocks the pleasurable effects of alcohol and decreases craving. Acamprosate reduces some of the unpleasant feelings (eg, tension, dysphoria, anxiety) brought on by alcohol abstinence. Of the three drugs, naltrexone appears most effective. However, even with this agent, benefits are modest.

Because of the risk of relapse, prolonged treatment is needed. The minimum duration is 3 months. However, continuing for a year or more is not unreasonable. If the first drug fails, clinicians often try another one.

Disulfiram Aversion Therapy

Therapeutic Effects.

Disulfiram [Antabuse] helps alcoholics avoid drinking. How? By causing unpleasant effects if alcohol is ingested. Disulfiram has no applications outside the treatment of alcoholism.

Although disulfiram has been employed for over 50 years, its efficacy is only moderate. In clinical trials, the drug is no better than placebo at maintaining abstinence: The proportion of patients who relapse and the time to relapse are the same as with placebo. However, although disulfiram doesn't prevent drinking, it does decrease the frequency of drinking after relapse has occurred—presumably because of the unpleasant reaction that the patient is now familiar with. There is some indication that supervised administration of disulfiram may be more effective than when patients self-administer the drug.

Mechanism of Action.

As indicated in Figure 38-1, disulfiram disrupts alcohol metabolism. Specifically, the drug causes *irreversible inhibition of aldehyde dehydrogenase,* the enzyme that converts acetaldehyde to acetic acid. As a result, if alcohol is ingested, *acetaldehyde* will accumulate to toxic levels, producing unpleasant and potentially harmful effects.

Pharmacologic Effects.

The constellation of effects caused by alcohol plus disulfiram is referred to as the *acetaldehyde syndrome,* a potentially dangerous event. In its "mild" form, the syndrome manifests as nausea, copious vomiting, flushing, palpitations, headache, sweating, thirst, chest pain, weakness, blurred vision, and hypotension; blood pressure may ultimately decline to shock levels. This reaction, which may last from 30 minutes to several hours, can be brought on by consuming as little as 7 mL of alcohol.

In its most severe manifestation, the acetaldehyde syndrome is life threatening. Possible reactions include marked respiratory depression, cardiovascular collapse, cardiac dysrhythmias, myocardial infarction, acute congestive heart failure, convulsions, and death. Clearly, the acetaldehyde syndrome is not simply unpleasant; this syndrome can be extremely hazardous and must be avoided.

In the absence of alcohol, disulfiram rarely causes significant effects. Drowsiness and skin eruptions may occur during initial use, but they diminish with time.

Patient Selection.

Because of the severity of the acetaldehyde syndrome, candidates must be carefully chosen. Alcoholics who lack the determination to stop drinking should not receive disulfiram. In other words, disulfiram must not be administered to alcoholics who are likely to attempt drinking while undergoing treatment.

Patient Education.

Patient education is an extremely important component of therapy. Patients must be thoroughly informed about the potential hazards of treatment. That is, they must be made aware that consuming any alcohol while taking disulfiram may produce a severe, potentially fatal, reaction. Patients must be warned to avoid all forms of alcohol, including alcohol found in sauces and cough syrups, and alcohol applied to the skin in aftershave lotions, colognes, and liniments. Patients should be made aware that the effects of disulfiram will persist about 2 weeks after the last dose, and hence continued abstinence is necessary. Individuals using disulfiram should be encouraged to carry identification indicating their status.

Preparations, Dosage, and Administration.

Disulfiram [Antabuse] is supplied in 250- and 500-mg tablets. At least 12 hours must elapse between the patient's last drink and starting treatment. The initial dosage is 500 mg once daily for 1 to 2 weeks. Maintenance dosages range from 125 to 500 mg/day, usually taken as a single dose in the morning. Therapy may last months or even years.

Naltrexone

Naltrexone [ReVia, Vivitrol] is a pure opioid antagonist that decreases craving for alcohol and blocks alcohol's reinforcing (pleasurable) effects. Alcoholics report that naltrexone decreases their “high.” Although the mechanism underlying these effects is uncertain, one possibility is blockade of dopamine release secondary to blockade of opioid receptors. Naltrexone is generally well tolerated. Nausea is the most common adverse effect (10%), followed by headache (7%), anxiety (2%), and sedation (2%). Since naltrexone is an opioid antagonist, the drug will precipitate withdrawal if given to individuals who are opioid dependent. Conversely, if a patient taking naltrexone needs emergency treatment with an opioid analgesic, high doses of the opioid will be required.

Naltrexone was approved for alcoholism on the basis of randomized clinical trials that combined extensive counseling along with the drug. In these trials, naltrexone cut the relapse rate by 50%. Compared with patients taking placebo, those taking naltrexone reported less craving for alcohol, fewer days drinking, fewer drinks per occasion, and reduced severity of alcohol-related problems. In contrast to the original trials, a more recent trial, conducted by the U.S. Department of Veterans Affairs, failed to show any benefit of naltrexone in maintaining abstinence. Why did naltrexone work in the original trials but not in the more recent one? The most likely reason is that the subjects in the two trials were very different: The alcoholic veterans suffered from long-term alcoholism, had little or no social support, and received minimal counseling during the trial, whereas subjects in the earlier studies were younger, had good support systems, and received extensive counseling along with naltrexone. Hence, the new study does not prove that naltrexone doesn't work. Rather, it only proves that naltrexone doesn't work for all drinkers, and doesn't work in the absence of adequate counseling.

Naltrexone is available in two formulations: 50-mg tablets [ReVia] for oral use, and a 380-mg depot formulation [Vivitrol] for IM injection. The oral dosage is 50 mg once a day. The IM dosage is 380 mg once a month. Depot naltrexone is especially good when patient adherence is a concern. As with disulfiram, patients must stop drinking before starting naltrexone.

The basic pharmacology of naltrexone is discussed in Chapter 28.

Acamprosate

Therapeutic Use.

Acamprosate [Campral] is approved for maintaining abstinence in patients with alcohol dependence following detoxification. Benefits derive from reducing unpleasant feelings (eg, tension, dysphoria, anxiety) brought on by abstinence. This effect contrasts with the effects of disulfiram (which makes drinking unpleasant) and naltrexone (which blocks the pleasant feelings that alcohol can cause). Acamprosate should be used only as part of a comprehensive management program that includes psychosocial support.

In clinical trials, acamprosate was moderately effective. Compared with patients taking placebo, those taking acamprosate abstained from their first drink longer, had greater rates of complete abstinence, and were abstinent for more total days. However, in patients who lacked psychosocial support, little or no benefit was seen. Acamprosate is somewhat less effective than naltrexone: Patients taking naltrexone abstain from their first drink longer and accumulate more days of abstinence. Combining acamprosate with naltrexone is more effective than acamprosate alone, but no better than naltrexone alone.

Mechanism of Action.

Just how acamprosate works is unknown. One theory suggests that acamprosate enhances inhibitory neurotransmission (mediated by GABA) and suppresses excitatory neurotransmission (mediated by glutamate), and thereby restores a balance between these transmitter systems. When given to alcohol-dependent animals, the drug reduces voluntary alcohol intake. Acamprosate is devoid of direct anxiolytic, anticonvulsant, and antidepressant activity, and does not cause alcohol aversion.

Pharmacokinetics.

Acamprosate is administered orally, and bioavailability is low (11%). Food reduces absorption even further. The drug has a long half-life (20 to 33 hours), and hence about 5 days are required for plasma levels to reach a plateau. Acamprosate does not undergo metabolism, and is excreted unchanged in the urine.

Adverse Effects and Drug Interactions.

Acamprosate is generally well tolerated. With most adverse effects, the incidence is no greater than with placebo. The principal exception is diarrhea, which occurs in 17% of acamprosate users compared with 10% of those taking placebo. Reports of suicide-related events (suicidal ideation, suicide attempts, completed suicide) are rare, but more common than with placebo. Acamprosate can cause fetal malformations in animals (at doses close to those used by humans). Accordingly, it would seem prudent to avoid this drug during pregnancy, especially since alternatives are available. Acamprosate has no potential for dependence or abuse, and appears devoid of significant drug interactions.

Preparations, Dosage, and Administration.

Acamprosate [Campral] is available in 333-mg delayed-release tablets. The recommended dosage is 2 tablets (666 mg) 3 times a day, taken with meals. (The reason for administration with meals is to promote compliance—not to influence absorption or GI effects.) Dosing should start immediately after detoxification is over, and should continue even if relapse occurs. For patients with *mild* renal impairment, the recommended initial dosage is 333 mg 3 times a day. If the patient has *severe* renal impairment, acamprosate should not be used.

Topiramate

Preliminary evidence suggests that topiramate [Topamax], a drug currently approved for epilepsy and migraine, can reduce craving for alcohol, and hence may reduce alcohol consumption in problem drinkers. In a double-blind, placebo-controlled study, subjects taking topiramate had fewer drinks per day (compared with subjects taking placebo), a lower percentage of drinking days, and a higher percentage of days with no drinking. Benefits took about 6 weeks to develop. As with acamprosate, benefits are believed to result from reducing neuronal excitation by glutamate and boosting neuronal inhibition by GABA. In addition, topiramate may normalize the activity of calcium channels, which can be disrupted by chronic alcohol exposure. To minimize adverse effects (tingling or numbness, altered taste, anorexia, difficulty concentrating, memory problems), dosages should be low initially (25 mg daily at bedtime)

and then gradually increased (by 25 to 50 mg daily each week) to a target dose of 200 mg/day. Compared with other drugs for maintaining abstinence, topiramate has one distinct advantage: Patients can start topiramate without first giving up drinking for several days. Despite its use in epilepsy, topiramate should not be given to manage convulsions triggered by alcohol withdrawal. The basic pharmacology of topiramate is discussed in Chapter 24.

Ondansetron

Ondansetron [Zofran], a selective 5-HT***3*** receptor antagonist, is under investigation as an aid for maintaining sobriety. The drug was originally developed to suppress nausea and vomiting caused by anticancer drugs (see Chapter 79). Why give ondansetron to alcoholics? Because, by blocking 5-HT***3*** receptors, the drug could, in theory, prevent alcohol from activating the brain's reward system, and hence could decrease motivation for drinking. In a preliminary trial, ondansetron did help suppress alcohol ingestion—but only among certain alcoholics: The drug reduced drinking by people with *early-onset* alcoholism (alcoholism that began before age 25) but had no effect on people with *late-onset* alcoholism (alcoholism that began after age 25). Among those with early-onset alcoholism, ondansetron increased the proportion of days spent without drinking (by 40% compared with placebo) and decreased the number of drinks consumed on drinking days (by 39% compared with placebo). The most effective dosage was 4 mg/kg twice a day. These results are important in that they suggest that dysfunction of serotonergic transmission is different in early-onset alcoholism compared with late-onset alcoholism. This implies that, for treatment to be most effective, it should be tailored to the patient's clinical subtype: early-onset alcoholism or late-onset alcoholism.

Nutritional Support, Fluid Replacement, and Antibiotics

Malnutrition is a common problem in the chronic alcoholic. The underlying causes are poor diet and malabsorption of nutrients and vitamins. Malabsorption results from alcohol-induced damage to the GI mucosa. Poor diet occurs in part because alcoholics meet up to 50% of their caloric needs with alcohol, and therefore consume subnormal amounts of foods with high nutritional value. Because of their poor nutritional state, alcoholics are in need of fat, protein, and vitamins. The B vitamins (thiamin, folic acid, cyanocobalamin)

are especially needed. To correct nutritional deficiencies, a program of dietary modification and vitamin supplements should be implemented.

Alcoholics frequently require fluid replacement therapy and antibiotics. Fluids are needed to replace fluids lost because of gastritis, or because of vomiting associated with withdrawal. Antibiotics may be needed to manage pneumonitis, a common complication of alcoholism.

KEY POINTS

- Alcohol is generally beneficial when consumed in moderation and always detrimental when consumed in excess.
- As blood levels of alcohol rise, CNS depression progresses from cortical areas to more primitive brain areas (eg, medulla).
- Long-term, excessive drinking reduces the size of the cerebrum.
- Alcohol produces a dose-dependent increase in blood pressure.
- Moderate drinking is defined as 2 drinks per day or less for men, and 1 drink per day or less for women.
- Moderate drinking significantly reduces the risk of CAD, MI, ischemic stroke, and heart failure—primarily by raising HDL cholesterol, and partly by suppressing platelet aggregation, enhancing fibrinolysis, and suppressing the inflammatory component of atherosclerosis.
- Excessive drinking causes direct damage to the myocardium.
- Like all other CNS depressants, alcohol depresses respiration.
- Chronic, heavy drinking can cause hepatitis and cirrhosis. People with liver disease should avoid alcohol.
- Heavy drinking can cause erosive gastritis.
- Alcohol is a diuretic.
- Alcohol increases the risk of breast cancer and colorectal cancer.
- Excessive drinkers die younger than the population at large.

- Because of the cardioprotective effects of alcohol, moderate drinkers live longer than those who abstain.
- Alcohol dehydrogenase is the rate-limiting enzyme in alcohol metabolism.
- Alcohol is metabolized at a constant rate, regardless of how high blood levels rise. In contrast, the rate of metabolism of most drugs increases as their blood levels rise.
- Most people can metabolize about 1 drink per hour—be it beer, wine, straight whiskey, or a cocktail. Consuming more than 1 drink per hour causes alcohol to accumulate.
- Chronic drinking produces tolerance to many of alcohol's effects—but not to respiratory depression.
- Tolerance to alcohol confers cross-tolerance to general anesthetics, barbiturates, and other general CNS depressants—but not to opioids.
- The CNS-depressant effects of alcohol are additive with those of other CNS depressants.
- The combined effects of alcohol and NSAIDs can cause significant gastric bleeding. People with peptic ulcer disease should avoid alcohol.
- The combination of alcohol and acetaminophen can cause fatal hepatic failure.
- Alcohol use during pregnancy can result in FASD (including FAS), stillbirth, and spontaneous abortion. Women who are pregnant or trying to conceive should not drink.
- Benzodiazepines (eg, chlordiazepoxide, diazepam, lorazepam) are drugs of choice for facilitating withdrawal in alcohol-dependent individuals. Benzodiazepines suppress symptoms because of cross-dependence with alcohol.
- Three drugs are approved for maintaining alcohol abstinence: disulfiram, naltrexone, and acamprosate.
- Disulfiram blocks aldehyde dehydrogenase. As a result, if alcohol is consumed, acetaldehyde will accumulate, thereby causing a host of unpleasant and potentially dangerous symptoms.

- Naltrexone blocks opioid receptors, and thereby decreases craving for alcohol and blocks alcohol's reinforcing effects.
- Acamprosate decreases tension, anxiety, and other unpleasant feelings caused by the absence of alcohol. The underlying mechanism is unclear.

Summary of Major Nursing Implications*

DISULFIRAM

Preadministration Assessment

Therapeutic Goal

Maintaining alcohol abstinence.

Patient Selection

Candidates for therapy must be chosen carefully. Disulfiram must not be given to alcoholics who are likely to attempt drinking while taking this drug.

Identifying High-Risk Patients

Disulfiram is *contraindicated* for patients suspected of being incapable of abstinence from alcohol; for patients with myocardial disease, coronary occlusion, or psychosis; and for patients who have recently received alcohol, metronidazole, or alcohol-containing medications (eg, cough syrups, tonics).

Implementation: Administration

Route

Oral.

Administration

Instruct the patient not to administer the first dose until at least 12 hours after his or her last drink.

Dosing is done once daily and may continue for months or even years.

Inform patients that tablets may be crushed or mixed with liquid.

Implementation: Measures to Enhance Therapeutic Effects

Patient education is essential for safety. **Inform patients about the potential hazards of treatment, and warn them to avoid all forms of alcohol, including alcohol in vinegar, sauces, and cough syrups, and alcohol applied to the skin in aftershave lotions, colognes, and liniments. Inform patients that the effects of disulfiram will persist about 2 weeks after the last dose and that alcohol must not be consumed during this time. Encourage patients to carry identification to alert emergency healthcare personnel to their condition.**

39 Drug Abuse III: Major Drugs of Abuse (Other Than Alcohol)

In this chapter, we discuss all of the major drugs of abuse except alcohol, which is discussed in Chapter 38. As indicated in Table 39-1, abused drugs fall into seven major categories: (1) opioids, (2) psychostimulants, (3) depressants, (4) psychedelics, (5) dissociative drugs, (6) anabolic steroids, and (7) miscellaneous drugs of abuse. The basic pharmacology of many of these drugs is presented in previous chapters, and hence their discussion here is brief. Agents that have not been addressed previously (eg, marijuana, *d*-lysergic acid diethylamide [LSD], nicotine) are discussed in depth. Structural formulas of representative controlled substances are shown in Figure 39-1. Street names for abused drugs are given in Table 39-2.

Category	Examples
Opioids	Heroin
	Morphine
	Meperidine
	Hydromorphone
Psychostimulants	Cocaine
	Dextroamphetamine
	Methamphetamine
	Methylphenidate
Depressants	
Barbiturates	Amobarbital
	Secobarbital
	Pentobarbital
	Phenobarbital
Benzodiazepines	Diazepam
	Flunitrazepam
	Lorazepam
Miscellaneous	Alcohol
	Methaqualone
	Gamma-hydroxybutyrate
	Meprobamate
Psychedelics	LSD
	Mescaline
	Psilocybin
	Dimethyltryptamine
Dissociative Drugs	Phencyclidine
	Ketamine
Anabolic Steroids	Nandrolone
	Oxandrolone
	Testosterone
Miscellaneous	Dextromethorphan
	Marijuana
	Nicotine
	Nitrous oxide
	Amyl nitrite

TABLE 39-1 Pharmacologic Categorization of Abused Drugs

Drug	Street Names
Opioids	
Heroin	H, Harry, horse, junk, smack, skag
Hydromorphone	Juice
Methadone	Dolly
Psychedelics	
d-Lysergic acid diethylamide	LSD, LSD-25, acid, blotter, microdot
Dimethyltryptamine	DMT, businessman's trip
Mescaline	Peyote, cactus buttons
2,5-Dimethoxy-4-methylamphetamine	DOM, STP
Psilocybin	Magic mushrooms
Psilocin	Magic mushrooms
Psychostimulants	
Amphetamine	Bennies, hearts, whites, cartwheels
Dextroamphetamine	Dexies, oranges, footballs
Methamphetamine	Speed, bombita, crank, crystal meth, ice, glass
Methylphenidate	Kiddie dope, R-ball, vitamin R
Biphetamine	Black beauties
Cocaine	Coke, crack, snow, blow, flake, nose candy, toot
General CNS Depressants	
Amobarbital	Blue devils
Flunitrazepam [Rohypnol]*	Forget-me pill, Roche, R2, roofies, rope, rophies
Gamma-hydroxybutyrate (GHB)*	Grievous bodily harm, Georgia homeboy, liquid ecstasy
Pentobarbital	Yellow jackets
Secobarbital	Red devils
Methaqualone	Ludes, sopors
Dissociative Drugs	
Phencyclidine	PCP, angel dust, dummy dust, hog, ozone, peace pill, rocket fuel, sheets, wack
Ketamine	Special K, vitamin K, cat Valium
Miscellaneous Agents	
3,4-Methylenedioxymethamphetamine	MDMA, ectasy, hug, XTC, the love drug
Marijuana	Pot, grass, reefer, weed, Panama red, Acapulco gold, Mary Jane, many others
Combinations	
Heroin + cocaine	Speedball
Heroin + crack cocaine	Moon rock
Heroin + marijuana	Atom bomb
Marijuana + phencyclidine	Killer joints, crystal supergrass

TABLE 39-2 Street Names for Abused Drugs

HEROIN AND OTHER OPIOIDS

The opioids (eg, heroin, oxycodone, morphine) are major drugs of abuse. As a result, most opioids are classified as Schedule II substances. The basic pharmacology of the opioids is discussed in Chapter 28.

Patterns of Use

In the United States, an estimated 3.7 million people have used heroin at some time in their lives. Of these, between 750,000 and 1 million are considered hardcore users. Use is greatest among persons 18 to 25 years old. In addition to people who abuse heroin, millions more abuse prescription opioids.

Opioid abuse is encountered in all segments of American society. Formerly, opioid use was limited almost exclusively to lower socioeconomic groups residing in cities. However, opioids are now used by people outside cities and by people of means.

For most abusers, initial exposure to opioids occurs either socially (ie, illicitly) or in the context of pain management in a medical setting. The overwhelming majority of individuals who go on to abuse opioids begin their drug use illicitly. Only an exceedingly small percentage of those exposed to opioids therapeutically develop a pattern of compulsive drug use.

Opioid abuse by healthcare providers deserves special consideration. It is well established that physicians, nurses, and pharmacists, as a group, abuse opioids to a greater extent than all other groups with similar educational backgrounds. The vulnerability of healthcare professionals to opioid abuse is due primarily to drug access.

Subjective and Behavioral Effects

Moments after IV injection, heroin produces a sensation in the lower abdomen similar to sexual orgasm. This initial reaction, known as a “rush” or “kick,” persists for about 45 seconds. After this, the user experiences a prolonged sense of euphoria (well-being); there is a feeling that “all is well with the world.” These extended effects, rather than the initial rush, are the primary reason for opioid abuse.

Interestingly, when individuals first use opioids, nausea and vomiting are prominent, and an overall sense of *dysphoria* may be felt. In many cases, were it not for peer pressure, individuals would not continue opioid use long enough to allow these unpleasant reactions to be replaced by a more agreeable experience.

Preferred Drugs and Routes of Administration

Heroin.

Among street users, heroin is the opioid of choice. This agent is easy to procure and is taken by about 90% of opioid abusers. The popularity of heroin is related to its high lipid solubility, which allows the drug to cross the blood-brain barrier with ease, thereby producing effects that are both immediate and intense. This combination of speed and intensity sets heroin apart from other opioids, and makes it such a desirable drug of abuse.

Heroin can be administered in several ways. The order of preference is IV injection, smoking, and nasal inhalation (known as sniffing or snorting). Intravenous injection produces effects with the greatest intensity and most rapid onset (7 to 8 seconds). When heroin is smoked or snorted, effects develop more slowly, reaching a peak in 10 to 15 minutes. Among users who seek addiction treatment, injection is the predominant method of administration. However, because sniffing and smoking are safer and easier than injection, these routes are becoming increasingly popular.

It should be noted that, when heroin is administered orally or subcutaneously, as opposed to intravenously, its effects cannot be distinguished from those of morphine and other opioids. This observation is not surprising given that, once in the brain, heroin is rapidly converted into morphine, its active form.

Meperidine.

Nurses and physicians who abuse opioids often select meperidine [Demerol], a drug with distinct advantages for these users. First, unlike heroin, meperidine is highly effective when administered orally, and hence abuse need not be associated with telltale signs of repeated injections. Second, meperidine produces less pupillary constriction than other opioids, thereby minimizing awkward questions about miosis. Lastly, meperidine has minimal effects on

smooth muscle function; hence, constipation and urinary retention are less problematic than with other opioids.

Oxycodone.

In some parts of the United States, people are abusing the *controlled-release* formulation of oxycodone [OxyContin], an opioid similar to morphine. The controlled-release tablets were designed to provide steady levels of oxycodone over an extended time, and are safe and effective when swallowed intact. However, abusers do not ingest the tablets whole. Rather, they crush the tablets, and then either snort the powder, or dissolve it in water and then inject it IV. As a result, the entire dose is absorbed *immediately,* producing blood levels that are dangerously high. Hundreds of deaths have been reported. The risk of respiratory depression and death is greatest in people who have not developed tolerance to opioids.

Tolerance and Physical Dependence

Tolerance.

With prolonged opioid use, tolerance develops to some pharmacologic effects, but not others. Effects to which tolerance does develop include euphoria, respiratory depression, and nausea. In contrast, little or no tolerance develops to constipation and miosis. Because tolerance to respiratory depression develops in parallel with tolerance to euphoria, respiratory depression does not increase as higher doses are taken to produce desired subjective effects. Persons tolerant to one opioid are cross-tolerant to other opioids. However, there is no cross-tolerance between opioids and general central nervous system (CNS) depressants (eg, barbiturates, benzodiazepines, alcohol).

Physical Dependence.

Long-term use produces substantial physical dependence. The abstinence syndrome resulting from opioid withdrawal is described in Chapter 28. It is important to note that, although the opioid withdrawal syndrome can be extremely unpleasant, it is rarely dangerous.

Following the acute abstinence syndrome, which fades in 10 days, opioid addicts may experience a milder but protracted phase of withdrawal. This

second phase, which may persist for months, is characterized by insomnia, irritability, and fatigue. Gastrointestinal hyperactivity and premature ejaculation may also occur.

Treatment of Acute Toxicity

Treatment of acute opioid toxicity is discussed at length in Chapter 28 and summarized here. Overdose produces a classic triad of symptoms: *respiratory depression, coma,* and *pinpoint pupils. Naloxone* [Narcan], an opioid antagonist, is the treatment of choice. This agent rapidly reverses all signs of opioid poisoning. However, dosage must be titrated carefully. Why? Because if too much is given, the addict will swing from a state of intoxication to one of withdrawal. Owing to its short half-life, naloxone must be re-administered every few hours until opioid concentrations have dropped to nontoxic levels, which may take days. Failure to repeat naloxone dosing may result in the death of patients who had earlier been rendered symptom free.

Nalmefene [Revex], a long-acting opioid antagonist, is an alternative to naloxone. Because of its long half-life, nalmefene does not require repeated dosing—an obvious advantage. However, if the dose is excessive, nalmefene will put opioid-dependent patients into prolonged withdrawal—an obvious disadvantage.

Detoxification

Persons who are physically dependent on opioids experience unpleasant symptoms if drug use is abruptly discontinued. Techniques for minimizing discomfort are presented below.

Methadone Substitution.

Methadone, a long-acting oral opioid, is the agent most commonly employed for easing withdrawal. The first step in methadone-aided withdrawal is to substitute methadone for the opioid upon which the addict is dependent. Because opioids display cross-dependence with one another, methadone will prevent an abstinence syndrome. Once the subject has been stabilized on methadone, withdrawal is accomplished by administering methadone in gradually smaller doses. The resultant abstinence syndrome is mild, with symptoms resembling

those of moderate influenza. The entire process of methadone substitution and withdrawal takes about 10 days.

When substituting methadone for another opioid, suppression of the abstinence syndrome requires that methadone dosage be closely matched to the existing degree of physical dependence. Hence, to ensure that methadone dosing is adequate, the extent of physical dependence must be assessed. This can be accomplished by taking a history on the extent of drug use and by observing the patient for symptoms of withdrawal. Of the two approaches, observation is the more reliable. Estimates of drug use based on patient histories may be unreliable because (1) street users don't know the purity of the drugs they have taken, (2) claims of drug use may be inflated in hopes of receiving larger doses of methadone, and (3) addicts from the ranks of the healthcare professions may report minimal consumption to downplay the extent of abuse. Because information from addicts is not likely to permit accurate assessment of dependence, it is essential to observe the patient to make certain methadone dosage is sufficient to suppress withdrawal.

Use of methadone for *maintenance therapy* and *suppressive therapy* is discussed separately below.

Clonidine-Assisted Withdrawal.

Clonidine is a centrally acting alpha*2*-adrenergic agonist. When administered to an individual physically dependent on opioids, clonidine can suppress some symptoms of abstinence. Clonidine is most effective against symptoms related to autonomic hyperactivity (nausea, vomiting, diarrhea). Modest relief is provided from muscle aches, restlessness, anxiety, and insomnia. Opioid craving is not diminished. The basic pharmacology of clonidine is discussed in Chapter 19.

Rapid and Ultrarapid Withdrawal.

In both procedures, the addict is given an opioid *antagonist* (naloxone or naltrexone) to precipitate immediate withdrawal, and thereby accelerate the withdrawal process. The ultrarapid procedure is carried out under general anesthesia or heavy sedation with IV midazolam [Versed]. In both procedures, clonidine may be added to ease symptoms. These procedures permit a rapid

switch to maintenance therapy with an opioid antagonist. However, they are no more effective than standard withdrawal techniques, and they are considerably more expensive.

Drugs for Long-Term Management of Opioid Addiction

Three kinds of drugs are employed for long-term management: *opioid agonists, opioid agonist-antagonists,* and *opioid antagonists*. Opioid agonists (eg, methadone) substitute for the abused opioid and are given to patients who are not yet ready for detoxification. In contrast, opioid antagonists (eg, naltrexone) are used to discourage renewed opioid use after detoxification has been accomplished. An opioid agonist-antagonist (eg, buprenorphine) can be used both for maintenance therapy and to facilitate detoxification.

Methadone.

In addition to its role in facilitating opioid withdrawal, methadone can be used for *maintenance therapy* and *suppressive therapy*. These strategies are employed to modify drug-using behavior in addicts who are not ready to try withdrawal.

Methadone maintenance consists of transferring the addict from the abused opioid to oral methadone. By taking methadone, the addict avoids both withdrawal and the need to procure illegal drugs. Maintenance dosing is done once a day. Maintenance is most effective when done in conjunction with nondrug measures directed at altering patterns of drug use.

Suppressive therapy is done to prevent the reinforcing effects of opioid-induced euphoria. Suppression is achieved by giving the addict progressively larger doses of methadone until a very high dose (120 mg/day) is reached. Building up to this dose creates a high degree of tolerance, and hence no subjective effects are experienced from the methadone itself. Because cross-tolerance exists among opioids, once the patient is tolerant to methadone, taking street drugs, even in high doses, cannot produce significant desirable effects. As a result, individuals made tolerant with methadone will be less likely to seek out illicit opioids.

Use of methadone to treat opioid addicts is restricted to agencies approved by the Food and Drug Administration (FDA) and state authorities. These restrictions on the nonanalgesic use of methadone are needed to control methadone

abuse, since the drug has about the same abuse liability as morphine and other strong opioids. Since the number of approved clinics is limited, gaining access to one is hard in many parts of the country.

Buprenorphine.

Buprenorphine [Subutex, Suboxone], an agonist-antagonist opioid, was approved in 2002 for treating addiction. As discussed in Chapter 28, the drug is a partial agonist at mu receptors and a full antagonist at kappa receptors. Buprenorphine can be used for maintenance therapy and to facilitate detoxification. When used for maintenance, buprenorphine alleviates craving, reduces use of illicit opioids, and increases retention in therapeutic programs. When used for detoxification, it reduces symptoms of withdrawal.

Unlike methadone, which is available only through approved treatment centers, buprenorphine can be prescribed by any physician or nurse practitioner who has (1) received at least 8 hours of authorized training and (2) registered with the Substance Abuse and Mental Health Services Administration. By 2005 more than 4500 prescribers had qualified.

Buprenorphine has several properties that make it attractive for treating addiction. Because it is a partial agonist at mu receptors, it has a low potential for abuse—but can still suppress craving for heroin. If the dosage is sufficiently high, the drug can completely block access of heroin to mu receptors, and can thereby prevent heroin-induced euphoria. With buprenorphine, there is a ceiling to respiratory depression, which makes it safer than methadone. Development of physical dependence is low, and hence withdrawal is relatively mild.

Buprenorphine is available in two *sublingual* formulations, marketed as *Subutex* (buprenorphine alone) and *Suboxone* (buprenorphine combined with naloxone). Subutex is used for the first few days of treatment, and then Suboxone is used for long-term maintenance. What's the purpose of the naloxone in Suboxone? It's there to discourage IV abuse. If taken IV, the naloxone in Suboxone will precipitate withdrawal. However, with sublingual administration, very little naloxone is absorbed, and hence, when the drug is administered as intended, the risk of withdrawal is low. Nonetheless, because there *is* a small risk with sublingual Suboxone, treatment is initiated with Subutex,

thereby allowing substitution of buprenorphine for the abused opioid. Thereafter, Suboxone is taken for maintenance.

Naltrexone.

Once a patient has undergone opioid detoxification, an opioid antagonist can be used to discourage renewed opioid abuse. Benefits derive from blocking euphoria and all other opioid-induced effects. By preventing pleasurable effects, opioid antagonists eliminate the reinforcing properties of drug use. When the former addict learns that taking an opioid cannot produce the desired response, drug-using behavior will cease. Of the opioid antagonists available, *naltrexone* is best suited for this application. Why? Because naltrexone can be taken orally and because its long half-life permits alternate-day dosing. Furthermore, an IM depot preparation, currently approved only for alcoholism, would permit dosing just once a month. In contrast, naloxone has low oral efficacy and, because its half-life is very short, would require multiple daily doses. These properties make naloxone impractical.

Sequelae of Compulsive Opioid Use

Surprisingly, chronic opioid use has very few *direct* detrimental effects. Addicts in treatment programs have been maintained on high doses of methadone for a decade with no significant impairment of health. Furthermore, individuals on methadone maintenance can be successful socially and at work. It appears, then, that opioid use is not necessarily associated with poor health, lack of productivity, or inadequate social interaction.

Although opioids have few direct ill effects, there are many *indirect* hazards. These risks stem largely from the lifestyle of the opioid user and from impurities common to street drugs. Infections secondary to sharing nonsterile needles occur frequently. The infections that opioid abusers acquire include septicemia, subcutaneous ulcers, tuberculosis, hepatitis C, and HIV. Foreign-body emboli have resulted from impurities in opioid preparations. Opioid users suffer an unusually high death rate. Some deaths reflect the violent nature of the subculture in which opioid use often takes place. Many others result from accidental overdose.

GENERAL CNS DEPRESSANTS

The family of CNS depressants consists of barbiturates, benzodiazepines, alcohol, and other agents. With the exception of the benzodiazepines, all of these drugs are more alike than different. The benzodiazepines have properties that set them apart. The basic pharmacology of the benzodiazepines, barbiturates, and most other CNS depressants is presented in Chapter 34; the pharmacology of alcohol is presented in Chapter 38. Discussion here is limited to abuse of these drugs. Two CNS depressants notorious for their roles in date rape are discussed in Box 39-1.

Barbiturates

The barbiturates embody all of the properties that typify general CNS depressants, and hence can be considered prototypes of the group. Depressant effects are dose dependent and range from mild sedation to sleep to coma to death. With prolonged use, barbiturates produce tolerance and physical dependence.

The abuse liability of the barbiturates stems from their ability to produce subjective effects similar to those of alcohol. The barbiturates with the highest potential for abuse have a short-to-intermediate duration of action. These agents—amobarbital, pentobarbital, and secobarbital—are classified under Schedule II of the Controlled Substances Act. Other barbiturates appear under Schedules III and IV (see Table 37-3). Despite legal restrictions, barbiturates are available cheaply and in abundance.

Tolerance.

Regular use of barbiturates produces tolerance to some effects, but not to others. Tolerance to subjective effects is significant. As a result, progressively larger doses are needed to produce desired psychologic responses. Unfortunately, very little tolerance develops to respiratory depression. Consequently, as barbiturate use continues, the dose needed to produce subjective effects moves closer and closer to the dose that can cause respiratory arrest. (Note that this differs from the pattern seen with opioids, in which tolerance to subjective effects and to respiratory depression develop in parallel.) Individuals tolerant to barbiturates show cross-tolerance with other CNS depressants (eg, alcohol, benzodiazepines, general anesthetics). However, little or no cross-tolerance develops to opioids.

BOX 39-1 DATE-RAPE DRUGS: ROHYPNOL AND GHB

Over the past decade, two drugs—Rohypnol and gamma-hydroxybutyrate (GHB)—have gained notoriety over their use to facilitate rape. Both agents are powerful sedative-hypnotics. Use of either drug to commit sexual assault is a federal crime, punishable under the *Drug-Induced Rape Prevention and Punishment Act*. Street names for Rohypnol include roofies, Roche, rope, rophies, R2, forget-me pill, and Mexican Valium. Street names for GHB include Georgia homeboy, grievous bodily harm, and liquid ecstasy.

Rohypnol

Rohypnol is the trade name for flunitrazepam, a potent benzodiazepine. Like diazepam [Valium] and other benzodiazepines, Rohypnol causes sedation, psychomotor slowing, muscle relaxation, and retrograde amnesia. When used to facilitate sexual assault, the drug is slipped into the victim's drink. The combination of alcohol and flunitrazepam produces a vulnerable state characterized by suggestibility, impaired judgment, loss of inhibition, extreme sleepiness, weakness, and inability to remember what happened after the drugs took effect; most victims eventually lose consciousness. Because an intoxicated person is considered legally incapable of consent, performing sex with such a person is considered an aggressive criminal act, and can be prosecuted as felony sexual assault. Unfortunately, because of Rohypnol-induced amnesia, the victim is often unsure that rape actually took place, and certainly can't attest to details. As a result, prosecution is difficult. Two precautions can reduce the risk of being secretly drugged: In public settings (parties, night-clubs, etc.), never leave a drink unattended and never accept a drink from a person you don't know and trust.

Facilitation of rape is neither the only nor the principal reason for Rohypnol abuse. Most people take it just to get high. As a rule, the drug is combined with another abused substance, typically alcohol or heroin. Because Rohypnol is relatively cheap (about $5 a dose), it is especially popular among high school and college students. In the United States, abuse of Rohypnol is most common in the East and Southwest.

Rohypnol, manufactured by Hoffmann LaRoche, is available for medical use in several countries, but not the United States. In Europe, Rohypnol is widely

prescribed for relieving insomnia. Effects begin within 30 minutes, peak in 2 hours, and persist for 8 hours. The principal difference between Rohypnol and other benzodiazepines is that Rohypnol is very potent—about 10 times more potent than diazepam. Hence, a small dose has a big effect. One source claims that taking 2 mg of Rohypnol is like drinking an entire six-pack of beer.

To make secretive use of Rohypnol more difficult, Hoffmann LaRoche has reformulated the pill. The new formulation dissolves more slowly than the old one and contains a dye that turns pale drinks bright blue and makes dark drinks murky. In addition, the pill contains insoluble particles that will float on top of all drinks. However, since flunitrazepam is also made in clandestine laboratories, not all formulations will produce these conspicuous effects.

Because of its abuse potential, the legal status of flunitrazepam has changed. Initially, this drug, like all other benzodiazepines, was classified under Schedule IV. In 1995, the World Health Organization reclassified it under Schedule III. In the United States, importation of flunitrazepam has been banned, and the Drug Enforcement Agency is considering placing it in Schedule I.

In 1996, Congress passed the *Drug-Induced Rape Prevention and Punishment Act*. The law imposes a maximum prison term of 20 years for importing and distributing 1 gm or more of flunitrazepam. The act also stiffens the penalty for administering a controlled substance without consent and with the intent of committing rape or any other violent crime.

GHB

Gamma-hydroxybutyrate, or GHB, has two notable actions: it depresses CNS function and, by causing release of growth hormone, it promotes muscle growth. During the 1990s, GHB gained popularity as a drug of abuse, primarily among adolescents and young adults. The drug is taken in social settings (parties, raves, clubs, etc.) to produce relaxation, euphoria, and disinhibition. It is taken by athletes to increase strength. And it is administered clandestinely to facilitate sexual assault. When used for assault, GHB is much like Rohypnol. The perpetrator simply slips a few drops of the colorless, odorless, tasteless liquid into the intended victim's drink; within 20 minutes, the GHB produces incoordination, confusion, and deep sedation, along with amnesia about what has taken place.

The pharmacology of GHB is similar to that of other CNS depressants. This is no surprise given that GHB is a metabolite of gamma-aminobutyric acid, the major inhibitory transmitter in the brain. When taken in moderate doses, GHB produces sedation, relaxation, and mild euphoria. Overdose produces significant respiratory depression, which is made worse by concurrent use of alcohol. Seizures may occur, especially with combined use of methamphetamine. Overdose can also cause nausea, vomiting, bradycardia, hypothermia, agitation, delirium, unconsciousness, and coma. GHB has been linked to more than 60 deaths and thousands of emergency department admissions.

Repeated use of GHB appears to cause tolerance and physical dependence. Tolerance is indicated by the need for bigger and bigger doses to produce relaxation and euphoria. Physical dependence is indicated by signs of withdrawal—agitation, delirium, tachycardia, insomnia, anxiety, tremors, sweating—when regular use stops.

GHB has only one approved use: reduction of cataplexy in patients with narcolepsy (see Chapter 106). The drug is regulated as a Schedule III substance.

A precursor of GHB, known as *1,4-butanediol,* undergoes conversion to GHB in the body, and hence has effects identical to those of GHB itself. Butanediol is used as an industrial solvent, and is also available as a "dietary supplement." The supplements are claimed to enhance muscle growth, fight aging, increase sexual desire, promote relaxation, and elevate mood. Trade names for the supplements include Thunder Nectar, Inner G, and Zen.

Physical Dependence and Withdrawal Techniques.

Chronic barbiturate use can produce substantial physical dependence. Cross-dependence exists between barbiturates and other CNS depressants but not with opioids. When physical dependence is great, the associated abstinence syndrome can be severe—sometimes fatal (see Chapter 34). In contrast, the opioid abstinence syndrome, although unpleasant, is rarely life threatening.

One technique for easing barbiturate withdrawal employs phenobarbital, a barbiturate with a long half-life. Because of cross-dependence, substitution of phenobarbital for the abused barbiturate suppresses symptoms of abstinence. Once the patient has been stabilized, the dosage of phenobarbital is gradually tapered off, thereby minimizing symptoms of abstinence.

Acute Toxicity.

Overdose with barbiturates produces a triad of symptoms: *respiratory depression, coma,* and *pinpoint pupils*—the same symptoms that accompany opioid poisoning. Treatment is directed at maintaining respiration and removing the drug; endotracheal intubation and ventilatory assistance may be required. Details of management are presented in Chapter 34. Barbiturate overdose has no specific antidote; naloxone, which reverses poisoning by opioids, is not effective against poisoning by barbiturates.

Benzodiazepines

Benzodiazepines differ significantly from barbiturates. Benzodiazepines are much safer than the barbiturates, and overdose with *oral* benzodiazepines *alone* is rarely lethal. However, the risk of death is greatly increased when oral benzodiazepines are combined with other CNS depressants (eg, alcohol, barbiturates) or when benzodiazepines are administered IV. If severe overdose occurs, signs and symptoms can be reversed with *flumazenil,* a benzodiazepine antagonist. As a rule, tolerance and physical dependence are only moderate when benzodiazepines are taken for legitimate indications, but can be substantial when these drugs are abused. In patients who develop physical dependence, the abstinence syndrome can be minimized by withdrawing benzodiazepines very slowly—over a period of months. The abuse liability of the benzodiazepines is much lower than that of the barbiturates. As a result, all benzodiazepines are classified under Drug Enforcement Agency (DEA) Schedule IV. Benzodiazepines are discussed at length in Chapter 34.

Alcohol and Miscellaneous CNS Depressants

Alcohol, alcohol abuse, and alcoholism treatment are discussed in Chapter 38.

In addition to barbiturates, benzodiazepines, and alcohol, other CNS depressants (eg, paraldehyde, meprobamate, chloral hydrate) are subject to abuse. The pharmacology of these drugs is similar to that of the barbiturates.

Methaqualone is unique among the CNS depressants and requires comment. At one time, methaqualone [Quaalude] was available legally for sedation. However, because of its high abuse potential and the availability of superior alternatives (ie, benzodiazepines), methaqualone was withdrawn from the

market. The drug differs from other depressants in that overdose is not characterized by obvious signs of CNS depression. Rather, poisoning can produce restlessness, hypertonia, and convulsions.

PSYCHOSTIMULANTS

Discussion here focuses on CNS stimulants that have a high potential for abuse: amphetamines, cocaine, and related substances. Because of their considerable abuse liability, these drugs are classified as Schedule II agents. (If they lacked approved medical uses, they would be classified in Schedule I.) In addition to stimulating the CNS, the amphetamines and cocaine can stimulate the heart, blood vessels, and other structures under sympathetic control. Because of these peripheral actions, these agents are also referred to as *sympathomimetics*.

Stimulants with little or no abuse potential are not addressed in this chapter. Included in this group are Schedule III stimulants (eg, benzphetamine), Schedule IV stimulants (eg, diethylpropion), and stimulants that are not regulated at all (eg, caffeine, ephedrine).

Cocaine

Cocaine is a stimulant extracted from the leaves of the coca plant. The drug has CNS effects similar to those of the amphetamines. In addition, cocaine can produce local anesthesia (see Chapter 26) as well as vasoconstriction and cardiac stimulation. Among abusers, a form of cocaine known as "crack" is used widely. Crack is extremely addictive, and the risk of lethal overdose is high.

According to the National Survey on Drug Use and Health (NSDUH), 5.5 million Americans reported using cocaine in 2005, and 1.4 million reported using crack. The number of new users in 2005 was 872,000, most of them over the age of 18.

Forms.

Cocaine is available in two forms: *cocaine hydrochloride* and *cocaine base* (alkaloidal cocaine, freebase cocaine, "crack"). Cocaine base is heat stabile, whereas cocaine hydrochloride is not. Cocaine hydrochloride is available as a white powder that is frequently diluted ("cut") before sale. Cocaine base is sold in

the form of crystals ("rocks") that consist of nearly pure cocaine. Cocaine base is widely known by the street name "crack," a term inspired by the sound the crystals make when heated.

Routes of Administration.

Cocaine *hydrochloride* is usually administered *intranasally*. The drug is "snorted" and absorbed across the nasal mucosa into the bloodstream. A few users (about 5%) administer cocaine hydrochloride IV. Cocaine hydrochloride cannot be smoked because it is unstable at high temperature.

Cocaine *base* is administered by *smoking,* a process referred to as "freebasing." Smoking delivers large amounts of cocaine to the lungs, where absorption is very rapid. Subjective and physiologic effects are equivalent to those elicited by IV injection.

Subjective Effects and Addiction.

At usual doses, cocaine produces euphoria similar to that produced by amphetamines. In a laboratory setting, individuals familiar with the effects of cocaine are unable to distinguish between cocaine and amphetamine. How does cocaine cause euphoria? The drug inhibits neuronal reuptake of dopamine, and thereby increases activation of dopamine receptors in the brain's reward circuit.

As with many other psychoactive drugs, the intensity of subjective responses depends on the rate at which plasma drug levels rise. Since cocaine levels rise relatively slowly with intranasal administration, and almost instantaneously with IV injection or smoking, responses produced by intranasal cocaine are much less intense than those produced by the other two routes.

When crack cocaine is smoked, desirable subjective effects begin to fade within minutes and are often replaced by dysphoria. In an attempt to avoid dysphoria and regain euphoria, the user may administer repeated doses at short intervals. This usage pattern—termed *binging*—can rapidly lead to addiction.

Acute Toxicity: Symptoms and Treatment.

Overdose is frequent, and deaths have occurred. Mild overdose produces agitation, dizziness, tremor, and blurred vision. Severe overdose can produce hy-

perpyrexia, convulsions, ventricular dysrhythmias, and hemorrhagic stroke. Angina pectoris and myocardial infarction may develop secondary to coronary artery spasm. Psychologic manifestations of overdose include severe anxiety, paranoid ideation, and hallucinations (visual, auditory, or tactile). Because cocaine has a short half-life, symptoms subside in 1 to 2 hours.

Although there is no specific antidote to cocaine toxicity, most symptoms can be controlled with drugs. Intravenous *diazepam* or *lorazepam* can reduce anxiety and suppress seizures. *Diazepam* may also alleviate hypertension and dysrhythmias, since these result from increased central sympathetic activity. If hypertension is severe, it can be corrected with intravenous *nitroprusside* or *phentolamine*. Dysrhythmias associated with prolonging the QT interval may respond to *hypertonic sodium bicarbonate*. Although beta blockers can suppress dysrhythmias, they can further compromise coronary perfusion (by preventing beta*2*-mediated coronary vasodilation). Reduction of thrombus formation with aspirin can lower the risk of myocardial ischemia. Hyperthermia should be reduced with external cooling.

Chronic Toxicity.

When administered intranasally on a long-term basis, cocaine can cause atrophy of the nasal mucosa and loss of sense of smell. In extreme cases, necrosis and perforation of the nasal septum have occurred. Nasal pathology results from local ischemia secondary to chronic vasoconstriction. Injury to the lungs can occur from smoking cocaine base.

Use During Pregnancy.

Cocaine is highly lipid soluble and readily crosses the placenta, allowing it to accumulate in the fetal circulation. However, according to a report in *JAMA* (March 28, 2001, pages 1613–1625), fetal injury from cocaine is minimal—and, in all likelihood, considerably less than injury caused by tobacco or alcohol. Specifically, the *JAMA* report noted that there is no solid proof that *in utero* exposure to cocaine diminishes growth, affects developmental scores during the first 6 years, produces any lasting effect on motor development, or causes significant alterations in responses to behavioral stimuli. In short, available data fail to show that prenatal cocaine exposure has *major* adverse developmental effects.

Tolerance, Dependence, and Withdrawal.

In animal models, regular administration of cocaine results in *increased* sensitivity to the drug, not tolerance. Whether this holds true for humans is not clear.

The degree of physical dependence produced by cocaine is in dispute. Some observers report little or no evidence of withdrawal following cocaine discontinuation. In contrast, others report symptoms similar to those associated with amphetamines: dysphoria, craving, fatigue, depression, and prolonged sleep.

Treatment of Cocaine Addiction.

Although achieving complete abstinence from cocaine is extremely difficult, treatment *can* greatly reduce cocaine use. For the cocaine addict, psychosocial therapy is the cornerstone of treatment. This therapy is directed at motivating users to commit to a drug-free life, and then helping them work toward that goal. A combination of individual therapy and group drug counseling is most effective, producing a 70% reduction in cocaine use at 12-month follow-up.

Can medication help with cocaine addiction? To date, no drug has been proved broadly effective in treating cocaine abuse. However, ongoing work with two agents—a *cocaine vaccine* and *disulfiram* [Antabuse]—is encouraging. Subjects receiving the vaccine develop antibodies that bind cocaine, and thereby render it inactive. The higher the antibody titer, the greater the reduction in cocaine use. In one study with disulfiram, subjects receiving a combination of disulfiram plus cognitive behavioral therapy reduced their cocaine use from 2 or 3 times daily to 0.5 times daily. Disulfiram is the same drug we discussed in Chapter 38 for treating alcohol abuse.

Amphetamines

The basic pharmacology of the amphetamines is discussed in Chapter 36. Discussion here is limited to amphetamine abuse.

Forms and Routes.

The amphetamine family includes dextroamphetamine, methamphetamine, lisdexamfetamine, and amphetamine (a racemic mixture of dextroamphetam-

ine and levoamphetamine). When taken for purposes of abuse, amphetamines are usually administered orally or IV. In addition, a form of dextroamphetamine known as "ice" or "crystal meth" can be smoked, snorted, or inserted in the rectum. Abuse of methamphetamine is a growing problem in the United States.

Subjective and Behavioral Effects.

Amphetamines produce arousal and elevation of mood. Euphoria is likely and talkativeness is prominent. A sense of increased physical strength and mental capacity occurs. Self-confidence rises. The amphetamine user feels little or no need for food and sleep. Orgasm is delayed, intensified, and more pleasurable.

Adverse CNS Effects.

Amphetamines can produce a psychotic state characterized by hallucinations and paranoid ideation, and hence presents much like schizophrenia. Although psychosis can be triggered by a single dose, it occurs more commonly in the context of long-term abuse. Amphetamine-induced psychosis usually resolves spontaneously following drug withdrawal. If needed, an antipsychotic agent (eg, haloperidol) can be given to suppress symptoms.

Adverse Cardiovascular Effects.

Because of their sympathomimetic actions, amphetamines can cause vasoconstriction and excessive stimulation of the heart. These actions can lead to hypertension, angina pectoris, and dysrhythmias. Overdose may also cause cerebral and systemic vasculitis and renal failure. Changes in cerebral blood vessels can lead to stroke. Vasoconstriction can be relieved with an alpha-adrenergic blocker (eg, phentolamine). Cardiac stimulation can be reduced with a beta blocker (eg, labetalol). Drug elimination can be accelerated by giving ammonium chloride to acidify the urine.

Tolerance, Dependence, and Withdrawal.

Prolonged amphetamine use results in tolerance to mood elevation, appetite suppression, and cardiovascular effects. Although physical dependence is only moderate, psychologic dependence can be intense. Amphetamine withdrawal can produce dysphoria and a strong sense of craving. Other symptoms include

fatigue, prolonged sleep, excessive eating, and depression. Depression can persist for months and is a common reason for resuming amphetamine use.

MARIJUANA AND RELATED PREPARATIONS

Marijuana is the most commonly used illicit drug in the United States. Over 95 million Americans have tried it at least once. In 2006, 14.8 million Americans age 12 and older used marijuana at least once in the month prior to being surveyed. Among young adults 18 to 25 years old, 54% used marijuana at least once in 2002, compared with only 5.1% in 1965.

Cannabis sativa, the Source of Marijuana

Marijuana is prepared from *Cannabis sativa,* the Indian hemp plant—an unusual plant in that it has separate male and female forms. Psychoactive compounds are present in all parts of the male and female plants. However, the greatest concentration of psychoactive substances is found in the flowering tops of the females.

The two most common *Cannabis* derivatives are *marijuana* and *hashish*. Marijuana is a preparation consisting of leaves and flowers of male and female plants. Alternative names for marijuana include *grass, weed, pot,* and *dope*. The terms *joint* and *reefer* refer to marijuana cigarettes. Hashish is a dried preparation of the resinous exudate from female flowers. Hashish is considerably more potent than marijuana.

Psychoactive Component

The major psychoactive substance in *Cannabis sativa* is *delta-9-tetrahydrocannabinol* (THC), an oily chemical with high lipid solubility. The structure of THC appears in Figure 39-1.

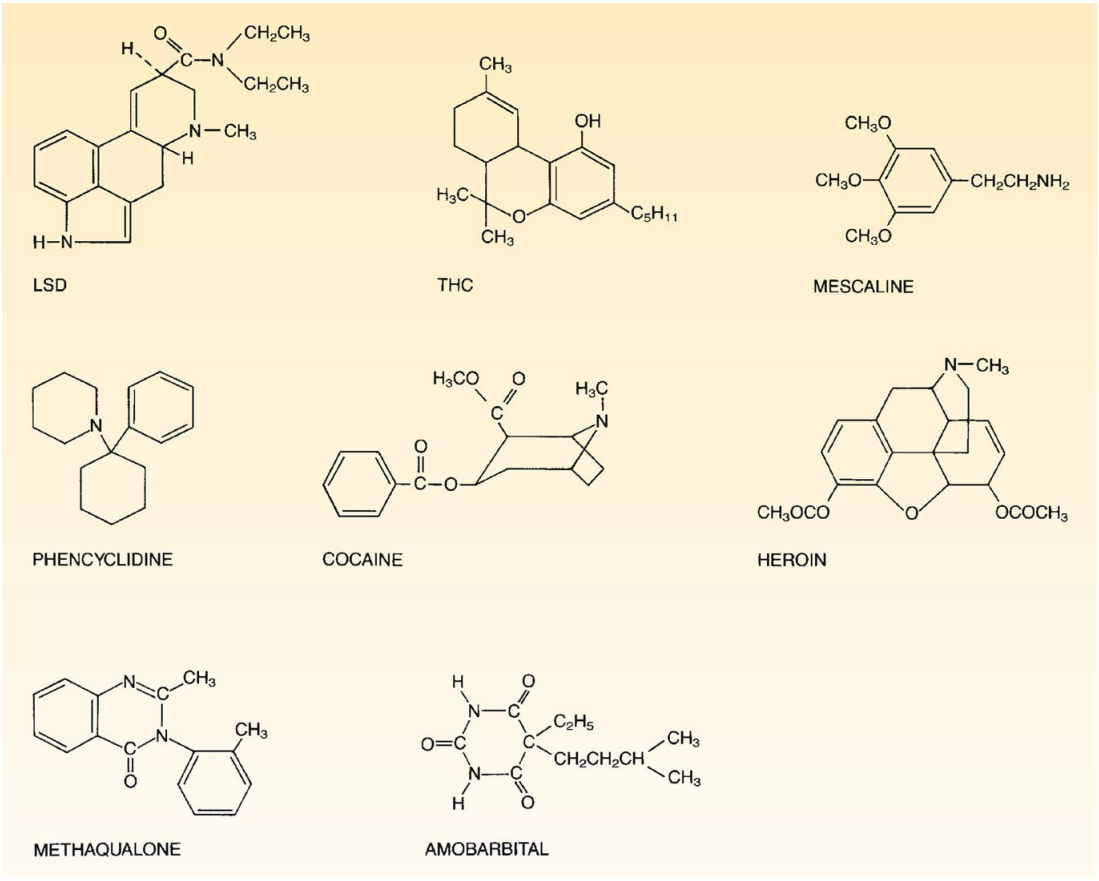


Figure 39-1 Structural formulas of representative drugs of abuse. (LSD = d-lysergic acid diethylamide; THC = tetrahydrocannabinol.)

The THC content of *Cannabis* preparations is variable. The highest concentrations are found in the flowers of the female plant. The lowest concentrations are in the seeds. Depending on growing conditions and the strain of the plant, THC in marijuana preparations may range from 1% to 11%.

Mechanism of Action

THC has several possible mechanisms. Perhaps the most important is activation of specific cannabinoid receptors found in various parts of the brain. The endogenous ligand for these receptors appears to be *anandamide,* a derivative of arachidonic acid unique to the brain. Other proposed mechanisms are (1) activation of phospholipase A2 in the brain, resulting in increased produc-

tion of prostaglandin E2, and (2) augmentation of neuronal membrane fluidity through interaction with membrane lipids.

There is evidence that marijuana may act in part through the same reward system as opioids and cocaine. Both heroin and cocaine produce pleasurable sensations by promoting release of dopamine in the brain's reward circuit. In rats, intravenous THC also causes dopamine release. Interestingly, release of dopamine by THC is blocked by naloxone, a drug that blocks the effects of opioids. This suggests that THC causes release of dopamine by first causing release of endogenous opioids.

Pharmacokinetics

Administration by Smoking.

When marijuana or hashish is smoked, about 60% of the THC content is absorbed. Absorption from the lungs is rapid. Subjective effects begin in minutes and peak 10 to 20 minutes later. Effects from a single marijuana cigarette may persist 2 to 3 hours. Termination results from metabolism of THC to inactive products.

Oral Administration.

When marijuana or hashish is ingested, practically all of the THC undergoes absorption. However, the majority is inactivated on its first pass through the liver. Hence only 6% to 20% of absorbed drug actually reaches the systemic circulation. Because of this extensive first-pass metabolism, oral doses must be 3 to 10 times greater than smoked doses to produce equivalent effects. With oral administration, effects are delayed and prolonged; responses begin 30 to 50 minutes after administration and persist up to 12 hours.

Behavioral and Subjective Effects

Marijuana produces three principal subjective effects: *euphoria, sedation,* and *hallucinations*. This set of responses is unique to marijuana; no other psychoactive drug causes all three. Because of this singular pattern of effects, marijuana is in a class by itself.

Effects of Low to Moderate Doses.

Responses to low doses of THC are variable and depend on several factors, including dosage size, route of administration, setting of drug use, and expectations and previous experience of the user. The following effects are common: euphoria and relaxation; gaiety and a heightened sense of the humorous; increased sensitivity to visual and auditory stimuli; enhanced sense of touch, taste, and smell; increased appetite and ability to appreciate the flavor of food; and distortion of time perception such that short spans seem much longer than they really are. In addition to these effects, which might be considered pleasurable (or at least innocuous), moderate doses can produce undesirable responses. Among these are impairment of short-term memory; decreased capacity to perform multistep tasks; impairment of driving skills (which can be substantially worsened by concurrent use of alcohol); temporal disintegration (inability to distinguish between past, present, and future); depersonalization (a sense of strangeness about the self); decreased ability to perceive the emotions of others; and reduced interpersonal interaction.

High-Dose Effects.

In high doses, marijuana can have serious adverse psychologic effects. The user may experience hallucinations, delusions, and paranoia. Euphoria may be displaced by intense anxiety, and a dissociative state may occur in which the user feels "outside of himself or herself." In extremely high doses, marijuana can produce a state resembling toxic psychosis, which may persist for weeks. Because of the widespread use of marijuana, psychiatric emergencies caused by the drug are relatively common.

Not all users are equally vulnerable to the adverse psychologic effects of marijuana. Some individuals experience ill effects only at extremely high doses. In contrast, others routinely experience adverse effects at moderate doses. Schizophrenics are at unusually high risk for adverse reactions. In the stabilized schizophrenic, marijuana can precipitate an acute psychotic episode.

Effects of Chronic Use.

Chronic, excessive use of marijuana is associated with a behavioral phenomenon known as an *amotivational syndrome,* characterized by apathy, dullness, poor grooming, reduced interest in achievement, and disinterest in the pursuit of

conventional goals. The precise relationship between marijuana and development of the syndrome is not known, nor is it certain what other factors may contribute. Available data do not suggest that the amotivational syndrome is due to organic brain damage.

Physiologic Effects

Cardiovascular Effects.

Marijuana produces a dose-related increase in heart rate. Increases of 20 to 50 beats/min are typical. However, rates up to 140 beats/min are not uncommon. Pretreatment with propranolol prevents marijuana-induced tachycardia but does not block the drug's subjective effects. Marijuana causes orthostatic hypotension and pronounced reddening of the conjunctivae. These responses apparently result from vasodilation.

Respiratory Effects.

When used *acutely,* marijuana produces *bronchodilation*. However, when smoked chronically, the drug causes airway constriction. In addition, chronic use is closely associated with development of bronchitis, sinusitis, and asthma. Lung cancer is another possible outcome. Animal studies have shown that tar from marijuana smoke is a more potent carcinogen than tar from cigarettes.

Effects on Reproduction.

Research in animals has shown multiple effects on reproduction. In males, marijuana decreases spermatogenesis and testosterone levels. In females, the drug reduces levels of follicle-stimulating hormone, luteinizing hormone, and prolactin.

Multiple effects may be seen in babies and children who were exposed to marijuana *in utero*. Some babies present with trembling, altered responses to visual stimuli, and a high-pitched cry. Preschoolers may have a decreased ability to perform tasks that involve memory and sustained attention. Schoolchildren may exhibit deficits in memory, attentiveness, and problem solving.

Altered Brain Structure.

Long-term marijuana use is associated with structural changes in the brain. Specifically, the volume of the hippocampus and amygdala is reduced, by an average of 12% and 7.1%, respectively. We don't know if volume reduction is due to reduced cell size, reduced synaptic density, or loss of glial cells and/or neurons. Interestingly, hippocampal volume loss occurred primarily in the left hemisphere.

Tolerance and Dependence

When taken in extremely high doses, marijuana can produce tolerance and physical dependence. Neither effect, however, is remarkable. Some tolerance develops to the cardiovascular, perceptual, and motor effects of marijuana. Little or no tolerance develops to subjective effects.

To demonstrate physical dependence on marijuana, the drug must be given in very high doses—and even then the degree of dependence is only moderate. Symptoms brought on by abrupt discontinuation of high-dose marijuana include irritability, restlessness, nervousness, insomnia, reduced appetite, and weight loss. Tremor, hyperthermia, and chills may occur too. Symptoms subside in 3 to 5 days. With moderate marijuana use, no withdrawal symptoms occur.

Therapeutic Uses

At this time, there are no approved medical uses for marijuana itself. However, there *are* approved uses for purified THC, the major active component of marijuana.

Therapeutic Uses for THC.

Suppression of Emesis.

Intense nausea and vomiting are common side effects of cancer chemotherapy. In certain patients, these responses can be suppressed more effectively with cannabinoids than with traditional antiemetics (eg, prochlorperazine, metoclopramide). At this time, only one cannabinoid—dronabinol (THC)—is available for antiemetic use. Dosage forms and dosages are presented in Chapter 79. Another cannabinoid—nabilone—has been withdrawn from the market.

Appetite Stimulation.

Dronabinol is approved for stimulating appetite in patients with AIDS. By relieving anorexia, treatment may prevent or reverse loss of weight.

Neuropathic Pain.

In 2005, Canadian regulators approved *Sativex*—a mouth-spray formulation of THC—for relieving neuropathic pain caused by multiple sclerosis (MS). Because the THC in Sativex is absorbed through the oral mucosa, the product has a rapid onset (like smoked marijuana), while being devoid of dangerous tars present in marijuana smoke. Sativex is not available in the United States, and cannot be legally imported, owing to classification in DEA Schedule I.

Medical Research on Marijuana.

Proponents of making marijuana available by prescription argue that smoked marijuana can reduce chronic pain, suppress nausea caused by chemotherapy, improve appetite in patients with AIDS, lower intraocular pressure in patients with glaucoma, and suppress spasticity associated with MS and spinal cord injury. However, the evidence supporting most of these claims is weak—largely because federal regulations effectively barred marijuana research.

In 1999, two developments opened the doors to marijuana research. First, an expert panel, convened by the National Academy of Sciences' Institute of Medicine, recommended that clinical trials on marijuana proceed. Because smoking marijuana poses a risk of lung cancer and other respiratory disorders, the panel also recommended development of a rapid-onset nonsmoked delivery system. In response to this report and to pressure from scientists and voters, the government created new guidelines that loosened restraints on marijuana research. Under the guidelines, researchers will be allowed to purchase marijuana directly from the federal government. (On behalf of the government, the University of Mississippi maintains a plot of marijuana on 1.8 closely guarded acres.) The only catch is that all proposed research must be approved by the FDA, the National Institute on Drug Abuse, and the DEA. Despite these formidable obstacles, at least one institute—the Center for Medicinal Cannabis Research (CMCR) at the University of California—has begun coordinating and supporting research on medical marijuana. Trials will focus on

HIV-related cachexia, neuropathic pain, nausea and vomiting associated with cancer chemotherapy, and muscle spasticity associated with MS and other diseases.

Legal Status of Medical Marijuana.

Eleven states have passed laws that legalize (or at least decriminalize) medical use of marijuana. However, in 2005, the U.S. Supreme Court ruled that federal DEA legislation trumps these state laws, and hence people who use or provide medical marijuana are still subject to federal prosecution, even in states where medical marijuana has been legalized. In Canada, medical use of marijuana has been legal since 2001. In fact, Canadian patients can purchase the drug directly from the government, at a price 3 to 5 times cheaper than on the street.

Comparison of Marijuana with Alcohol

In several important ways, responses to marijuana and alcohol are quite different. Whereas increased hostility and aggression are common sequelae of alcohol consumption, aggressive behavior is rare among marijuana users. Although loss of judgment and control can occur with either drug, these losses are greater with alcohol. For the marijuana user, increased appetite and food intake are typical. In contrast, heavy drinkers often suffer nutritional deficiencies. Lastly, whereas marijuana can cause toxic psychosis, dissociative phenomena, and paranoia, these severe psychologic reactions rarely occur with alcohol.

PSYCHEDELICS

The psychedelics are a fascinating drug family for which LSD can be considered the prototype. Other family members include mescaline, dimethyltryptamine (DMT), and psilocin. The psychedelics are so named because of their ability to produce what has been termed a *psychedelic state*. Individuals in this state show an increased awareness of sensory stimuli and are likely to perceive the world around them as beautiful and harmonious; the normally insignificant may assume exceptional meaning, the "self" may seem split into an "observer" and a "doer," and boundaries between "self" and "nonself" may fade, producing a sense of unity with the cosmos.

Psychedelic drugs are often referred to as *hallucinogens* or *psychotomimetics*. These names reflect an ability to produce hallucinations as well as mental states that resemble psychoses.

Although psychedelics can cause hallucinations and psychotic-like states, these are not their most characteristic effects. The characteristic that truly distinguishes the psychedelics from other agents is their *ability to bring on the same types of alterations in thought, perception, and feeling that otherwise occur only in dreams*. In essence, the psychedelics seem able to activate mechanisms for dreaming without causing unconsciousness.

d-Lysergic Acid Diethylamide (LSD)

History.

The first person to experience LSD was a Swiss chemist named Albert Hofmann. In 1943, 5 years after LSD was first synthesized, Hofmann accidentally ingested a minute amount of the drug. The result was a dream-like state accompanied by perceptual distortions and vivid hallucinations. The high potency and unusual actions of LSD led to speculation that it might provide a model for studying psychosis. Unfortunately, that speculation did not prove correct: Extensive research has shown that the effects of LSD cannot be equated with idiopathic psychosis. With the realization that LSD did not produce a "model psychosis," medical interest in the drug declined. Not everyone, however, lost interest; during the 1960s, nonmedical experimentation flourished. This widespread use caused substantial societal concern, and, by 1970, LSD had been classified as a Schedule I substance. Nonetheless, street use of LSD continues.

Mechanism of Action.

LSD acts at multiple sites in the brain and spinal cord. However, effects are most prominent in the cerebral cortex and the locus ceruleus. Effects are thought to result from activation of serotonin*2* receptors. This concept has been reinforced by the observation that *ritanserin,* a selective blocker of serotonin*2* receptors, can prevent the effects of LSD in animals.

Time Course.

LSD is usually administered orally but can also be injected or smoked. With oral administration, initial effects can be felt in minutes. Over the next few hours, responses become progressively more intense, and then subside 8 to 12 hours later.

Subjective and Behavioral Effects.

Responses to LSD can be diverse, complex, and changeable. The drug can alter thinking, feeling, perception, sense of self, and sense of relationship with the environment and other people. LSD-induced experiences may be sublime or terrifying. Just what will be experienced during any particular "trip" cannot be predicted.

Perceptual alterations can be dramatic. Colors may appear iridescent or glowing, kaleidoscopic images may appear, and vivid hallucinations may occur. Sensory experiences may merge so that colors seem to be heard and sounds seem to be visible. Afterimages may occur, causing current perceptions to overlap with preceding perceptions. The LSD user may feel a sense of wonderment and awe at the beauty of commonplace things.

LSD can have a profound impact on affect. Emotions may range from elation, good humor, and euphoria to sadness, dysphoria, and fear. The intensity of emotion may be overwhelming.

Thoughts may turn inward. Attitudes may be re-evaluated, and old values assigned new priorities. A sense of new and important insight may be felt. However, despite the intensity of these experiences, enduring changes in beliefs, behavior, and personality are rare.

Physiologic Effects.

LSD has few physiologic effects. Activation of the sympathetic nervous system can produce tachycardia, elevation of blood pressure, mydriasis, piloerection, and hyperthermia. Neuromuscular effects (tremor, incoordination, hyperreflexia, and muscular weakness) may also occur.

Tolerance and Dependence.

Tolerance to LSD develops rapidly. Substantial tolerance can be seen after just three or four daily doses. Tolerance to subjective and behavioral effects devel-

ops to a greater extent than to cardiovascular effects. Cross-tolerance exists with LSD, mescaline, and psilocybin, but not with DMT. Since DMT is similar to LSD, the absence of cross-tolerance is surprising. There is no cross-tolerance with amphetamines or THC. Upon cessation of LSD use, tolerance rapidly fades. Abrupt withdrawal of LSD is not associated with an abstinence syndrome. Hence there is no evidence for physical dependence.

Toxicity.

Toxic reactions are primarily psychologic. LSD has never been a direct cause of death, although fatalities have occurred from accidents and suicides.

Acute panic reactions are relatively common and may be associated with a fear of disintegration of the self. Such "bad trips" can usually be managed by a process of "talking down" (providing emotional support and reassurance in a nonthreatening environment). Panic episodes can also be managed with an antianxiety agent, such as diazepam. Neuroleptics (eg, haloperidol, chlorpromazine) may actually intensify the experience, and hence their use is questionable.

A small percentage of former LSD users experience episodic visual disturbances, referred to as *flashbacks* by users and *hallucinogen persisting perception disorder* (HPPD) by clinicians. These disturbances may manifest as geometric pseudohallucinations, flashes of color, or positive afterimages. Visual disturbances may be precipitated by several factors, including marijuana use, fatigue, stress, and anxiety. Phenothiazines exacerbate these experiences rather than provide relief. HPPD appears to be caused by permanent changes in the visual system.

In addition to panic reactions and visual disturbances, LSD can cause other adverse psychologic effects. Depressive episodes, dissociative reactions, and distortions of body image may occur. When an LSD experience has been intensely terrifying, the user may be left with persistent residual fear. The drug may also cause prolonged psychotic reactions. In contrast to acute effects, which differ substantially from symptoms of schizophrenia, prolonged psychotic reactions mimic schizophrenia faithfully.

Potential Therapeutic Uses.

LSD has no recognized therapeutic applications. The drug has been evaluated for possible use in treating alcoholism, opioid addiction, and psychiatric disorders. In addition, LSD has been studied as a possible means of promoting psychologic well-being in patients with terminal cancer. However, for all of these potential uses, LSD proved either ineffective or impractical.

Mescaline, Psilocybin, Psilocin, and Dimethyltryptamine

In addition to LSD, the family of psychedelic drugs includes mescaline, psilocin, psilocybin, dimethyltryptamine (DMT), and several related compounds. Some psychedelics are synthetic and some occur naturally. DMT and LSD represent the synthetic compounds. Mescaline, a constituent of the peyote cactus, and psilocin and psilocybin, constituents of "magic mushrooms," represent compounds found in nature.

The subjective and behavioral effects of the miscellaneous psychedelic drugs are similar to those of LSD. Like LSD, these drugs can elicit modes of thought, perception, and feeling that are normally restricted to dreams. In addition, they can cause hallucinations and induce mental states that resemble psychosis.

The miscellaneous psychedelics differ from LSD with respect to potency and time course. LSD is the most potent of the psychedelics, producing its full spectrum of effects at doses as low as 0.5 mcg/kg. Psilocin and psilocybin are 100 times less potent than LSD, and mescaline is 4000 times less potent than LSD. Whereas the effects of LSD are prolonged (responses may last 12 or more hours), the effects of mescaline and DMT are shorter: responses to mescaline usually terminate within 8 to 12 hours, and responses to DMT terminate within 1 to 2 hours.

None of these psychedelics is approved for medical use. The use of psilocybin in patients with terminal cancer and obsessive-compulsive disorder is under investigation.

DISSOCIATIVE DRUGS

The dissociative drugs—phencyclidine and ketamine—were originally developed as surgical anesthetics. When taken recreationally, these drugs distort perception of sight and sound, and produce feelings of dissociation (detach-

ment) from the environment. High doses can produce sedation, immobility, analgesia, and amnesia.

Phencyclidine

Phencyclidine ("PCP," "angel dust," "peace pill") was originally developed as an anesthetic for animals. The drug was tried briefly as a general anesthetic for humans but was withdrawn owing to severe emergence delirium. Although rejected for therapeutic use, phencyclidine has become widely used as a drug of abuse, largely because it can be synthesized easily by amateur chemists, making it cheap and abundant. The popularity of phencyclidine is disturbing in that the drug causes a high incidence of severe adverse effects, which make phencyclidine one of the most dangerous drugs of abuse.

Chemistry and Pharmacokinetics

Chemistry.

Phencyclidine is a weak organic base with high lipid solubility. The drug is chemically related to ketamine, an unusual general anesthetic (see Chapter 27 and below). The structural formula of phencyclidine appears in Figure 39-1.

Pharmacokinetics.

Phencyclidine can be administered orally, intranasally, intravenously, and by smoking. For administration by smoking, the drug is usually sprinkled on plant matter (eg, oregano, parsley, tobacco, marijuana). Because of its high lipid solubility, phencyclidine is readily absorbed from all sites.

Once absorbed, phencyclidine undergoes substantial gastroenteric recirculation. Because it is a base, phencyclidine in the blood can be drawn into the acidic environment of the stomach (by the pH partitioning effect); from the stomach, the drug re-enters the intestine, from which it is reabsorbed into the blood. This cycling from blood to GI tract and back prolongs the drug's sojourn in the body. Elimination occurs eventually through a combination of hepatic metabolism and renal excretion.

Mechanism of Action

Phencyclidine acts in the cerebral cortex and limbic system, where it blocks a subset of receptors for glutamate, known as *N*-methyl-D-aspartate (NMDA) receptor complexes. These glutamate receptors are involved in multiple processes, including learning, memory, emotionality, and perception of pain.

Subjective and Behavioral Effects

Phencyclidine produces a unique set of effects. Hallucinations are prominent. In addition, the drug can produce CNS depression, CNS excitation, and analgesia.

Effects of Low to Moderate Doses.

At low doses, phencyclidine produces effects like those of alcohol. Low-dose intoxication is characterized by euphoria, release of inhibitions, and emotional lability. Nystagmus, slurred speech, and motor incoordination may occur too.

As dosage increases, the clinical picture becomes more variable and complex. Symptoms include excitation, disorientation, anxiety, disorganized thoughts, altered body image, and reduced perception of tactile and painful stimuli. Mood may be volatile and hostile. Bizarre behavior may develop. Heart rate and blood pressure are elevated.

High-Dose (Toxic) Effects.

High doses can cause severe adverse physiologic and psychologic effects. Death may result from a variety of causes.

Psychologic effects include hallucinations, confusional states, combativeness, and psychosis. The psychosis closely resembles schizophrenia and may persist for weeks. Individuals with pre-existing psychoses are especially vulnerable to psychotogenic effects. Suicide has been attempted.

The physiologic effects of high-dose phencyclidine are varied. Extreme overdose can produce hypertension, coma, seizures, and muscular rigidity associated with severe hyperthermia and rhabdomyolysis.

Treatment of Toxicity.

Treatment is primarily supportive. Psychotic reactions are best managed by isolation from external stimuli. “Talking down” is not effective, and the benefits of antipsychotic drugs, such as haloperidol, are limited. Physical restraint may be needed to prevent self-inflicted harm and to protect others from assault. If respiration is depressed, mechanical support of ventilation may be needed. Severe hypertension can be managed with diazoxide, a vasodilator. Seizures can be controlled with IV diazepam. If fever is high, external cooling can lower temperature. By promoting muscle relaxation, dantrolene can reduce heat generation and rhabdomyolysis.

Elimination of phencyclidine can be accelerated by continuous gastric lavage and acidification of the urine with ammonium chloride. Continuous lavage is effective because gastroenteric recirculation keeps delivering drug to the stomach. Acidification of urine may promote phencyclidine excretion by reducing tubular reabsorption of this weak base.

Ketamine

Ketamine is a dissociative anesthetic used in animals and humans (see Chapter 27, General Anesthetics). Medicinal ketamine is formulated as an injectable liquid. For recreational use, the liquid is evaporated off, leaving a powder that can be snorted or ingested. Doses typically range from 50 to 200 mg. Much of the ketamine sold on the street was diverted from veterinary offices.

Ketamine is similar to phencyclidine in structure, mechanism, and effects, although its duration of action is shorter. When the drug is snorted, effects begin in 5 to 15 minutes and persist about an hour. Moderate doses produce effects ranging from a dream-like state to a pleasant sensation of floating to a sense of being separated from one's body. Some users experience a state known as the *K-hole,* likened to a near-death experience in which there is a sense of rising above one's body. For some, the K-hole experience is accompanied by a sense of inner peace and radiant light. For others, the K-hole experience is characterized by a terrifying sense of nearly complete sensory detachment. At high doses, ketamine can cause hallucinations, delirium, amnesia, elevation of blood pressure, and potentially fatal disruption of respiration. Even higher doses can produce unconsciousness and fatal cardiovascular collapse.

Because of it depressant and amnesic effects, ketamine has been used to facilitate sexual assault. The drug is colorless, tasteless, and odorless, and hence can be added to a beverage without detection. The use of two other drugs—gamma-hydroxybutyrate (GHB) and Rohypnol—to facilitate sexual assault is discussed in Box 39-1.

DEXTROMETHORPHAN

Dextromethorphan (DXM) is a cough suppressant widely available in over-the-counter cough and cold remedies (see Chapter 76). At the low doses needed for cough suppression, DXM is devoid of psychologic effects. However, at doses 5 to 10 times higher, DXM can produce euphoria, disorientation, paranoia, and altered sense of time, as well as visual, auditory, and tactile hallucinations. These effects are produced by dextrorphan, a metabolite of DXM that blocks receptors for NMDA. Note that this is the same mechanism used by phencyclidine and ketamine. Many of the products that contain DXM also contain other drugs, including acetaminophen, antihistamines, phenylephrine, and pseudoephedrine. Therefore, when excessive doses are taken, users are subject to toxicity from these compounds as well as from DXM itself. The principal users of DXM are adolescents and teenagers. Between 1999 and 2004, reports of DXM abuse in these groups rose 10-fold. Products that contain DXM include Coricidin HBP Cough & Cold, Robitussin, Day Quil Cold, and Theraflu Thin Strips.

3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, ECSTASY)

MDMA, also known as "ecstasy," is a complex drug with stimulant and psychedelic properties. The drug is structurally related to methamphetamine (a stimulant) and mescaline (a hallucinogen). Low doses produce mild LSD-like psychedelic effects; higher doses produce amphetamine-like stimulant effects. These effects result from promoting the release of at least three neurotransmitters: serotonin, dopamine, and norepinephrine. Although MDMA can produce effects that are clearly pleasurable, it can also be dangerous; the biggest concerns are neurotoxicity, seizures, hyperthermia and its sequelae, and excessive cardiovascular stimulation. MDMA is classified as a Schedule I drug.

Time Course and Dosage.

MDMA is usually administered orally, but may also be snorted, injected, or inserted as a rectal suppository. With oral administration, effects begin in 20 minutes, peak in 2 to 3 hours, and persist 4 to 5 hours. The usual dose is 100 mg or less.

Who Uses MDMA and Why?

MDMA is used primarily by adolescents and young adults, who often take it at nightclubs and all-night dance parties, known as "raves." The drug is used by young people in cities, in the suburbs, and in the country. According to a survey conducted in 2007, 1.5% of 8th-graders, 3.5% of 10th-graders, and 4.5% of 12th-graders had used MDMA in the past year.

Why do people take MDMA? Because it makes them feel really good. The drug can elevate mood, increase sensory awareness, and heighten sensitivity to music. It can also facilitate interpersonal relationships: Users report a sense of closeness with others, lowering of defenses, reduced anxiety, enhanced communication, and increased sociability.

Adverse Effects.

Unfortunately, MDMA is not free of risks. The drug can injure serotonergic neurons, stimulate the heart, and raise body temperature to a dangerous level. In addition, it can cause neurologic effects (eg, seizures, spasmodic jerking, jaw clenching, teeth grinding) and a host of adverse psychologic effects (eg, confusion, anxiety, paranoia, panic attacks, visual hallucinations, and suicidal thoughts and behavior). Every year, MDMA is associated with several thousand admissions to emergency departments, mainly because of seizures.

MDMA can damage serotonergic neurons, perhaps irreversibly. When administered to rats and primates in doses only 2 to 4 times greater than those that produce hallucinations in humans, MDMA causes *irreversible destruction of serotonergic neurons,* resulting in passivity and insomnia. At least three lines of evidence suggest that MDMA is also neurotoxic in humans: (1) MDMA causes dose-related impairment of memory, a brain function mediated in part by serotonin. Memory impairment persists long after MDMA was last taken. (2) The cerebrospinal fluid of long-term MDMA users contains abnormally

low concentrations of serotonin metabolites, suggesting a loss of serotonergic neurons. (3) Using positron emission tomography to study former MDMA users, researchers demonstrated decreased binding of a ligand selective for the serotonin transporter, indicating damage to serotonergic neurons. In this study, reductions in ligand binding correlated with the extent of MDMA use, and not with the duration of abstinence.

MDMA can cause hyperthermia in association with dehydration, hyponatremia, and rhabdomyolysis (disintegration of muscle tissue). Treatment consists of rapid cooling, rehydration, and administering dantrolene [Dantrium], a drug that relaxes skeletal muscle, thereby reducing heat generation and the risk of rhabdomyolysis. The risk of hyperthermia and dehydration could be greatly reduced by providing ample fluids at raves and other events where MDMA is likely to be used.

Because of its amphetamine-like actions, MDMA can increase heart rate, blood pressure, and myocardial oxygen consumption. Remarkably, the increases in heart rate and blood pressure equal those produced by maximal doses of dobutamine, a powerful adrenergic agonist (see Chapter 17). Cardiovascular stimulation poses a special risk to users with heart disease.

Potential Medical Use.

Despite its potential for adverse effects, MDMA also has the potential for therapeutic good, owing largely to its ability to decrease feelings of fear and defensiveness and promote feelings of love, trust, and compassion. In 2004, the FDA approved two small clinical trials of MDMA, one in patients with posttraumatic stress disorder, and the other in patients with severe anxiety related to terminal cancer.

INHALANTS

The inhalants are a diverse group of drugs that have one characteristic in common: administration by inhalation. These drugs can be divided into three classes: anesthetics, volatile nitrites, and organic solvents.

Anesthetics

Provided that dosage is modest, anesthetics produce subjective effects similar to those of alcohol (euphoria, exhilaration, loss of inhibitions). The anesthetics that have been abused most are *nitrous oxide* ("laughing gas") and *ether*. One reason for the popularity of these drugs is ease of administration: Both agents can be used without exotic equipment. For nitrous oxide, ready availability also promotes use: Small cylinders of the drug, marketed for aerating whipping cream, can be purchased without restriction.

Volatile Nitrites

Four volatile nitrites—*amyl nitrite, butyl nitrite, isobutyl nitrite,* and *cyclohexyl nitrite*—are subject to abuse. These drugs are abused by homosexual males because of an ability to relax the anal sphincter, and by males in general because of a reputed ability to prolong and intensify sexual orgasm.

The most pronounced pharmacologic effect of volatile nitrites is *venodilation,* which causes pooling of blood in veins, which in turn causes a profound drop in systolic blood pressure. The result is dizziness, lightheadedness, palpitations, and possibly pulsatile headache. Effects begin seconds after inhalation and fade rapidly. The primary toxicity is methemoglobinemia, which can be treated with methylene blue and supplemental oxygen.

Nitrites are available from medical and nonmedical sources. Amyl nitrite is used for angina pectoris. Cyclohexyl nitrite is present in room odorizers. Butyl nitrite and isobutyl nitrite are present in products made solely for recreational use. Trade names for butyl nitrite and isobutyl nitrite include Climax, Rush, and Locker Room. On the street, preparations of amyl nitrite are known as "poppers" or "snappers." These terms reflect the fact that amyl nitrite is packaged in glass ampules that make a popping sound when snapped open to allow inhalation.

Organic Solvents

A wide assortment of solvents have been inhaled to induce intoxication. These compounds include *toluene, gasoline, lighter fluid, paint thinner, nail-polish remover, benzene, acetone, chloroform,* and *model-airplane glue*. These agents are used primarily by children and the very poor—people who, because of age or

insufficient funds, lack access to more conventional drugs of abuse. In recent years, use of inhalants by young children and teens has been rising.

Administration.

Solvents are administered by three processes, referred to as "bagging," "huffing," and "sniffing." Bagging is performed by pouring solvent in a bag and inhaling the vapor. Huffing is performed by pouring the solvent on a rag and inhaling the vapor. Sniffing is performed by inhaling the solvent directly from its container.

Acute Pharmacologic Effects.

The acute effects of organic solvents are somewhat like those of alcohol (euphoria, impaired judgment, slurred speech, flushing, CNS depression). In addition, these compounds can cause visual hallucinations and disorientation with respect to time and place. High doses can cause sudden death. Possible causes include anoxia, respiratory depression, vagal stimulation (which slows heart rate), and dysrhythmias.

Chronic Toxicity.

Prolonged use is associated with multiple toxicities. For example, chloroform is toxic to the heart, liver, and kidneys; and toluene can cause severe brain damage and bone marrow depression. Many solvents can damage the heart; fatal dysrhythmias have occurred secondary to drug-induced heart block.

Management.

Management of acute toxicity is strictly supportive. The objective is to stabilize vital signs. We have no antidotes for volatile solvents.

NICOTINE AND SMOKING

Cigarette smoking remains the greatest single cause of preventable illness and premature death. In the United States, smoking kills nearly 400,000 adults each year—over 242,000 males and 155,000 females. Around the world, tobacco kills 5 million people each year. On average, male smokers die 13.2 years prematurely, and females die 14.5 years prematurely. As shown in Table 39-3, most deaths result from lung cancer (123,836), heart disease (107,774), and

chronic airway obstruction (75,074). Not only do cigarettes kill the people who smoke them, every year they also kill thousands of nonsmokers who inhaled secondhand smoke. The direct medical costs of smoking exceed $95 billion a year. Indirect costs, including lost time from work and disability, add up to an additional $97 billion.

Although tobacco smoke contains many dangerous compounds, nicotine is of greatest concern. Other hazardous components in tobacco smoke include carbon monoxide, hydrogen cyanide, ammonia, nitrosamines, and tar. Tar is composed of various polycyclic hydrocarbons, some of which are proven carcinogens.

What is the regulatory status of cigarettes? Good question, given that cigarettes are the single most dangerous product available to U.S. consumers. Until recently, cigarettes had avoided virtually all federal regulation. However, strong regulations are now in place. Under the *Family Smoking Prevention and Tobacco Control Act*, passed in June 2009, the FDA now has the authority to

- Strengthen advertising restrictions, including the prohibition on marketing to youth.
- Require revised and more prominent warning labels.
- Require disclosure of all ingredients in tobacco products and restrict harmful additives.
- Monitor nicotine yields, and mandate gradual nicotine reduction to nonaddictive levels.

Basic Pharmacology of Nicotine

Mechanism of Action

The effects of nicotine result from actions at nicotinic receptors. Whether these receptors are activated or inhibited depends on nicotine dosage. *Low* doses *activate* nicotinic receptors; *high* doses *block* them. The amount of nicotine received from cigarettes is relatively low. Accordingly, cigarette smoking causes receptor *activation*.

Nicotine can activate nicotinic receptors at several locations. Most effects result from activating nicotinic receptors in autonomic ganglia and the adrenal

medulla. In addition, nicotine can activate nicotinic receptors in the carotid body, aortic arch, and CNS. As discussed below, actions in the CNS mimic those of cocaine and other highly addictive substances. When present at the levels produced by smoking, nicotine has no significant effect on nicotinic receptors of the neuromuscular junction.

Pharmacokinetics

Absorption of nicotine depends on whether the delivery system is a cigarette, a cigar, or smokeless tobacco. Nicotine in cigarette smoke is absorbed primarily from the lungs. When cigarette smoke is inhaled, between 90% and 98% of nicotine in the lungs enters the blood. Unlike nicotine in cigarette smoke, nicotine in cigar smoke is absorbed primarily from the mouth, as is nicotine in smokeless tobacco.

Nicotine can cross membranes easily and is widely distributed throughout the body. The drug readily enters breast milk, reaching levels that can be toxic to the nursing infant. Nicotine also crosses the placental barrier and can cause fetal harm. When inhaled in cigarette smoke, nicotine reaches the brain in just 10 seconds.

Nicotine is rapidly metabolized to inactive products. Nicotine and its metabolites are excreted by the kidney. The drug's half-life is 1 to 2 hours.

Pharmacologic Effects

The pharmacologic effects discussed in this section are associated with *low* doses of nicotine. These are the effects caused by smoking cigarettes. Responses to *high* doses are discussed under *Acute Poisoning*.

Cardiovascular Effects.

The cardiovascular effects of nicotine result primarily from activating nicotinic receptors in *sympathetic ganglia* and the *adrenal medulla*. Activation of these receptors promotes release of norepinephrine from sympathetic nerves and release of epinephrine (and some norepinephrine) from the adrenals. Norepinephrine and epinephrine act on the cardiovascular system to constrict blood vessels, accelerate the heart, and increase the force of ventricular con-

traction. The net result is elevation of blood pressure and increased cardiac work. These effects underlie cardiovascular deaths.

GI Effects.

Nicotine influences GI function primarily by activating nicotinic receptors in *parasympathetic* ganglia. The result is increased secretion of gastric acid and increased tone and motility of GI smooth muscle. In addition, nicotine can promote vomiting. Nicotine-induced vomiting results from a complex process that involves nicotinic receptors in the aortic arch, the carotid sinus, and the CNS.

CNS Effects.

Nicotine is a CNS stimulant. The drug stimulates respiration and produces an arousal pattern on the electroencephalogram. Moderate doses can cause tremors, and high doses can cause convulsions.

Nicotine has multiple psychologic effects. The drug increases alertness, facilitates memory, improves cognition, reduces aggression, and suppresses appetite. In addition, by promoting release of dopamine, nicotine activates the brain's "pleasure system" located in the mesolimbic area. The effects of nicotine on the pleasure system are identical to those of other highly addictive drugs, including cocaine, amphetamines, and opioids.

Effects During Pregnancy and Lactation.

Exposure to nicotine can harm the fetus. Nicotine in breast milk can harm the nursing infant. Accordingly, therapeutic formulations of nicotine (eg, nicotine chewing gum, nicotine transdermal patches, nicotine nasal spray) are contraindicated during pregnancy, and their use by nursing mothers is not recommended.

Tolerance and Dependence

Tolerance.

Tolerance develops to some effects of nicotine but not to others. Tolerance does develop to nausea and dizziness, which are common in the unseasoned smoker. In contrast, *very little tolerance develops to the cardiovascular actions of*

nicotine: Veteran smokers continue to experience increased blood pressure and increased cardiac work whenever they smoke.

Dependence.

Chronic cigarette smoking results in dependence. By definition, this means that individuals who discontinue smoking will experience an abstinence syndrome. Prominent symptoms are craving, nervousness, restlessness, irritability, impatience, increased hostility, insomnia, impaired concentration, increased appetite, and weight gain. Symptoms begin about 24 hours after smoking has ceased, and can last for weeks to months. Women report more discomfort than men. Experience has shown that abrupt discontinuation may be preferable to gradual reduction. (All that gradual reduction seems to do is prolong suffering.)

Acute Poisoning

Nicotine is highly toxic. Doses as low as 40 mg can be fatal. Toxicity is underscored by the use of nicotine as an insecticide. Common causes of nicotine poisoning include ingestion of tobacco by children and exposure to nicotine-containing insecticides.

Symptoms.

The most prominent symptoms involve the cardiovascular, GI, and central nervous systems. Specific symptoms include nausea, salivation, vomiting, diarrhea, cold sweat, disturbed hearing and vision, confusion, and faintness; pulses may be rapid, weak, and irregular. Death results from respiratory paralysis, which is caused by direct effects of nicotine on the muscles of respiration, as well as by effects in the CNS.

Treatment.

Management centers on reducing nicotine absorption and supporting respiration; there is no specific antidote to nicotine poisoning. Absorption of ingested nicotine can be reduced by giving activated charcoal. If respiration is depressed, ventilatory assistance should be provided. Since nicotine undergoes rapid metabolic inactivation, recovery from the acute phase of poisoning can occur within hours.

Chronic Toxicity from Smoking

According to a 2004 report from the U.S. Surgeon General, the adverse consequences of smoking are more extensive than previously understood. It is now clear that chronic smoking can injure nearly every organ of the body. We already knew that smoking could cause cardiovascular disease, chronic lung disease, and cancers of the larynx, lung, esophagus, oral cavity, and bladder. New additions to the list include leukemia, cataracts, pneumonia, periodontal disease, type 2 diabetes, abdominal aortic aneurysm, and cancers of the cervix, kidney, pancreas, and stomach. Smoking during pregnancy increases the risk of low birth weight, preterm labor, stillbirth, miscarriage, spontaneous abortion, perinatal mortality, and sudden infant death. As shown in Table 39-3, the leading causes of smoking-related death are lung cancer, ischemic heart disease, and chronic airway obstruction.

Pharmacologic Aids to Smoking Cessation

Cigarettes are highly addictive, and hence giving them up is very hard. Nonetheless, abstinence *can* be achieved. Every year, about 41% of Americans who smoke make one or more attempts to quit. Of those who try to quit *without formal help,* only 3% to 5% achieve long-term success. In contrast, when a combination of counseling and drugs is employed, the 1-year abstinence rate approaches 30%. However, even with the aid of counseling and drugs, the first attempt usually fails. In fact, most people try quitting 5 to 7 times before they ultimately succeed. As time without a cigarette increases, the chances of relapse get progressively smaller: Of those who quit for a year, only 15% smoke again; and of those who quit for 5 years, only 3% smoke again.

Long-term smokers should be assured that quitting offers important health benefits. Regardless of how long one has smoked, quitting can reduce the risk of developing a tobacco-related disease, slow the progression of an established tobacco-related disease, and increase life expectancy. These benefits apply not only to people who quit while they are young and healthy, but also to people who quit after age 65 and to those with established tobacco-related disease. Data from the Nurses' Health Study indicate that former smokers eventually achieve the same disease-risk status as never smokers, even with respect to lung cancer. The risk of chronic obstructive pulmonary disease or death from

a heart attack declines to that of never smokers in 20 years, and the risk of lung cancer reaches that of never smokers in 30 years.

Nine drug products have been shown to aid smoking cessation (Table 39-4). Of these, seven are specifically approved by the FDA for this use, and are considered first-line treatments. The other two—nortriptyline and clonidine—are considered second-line treatments. Of the seven first-line products, five contain nicotine and two do not. The nicotine-based products—nicotine gum, nicotine lozenge, nicotine patch, nicotine inhaler, and nicotine nasal spray—are employed as nicotine replacement therapy (NRT). The nicotine-free products—sustained-release bupropion (bupropion SR) [Zyban] and varenicline [Chantix]—are taken to decrease nicotine craving and suppress symptoms of withdrawal. The most effective drug therapies for smoking cessation are varenicline alone and the nicotine patch combined with a short-acting nicotine product (ie, nasal spray or gum).

Product	Common Side Effects	Advantages	Disadvantages
FIRST-LINE AGENTS			
Nicotine-Based Products			
Nicotine patch [Nicotrol, Nicoderm CQ]	Transient itching, burning, and redness under the patch; insomnia	Nonprescription; provides a steady level of nicotine; easy to use; unobtrusive	User cannot adjust dose if craving occurs; nicotine released more slowly than in other products
Nicotine gum [Nicorette]	Mouth and throat irritation, aching jaw muscles, dyspepsia	Nonprescription; user controls dose	Unpleasant taste; requires proper chewing technique; cannot eat or drink while chewing the gum; can damage dental work and is difficult for denture wearers to use
Nicotine lozenge [Commit]	Hiccups, dyspepsia, mouth irritation, nausea	Nonprescription; user controls dose; easier to use than nicotine gum	Cannot eat or drink while the lozenge is in the mouth
Nicotine nasal spray [Nicotrol NS]	During 1st week: mouth and throat irritation, rhinitis, sneezing, coughing, teary eyes	User controls dose; fastest nicotine delivery and highest nicotine levels of all nicotine-based products	Prescription required; most irritating nicotine-based product; device visible when used
Nicotine inhaler [Nicotrol Inhaler]	Mouth and throat irritation, cough	User controls dose; mimics hand-to-mouth motion of smoking	Prescription required; slow onset and low nicotine levels; frequent puffing needed; device visible when used
Nicotine-Free Products			
Varenicline [Chantix]	Nausea, sleep disturbances, headaches, abnormal dreams	Easy to use (pill); no nicotine; most effective pharmacologic aid to smoking cessation	Prescription required; does not counter weight gain associated with smoking cessation; may cause neuropsychiatric disturbances, including suicidal thoughts and actions
Bupropion [Zyban]	Insomnia, dry mouth, agitation	Easy to use (pill); no nicotine; promotes weight loss, which may limit cessation-related weight gain; first-choice drug for smokers with depression	Prescription required; carries a small risk of seizures
SECOND-LINE AGENTS			
Nortriptyline* [Aventyl, Pamelor]	Dry mouth, sedation, dizziness	Easy to use (pill); no nicotine	Prescription required; side effects are common; caution required in patients with heart disease
Clonidine* [Catapres]	Dry mouth, sedation, dizziness	Easy to use (pill); no nicotine	Prescription required; side effects limit use

TABLE 39-4 Pharmacologic Aids for Smoking Cessation

* Not FDA-approved for use as a smoking cessation aid.

At this time, we cannot predict who will respond best to a particular product. Accordingly, selection among the first-line drugs should be based on patient preference, success with a particular product in the past, and side effects. The second-line drugs should be reserved for patients who cannot use the first-line drugs or who failed to quit while using them.

Interventions for smoking cessation can be found in *Treating Tobacco Use and Dependence: 2008 Update,* a clinical practice guideline issued by the U.S. Public Health Service. As stated in the guideline, tobacco dependence is a chronic condition that warrants repeated intervention until long-term abstinence is achieved. This is the same philosophy that guides treatment of dependence on other highly addictive substances, including cocaine and heroin. Tobacco dependence can be treated with two methods: counseling and drugs. Both methods are effective, but the combination of both is more effective than either one alone. Accordingly, the guidelines recommend that all patients who want to quit be offered counseling—either individual, group, or by phone (available in all states by dialing 1-800-QUITNOW)—along with at least one first-line drug: bupropion, varenicline, or a nicotine-based product. The overall intervention strategy is summarized in the "5 A's" model for treating tobacco use and dependence:

Ask (screen all patients for tobacco use).

Advise tobacco users to quit.

Assess willingness to make a quit attempt.

Assist with quitting (offer medication and provide or refer to counseling).

Arrange follow-up contacts, beginning within the first week after the quit date.

Nicotine Replacement Therapy (NRT)

NRT allows smokers to substitute a pharmaceutical source of nicotine for the nicotine in cigarettes—and then gradually withdraw the replacement nicotine. This is analogous to using methadone to wean addicts from heroin.

Five formulations of nicotine are available: chewing gum, lozenges, transdermal patches, a nasal spray, and an inhaler (see Table 39-4). With the gum,

lozenges, patches, and inhaler, blood levels of nicotine rise slowly and remain relatively steady. Because nicotine levels rise slowly, these delivery systems produce less pleasure than cigarettes, but nonetheless do relieve symptoms of withdrawal. With the nasal spray, blood levels of nicotine rise rapidly, much as they do with smoking. Hence the nasal spray provides some of the subjective pleasure that smoking does.

Long-term quitting rates are significantly greater with NRT than with placebo—although absolute success rates remain low. For example, the 1-year success with nicotine patches is about 25%, compared with 9% for placebo. Success rates are highest when replacement therapy is combined with counseling.

Nicotine Chewing Gum (Nicotine Polacrilex).

Nicotine chewing gum [Nicorette] is composed of a gum base plus nicotine polacrilex, an ion exchange resin to which nicotine is bound. The gum must be chewed to release the nicotine. Following release, nicotine is absorbed across the oral mucosa into the systemic circulation. Like other forms of NRT, nicotine gum doubles the cessation success rate.

The most common adverse effects are mouth and throat soreness, jaw muscle ache, eructation (belching), and hiccups. Using optimal chewing technique minimizes these problems. Nicotine gum and all other nicotine-containing products should be avoided during pregnancy and lactation.

Patients should be advised to chew the gum slowly and intermittently for about 30 minutes. Rapid chewing can release too much nicotine at one time, resulting in effects similar to those of excessive smoking (eg, nausea, throat irritation, hiccups). Since foods and beverages can reduce nicotine absorption, patients should not eat or drink while chewing or for 15 minutes before chewing.

Nicotine gum is available in two strengths: 2 mg/piece and 4 mg/piece. Dosing is individualized and based on the degree of nicotine dependence. For initial therapy, patients with low to moderate nicotine dependence should use the 2-mg strength; highly dependent patients (those who smoke more than 25 cigarettes a day) should use the 4-mg strength. The average adult dosage is 9 to 12 pieces/day. The maximum daily dosage is 30 pieces of the 2-mg strength

or 20 pieces of the 4-mg strength. Experience indicates that dosing on a fixed schedule (one piece every 2 to 3 hours) is more effective than PRN dosing for achieving abstinence.

After 3 months without cigarettes, patients should discontinue nicotine use. Withdrawal should be done gradually. Use of nicotine gum beyond 6 months is not recommended.

Nicotine Lozenges (Nicotine Polacrilex).

The pharmacology of nicotine lozenges [Commit] is very similar to that of nicotine gum. Both products contain nicotine bound to polacrilex. Sucking on the lozenge releases nicotine, which is then absorbed across the oral mucosa into the systemic circulation. As with nicotine gum and other forms of NRT, nicotine lozenges double the cessation success rate.

The most common adverse effects are mouth irritation, dyspepsia, nausea, and hiccups—all of which can be increased by taking two lozenges at once or by taking several lozenges in immediate succession. Like all other nicotine-containing products, the lozenges should be avoided during pregnancy and lactation.

Administration consists of placing the lozenge in the mouth and allowing it to dissolve, which takes 20 to 30 minutes. Users should not eat or drink for 15 minutes before dosing and while the lozenge is in the mouth. Also, they should not chew or swallow the lozenge, and they should minimize swallowing saliva.

Like nicotine gum, nicotine lozenges are available in two strengths: 2 mg and 4 mg. However, in contrast to nicotine gum, which is dosed on the basis of total cigarettes smoked per day, dosing with the lozenges is based on *when* the first cigarette of the day is smoked: The 2-mg strength is indicated for people who start smoking 30 minutes or more after waking; the 4-mg strength is indicated for those who smoke sooner. Users should consume no more than 5 lozenges every 6 hours, and no more than 20 lozenges per day. The recommended dosing schedule is 1 lozenge every 1 to 2 hours for the first 6 weeks; 1 every 2 to 4 hours for the next 3 weeks; and 1 every 4 to 8 hours for the next 3 weeks, after which dosing should stop.

Nicotine Transdermal Systems (Patches).

Nicotine transdermal systems are nicotine-containing adhesive patches that, after application to the skin, slowly release their nicotine content. The nicotine is absorbed into the skin and then into the blood, producing steady blood levels. Use of the patch about doubles the cessation success rate.

Two systems are available: Nicoderm CQ and Nicotrol. Both can be purchased without a prescription. As indicated in Table 39-4, the patches come in different sizes. The larger patches release more nicotine.

Nicotine patches are applied once a day to clean, dry, non-hairy skin of the upper body or upper arm. The site should be changed daily and not reused for at least 1 week. Nicoderm CQ patches are left in place for 24 hours and then immediately replaced with a fresh one. In contrast, Nicotrol patches are applied in the morning and removed 16 hours later at bedtime. This pattern is intended to simulate nicotine dosing produced by smoking.

Most patients begin treatment with a large patch and then progress to smaller patches over several weeks (Table 39-5). Certain patients (those with cardiovascular disease, those who weigh less than 100 pounds, or those who smoke less than one-half pack of cigarettes a day) should begin with a smaller patch.

Trade Name	Surface Area (cm^2)	Hours/Day in Place	Dose Absorbed	Duration of Use	
				Per Patch Size	Total
Nicoderm CQ Step 1	30	24	21 mg over 24 hr	First 4–6 wk	8–10 wk
Nicoderm CQ Step 2	20	24	14 mg over 24 hr	Next 2 wk	
Nicoderm CQ Step 3	10	24	7 mg over 24 hr	Next 2 wk	
Nicotrol Step 1	30	16	15 mg over 16 hr	First 6 wk	10 wk
Nicotrol Step 2	20	16	10 mg over 16 hr	Next 2 wk	
Nicotrol Step 3	10	16	5 mg over 16 hr	Next 2 wk	

TABLE 39-5 Nicotine Transdermal Systems (Patches)

Adverse effects are generally mild. Short-lived erythema, itching, and burning occur under the patch in 35% to 50% of users. In 14% to 17% of users, persistent erythema occurs, lasting up to 24 hours after patch removal. Patients who experience severe, persistent local reactions (eg, severe erythema, itching, edema) should discontinue the patch and contact a physician or nurse practitioner. Nicotine patches and all other nicotine-containing products should be avoided during pregnancy and lactation.

Nicotine Inhaler.

The nicotine inhaler [Nicotrol Inhaler] differs from other NRT products in that it looks much like a cigarette. Puffing on it delivers the nicotine. Because of this delivery method, using the inhaler can substitute for the hand-to-mouth behavior of smoking. In addition to nicotine, the inhaler contains menthol, whose purpose is to create a sensation in the back of the throat reminiscent of

that caused by smoke. Like other forms of NRT, the inhaler doubles cessation success rates.

The nicotine inhaler consists of a mouthpiece and a sealed, tubular cartridge. Inside the cartridge is a porous plug containing 10 mg of nicotine. Inserting the cartridge into the mouthpiece breaks the seal. Puffing on the mouthpiece draws air over the plug, and thereby draws nicotine vapor into the mouth. Most of the nicotine is absorbed through the *oral mucosa*—not in the lungs. As a result, blood levels rise slowly, and peak 10 to 15 minutes after puffing stops. Blood levels are less than half those achieved with cigarettes. Each cartridge can deliver 300 to 400 puffs. Benefits are greatest with frequent puffing over 20 minutes, after which the cartridge is discarded. Patients generally use 6 to 16 cartridges a day for 3 months, and then taper off over 2 to 3 months.

Adverse effects are mild. The most frequent are dyspepsia, coughing, throat irritation, oral burning, and rhinitis. The inhaler should not be used by patients with asthma. Because the cartridges contain dangerous amounts of nicotine, they should be kept away from children and pets.

Nicotine Nasal Spray.

Nicotine nasal spray [Nicotrol NS] differs from other NRT formulations in that blood levels of nicotine rise *rapidly* after each administration, thereby closely simulating smoking. Because nicotine levels rise rapidly, the spray provides some of the subjective pleasure associated with cigarettes. As with other forms of NRT, the spray doubles smoking cessation rates.

The spray device delivers 0.5 mg of nicotine per activation. Two sprays (one in each nostril) constitute one dose and are equivalent to the amount of nicotine absorbed from one cigarette. Treatment should be started with 1 or 2 doses per hour—and never more than 5 doses per hour, or 40 doses a day. After 4 to 6 weeks, dosing should be gradually reduced and then stopped.

Quitting success with the spray has been good news and bad news. The good news, as reported in one study, is that 27% of users avoided smoking for 1 year—about twice the abstinence rate achieved with placebo. The bad news is that many patients continued to use the spray, being unwilling or unable to give it up. Nonetheless, since the spray delivers nicotine without the additional hazards in cigarettes, using the spray is clearly preferable to smoking.

Adverse effects are mild and temporary. At first, most users experience rhinitis, sneezing, coughing, watering eyes, and nasal and throat irritation. Fortunately, these effects abate in a few days. Nicotine nasal spray should be avoided by patients with sinus problems, allergies, or asthma.

Bupropion SR

Bupropion SR [Zyban], an atypical antidepressant, was the first non-nicotine drug approved as an aid to quit smoking. The drug is structurally similar to amphetamine and, like amphetamine, causes CNS stimulation and suppresses appetite. In people trying to quit cigarettes, bupropion reduces the urge to smoke and reduces some symptoms of nicotine withdrawal (eg, irritability, anxiety). The drug is effective in the presence and absence of depression. Although the mechanism of action is uncertain, benefits may derive from blocking uptake of norepinephrine and dopamine. For use in depression, bupropion is sold under the trade name Wellbutrin.

Like the NRT products, bupropion SR doubles the cessation success rate. In one trial, patients were given bupropion SR (100, 150, or 300 mg/day) or placebo. At 7 weeks, abstinence rates were 19% with placebo, and 29%, 39%, and 44% with increasing dosages of bupropion SR. At 12 weeks, abstinence rates were lower: 12% with placebo and 20%, 23%, and 23% with increasing dosages of bupropion SR. Combining a nicotine patch with bupropion SR is somewhat more effective than either treatment alone.

Adverse effects are generally mild. The most common are dry mouth and insomnia. High doses (above 450 mg/day) are associated with a 0.4% risk of seizures. However, at the doses employed for smoking cessation (300 mg/day), seizures have not been reported. Nonetheless, bupropion SR should be avoided in patients with seizure risk factors, such as head trauma, history of seizures, anorexia nervosa, cocaine use, and alcohol withdrawal. Because it suppresses appetite, bupropion SR can cause weight loss. However, since weight gain is common among ex-smokers, appetite reduction may be an added benefit rather than a drawback. Bupropion SR should not be combined with a monoamine oxidase inhibitor. Nor should it be given to patients taking Wellbutrin, which is just another name for bupropion itself.

The usual regimen is 150 mg in the morning for 3 days, followed by 150 mg twice a day for 7 to 12 weeks. To minimize interference with sleep, the second dose should be taken as early in the day as possible—but at least 8 hours after the morning dose. Because onset of effects is delayed, dosing should begin 1 to 2 weeks before attempting to give up cigarettes.

The basic pharmacology of bupropion is discussed in Chapter 32.

Varenicline

Varenicline [Chantix], a partial agonist at nicotinic receptors, is our most effective aid to smoking cessation. In clinical trials, more patients achieved abstinence with varenicline than with bupropion SR or the nicotine patch. Estimated abstinence rates after 6 months were 33.2% with varenicline, 24.2% with bupropion SR, and 23.4% with the nicotine patch. The most common side effect is nausea. Unlike bupropion SR and NRT, varenicline does *not* reduce weight gain that occurs with smoking cessation. Since being approved in 2006, varenicline has been used by more than 5 million people.

Mechanism of Action.

Varenicline acts as a *partial agonist* at a subset of nicotinic receptors—known as alpha***4***beta***2*** nicotinic receptors—whose activation promotes release of dopamine, the compound that mediates the pleasurable effects of nicotine. Compared with nicotine, varenicline binds alpha***4***beta***2*** receptors with greater affinity. Hence, when varenicline is present, access of nicotine to these receptors is blocked. Because varenicline is a partial agonist, receptor binding results in mild activation, which promotes some dopamine release, and thereby helps reduce both nicotine craving and the intensity of withdrawal symptoms. At the same time, the presence of varenicline prevents intense receptor activation by nicotine itself, and thereby blocks the reward that nicotine can provide.

Pharmacokinetics.

Varenicline is readily absorbed from the GI tract, both in the presence and absence of food. Plasma levels peak about 4 hours after dosing. Binding to plasma proteins is low (20%). Metabolism is minimal, and hence most of each dose (92%) is excreted unchanged in the urine. The plasma half-life is 17 to

24 hours. Moderate to severe renal impairment delays excretion and increases varenicline blood levels.

Adverse Effects.

In clinical trials, dose-dependent *nausea* was the most common adverse effect, occurring in 30% to 40% of users. Nausea is mild to moderate initially, and becomes less severe over time. Other common reactions include sleep disturbances (18%), headaches (15%), abnormal dreams (13%), constipation (8%), dry mouth (6%), flatulence (6%), vomiting (5%), and altered sense of taste (5% to 8%). Mild physical dependence develops, but there have been no reports of abuse or addictive behavior.

Postmarketing reports indicate that varenicline can cause serious *neuropsychiatric effects,* including mood changes, erratic behavior, and suicidality. As of February 2008, there were 391 reports of suicidal thoughts and 39 successful suicides—out of more than 5 million people using the drug. At this time, we don't know if varenicline was the cause of suicidality, or if these patients had an underlying psychiatric illness. All patients should be advised to contact their prescriber if they experience a significant change in behavior or mental status. Varenicline should be used with caution in patients with a history of psychiatric disease.

Most recently, varenicline has been associated with rare reports of heart attacks, dysrhythmias, seizures, diabetes, dizziness, disturbed vision, and moderate and severe skin reactions. However, a causal relationship has not been established.

Drug Interactions.

Varenicline does not affect the major components of the cytochrome P450 system. Studies with bupropion, transdermal nicotine, digoxin, warfarin, cimetidine, and metformin have shown no significant interactions. To date, no clinically significant interactions with other drugs have been reported.

Preparations, Dosage, and Administration.

Varenicline is formulated in 0.5- and 1-mg tablets. To reduce nausea, each dose should be taken after eating and with a full glass of water. Dosage should

be titrated as follows: days 1 to 3, 0.5 mg once daily; days 4 to 7, 0.5 mg twice daily; day 8 to the end of treatment, 1 mg twice daily. Dosing should begin 1 week before smoking is scheduled to stop, and should continue for 12 weeks. If abstinence has been achieved, an additional 12 weeks of treatment is recommended. Patients who fail to stop smoking after the initial 12 weeks, or who relapse after a full course of treatment, should be encouraged to try again when conditions are deemed favorable. Patients with severe renal impairment should begin therapy at 0.5 mg once daily and increase to 0.5 mg twice daily, if tolerated. Patients with end-stage renal disease undergoing dialysis should take a maximum of 0.5 mg once daily. Dosage adjustment is unnecessary in patients with mild to moderate renal impairment.

Nortriptyline and Clonidine

Nortriptyline [Aventyl, Pamelor] and clonidine [Catapres] are second-line drugs for helping people quit smoking. Neither agent is FDA approved for this use. Nortriptyline is a tricyclic antidepressant (see Chapter 32). Clonidine is a centrally acting alpha***2*** agonist used primarily for hypertension (see Chapter 19). Both drugs cause dry mouth, sedation, and dizziness—but the intensity is greater with clonidine. For nortriptyline, dosing is initiated at 25 mg/day starting 10 to 28 days before the quitting date, and then gradually increased to 75 to 100 mg/day. For clonidine, the dosage is 0.1 to 0.3 mg twice a day.

Drugs That Are Not Recommended

According to *Treating Tobacco Use and Dependence: 2008 Update,* there is insufficient proof to recommend the following drugs as aids to smoking cessation: naltrexone, mecamylamine, silver acetate, beta blockers, benzodiazepines, and antidepressants other than bupropion SR and nortriptyline, including the selective serotonin reuptake inhibitors.

ANABOLIC STEROIDS

Many athletes take anabolic steroids (androgens) to enhance athletic performance. The principal benefit is increased muscle mass and strength. Because of the massive doses that are employed, the risk of adverse effects is substantial. With long-term steroid use, an addiction syndrome develops. Because of their abuse potential, most androgens are now classified as Schedule III drugs (see

Table 37-3). The basic pharmacology of androgens and their abuse by athletes are discussed in Chapter 64.

KEY POINTS

- Because heroin is very lipid soluble, initial effects are more intense and occur faster than with other opioids. As a result, heroin is the opioid of choice among abusers.
- Among healthcare providers who abuse opioids, meperidine [Demerol] is a drug of choice. Why? Because meperidine is orally active, causes minimal pupillary constriction, and causes less constipation and urinary retention than other opioids.
- With opioids, tolerance to respiratory depression develops in parallel with tolerance to euphoria. As a result, respiratory depression does not increase as higher doses are taken to produce desired subjective effects.
- Persons tolerant to one opioid are cross-tolerant to all other opioids.
- Although the opioid withdrawal syndrome can be extremely unpleasant, it is rarely dangerous.
- Opioid overdose produces a classic triad of symptoms: respiratory depression, coma, and pinpoint pupils. Death can result.
- Naloxone, an opioid antagonist, is the treatment of choice for opioid overdose.

•Naloxone dosage must be titrated carefully, because too much naloxone will transport the patient from a state of intoxication to one of withdrawal. Also, since the half-life of naloxone is shorter than the half-lives of the opioids, naloxone must be administered repeatedly until the crisis is over.

- Because of cross-dependence, methadone can ease withdrawal symptoms in opioid-dependent individuals. To ease withdrawal, methadone is substituted for the abused opioid and then gradually tapered.
- In opioid abusers who are not ready for withdrawal, methadone can be used for maintenance therapy or suppressive therapy. In maintenance ther-

apy, the methadone dosage is equivalent to the dosage of the abused opioid, thereby preventing withdrawal. In suppressive therapy, the abuser is rendered opioid tolerant with very high doses of methadone; as a result, use of street opioids can no longer produce subjective effects.

- Buprenorphine is an alternative to methadone for detoxification and maintenance of opioid addicts.
- In contrast to methadone, which is available only through approved treatment facilities, buprenorphine can be prescribed by any physician or nurse practitioner who has (1) received at least 8 hours of approved training and (2) registered with the Substance Abuse and Mental Health Services Administration.
- With barbiturates, tolerance develops to subjective effects but not to respiratory depression. As a result, as increasingly large doses are taken to produce subjective effects, the risk of serious respiratory depression increases. (Note that this differs from the situation with opioids.)
- Individuals who are tolerant to barbiturates show cross-tolerance with other CNS depressants (eg, alcohol, benzodiazepines, general anesthetics) but not with opioids.
- Individuals who are physically dependent on barbiturates show cross-dependence with other CNS depressants, but not with opioids.
- When physical dependence on barbiturates (and other CNS depressants) is great, the associated abstinence syndrome can be severe—sometimes fatal. (Note that this differs from the situation with opioids.)
- Overdose with barbiturates produces the same triad of symptoms seen with opioids: respiratory depression, coma, and pinpoint pupils. Death can result.
- In contrast to opioid overdose, barbiturate overdose has no antidote, and hence treatment is only supportive.
- In contrast to overdose with opioids or barbiturates, overdose with benzodiazepines alone is rarely fatal.
- If necessary, benzodiazepine overdose can be treated with flumazenil, a benzodiazepine antagonist.

- The psychologic effects of cocaine result from activation of dopamine receptors secondary to cocaine-induced blockade of dopamine reuptake.
- Severe overdose with cocaine can produce hyperpyrexia, convulsions, ventricular dysrhythmias, and hemorrhagic stroke; death has occurred. Psychologic effects of overdose include severe anxiety, paranoid ideation, and hallucinations.
- There is no specific antidote to cocaine overdose. Intravenous diazepam can suppress anxiety, seizures, hypertension, and dysrhythmias. Intravenous nitroprusside or phentolamine can treat severe hypertension.
- In animals, regular use of cocaine produces sensitization—not tolerance. Whether this is true for humans is unclear.
- Whether cocaine causes significant physical dependence is in dispute.
- Psychosocial therapy is considered the cornerstone of cocaine addiction treatment. Adding disulfiram may also help.
- In addition to CNS stimulation, amphetamines cause vasoconstriction and stimulate the heart. Cardiovascular stimulation may result in hypertension, angina, and dysrhythmias.
- Regular use of amphetamines can produce a state that closely resembles paranoid schizophrenia.
- Although physical dependence on amphetamines is only moderate, psychologic dependence can be intense. Withdrawal can produce dysphoria and a strong sense of craving.
- The major psychoactive substance in marijuana is delta-9-tetrahydrocannabinol (THC).
- HC acts through specific receptors in the brain.
- Marijuana has three principal subjective effects: euphoria, sedation, and hallucinations.
- Physiologic effects of marijuana, as well as tolerance and physical dependence, are minimal.
- Marijuana has no approved medical uses, although its major active component—THC—does.

- Psychedelic drugs produce alterations in thought, perception, and feeling that otherwise occur only in dreams.
- Psychedelic drugs are also known as hallucinogens or psychotomimetics—names that reflect their ability to produce hallucinations and mental states that resemble psychosis.
- Lysergic acid diethylamide (LSD) can be considered the prototype of the psychedelic drugs.
- LSD produces its effects by activating serotonin*2* receptors in the brain.
- Although tolerance develops to LSD, physiologic effects and physical dependence are minimal.
- Acute panic reactions to LSD can be managed by "talking down" and by treatment with benzodiazepines. Neuroleptic drugs (eg, haloperidol) may intensify the reaction.
- LSD users may experience episodic visual disturbances after discontinuing the drug. In many cases, the underlying cause is a permanent change in the visual system.
- Some LSD users experience prolonged psychotic reactions that closely resemble schizophrenia.
- Phencyclidine (PCP) is a dissociative anesthetic that produces alcohol-like effects at low doses and hallucinations and psychotic reactions at high doses.
- Extreme overdose with phencyclidine can produce hypertension, coma, and seizures, as well as muscular rigidity associated with severe hyperthermia and rhabdomyolysis.
- There is no specific antidote to phencyclidine overdose. "Talking down" is not effective, and antipsychotic drugs are of limited help.
- Ecstasy (MDMA) produces psychedelic effects at low doses and amphetamine-like stimulation at higher doses.
- Ecstasy can cause irreversible destruction of serotonergic neurons.
- Cigarette smoking kills nearly 400,000 American adults each year, making smoking the largest preventable cause of premature death.

- The principal cause of death among smokers is lung cancer, followed closely by heart disease.
- Nicotine in cigarette smoke is absorbed from the lungs, whereas nicotine in cigar smoke and smokeless tobacco is absorbed from the mouth.
- By activating nicotinic receptors in sympathetic ganglia and the adrenal medulla, nicotine promotes vasoconstriction, acceleration of heart rate, and increased force of ventricular contraction, thereby elevating blood pressure and increasing cardiac work. These effects underlie cardiovascular deaths.
- Through actions in the CNS, nicotine increases alertness, facilitates memory, improves cognitive function, reduces aggression, and suppresses appetite. In addition, by promoting release of dopamine, nicotine activates the same pleasure circuit involved in addiction to cocaine, amphetamines, and opioids.
- Although tolerance develops to some effects of nicotine, very little tolerance develops to cardiovascular effects: Veteran smokers continue to experience an increase in blood pressure and cardiac work whenever they light up.
- Nicotine causes physical dependence. Withdrawal is characterized by craving, nervousness, restlessness, irritability, impatience, increased hostility, insomnia, impaired concentration, increased appetite, and weight gain.
- Nicotine for replacement therapy is available in five delivery systems: chewing gum, lozenges, transdermal patches, nasal spray, and an inhaler.
- Bupropion SR [Zyban], which blocks reuptake of norepinephrine and dopamine, helps smokers quit by reducing nicotine craving and withdrawal symptoms.
- Varenicline [Chantix] acts as a partial agonist at specific nicotine receptors, and thereby reduces nicotine craving and withdrawal symptoms. In addition, the drug blocks access of nicotine itself to nicotine receptors, and thereby prevents nicotine from producing pleasurable effects.
- The most effective drug/therapies for smoking cessation are varenicline alone and the nicotine patch combined with PRN nicotine nasal spray or nicotine gum.

- With the aid of counseling and pharmacotherapy, about 30% of smokers who attempt to quit can expect to achieve long-term abstinence.

VI. DRUGS THAT AFFECT FLUID AND ELECTROLYTE BALANCE

40 Diuretics

Diuretics are drugs that increase the output of urine. These agents have two major applications: (1) treatment of hypertension and (2) mobilization of edematous fluid (associated with heart failure, cirrhosis, and kidney disease). In addition, because of their ability to maintain urine flow, diuretics are used to prevent renal failure.

REVIEW OF RENAL ANATOMY AND PHYSIOLOGY

Understanding the diuretic drugs requires a basic knowledge of the anatomy and physiology of the kidney. Accordingly, we review these topics before discussing the diuretics themselves.

Anatomy

The basic functional unit of the kidney is the *nephron*. As indicated in Figure 40-1, the nephron has four functionally distinct regions: (1) the *glomerulus,* (2) the *proximal convoluted tubule,* (3) the *loop of Henle,* and (4a, 4b) the *distal convoluted tubule*. All nephrons are oriented within the kidney such that the upper portion of Henle's loop is located within the renal cortex and the lower end of the loop descends toward the renal *medulla*. Without this orientation, the kidney could not produce concentrated urine.

In addition to the nephrons, the *collecting ducts* (the tubules into which the nephrons pour their contents) play a critical role in kidney function. As suggested by Figure 40-1, the final segment of the distal convoluted tubule (4b) plus the collecting duct into which it empties (5) can be considered a single functional unit: the *distal nephron*.

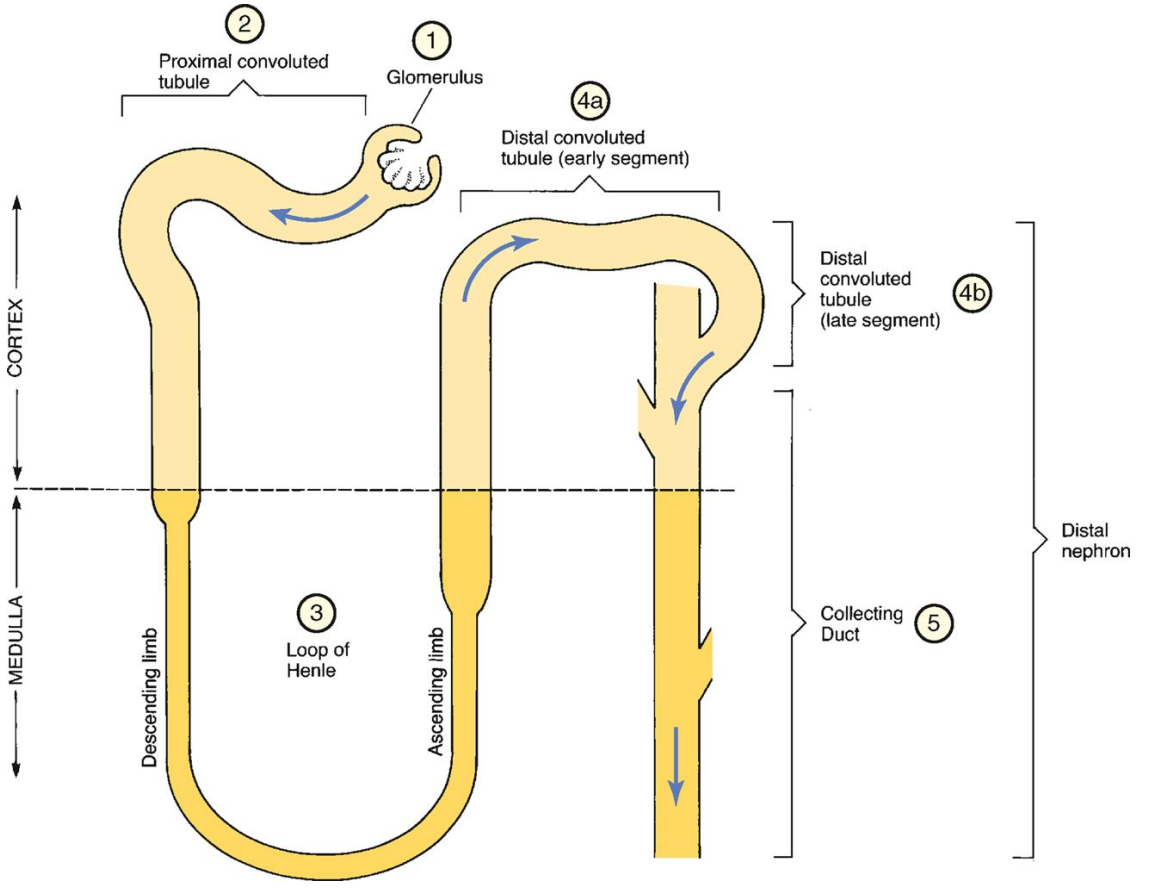


Figure 40-1 Schematic representation of a nephron and collecting duct.

Physiology

Overview of Kidney Functions

The kidney serves three basic functions: (1) cleansing of extracellular fluid (ECF) and maintenance of ECF volume and composition; (2) maintenance of acid-base balance; and (3) excretion of metabolic wastes and foreign substances (eg, drugs, toxins). Of the three, maintenance of ECF volume and composition is the one that diuretics affect most.

The Three Basic Renal Processes

Effects of the kidney on ECF are the net result of three basic processes: (1) *filtration,* (2) *reabsorption,* and (3) *active secretion*. In order to cleanse the entire ECF, huge volumes of plasma must be filtered. Furthermore, in order to maintain homeostasis, practically everything that has been filtered must be reabsorbed—leaving behind only a small volume of urine for excretion.

Filtration.

Filtration occurs at the *glomerulus* and is the first step in urine formation. Virtually all small molecules (electrolytes, amino acids, glucose, drugs, metabolic wastes) present in plasma undergo filtration. In contrast, cells and large molecules (lipids, proteins) remain behind in the blood. The most prevalent constituents of the filtrate are sodium ions and chloride ions. Bicarbonate ions and potassium ions are also present, but in smaller amounts.

The filtration capacity of the kidney is very large. Each minute the kidney produces 125 mL of filtrate, which adds up to 180 L/day. Since the total volume of ECF is only 12.5 L, the kidney can process the equivalent of all the ECF in the body every 100 minutes. Hence, the ECF undergoes complete cleansing many times each day.

Be aware that filtration is a *nonselective process,* and therefore cannot regulate the composition of urine. Reabsorption and secretion—processes that display a significant degree of selectivity—are the primary determinants of what the urine ultimately contains. Of the two, reabsorption is by far the more important.

Reabsorption.

Greater than 99% of the water, electrolytes, and nutrients that are filtered at the glomerulus undergo reabsorption. This conserves valuable constituents of the filtrate while allowing wastes to undergo excretion. Reabsorption of solutes (eg, electrolytes, amino acids, glucose) takes place by way of *active transport*. Water then follows passively along the osmotic gradient created by solute reuptake. Specific sites along the nephron at which reabsorption takes place are discussed below. Diuretics work primarily by interfering with reabsorption.

Active Tubular Secretion.

The kidney has two major kinds of "pumps" for active secretion. These pumps transport compounds from the plasma into the lumen of the nephron. One pump transports *organic acids* and the other transports *organic bases*. Together, these pumps can promote the excretion of a wide assortment of molecules, including metabolic wastes, drugs, and toxins. The pumps for active secretion are located in the *proximal convoluted tubule*.

Processes of Reabsorption That Occur at Specific Sites Along the Nephron

Because most diuretics act by disrupting solute reabsorption, to understand the diuretics, we must first understand the major processes by which nephrons reabsorb filtered solutes. Because sodium and chloride ions are the predominant solutes in the filtrate, reabsorption of these ions is of greatest interest. As we discuss reabsorption, numeric values are given for the percentage of solute reabsorbed at specific sites along the nephron. Bear in mind that these values are only approximate. Figure 40-2 provides a summary of the sites of sodium and chloride reabsorption, indicating the amount of reabsorption that occurs at each site.

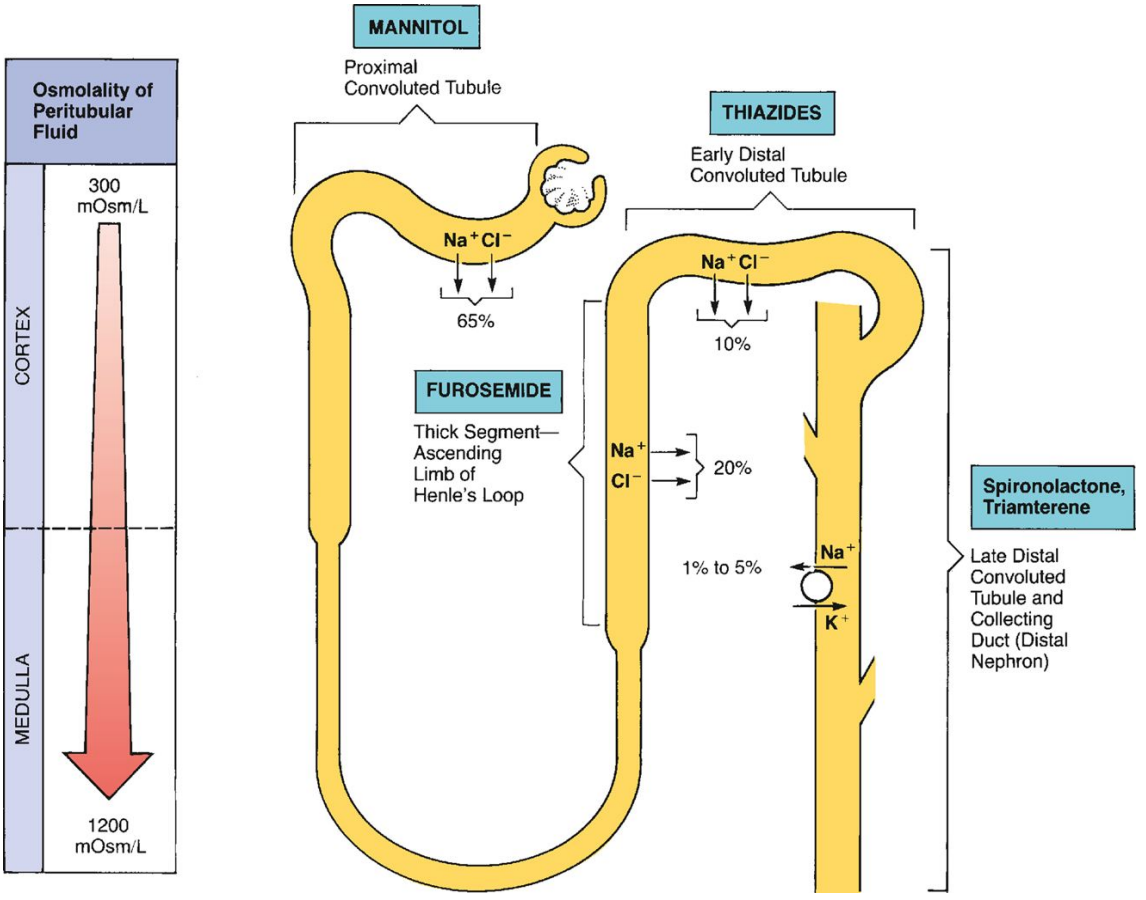


Figure 40-2 Schematic diagram of a nephron showing sites of sodium absorption and diuretic action. The percentages indicate how much of the filtered sodium and chloride is reabsorbed at each site.

Proximal Convoluted Tubule.

The proximal convoluted tubule (PCT) has a high reabsorptive capacity. As indicated in Figure 40-2, *a large fraction (about 65%) of filtered sodium and chloride is reabsorbed at the PCT*. In addition, essentially all of the bicarbonate and potassium in the filtrate is reabsorbed here. As sodium, chloride, and other solutes are actively reabsorbed, water follows passively. Since solutes and water are reabsorbed to an equal extent, the tubular urine remains isotonic (300 mOsm/L). By the time the filtrate leaves the PCT, sodium and chloride are the only solutes that remain in significant amounts.

Loop of Henle.

The *descending limb* of the loop of Henle is freely permeable to water. Hence, as tubular urine moves down the loop and passes through the hypertonic environment of the renal medulla, water is drawn from the loop into the interstitial space. This process decreases the volume of the tubular urine and causes the urine to become concentrated (tonicity increases to about 1200 mOsm/L).

Within the thick segment of the *ascending limb* of the loop of Henle, about *20% of filtered sodium and chloride is reabsorbed* (see Fig. 40-2). Since, unlike the descending limb, the ascending limb is not permeable to water, water must remain in the loop as reabsorption of sodium and chloride takes place. This process causes the tonicity of the tubular urine to return to that of the original filtrate (300 mOsm/L).

Distal Convoluted Tubule (Early Segment).

About 10% of filtered sodium and chloride is reabsorbed in the early segment of the distal convoluted tubule. Water follows passively.

Late Distal Convoluted Tubule and Collecting Duct (Distal Nephron).

The distal nephron is the site of two important processes. The first involves exchange of sodium for potassium and is under the influence of aldosterone. The second determines the final concentration of the urine and is regulated by antidiuretic hormone (ADH).

Sodium-Potassium Exchange.

Aldosterone, the principal mineralocorticoid of the adrenal cortex, stimulates reabsorption of sodium from the distal nephron. At the same time, aldosterone causes potassium to be secreted. Although not directly coupled, these two processes—sodium retention and potassium excretion—can be viewed as an exchange mechanism. This exchange is shown schematically in Figure 40-2. Aldosterone promotes sodium-potassium exchange by stimulating cells of the distal nephron to synthesize more of the pumps responsible for sodium and potassium transport.

Regulation of Urine Concentration by ADH.

Although of great physiologic significance, ADH has little to do with the actions of diuretics. Hence, discussion of this physiologically important topic is presented in small type.

ADH acts on the collecting duct to regulate conservation of water. To understand the effects of ADH, we need to know four facts:

- In the absence of ADH, the collecting duct is impermeable to water.
- The collecting duct is oriented such that it begins in the cortex of the kidney and then passes down through the hypertonic renal medulla (see Fig. 40-2).
- Tubular urine entering the collecting duct is isotonic (300 mOsm/L).
- ADH acts on the collecting duct to increase its permeability to water.

By rendering the collecting duct permeable to water, ADH allows water to be drawn from the duct as it passes through the hypertonic renal medulla. Because of this water reabsorption, urine that entered the duct in a relatively dilute state becomes concentrated and reduced in volume.

In the absence of ADH, water cannot be reabsorbed in the collecting duct. As a result, large volumes of dilute urine are produced. The clinical syndrome resulting from ADH deficiency is known as *diabetes insipidus*.

INTRODUCTION TO DIURETICS

How Diuretics Work

Most diuretics share the same basic mechanism of action: blockade of sodium and chloride reabsorption. By blocking the reabsorption of these prominent solutes, diuretics create osmotic pressure within the nephron that prevents the passive reabsorption of water. Hence, diuretics cause water and solutes to be retained within the nephron, and thereby promote the excretion of both.

The increase in urine flow that a diuretic produces is directly related to the amount of sodium and chloride reabsorption that it blocks. Accordingly, drugs that block solute reabsorption to the greatest degree produce the most profound diuresis. Since the amount of solute in the nephron becomes progressively smaller as filtrate flows from the proximal tubule to the collecting duct, *drugs that act early in the nephron have the opportunity to block the greatest amount of solute reab-*

sorption. Accordingly, these agents produce the greatest diuresis. Conversely, since most of the filtered solute has already been reabsorbed by the time the filtrate reaches the distal parts of the nephron, diuretics that act at distal sites have very little reabsorption available to block. Consequently, such agents produce relatively scant diuresis.

It is instructive to look at the quantitative relationship between blockade of solute reabsorption and production of diuresis. Recall that the kidney produces 180 L of filtrate a day, practically all of which is normally reabsorbed. With filtrate production at this volume, a diuretic will increase daily urine output by 1.8 L for each 1% of solute reabsorption that is blocked. A 3% blockade of solute reabsorption will produce 5.4 L of urine a day—a rate of fluid loss that would reduce body weight by 12 pounds in 24 hours. Clearly, with only a small blockade of reabsorption, diuretics can produce a profound effect on the fluid and electrolyte composition of the body.

Adverse Impact on Extracellular Fluid

In order to promote excretion of water, diuretics must interfere with the normal operation of the kidney. By doing so, diuretics can cause *hypovolemia* (from excessive fluid loss), *acid-base imbalance,* and *disturbance of electrolyte levels*. These adverse effects can be minimized by using short-acting diuretics and by timing drug administration such that the kidney is allowed to operate in a drug-free manner between periods of diuresis. Both measures will give the kidney periodic opportunities to readjust the ECF so as to compensate for any undesired alterations produced under the influence of diuretics.

Classification of Diuretics

There are four major categories of diuretic drugs: (1) *high-ceiling (loop) diuretics* (eg, furosemide); (2) *thiazide diuretics* (eg, hydrochlorothiazide); (3) *osmotic diuretics* (eg, mannitol); and (4) *potassium-sparing diuretics*. The last group, the potassium-sparing agents, can be subdivided into *aldosterone antagonists* (eg, spironolactone) and *nonaldosterone antagonists* (eg, triamterene).

In addition to the four major categories of diuretics, there is a fifth group: the *carbonic anhydrase inhibitors*. Although the carbonic anhydrase inhibitors are classified as diuretics, these drugs are employed primarily to lower intraocu-

lar pressure (IOP) and not to increase urine production. Consequently, the carbonic anhydrase inhibitors are discussed in Chapter 103 (Drugs for the Eye) rather than here.

HIGH-CEILING (LOOP) DIURETICS

The high-ceiling agents are the most effective diuretics available. These drugs produce more loss of fluid and electrolytes than any other diuretics. Because their site of action is in the loop of Henle, the high-ceiling agents are also known as *loop diuretics*.

Furosemide

Furosemide [Lasix] is the most frequently prescribed loop diuretic and will serve as our prototype for the group.

Mechanism of Action

Furosemide acts in the thick segment of the ascending limb of Henle's loop to block reabsorption of sodium and chloride (see Fig. 40-2). By blocking solute reabsorption, furosemide prevents passive reabsorption of water. Since a substantial amount (20%) of filtered NaCl is normally reabsorbed in the loop of Henle, interference with reabsorption here can produce profound diuresis.

Pharmacokinetics

Furosemide can be administered orally, IV, and IM. With oral administration, diuresis begins in 60 minutes and persists for 8 hours. Oral therapy is used when rapid onset is not required. Effects of intravenous furosemide begin within 5 minutes and last for 2 hours. Intravenous therapy is used in critical situations (eg, pulmonary edema) that demand immediate mobilization of fluid. Furosemide undergoes hepatic metabolism followed by renal excretion.

Therapeutic Uses

Furosemide is a powerful drug that is generally reserved for situations that require rapid or massive mobilization of fluid. This drug should be avoided when less efficacious diuretics (thiazides) will suffice. Conditions that justify use of furosemide include (1) pulmonary edema associated with congestive heart failure (CHF); (2) edema of hepatic, cardiac, or renal origin that has been unre-

sponsive to less efficacious diuretics; and (3) hypertension that cannot be controlled with other diuretics. Furosemide is especially useful in patients with severe renal impairment, since, unlike the thiazides (see below), the drug can promote diuresis even when renal blood flow and glomerular filtration rate (GFR) are low. If treatment with furosemide alone is insufficient, a thiazide diuretic may be added to the regimen. There is no benefit to combining furosemide with another high-ceiling agent.

Adverse Effects

Hyponatremia, Hypochloremia, and Dehydration.

Furosemide can produce excessive loss of sodium, chloride, and water. Severe dehydration can result. Signs of evolving dehydration include dry mouth, unusual thirst, and oliguria (scanty urine output). Impending dehydration can also be anticipated from excessive loss of weight. If dehydration occurs, furosemide should be withheld.

Dehydration can promote thrombosis and embolism. Symptoms include headache and pain in the chest, calves, or pelvis. The prescriber should be notified if these develop.

The risk of dehydration and its sequelae can be minimized by initiating therapy with low doses, adjusting the dosage carefully, monitoring weight loss every day, and administering furosemide on an intermittent schedule.

Hypotension.

Furosemide can cause a substantial drop in blood pressure. At least two mechanisms are involved: (1) loss of volume and (2) relaxation of venous smooth muscle, which reduces venous return to the heart. Signs of hypotension include dizziness, lightheadedness, and fainting. If blood pressure falls precipitously, furosemide should be discontinued. Because of the risk of hypotension, blood pressure should be monitored routinely.

Outpatients should be taught to monitor their blood pressure and instructed to notify the prescriber if it drops substantially. Also, patients should be informed about symptoms of postural hypotension (dizziness, lightheadedness)

and advised to sit or lie down if these occur. Patients should be taught that postural hypotension can be minimized by getting up slowly.

Hypokalemia.

Potassium is lost through increased secretion in the distal nephron. If serum potassium falls below 3.5 mEq/L, fatal dysrhythmias may result. As discussed below under *Drug Interactions,* loss of potassium is of special concern for patients taking digoxin, a drug used for heart failure. Hypokalemia can be minimized by consuming potassium-rich foods (eg, dried fruits, nuts, spinach, citrus fruits, potatoes, bananas), taking potassium supplements, or using a potassium-sparing diuretic.

Ototoxicity.

Rarely, loop diuretics cause hearing impairment. With furosemide, deafness is transient. With ethacrynic acid (another loop diuretic), irreversible hearing loss has occurred. The ability to impair hearing is unique to the high-ceiling agents; diuretics in other classes are not ototoxic. Because of the risk of hearing loss, caution is needed when high-ceiling diuretics are used in combination with other ototoxic drugs (eg, aminoglycoside antibiotics).

Hyperglycemia.

Elevation of plasma glucose is a potential, albeit uncommon, complication of furosemide therapy. Hyperglycemia appears to result from inhibition of insulin release. Increased glycogenolysis and decreased glycogen synthesis may also contribute. When furosemide is taken by a diabetic patient, he or she should be especially diligent about monitoring blood glucose content.

Hyperuricemia.

Elevation of plasma uric acid is a frequent side effect of treatment. For most patients, furosemide-induced hyperuricemia is asymptomatic. However, for patients predisposed to gout, elevation of uric acid may precipitate a gouty attack. Patients should be informed about symptoms of gout (tenderness or swelling in joints) and instructed to notify the prescriber if these develop.

Use in Pregnancy.

When administered to pregnant laboratory animals, high-ceiling diuretics have caused maternal death, abortion, fetal resorption, and other adverse effects. There are no definitive studies on loop diuretics during human pregnancy. However, given the toxicity displayed in animals, prudence dictates that pregnant women use these drugs only if absolutely required.

Impact on Lipids, Calcium, and Magnesium.

Furosemide reduces high-density lipoprotein (HDL) cholesterol and raises low-density lipoprotein (LDL) cholesterol and triglycerides. Although these undesirable effects by themselves can increase the risk of coronary heart disease, they are more than balanced by the beneficial effects of the diuretic therapy on the heart. That is, despite adverse effects on lipids, high-ceiling diuretics reduce the risk of coronary mortality by 25%.

Furosemide increases urinary excretion of magnesium, posing a risk of magnesium deficiency. Symptoms include muscle weakness, tremor, twitching, and dysrhythmias.

Furosemide increases urinary excretion of calcium. This action has been exploited to treat hypercalcemia.

Drug Interactions

Digoxin.

Digoxin is used for heart failure (see Chapter 47) and cardiac dysrhythmias (see Chapter 48). In the presence of low potassium, the risk of serious digoxin-induced toxicity (ventricular dysrhythmias) is greatly increased. Since high-ceiling diuretics promote potassium loss, use of these drugs in combination with digoxin can increase the risk of dysrhythmias. This interaction is unfortunate in that most patients who take digoxin for heart failure must also take a diuretic as part of their therapy. To reduce the risk of toxicity, potassium levels should be monitored routinely, and, when indicated, potassium supplements or a potassium-sparing diuretic should be given.

Ototoxic Drugs.

The risk of furosemide-induced hearing loss is increased by concurrent use of other ototoxic drugs—especially aminoglycoside antibiotics (eg, gentamicin). Accordingly, combined use of these drugs should be avoided.

Potassium-Sparing Diuretics.

The potassium-sparing diuretics (eg, spironolactone, triamterene) can help counterbalance the potassium-wasting effects of furosemide, thereby reducing the risk of hypokalemia.

Lithium.

Lithium is used to treat bipolar disorder (see Chapter 33). In patients with low sodium, excretion of lithium is reduced. Hence, by lowering sodium levels, furosemide can cause lithium to accumulate to toxic levels. Accordingly, lithium levels should be monitored, and, if they climb too high, lithium dosage should be reduced.

Antihypertensive Agents.

The hypotensive effects of furosemide add with those of other hypotensive drugs. To avoid excessive reduction of blood pressure, patients may need to reduce or eliminate use of other hypotensive medications.

Nonsteroidal Anti-inflammatory Drugs.

The nonsteroidal anti-inflammatory drugs (NSAIDs; eg, aspirin) can attenuate the diuretic effects of furosemide. The mechanism appears to be inhibition of prostaglandin synthesis in the kidney. (Part of the diuretic effect of furosemide results from increasing renal blood flow, which is thought to occur through a prostaglandin-mediated process. By inhibiting prostaglandin synthesis, NSAIDs prevent the increase in renal blood flow, and thereby partially blunt diuretic effects.)

Preparations, Dosage, and Administration

Oral.

Furosemide [Lasix] is available in tablets (20, 40, and 80 mg) and in solution (8 and 10 mg/mL) for oral use. The initial dosage for adults is 20 to 80 mg/day as

a single dose. The maximum daily dosage is 600 mg. Twice-daily dosing (8:00 AM and 2:00 PM) is common. Administration late in the day produces nocturia and should be avoided.

Parenteral.

Furosemide is available in solution (10 mg/mL) for IV and IM administration. The usual dosage for adults is 20 to 40 mg, repeated in 1 or 2 hours if needed. Intravenous administration should be done slowly (over 1 to 2 minutes). For high-dose therapy, furosemide can be administered by continuous infusion at a rate of 4 mg/min or slower.

Other High-Ceiling Diuretics

In addition to furosemide, three other high-ceiling agents are available: *ethacrynic acid* [Edecrin], *bumetanide* [Bumex], and *torsemide* [Demadex]. All three are much like furosemide. They all promote diuresis by inhibiting sodium and chloride reabsorption in the thick ascending limb of the loop of Henle. All are approved for edema caused by heart failure, chronic renal disease, and cirrhosis, but only torsemide, like furosemide, is also approved for hypertension. All can cause ototoxicity, hypovolemia, hypotension, hypokalemia, hyperuricemia, hyperglycemia, and disruption of lipid metabolism (ie, reduction of HDL cholesterol and elevation of LDL cholesterol and triglycerides). Lastly, they all share the same drug interactions: their effects can be blunted by NSAIDs, they can intensify ototoxicity caused by aminoglycosides, they can increase cardiotoxicity caused by digoxin, and they can cause lithium to accumulate to toxic levels. Routes, dosages, and time courses are summarized in Table 40-1.

Drug	Route	Onset (min)	Duration (hr)	Dosage (mg)	Doses/Day
Furosemide [Lasix]	Oral	Within 60	6–8	20–80	1–2
	IV or IM	Within 5	2	20–40	
Ethacrynic acid [Edecrin]	Oral	Within 30	6–8	50–100	1–2
	IV	Within 5	2	50	1–2
Bumetanide [Bumex]	Oral	30–60	4–6	0.5–2	1
	IV	Within a few	0.5–1	0.5–1	1–3
Torsemide [Demadex]	Oral	Within 60	6–8	5–20	1
	IV	Within 10	6–8	5–20	1

TABLE 40-1 High-Ceiling (Loop) Diuretics: Routes, Time Course, and Dosage

THIAZIDES AND RELATED DIURETICS

The thiazide diuretics (also known as benzothiadiazides) have effects similar to those of the loop diuretics. Like the loop diuretics, thiazides increase renal excretion of sodium, chloride, potassium, and water. In addition, thiazides elevate plasma levels of uric acid and glucose. The principal difference between the thiazides and high-ceiling agents is that the maximum diuresis produced by the thiazides is considerably lower than the maximum diuresis produced by the high-ceiling drugs. In addition, whereas loop diuretics can be effective even when urine flow is scant, thiazides cannot.

Hydrochlorothiazide

Hydrochlorothiazide [HydroDIURIL, others] is the most widely used thiazide diuretic and will serve as our prototype for the group. Because of its use in hypertension, a very common disorder, hydrochlorothiazide is one of our most widely used drugs.

Mechanism of Action

Hydrochlorothiazide promotes urine production by blocking the reabsorption of sodium and chloride in the *early segment of the distal convoluted tubule* (see Fig. 40-2). Retention of sodium and chloride in the nephron causes water to be retained as well, thereby producing an increased flow of urine. Since only 10% of filtered sodium and chloride is normally reabsorbed at the site where thiazides act, the maximum urine flow these drugs can produce is lower than with the high-ceiling drugs.

The ability of thiazides to promote diuresis is dependent on adequate kidney function. These drugs are ineffective when GFR is low (less than 15 to 20 mL/min). Hence, in contrast to the high-ceiling agents, thiazides cannot be used to promote fluid loss in patients with severe renal impairment.

Pharmacokinetics

Diuresis begins about 2 hours after oral administration. Effects peak within 4 to 6 hours, and may persist up to 12 hours. Most of the drug is excreted unchanged in the urine.

Therapeutic Uses

Essential Hypertension.

The primary indication for hydrochlorothiazide is hypertension, a condition for which thiazides are often drugs of first choice. For many hypertensive patients, blood pressure can be controlled with a thiazide alone, although many other patients require multiple-drug therapy. The role of thiazides in hypertension is discussed in Chapter 46.

Edema.

Thiazides are preferred drugs for mobilizing edema associated with mild to moderate heart failure. They are also given to mobilize edema associated with hepatic or renal disease.

Diabetes Insipidus.

Diabetes insipidus is a rare condition characterized by excessive production of urine. In patients with this disorder, thiazides reduce urine production by 30% to 50%. The mechanism of this paradoxical effect is unclear.

Adverse Effects

The adverse effects of thiazide diuretics are similar to those of the high-ceiling agents. In fact, with the exception that thiazides lack ototoxic actions, the adverse effects of the thiazides and loop diuretics are nearly identical.

Hyponatremia, Hypochloremia, and Dehydration.

Loss of sodium, chloride, and water can lead to hyponatremia, hypochloremia, and dehydration. It should be noted, however, that since the diuresis produced by thiazides is moderate, these drugs have a smaller impact on sodium, chloride, and water than do the loop diuretics. To evaluate fluid and electrolyte status, electrolyte levels should be determined periodically, and the patient should be weighed on a regular basis.

Hypokalemia.

Like the high-ceiling diuretics, the thiazides can cause hypokalemia from excessive potassium excretion. As noted, potassium loss is of particular concern for patients taking digoxin. Potassium levels should be measured periodically, and, if serum potassium falls below 3.5 mEq/L, treatment with potassium supplements or a potassium-sparing diuretic should be instituted. Hypokalemia can be minimized by eating potassium-rich foods.

Use in Pregnancy and Lactation.

The thiazides have direct and indirect effects on the developing fetus. By reducing blood volume, thiazides can decrease placental perfusion, and may thereby compromise fetal nutrition and growth. Furthermore, thiazides can cross the placental barrier to produce fetal harm directly. Potential effects include electrolyte imbalance, hypoglycemia, jaundice, and hemolytic anemia. Because of the potential for fetal harm, *thiazides should not be used routinely during pregnancy*. Edema of pregnancy is not an indication for diuretic therapy, except when severe. In contrast, edema from pathologic causes (eg, heart failure, cirrhosis) does constitute a legitimate indication for thiazide use.

Thiazides enter breast milk and can be hazardous to the nursing infant. Women taking thiazides should be cautioned against breast-feeding.

Hyperglycemia.

Like the loop diuretics, the thiazides can elevate plasma levels of glucose. Significant hyperglycemia develops only in diabetic patients, who should be especially diligent about monitoring blood glucose. To maintain normal glucose levels, the diabetic patient may require larger doses of insulin or an oral hypoglycemic drug.

Hyperuricemia.

The thiazides, like the loop diuretics, can cause retention of uric acid, thereby elevating plasma uric acid levels. Although hyperuricemia is usually asymptomatic, it may precipitate gouty arthritis in patients with a history of the disorder. Plasma levels of uric acid should be measured periodically.

Impact on Lipids, Calcium, and Magnesium.

Thiazides can increase levels of LDL cholesterol, total cholesterol, and triglycerides. Thiazides reduce urinary excretion of calcium, an effect that has been used to treat calcium-related kidney stones. Thiazides increase excretion of magnesium, sometimes causing magnesium deficiency. Symptoms include muscle weakness, tremor, twitching, and dysrhythmias.

Drug Interactions

The important drug interactions of the thiazides are nearly identical to those of the loop diuretics. By promoting potassium loss, thiazides can increase the risk of toxicity from *digoxin*. By counterbalancing the potassium-wasting effects of the thiazides, the *potassium-sparing diuretics* can help prevent excessive potassium loss. By lowering blood pressure, thiazides can augment the effects of other *antihypertensive drugs*. By promoting sodium loss, thiazides can reduce renal excretion of *lithium,* thereby causing the drug to accumulate, possibly to toxic levels. *NSAIDs* may blunt the diuretic effects of thiazides. In contrast to the loop diuretics, the thiazides can be combined with *ototoxic agents* without an increased risk of hearing loss.

Preparations, Dosage, and Administration

Hydrochlorothiazide [HydroDIURIL, others] is supplied in capsules (12.5 mg) and tablets (12.5, 25, 50, and 100 mg). Like most other thiazides, hydro-

chlorothiazide is administered only by mouth. The usual adult dosage is 25 to 50 mg once or twice daily. To minimize nocturia, the drug should not be administered late in the day. To minimize electrolyte imbalance, the drug should be administered on an intermittent basis (eg, every other day). In addition to being marketed alone, hydrochlorothiazide is available in fixed-dose combinations with potassium-sparing diuretics and a long list of other drugs: beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, reserpine, hydralazine, clonidine, methyldopa, and prazosin (see Table 46-6).

Other Thiazide-Type Diuretics

In addition to hydrochlorothiazide, five other thiazides (and related drugs) are approved for use in the United States (Table 40-2). All have pharmacologic properties similar to those of hydrochlorothiazide. With the exception of chlorothiazide, these drugs are administered only by mouth. Chlorothiazide can be administered IV as well as PO. Although the thiazides differ from one another in milligram potency (see Table 40-2), at therapeutically equivalent doses, all elicit the same degree of diuresis. Although most have the same onset time (1 to 2 hours), these drugs differ significantly with respect to duration of action. As with hydrochlorothiazide, disturbance of electrolyte balance can be minimized through alternate-day dosing. Nocturia can be minimized by avoiding dosing in the late afternoon. Table 40-2 lists three drugs—chlorthalidone, indapamide, and metolazone—that are not true thiazides. However, these agents are very similar to thiazides both in structure and function, hence their inclusion in this group.

POTASSIUM-SPARING DIURETICS

The potassium-sparing diuretics can elicit two potentially useful responses. First, they produce a modest increase in urine production. Second, they produce a substantial *decrease in potassium excretion*. Because their diuretic effects are limited, the potassium-sparing drugs are rarely employed alone to promote diuresis. However, because of their marked ability to decrease potassium excretion, these drugs are often used to counteract potassium loss caused by thiazide and loop diuretics.

There are two subcategories of potassium-sparing diuretics: *aldosterone antagonists* and *nonaldosterone antagonists*. In the United States, only one aldosterone antagonist—spironolactone—is used for diuresis.* Two nonaldosterone antagonists—triamterene and amiloride—are currently employed.

Spironolactone

Mechanism of Action

Spironolactone [Aldactone] blocks the actions of aldosterone in the distal nephron. Since aldosterone acts to promote sodium uptake in exchange for potassium secretion (see Fig. 40-2), inhibition of aldosterone has the opposite effect: *retention of potassium and increased excretion of sodium*. The diuresis caused by spironolactone is scanty because most of the filtered sodium load has already been reabsorbed by the time the filtrate reaches the distal nephron. (Recall that the degree of diuresis a drug produces is directly proportional to the amount of sodium reuptake that it blocks.)

Generic Name	Trade Name	Time Course		Optimal Oral Adult Dosage (mg/day)
		Onset (hr)	Duration (hr)	
Thiazides				
Chlorothiazide	Diuril	1–2	6–12	500–1000
Hydrochlorothiazide	HydroDIURIL, Hydro-Par, Ezide, Microzide	2	6–12	12.5–25
Methyclothiazide	Enduron	2	24	2.5–5
Related Drugs				
Chlorthalidone	Hygroton, Thalitone	2	24–72	50–100
Indapamide	Lozol	1–2	Up to 36	2.5–5
Metolazone	Zaroxolyn	1	12–24	2.5–20

TABLE 40-2 Thiazides and Related Diuretics: Dosages and Time Course of Effects

* Another aldosterone antagonist—*eplerenone*—is available, but the drug is not considered a diuretic. The basic pharmacology of eplerenone and its main use (heart failure) are discussed in Chapters 43 and 47, respectively.

As indicated in Table 40-3, the effects of spironolactone are delayed, taking up to 48 hours to develop. Why the delay? Recall that aldosterone acts by stimulating cells of the distal nephron to synthesize the proteins required for sodium and potassium transport. By preventing aldosterone's action, spironolactone blocks the synthesis of *new* proteins, but does not stop existing transport proteins from doing their job. Hence, effects are not visible until the existing proteins complete their normal life cycle—a process that takes 1 or 2 days.

Generic Name	Trade Name	Time Course		Usual Adult Dosage (mg/day)
		Onset (hr)	Duration (hr)	
Spironolactone	Aldactone	24–48	48–72	25–200
Triamterene	Dyrenium	2–4	12–16	200–300
Amiloride	Midamor	2	24	5–20

TABLE 40-3 Potassium-Sparing Diuretics: Names, Dosages and Time Course of Effects

Therapeutic Uses

Hypertension and Edema.

Spironolactone is used primarily for hypertension and edema. Although it can be employed alone, the drug is used most commonly in combination with a thiazide or loop diuretic. The purpose of spironolactone in these combinations is to counteract the potassium-wasting effects of the more powerful diuretics. Spironolactone also makes a small contribution to diuresis.

Heart Failure.

In patients with severe heart failure, spironolactone greatly reduces mortality and hospital admissions. Benefits derive from protective effects of aldosterone blockade in the heart and blood vessels (see Chapter 47).

Other Uses.

In addition to the applications discussed above, spironolactone can be used for primary hyperaldosteronism (Chapter 59), premenstrual syndrome (Chapter 60), polycystic ovary syndrome (Chapter 62), and acne in young women (Chapter 104).

Adverse Effects

Hyperkalemia.

The potassium-sparing effects of spironolactone can result in hyperkalemia, a condition that can produce fatal dysrhythmias. Although hyperkalemia is most likely when spironolactone is used alone, it can also develop when spironolactone is used in conjunction with potassium-wasting agents (thiazides and high-ceiling diuretics). If serum potassium rises above 5 mEq/L, or if signs of hyperkalemia develop (eg, abnormal cardiac rhythm), spironolactone should be discontinued and potassium intake restricted. Injection of insulin can help lower potassium levels by promoting potassium uptake into cells.

Benign and Malignant Tumors.

When given long term to rats in doses 25 to 250 times those used in humans, spironolactone caused benign adenomas of the thyroid and testes, malignant mammary tumors, and proliferative changes in the liver. The risk of tumors in humans from use of normal doses is unknown.

Endocrine Effects.

Spironolactone is a steroid derivative with a structure similar to that of steroid hormones (eg, progesterone, estradiol, testosterone). As a result, spironolactone can cause a variety of endocrine effects, including *gynecomastia, menstrual irregularities, impotence, hirsutism,* and *deepening of the voice*.

Drug Interactions

Thiazide and Loop Diuretics.

Spironolactone is frequently combined with thiazide and loop diuretics. The goal is to counteract the potassium-wasting effects of the more powerful diuretic.

Agents That Raise Potassium Levels.

Because of the risk of hyperkalemia, *spironolactone must never be combined with potassium supplements, salt substitutes (which contain potassium chloride), or another potassium-sparing diuretic*. In addition, three groups of drugs—*angiotensin-converting enzyme* (ACE) *inhibitors, angiotensin receptor blockers,* and *direct renin inhibitors*—can elevate potassium levels (by suppressing aldosterone secre-

tion), and hence should be combined with spironolactone only when clearly necessary.

Preparations, Dosage, and Administration

Spironolactone [Aldactone] is dispensed in tablets (25, 50, and 100 mg) for oral administration. The usual adult dosage is 25 to 100 mg/day. Spironolactone is also marketed in a fixed-dose combination with hydrochlorothiazide under the trade name Aldactazide.

Triamterene

Mechanism of Action

Like spironolactone, triamterene [Dyrenium] disrupts sodium-potassium exchange in the distal nephron. However, in contrast to spironolactone, which reduces ion transport *indirectly* through blockade of aldosterone, triamterene is a *direct inhibitor of the exchange mechanism itself*. The net effect of inhibition is a decrease in sodium reuptake and a reduction in potassium secretion. Hence, sodium excretion is increased, while potassium is conserved. Because it inhibits ion transport directly, triamterene acts much more quickly than spironolactone. As indicated in Table 40-3, initial responses develop in hours, compared with days for spironolactone. As with spironolactone, diuresis with triamterene is scant.

Therapeutic Uses

Triamterene can be used alone or in combination with other diuretics to treat *hypertension* and *edema*. When used alone, triamterene produces mild diuresis. When combined with other diuretics (eg, furosemide, hydrochlorothiazide), triamterene augments diuresis and helps counteract the potassium-wasting effects of the more powerful diuretic. It is the latter effect for which triamterene is principally employed.

Adverse Effects

Hyperkalemia.

Excessive potassium accumulation is the most significant adverse effect. Hyperkalemia is most likely when triamterene is used alone, but can also occur when the drug is combined with thiazides or high-ceiling agents. Triamterene should never be used in conjunction with another potassium-sparing diuretic or with potassium supplements or salt substitutes. In addition, caution is needed if the drug is combined with an ACE inhibitor, angiotensin receptor blocker, or direct renin inhibitor.

Other Adverse Effects.

Relatively common side effects include *nausea, vomiting, leg cramps,* and *dizziness*. Blood dyscrasias occur rarely.

Preparations, Dosage, and Administration

Triamterene [Dyrenium] is available in 50- and 100-mg capsules for oral use. The usual initial dosage is 100 mg twice a day. The maximum daily dosage is 300 mg. Triamterene is also marketed in fixed-dose combinations with hydrochlorothiazide under the trade names Dyazide and Maxzide.

Amiloride

Pharmacologic Properties.

Amiloride [Midamor] has actions similar to those of triamterene. Both drugs inhibit potassium loss by direct blockade of sodium-potassium exchange in the distal nephron. Also, both drugs produce only modest diuresis. Although it can be employed alone as a diuretic, amiloride is used primarily to counteract potassium loss caused by more powerful diuretics (thiazides, high-ceiling agents). The major adverse effect is hyperkalemia. Accordingly, concurrent use of other potassium-sparing diuretics or potassium supplements must be avoided. Caution is needed if the drug is combined with an ACE inhibitor, angiotensin receptor blocker, or direct renin inhibitor.

Preparations, Dosage, and Administration.

Amiloride [Midamor] is supplied in 5-mg tablets for oral use. Dosing is begun at 5 mg/day and may be increased to a maximum of 20 mg/day. Amiloride

is available in a fixed-dose combination with hydrochlorothiazide under the trade name Moduretic.

OSMOTIC DIURETICS

Four compounds—mannitol, urea, glycerin, and isosorbide—are classified as osmotic diuretics. However, of the four, only mannitol is used for its diuretic actions. The osmotic agents differ from other diuretics in both mechanism and indications.

Mannitol

Mannitol [Osmitrol] is a simple six-carbon sugar that possesses the four properties characteristic of an osmotic diuretic:

- It is freely filtered at the glomerulus.
- It undergoes minimal reabsorption.
- It is not metabolized to a significant degree.
- It is pharmacologically inert (ie, it has no direct effects on the biochemistry or physiology of cells).

Mechanism of Diuretic Action

Mannitol promotes diuresis by creating an osmotic force within the lumen of the nephron. Unlike other solutes, mannitol undergoes minimal reabsorption after filtration. As a result, most of the drug remains within the nephron, creating an osmotic force that inhibits passive reabsorption of water. Hence, urine flow increases. The degree of diuresis produced is directly related to the concentration of mannitol in the filtrate; the more mannitol present, the greater the diuresis. Mannitol has no significant effect on the excretion of potassium and other electrolytes.

Pharmacokinetics

Mannitol does not diffuse across the GI epithelium and cannot be transported by the uptake systems that absorb dietary sugars. Accordingly, in order to reach the circulation, the drug must be given parenterally. Following IV injection, mannitol distributes freely to extracellular water. Diuresis begins in 30

to 60 minutes and persists 6 to 8 hours. Most of the drug is excreted intact in the urine.

Therapeutic Uses

Prophylaxis of Renal Failure.

Under certain conditions (eg, dehydration, severe hypotension, hypovolemic shock), blood flow to the kidney is decreased, causing a great reduction in filtrate volume. When the volume of filtrate is this low, transport mechanisms of the nephron are able to reabsorb virtually all of the sodium and chloride present, causing complete reabsorption of water as well. As a result, urine production ceases, and kidney failure ensues. The risk of renal failure can be reduced with mannitol. Because filtered mannitol is not reabsorbed—even when filtrate volume is small—filtered mannitol will remain in the nephron, drawing water with it. Hence, mannitol can preserve urine flow and may thereby prevent renal failure. Thiazides and loop diuretics are not as effective for this application because, under conditions of low filtrate production, there is such an excess of reabsorptive capacity (relative to the amount of filtrate) that these drugs are unable to produce sufficient blockade of reabsorption to promote diuresis.

Reduction of Intracranial Pressure.

Intracranial pressure (ICP) that has been elevated by cerebral edema can be reduced with mannitol. The drug lowers ICP because its presence in the cerebral vasculature creates an osmotic force that draws edematous fluid out of the brain. There is no risk of increasing cerebral edema because mannitol cannot exit the capillary beds of the brain.

Reduction of Intraocular Pressure.

Mannitol and other osmotic agents can lower IOP. Mannitol reduces IOP by rendering the plasma hyperosmotic with respect to intraocular fluids, thereby creating an osmotic force that draws ocular fluid into the blood. Use of mannitol to lower IOP is reserved for patients who have not responded to more conventional treatment.

Adverse Effects

Edema.

Mannitol can leave the vascular system at all capillary beds except those of the brain. When the drug exits capillaries, it draws water along, causing edema. Mannitol must be used with extreme caution in patients with heart disease, since it may precipitate CHF and pulmonary edema. If signs of pulmonary congestion or CHF develop, use of the drug must cease immediately. Mannitol must also be discontinued if patients with heart failure or pulmonary edema develop renal failure, because the resultant accumulation of mannitol would increase the risk of cardiac or pulmonary injury.

Other Adverse Effects.

Common responses include headache, nausea, and vomiting. Fluid and electrolyte imbalance may also occur.

Preparations, Dosage, and Administration

Mannitol [Osmitrol] is administered by IV infusion. Solutions for IV use range in concentration from 5% to 25%. Dosing is complex and varies with the objective of therapy (prevention of renal failure, lowering of ICP, lowering of IOP). The usual adult dosage for preventing renal failure is 50 to 100 gm over 24 hours. The infusion rate should be set to elicit a urine flow of at least 30 to 50 mL/hr. It should be noted that mannitol may crystallize out of solution if exposed to low temperature. Accordingly, preparations should be observed for crystals prior to use. Preparations that contain crystals should be warmed (to redissolve the mannitol) and then cooled to body temperature for administration. A filter needle is employed to withdraw mannitol from the vial, and an in-line filter is used to prevent crystals from entering the circulation. If urine flow declines to a very low rate or ceases entirely, the infusion should be stopped.

Urea, Glycerin, and Isosorbide

In addition to mannitol, three other drugs—urea, glycerin, and isosorbide—are classified as osmotic diuretics. Like mannitol, these agents are freely filtered at the glomerulus and undergo limited reabsorption. These properties pro-

mote osmotic diuresis. It must be noted, however, that although urea, glycerin, and isosorbide can produce diuresis, they are not actually used for this purpose. Rather, they are used only to reduce IOP and ICP. Urea [Ureaphil] is administered intravenously. Glycerin [Osmoglyn] and isosorbide [Ismotic] are administered by mouth.

KEY POINTS

- More than 99% of the water, electrolytes, and nutrients that are filtered at the glomerulus undergo reabsorption.
- Most diuretics block active reabsorption of sodium and chloride, and thereby prevent passive reabsorption of water.
- The amount of diuresis produced is directly related to the amount of sodium and chloride reabsorption blocked.
- Drugs that act early in the nephron are in a position to block the greatest amount of solute reabsorption, and hence produce the greatest diuresis.
- High-ceiling diuretics (loop diuretics) block sodium and chloride reabsorption in the loop of Henle.
- High-ceiling diuretics produce the greatest diuresis.
- In contrast to thiazide diuretics, high-ceiling diuretics are effective even when the glomerular filtration rate is low.
- High-ceiling diuretics can cause dehydration through excessive fluid loss.
- High-ceiling diuretics can cause hypotension by decreasing blood volume and relaxing venous smooth muscle.
- High-ceiling diuretics can cause hearing loss, which is usually reversible.
- Hypokalemia caused by high-ceiling diuretics is a special problem for patients taking digoxin.
- Thiazide diuretics block sodium and water reabsorption in the early distal convoluted tubule.
- Thiazide diuretics produce less diuresis than high-ceiling diuretics.

- Thiazide diuretics are ineffective when glomerular filtration rate is low.
- Like the high-ceiling diuretics, thiazide diuretics can cause dehydration and hypokalemia. However, thiazides do not cause hearing loss.
- Thiazide-induced hypokalemia is a special problem for patients taking digoxin.
- Potassium-sparing diuretics act by directly or indirectly blocking sodium-potassium "exchange" in the distal convoluted tubule.
- Potassium-sparing diuretics cause only modest diuresis.
- Potassium-sparing diuretics are used primarily to counteract potassium loss in patients taking high-ceiling diuretics or thiazides.
- The principal adverse effect of potassium-sparing diuretics is hyperkalemia.
- Because of the risk of hyperkalemia, potassium-sparing diuretics should not be combined with one another or with potassium supplements, and they should be used cautiously in patients taking ACE inhibitors, angiotensin receptor blockers, or direct renin inhibitors.
- High-ceiling diuretics and thiazides are used to treat hypertension and edema associated with heart failure, cirrhosis, and kidney disease.

Summary of Major Nursing Implications*

HIGH-CEILING (LOOP) DIURETICS

Bumetanide

Ethacrynic acid

Furosemide

Torsemide

Preadministration Assessment

Therapeutic Goal

High-ceiling diuretics are indicated for patients with (1) pulmonary edema associated with congestive heart failure; (2) edema of hepatic, cardiac, or renal origin that has been unresponsive to less effective diuretics; (3) hypertension that cannot be controlled with thiazide and potassium-sparing diuretics; and (4) all patients who need diuretic therapy but have low renal blood flow.

Baseline Data

For all patients, obtain baseline values for weight, blood pressure (sitting and supine), pulse, respiration, and electrolytes (sodium, potassium, chloride). For patients with edema, record sites and extent of edema. For patients with ascites, measure abdominal girth. For acutely ill patients (eg, severe CHF), assess lung sounds.

Identifying High-Risk Patients

Use with *caution* in patients with cardiovascular disease, renal impairment, diabetes mellitus, or a history of gout, and in patients who are pregnant or taking digoxin, lithium, ototoxic drugs, NSAIDs, or antihypertensive drugs.

Implementation: Administration

Routes

Furosemide and Bumetanide. Oral, IV, IM.

Ethacrynic Acid and Torsemide. Oral, IV.

Administration

Oral.

Dosing may be done once daily, twice daily, or on alternate days. **Instruct patients who are using once-a-day or alternate-day dosing to take their medication in the morning. Instruct patients using Twice-A-Day dosing to take their medication at 8:00 AM and 2:00 PM (to minimize nocturia).**

Advise patients to administer furosemide with food if GI upset occurs.

Parenteral.

Administer IV injections slowly (over 1 to 2 minutes). For high-dose therapy, administer by continuous infusion. Discard discolored solutions.

Promoting Adherence

Increased frequency of urination is inconvenient and can discourage adherence. **To promote adherence, inform patients that treatment will increase urine volume and frequency of voiding, and that these effects will subside 6 to 8 hours after dosing. Inform patients that nighttime diuresis can be minimized by avoiding dosing late in the day.**

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor blood pressure and pulse rate, weigh the patient daily, and evaluate for decreased edema.

Monitor intake and output. Notify the prescriber if oliguria (urine output less than 25 mL/hr) or anuria (no urine output) develops.

Instruct outpatients to weigh themselves daily (using the same scale), preferably in the morning before eating. Also, instruct them to maintain a weight record, and to report excessive weight gain or weight loss.

In acute conditions requiring rapid diuresis and careful monitoring, a Foley catheter may be used. The catheter should be emptied prior to drug injection, and output should be monitored hourly and recorded.

Minimizing Adverse Effects

Hyponatremia, Hypochloremia, and Dehydration.

Loss of sodium, chloride, and water can cause hyponatremia, hypochloremia, and severe dehydration. Signs of dehydration include dry mouth, unusual thirst, and oliguria. Withhold the drug if these appear.

Dehydration can promote thromboembolism. Monitor the patient for symptoms (headache; pain in the chest, calves, or pelvis), and notify the prescriber if these develop.

The risk of dehydration and its sequelae can be minimized by (1) initiating therapy with low doses, (2) adjusting the dosage carefully, (3) monitoring weight loss daily, and (4) using an intermittent dosing schedule.

Hypotension.

Monitor blood pressure. If it falls precipitously, withhold medication and notify the prescriber.

Teach patients to monitor their blood pressure and instruct them to notify the prescriber if it drops substantially.

Inform patients about signs of postural hypotension (dizziness, lightheadedness), and advise them to sit or lie down if these occur. Inform patients that postural hypotension can be minimized by getting up slowly, and by dangling legs off the bed before standing.

Hypokalemia.

If serum potassium falls below 3.5 mEq/L, fatal dysrhythmias may result. Hypokalemia can be minimized by consuming potassium-rich foods (eg, nuts, dried fruits, spinach, citrus fruits, potatoes, bananas), taking potassium supplements, or using a potassium-sparing diuretic. **Teach patients the signs and symptoms of hypokalemia (eg, irregular heartbeat, muscle weakness, cramping, flaccid paralysis, leg discomfort, extreme thirst, confusion), and stress the importance of showing up for regular blood tests.**

Ototoxicity.

Inform patients about possible hearing loss and instruct them to notify the prescriber if a hearing deficit develops. Exercise caution when high-ceiling diuretics are used concurrently with other ototoxic drugs, especially aminoglycosides.

Hyperglycemia.

High-ceiling diuretics may elevate blood glucose levels in diabetic patients. **Advise these patients to be especially diligent about monitoring blood glucose.**

Hyperuricemia.

High-ceiling diuretics frequently cause *asymptomatic* hyperuricemia, although gout-prone patients may experience a gouty attack. **Inform patients about signs of gout (tenderness or swelling in joints), and instruct them to notify the prescriber if these occur.**

Minimizing Adverse Interactions

Digoxin.

By lowering potassium levels, high-ceiling diuretics increase the risk of fatal dysrhythmias from digoxin. Serum potassium levels must be monitored and maintained above 3.5 mEq/L.

Lithium.

High-ceiling diuretics can suppress lithium excretion, thereby causing the drug to accumulate, possibly to toxic levels. Plasma lithium should be monitored routinely. If drug levels become elevated, lithium dosage should be reduced.

Ototoxic Drugs.

The risk of hearing loss from high-ceiling diuretics is increased in the presence of other ototoxic drugs, especially aminoglycosides. Exercise caution when such combinations are employed.

THIAZIDES AND RELATED DIURETICS

Chlorothiazide

Chlorthalidone

Hydrochlorothiazide

Indapamide

Methyclothiazide

Metolazone

Thiazide diuretics have actions much like those of the high-ceiling diuretics. Hence, nursing implications for the thiazides are nearly identical to those of the high-ceiling agents.

Preadministration Assessment

Therapeutic Goal

Thiazide diuretics are used to treat hypertension and edema.

Baseline Data

For all patients, obtain baseline values for weight, blood pressure (sitting and supine), pulse, respiration, and electrolytes (sodium, chloride, potassium). For patients with edema, record sites and extent of edema.

Identifying High-Risk Patients

Use with *caution* in patients with cardiovascular disease, renal impairment, diabetes mellitus, or a history of gout and in patients taking digoxin, lithium, or antihypertensive drugs. *Generally avoid* in women who are pregnant or breast-feeding.

Implementation: Administration

Routes

Oral. All thiazide-type diuretics.

Intravenous. Chlorothiazide.

Administration

Dosing may be done once daily, twice daily, or on alternate days. **When once-a-day dosing is employed, instruct patients to take their medicine early in the day to minimize nocturia. When Twice-A-Day dosing is employed, instruct patients to take their medicine at 8:00 AM and 2:00 PM.**

Advise patients to administer thiazides with or after meals if GI upset occurs.

Promoting Adherence

See nursing implications for *High-Ceiling (Loop) Diuretics*.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

See nursing implications for *High-Ceiling (Loop) Diuretics*.

Minimizing Adverse Effects

Like the high-ceiling diuretics, thiazides can cause *hyponatremia, hypochloremia, dehydration, hypokalemia, hypotension, hyperglycemia,* and *hyperuricemia*. For implications regarding these effects, see nursing implications for *High-Ceiling (Loop) Diuretics*.

Thiazides can cause fetal harm and can enter breast milk. Avoid these drugs during pregnancy unless absolutely required. **Caution women not to breast-feed.**

Minimizing Adverse Interactions

Like high-ceiling diuretics, thiazides can interact adversely with *digoxin* and *lithium*. For implications regarding these interactions, see nursing implications for *High-Ceiling (Loop) Diuretics*.

POTASSIUM-SPARING DIURETICS

Amiloride

Spironolactone

Triamterene

Preadministration Assessment

Therapeutic Goal

Potassium-sparing diuretics are given primarily to counterbalance the potassium-losing effects of thiazides and high-ceiling diuretics.

Baseline Data

Obtain baseline values for serum potassium, along with baseline values for weight, blood pressure (sitting and supine), pulse, respiration, sodium, and chloride. For patients with edema, record sites and extent of edema.

Identifying High-Risk Patients

Potassium-sparing diuretics are *contraindicated* for patients with hyperkalemia and for patients taking potassium supplements or another potassium-sparing diuretic. Use with *caution* in patients taking ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors.

Implementation: Administration

Route

Oral.

Administration

Advise patients to take these drugs with or after meals if GI upset occurs.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor serum potassium levels on a regular basis. The objective is to maintain serum potassium levels between 3.5 and 5 mEq/L.

Minimizing Adverse Effects

Hyperkalemia.

Hyperkalemia is the principal adverse effect. **Instruct patients to restrict intake of potassium-rich foods (eg, nuts, dried fruits, spinach, citrus fruits, potatoes, bananas).** If serum potassium levels rise above 5 mEq/L, or if signs of hyperkalemia develop (eg, abnormal cardiac rhythm), withhold medication and notify the prescriber. Insulin can be given to (temporarily) drive potassium levels down.

Endocrine Effects.

Spironolactone may cause *menstrual irregularities* and *impotence*. **Inform patients about these effects, and instruct them to notify the prescriber if they occur.**

Minimizing Adverse Interactions

Drugs That Raise Potassium Levels.

Because of the risk of hyperkalemia, don't combine a potassium-sparing diuretic with potassium supplements, salt substitutes, or with another potassium-sparing diuretic. Generally avoid combined use with ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors.

41 Agents Affecting the Volume and Ion Content of Body Fluids

The drugs discussed in this chapter are used to correct disturbances in the volume and ionic composition of body fluids. Three groups of agents are considered: (1) drugs used to correct disorders of fluid volume and osmolality, (2) drugs used to correct disturbances of hydrogen ion concentration (acid-base status), and (3) drugs used to correct electrolyte imbalances.

DISORDERS OF FLUID VOLUME AND OSMOLALITY

Good health requires that both the volume and osmolality of extracellular and intracellular fluids remain within a normal range. If a substantial alteration in either the volume or osmolality of these fluids develops, significant harm can result.

Maintenance of fluid volume and osmolality is primarily the job of the kidneys, and, even under adverse conditions, renal mechanisms usually succeed in keeping the volume and composition of body fluids within acceptable limits. However, circumstances can arise in which the regulatory capacity of the kidneys is exceeded. When this occurs, disruption of fluid volume, osmolality, or both can result.

Abnormal states of hydration can be divided into two major categories: volume contraction and volume expansion. *Volume contraction* is defined as *a decrease* in total body water; conversely, *volume expansion* is defined as an *increase* in total body water. States of volume contraction and volume expansion have three subclassifications based on alterations in extracellular osmolality. For volume contraction, the subcategories are *isotonic contraction, hypertonic contraction,* and *hypotonic contraction*. Volume expansion may also be subclassified as *isotonic, hypertonic,* or *hypotonic*. Descriptions and causes of these abnormal states are discussed below.

In the clinical setting, changes in osmolality are described in terms of the sodium content of plasma. Sodium is used as the reference for classification because this ion is the principal extracellular solute. (Recall that plasma sodium content ranges from 135 to 145 mEq/L.) In most cases, the total osmolality of

plasma is equal to approximately twice the osmolality of sodium. That is, total plasma osmolality usually ranges from 280 to 300 mOsm/kg water.

Volume Contraction

Isotonic Contraction

Definition and Causes.

Isotonic contraction is defined as volume contraction in which *sodium and water are lost in isotonic proportions*. Hence, although there is a decrease in the total volume of extracellular fluid, there is no change in osmolality. Causes of isotonic contraction include vomiting, diarrhea, kidney disease, and misuse of diuretics. Isotonic contraction is characteristic of cholera, an infection that produces vomiting and severe diarrhea.

Treatment.

Lost volume should be replaced with fluids that are isotonic to plasma. This can be accomplished by infusing isotonic (0.9%) sodium chloride in sterile water, a solution in which both sodium and chloride are present at a concentration of 145 mEq/L. Volume should be replenished slowly to avoid pulmonary edema.

Hypertonic Contraction

Definition and Causes.

Hypertonic contraction is defined as volume contraction in which *loss of water exceeds loss of sodium*. Hence, there is a reduction in extracellular fluid volume coupled with an increase in osmolality. Because of extracellular hypertonicity, water is drawn out of cells, thereby producing intracellular dehydration and partial compensation for lost extracellular volume.

Causes of hypertonic contraction include excessive sweating, osmotic diuresis, and feeding excessively concentrated foods to infants. Hypertonic contraction may also develop secondary to extensive burns or disorders of the central nervous system (CNS) that render the patient unable to experience or report thirst.

Treatment.

Volume replacement in hypertonic contraction should be accomplished with hypotonic fluids (eg, 0.11% sodium chloride) or with fluids that contain no solutes at all. Initial therapy may consist simply of drinking water. Alternatively, 5% dextrose can be infused intravenously. (Since dextrose is rapidly metabolized to carbon dioxide and water, dextrose solutions can be viewed as the osmotic equivalent of water alone.) Volume replenishment should be done in stages. About 50% of the estimated loss should be replaced during the first few hours of treatment. The remainder should be replenished over 1 to 2 days.

Hypotonic Contraction

Definition and Causes.

Hypotonic contraction is defined as volume contraction in which *loss of sodium exceeds loss of water*. Hence, both the volume and osmolality of extracellular fluid are reduced. Because intracellular osmolality now exceeds extracellular osmolality, extracellular volume becomes diminished further by movement of water into cells.

The principal cause of hypotonic contraction is excessive loss of sodium through the kidneys. This may occur because of diuretic therapy, chronic renal insufficiency, or lack of aldosterone (the adrenocortical hormone that promotes renal retention of sodium).

Treatment.

If hyponatremia is mild, and if renal function is adequate, hypotonic contraction can be corrected by infusing *isotonic* sodium chloride solution for injection. When this is done, plasma tonicity will be adjusted by the kidneys. However, if the sodium loss is severe, a *hypertonic* (eg, 3%) solution of sodium chloride should be infused. Administration should continue until plasma sodium concentration has been raised to about 130 mEq/L. Patients should be monitored for signs of fluid overload (distention of neck veins, peripheral or pulmonary edema). When hypotonic contraction is due to aldosterone insufficiency, patients should receive hormone replacement therapy along with intravenous infusion of isotonic sodium chloride.

Volume Expansion

Volume expansion is defined as an *increase in the total volume of body fluid*. As with volume contraction, volume expansion may be *isotonic, hypertonic,* or *hypotonic*. Volume expansion may result from an overdose with therapeutic fluids (eg, sodium chloride infusion) or may be associated with disease states, such as heart failure, nephrotic syndrome, or cirrhosis of the liver with ascites. The principal drugs employed to correct volume expansion are *diuretics* and the *agents used for heart failure*. These drugs are discussed in Chapters 40 and 47, respectively.

ACID-BASE DISTURBANCES

Maintenance of acid-base balance is a complex process, the full discussion of which is beyond the scope of this text. Hence, discussion here is condensed.

Acid-base status is regulated by multiple systems. The most important are (1) the bicarbonate–carbonic acid buffer system, (2) the respiratory system, and (3) the kidneys. The respiratory system influences pH through control of CO_2 exhalation. Because CO_2 represents volatile carbonic acid, exhalation of CO_2 tends to elevate pH (reduce acidity), whereas retention of CO_2 (secondary to respiratory slowing) tends to lower pH. The kidneys influence pH by regulating bicarbonate excretion. By *retaining* bicarbonate, the kidneys can raise pH. Conversely, by increasing bicarbonate *excretion,* the kidneys can lower pH, and thereby compensate for alkalosis.

There are four principal types of acid-base imbalance: (1) respiratory alkalosis, (2) respiratory acidosis, (3) metabolic alkalosis, and (4) metabolic acidosis. Causes and treatments are discussed below.

Respiratory Alkalosis

Causes.

Respiratory alkalosis is produced by hyperventilation. Deep and rapid breathing increases CO_2 loss, which in turn lowers the pCO_2* of blood, and thereby increases pH. Mild hyperventilation may result from a number of causes, including hypoxia, pulmonary disease, and drugs (especially aspirin and other salicylates). Severe hyperventilation can be caused by CNS injury and hysteria.

* pCO_2 is the partial pressure of carbon dioxide in blood.

Treatment.

Management of respiratory alkalosis is dictated by the severity of pH elevation. When alkalosis is mild, no specific treatment is indicated. Severe respiratory alkalosis resulting from hysteria can be controlled by having the patient rebreathe his or her CO_2-laden expired breath. This can be accomplished by holding a paper bag over the nose and mouth. A similar effect can be achieved by having the patient inhale a gas mixture containing 5% CO_2. A sedative (eg, diazepam [Valium]) can help suppress the hysteria.

Respiratory Acidosis

Causes.

Respiratory acidosis results from retention of CO_2 secondary to hypoventilation. Reduced CO_2 exhalation raises plasma pCO_2, which in turn causes plasma pH to fall. Primary causes of impaired ventilation are (1) depression of the medullary respiratory center, and (2) pathologic changes in the lungs (eg, status asthmaticus, airway obstruction). Over time, the kidneys compensate for respiratory acidosis by excreting less bicarbonate.

Treatment.

Primary treatment of respiratory acidosis is directed at correcting respiratory impairment. The patient may also need oxygen and ventilatory assistance. Infusion of sodium bicarbonate may be indicated if acidosis is severe.

Metabolic Alkalosis

Causes.

Metabolic alkalosis is characterized by increases in both the pH and bicarbonate content of plasma. Causes include excessive loss of gastric acid (through vomiting or suctioning) and administration of alkalinizing salts (eg, sodium bicarbonate). The body compensates for metabolic alkalosis by (1) hypoventilation (which causes retention of CO_2), (2) increased renal excretion of bicarbonate, and (3) accumulation of organic acids.

Treatment.

In most cases, metabolic alkalosis can be corrected by infusing a solution of *sodium chloride plus potassium chloride*. This facilitates renal excretion of bicarbonate, and thereby promotes normalization of plasma pH. When alkalosis is severe, direct correction of pH is indicated. This can be accomplished by infusing dilute (0.1 N) *hydrochloric acid* through a central venous catheter or by administering an acid-forming salt, such as *ammonium chloride*. However, ammonium chloride must not be given to patients with liver failure, because the drug is likely to cause hepatic encephalopathy in these patients.

Metabolic Acidosis

Causes.

Principal causes of metabolic acidosis are chronic renal failure, loss of bicarbonate during severe diarrhea, and metabolic disorders that result in overproduction of lactic acid (lactic acidosis) or ketoacids (ketoacidosis). Metabolic acidosis may also result from poisoning by methanol and certain medications (eg, aspirin and other salicylates).

Treatment.

Treatment consists of correcting the underlying cause of acidosis, and, if the acidosis is severe, administering an alkalinizing salt (eg, sodium bicarbonate, sodium carbonate).

When an alkalinizing salt is indicated, *sodium bicarbonate* is generally preferred. Administration may be oral or intravenous. If acidosis is mild, oral administration is preferred. Intravenous infusion is usually reserved for severe reductions of pH. When sodium bicarbonate is given IV to treat acute, severe acidosis, caution must be exercised to avoid excessive elevation of plasma pH. Why? Because rapid conversion from acidosis to alkalosis can be hazardous. Also, because of the sodium content of sodium bicarbonate, care should be taken to avoid hypernatremia.

POTASSIUM IMBALANCES

Potassium is the most abundant *intracellular* cation, having a concentration within cells of about 150 mEq/L. In contrast, *extracellular* concentrations are low (4 to 5 mEq/L). Potassium plays a major role in conducting nerve impulses and maintaining the electrical excitability of muscle. Potassium also helps regulate acid-base balance.

Regulation of Potassium Levels

Serum levels of potassium are regulated primarily by the kidneys. Under steady-state conditions, urinary output of potassium equals intake. Renal excretion of potassium is increased by aldosterone, an adrenal steroid that promotes conservation of sodium while increasing potassium loss. Potassium excretion is also increased by most diuretics. Potassium-sparing diuretics (eg, spironolactone) are the exception.

Potassium levels are influenced by extracellular pH. In the presence of extracellular *alkalosis,* potassium uptake by cells is *enhanced,* causing a *reduction* in extracellular potassium levels. Conversely, extracellular *acidosis* promotes the exit of potassium from cells, thereby causing extracellular *hyperkalemia*.

Insulin has a profound effect on potassium: In high doses, insulin stimulates potassium uptake by cells—an ability that has been exploited to treat hyperkalemia.

Hypokalemia

Causes and Consequences

Hypokalemia is defined as a deficiency of potassium in the blood. By definition, hypokalemia exists when serum potassium levels fall below 3.5 mEq/L. The most common cause is treatment with a thiazide or loop diuretic (see Chapter 40). Other causes include insufficient potassium intake; alkalosis and excessive insulin (both of which decrease extracellular potassium levels by driving potassium into cells); increased renal excretion of potassium (eg, as caused by aldosterone); and potassium loss associated with vomiting, diarrhea, and abuse of laxatives. Hypokalemia may also occur because of excessive potassium loss in sweat. As a rule, potassium depletion is accompanied by loss of chloride. Insufficiency of both ions produces *hypokalemic alkalosis*.

Hypokalemia has adverse effects on skeletal muscle, smooth muscle, blood pressure, and the heart. Symptoms include weakness or paralysis of skeletal muscle, a risk of fatal dysrhythmias, and intestinal dilation and ileus. In patients taking digoxin (a cardiac drug), hypokalemia is the principal cause of digoxin toxicity. For all people, hypokalemia increases the risk of hypertension and stroke.

Prevention and Treatment

Potassium depletion can be treated with three potassium salts: potassium chloride, potassium phosphate, and potassium bicarbonate. These may also be used for prophylaxis against potassium insufficiency. For either treatment or prophylaxis, the preferred salt is *potassium chloride*. Why? Because chloride deficiency frequently coexists with potassium deficiency.

Potassium chloride may be administered PO or IV. Oral therapy is preferred for prophylaxis and for treating mild deficiency. Intravenous therapy is reserved for severe deficiency and for patients who cannot take potassium by mouth.

Oral Potassium Chloride.

Uses, Dosage, and Preparations.

Oral potassium chloride may be used for both prevention and treatment of potassium deficiency. Dosages for prevention range from 16 to 24 mEq/day. Dosages for deficiency range from 40 to 100 mEq/day.

Oral potassium chloride is available in solution and in solid formulations: immediate-release tablets, sustained-release tablets, effervescent tablets, and powders. *The sustained-release tablets (eg, K-Dur, Micro-K) are preferred*. Why? Because they are more convenient and better tolerated than the other formulations, and hence offer the best chance of patient adherence.

Adverse Effects.

Potassium chloride irritates the GI tract, frequently causing abdominal discomfort, nausea, vomiting, and diarrhea. With the exception of the sustained-release tablets, solid formulations can produce high local concentrations of

potassium, resulting in severe intestinal injury (ulcerative lesions, bleeding, perforation); death has occurred. To minimize GI effects, oral potassium chloride should be taken with meals or a full glass of water. If symptoms of irritation occur, administration should be discontinued. Rarely, oral potassium chloride produces hyperkalemia. This dangerous development is much more likely with IV therapy.

Intravenous Potassium Chloride.

Intravenous potassium chloride is indicated for prevention and treatment of hypokalemia. Intravenous solutions must be diluted (preferably to 40 mEq/L or less) and infused slowly (generally no faster than 10 mEq/hr in adults).

The principal complication is *hyper*kalemia, which can prove fatal. To reduce the risk of hyperkalemia, serum potassium levels should be measured prior to the infusion and periodically throughout the treatment interval. Also, renal function should be assessed before and during treatment to ensure adequate output of urine. If renal failure develops, the infusion should be stopped immediately. Changes in the electrocardiogram (ECG) can be an early indication that potassium toxicity is developing.

Contraindications to Potassium Use.

Potassium should be avoided under conditions that predispose the patient to hyperkalemia (eg, severe renal impairment, use of potassium-sparing diuretics, hypoaldosteronism). Potassium must also be avoided when hyperkalemia already exists.

Hyperkalemia

Causes.

Hyperkalemia (excessive elevation of serum potassium) can result from a number of causes. These include severe tissue trauma, untreated Addison's disease, acute acidosis (which draws potassium out of cells), misuse of potassium-sparing diuretics, and overdose with IV potassium.

Consequences.

The most serious consequence of hyperkalemia is disruption of the electrical activity of the heart. Because hyperkalemia alters the generation and conduction of cardiac impulses, alterations in the ECG and cardiac rhythm are usually the earliest signs that potassium levels are growing dangerously high. With mild elevation of serum potassium (5 to 7 mEq/L), the T wave heightens and the PR interval becomes prolonged. When serum potassium reaches 8 to 9 mEq/L, cardiac arrest can occur, possibly preceded by ventricular tachycardia or fibrillation.

Effects of hyperkalemia are not limited to the heart. Noncardiac effects include confusion, anxiety, dyspnea, weakness or heaviness of the legs, and numbness or tingling of the hands, feet, and lips.

Treatment.

Treatment is begun by withholding any foods that contain potassium and any medicines that promote potassium accumulation (eg, potassium-sparing diuretics, potassium supplements). After this, management consists of measures that (1) counteract potassium-induced cardiotoxicity and (2) lower extracellular levels of potassium. Specific steps include (1) infusion of a *calcium salt* (eg, calcium gluconate) to offset effects of hyperkalemia on the heart; (2) infusion of *glucose* and *insulin* to promote uptake of potassium by cells and thereby decrease extracellular potassium levels; and (3) if acidosis is present (which is likely), infusion of *sodium bicarbonate* to move pH toward alkalinity, and thereby increase cellular uptake of potassium. If these measures prove inadequate, steps can be taken to remove potassium. These include (1) oral or rectal administration of *sodium polystyrene sulfonate* [Kayexalate], an exchange resin that absorbs potassium; and (2) peritoneal or extracorporeal dialysis.

MAGNESIUM IMBALANCES

Magnesium is required for the activity of many enzymes and for binding of messenger RNA to ribosomes. In addition, magnesium helps regulate neurochemical transmission and the excitability of muscle. The concentration of magnesium within cells is about 40 mEq/L, much higher than its concentration outside cells (about 2 mEq/L).

Hypomagnesemia

Causes and Consequences

Low levels of magnesium may result from a variety of causes, including diarrhea, hemodialysis, kidney disease, and prolonged intravenous feeding with magnesium-free solutions. Hypomagnesemia may also be seen in chronic alcoholics and in people with diabetes or pancreatitis. Frequently, patients with magnesium deficiency also present with hypocalcemia and hypokalemia.

Prominent symptoms of hypomagnesemia involve cardiac and skeletal muscle. In the presence of low levels of magnesium, release of acetylcholine at the neuromuscular junction is enhanced. This can increase muscle excitability to the point of tetany. Hypomagnesemia also increases excitability of neurons in the CNS, causing disorientation, psychoses, and seizures.

In the kidneys, hypomagnesemia may lead to nephrocalcinosis (formation of minuscule calcium stones within nephrons). Renal injury occurs when the stones become large enough to block the flow of tubular urine.

Prevention and Treatment

Frank hypomagnesemia is treated with parenteral magnesium sulfate. For prophylaxis against magnesium deficiency, an oral preparation (magnesium gluconate, magnesium hydroxide) may be used.

Magnesium Gluconate and Magnesium Hydroxide.

Tablets of magnesium gluconate or magnesium hydroxide may be taken as supplements to dietary magnesium to help prevent hypomagnesemia. Milk of magnesia (a liquid formulation of magnesium hydroxide) may also be used for prophylaxis. With any oral magnesium preparation, excessive doses may cause diarrhea. The adult and pediatric dosage for preventing deficiency is 5 mg/kg/day.

Magnesium Sulfate.

Uses, Administration, and Dosage.

Magnesium sulfate (IM or IV) is the preferred treatment for severe hypomagnesemia. The IM dosage is 0.5 to 1 gm 4 times a day. For IV therapy, a 10% solution can be used, infused at a rate of 1.5 mL/min or less.

Adverse Effects.

Excessive levels of magnesium cause *neuromuscular blockade*. Paralysis of the respiratory muscles is of particular concern. By suppressing neuromuscular transmission, magnesium excess can intensify the effects of neuromuscular blocking agents (eg, tubocurarine, succinylcholine). Hence, caution must be exercised in patients receiving these drugs. The neuromuscular blocking actions of magnesium can be counteracted with calcium. Accordingly, when parenteral magnesium is being employed, an injectable form of calcium (eg, calcium gluconate) should be immediately available.

In the heart, excessive magnesium can suppress impulse conduction through the atrioventricular (AV) node. Accordingly, magnesium sulfate is contraindicated for patients with AV heart block.

To minimize the risk of toxicity, serum magnesium levels should be monitored. Respiratory paralysis occurs at 12 to 15 mEq/L. When magnesium levels exceed 25 mEq/L, cardiac arrest may set in.

Hypermagnesemia

Toxic elevation of magnesium levels is most common in patients with renal insufficiency, especially when magnesium-containing antacids or cathartics are being used. Symptoms of mild intoxication include muscle weakness (resulting from inhibition of acetylcholine release), hypotension, sedation, and ECG changes. As noted, respiratory paralysis is likely when plasma levels reach 12 to 15 mEq/L. At higher magnesium concentrations, there is a risk of cardiac arrest. Muscle weakness and paralysis can be counteracted with intravenous calcium.

KEY POINTS

- Treat isotonic volume contraction with isotonic (0.9%) sodium chloride.
- Treat hypertonic volume contraction with hypotonic (eg, 0.11%) sodium chloride.
- Treat hypotonic volume contraction with hypertonic (eg, 3%) sodium chloride.

- Treat volume expansion with diuretics.
- Treat respiratory or metabolic acidosis with sodium bicarbonate.
- Treat respiratory alkalosis by having patients inhale 5% CO_2 or rebreathe their expired air.
- Treat metabolic alkalosis with an infusion of sodium chloride plus potassium chloride. For severe cases, infuse 0.1% hydrochloric acid or ammonium chloride.
- Treat moderate hypokalemia with potassium chloride in sustained-release tablets.
- Treat severe hypokalemia with IV potassium chloride.
- To treat hyperkalemia, begin by withdrawing potassium-containing foods and drugs that promote potassium accumulation (eg, potassium supplements, potassium-sparing diuretics). Subsequent measures include (1) infusing a calcium salt to offset the cardiac effects of potassium, (2) infusing glucose and insulin to promote potassium uptake by cells, and (3) infusing sodium bicarbonate if acidosis is present.
- Treat hypomagnesemia with IM or IV magnesium sulfate. For prophylaxis, give oral magnesium (eg, magnesium gluconate).

VII. DRUGS THAT AFFECT THE HEART, BLOOD VESSELS, AND BLOOD

42 Review of Hemodynamics

Hemodynamics is the study of the movement of blood throughout the circulatory system, along with the regulatory mechanisms and driving forces involved. Concepts introduced here reappear throughout the chapters on cardiovascular drugs. Accordingly, I urge you to review these now. Because this is a pharmacology text, and not a physiology text, discussion is limited to hemodynamic factors that have particular relevance to the actions of drugs.

OVERVIEW OF THE CIRCULATORY SYSTEM

The circulatory system has two primary functions: (1) delivery of oxygen, nutrients, hormones, electrolytes, and other essentials to cells; and (2) removal of carbon dioxide, metabolic wastes, and other detritus from cells. In addition, the system helps fight infection.

The circulatory system has two major divisions: the *pulmonary circulation* and the *systemic circulation*. The pulmonary circulation delivers blood to the lungs. The systemic circulation delivers blood to all other tissues. The systemic circulation is also known as the *greater circulation* or *peripheral circulation*.

Components of the Circulatory System

The circulatory system is composed of the *heart* and *blood vessels*. The heart is the pump that moves blood through the arterial tree. The blood vessels have several functions:

- *Arteries* transport blood under high pressure to tissues.
- *Arterioles* are control valves that regulate local blood flow.
- *Capillaries* are the sites for exchange of fluid, oxygen, carbon dioxide, nutrients, hormones, wastes, and so forth.
- *Venules* collect blood from the capillaries.

- *Veins* transport blood back to the heart. In addition, veins serve as a major reservoir for blood.

Arteries and veins differ with respect to distensibility (elasticity). Arteries are very muscular, and hence do not readily stretch. As a result, large increases in arterial pressure (AP) cause only small increases in arterial diameter. Veins are much less muscular, and hence are 6 to 10 times more distensible. As a result, small increases in venous pressure cause large increases in vessel diameter, which produces a large increase in venous volume.

Distribution of Blood

The adult circulatory system contains about 5 L of blood, which is distributed throughout the system. As indicated in Figure 42-1, 9% is in the pulmonary circulation, 7% is in the heart, and 84% is in the systemic circulation. Within the systemic circulation, however, distribution is uneven: most (64%) of the blood is in veins, venules, and venous sinuses; the remaining 20% is in arteries (13%) and arterioles or capillaries (7%). The large volume of blood in the venous system serves as a reservoir.

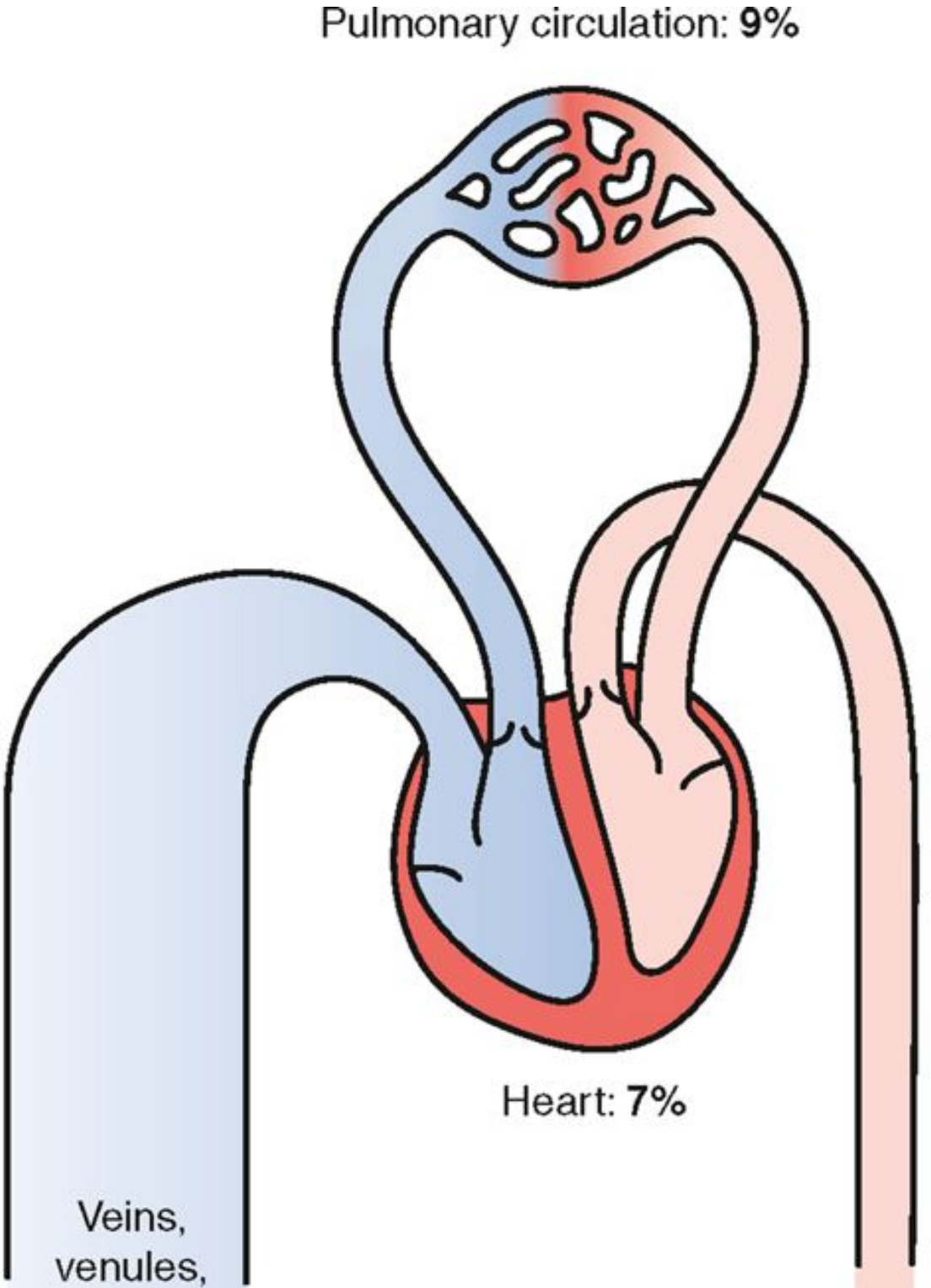

Pulmonary circulation: 9%
Heart: 7%
Veins,
venules,

Figure 42-1 Distribution of blood in the circulatory system. Note that a large percentage of the blood resides in the venous system.

What Makes Blood Flow?

Blood moves within vessels because the force that drives flow is greater than the resistance to flow. As indicated in Figure 42-2, the force that drives blood flow is the pressure gradient between two points in a vessel. Obviously, blood will flow from the point where pressure is higher toward the point where pressure is lower. Resistance to flow is determined by the diameter and length of the vessel, and by blood viscosity. From a pharmacologic viewpoint, the most important determinant of resistance is vessel diameter: the larger the vessel, the smaller the resistance, and vice versa. Accordingly, when vessels dilate, resistance declines, causing blood flow to increase—and when vessels constrict, resistance rises, causing blood flow to decline. In order to maintain adequate flow when resistance rises, blood pressure must rise as well.

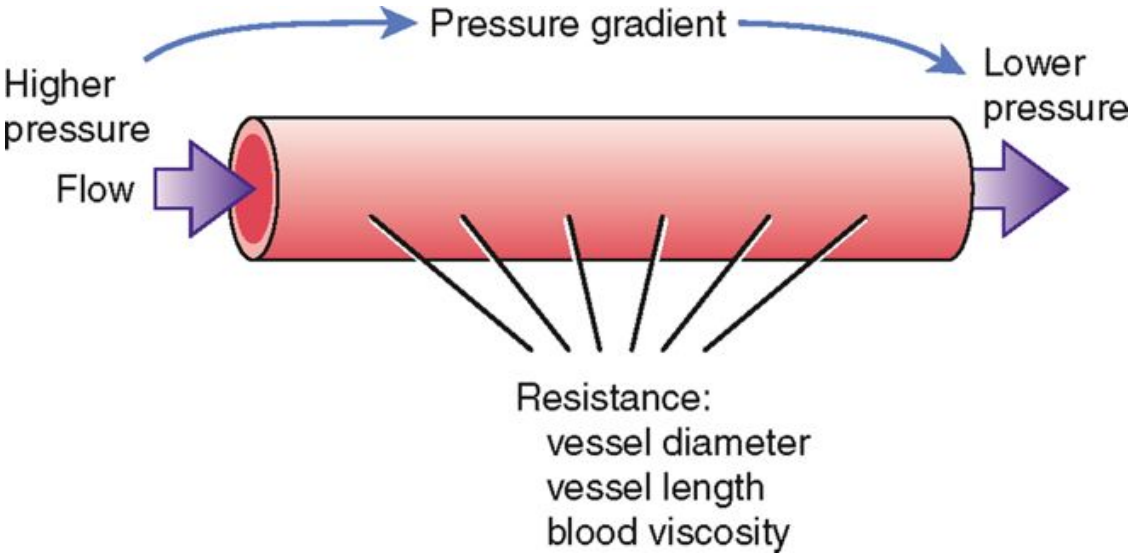


Figure 42-2 Forces that promote and impede flow of blood. Blood flows from the point of higher pressure toward the point of lower pressure. Resistance to flow is determined by vessel diameter, vessel length, and blood viscosity.

How Does Blood Get Back to the Heart?

As indicated in Figure 42-3, pressure falls progressively as blood moves through the systemic circulation. Pressure is 120 mm Hg when blood enters the aorta, 30 mm Hg when blood enters capillaries, and only 18 mm Hg when blood leaves capillaries, and then drops to negative values (0 to –5 mm Hg) in the right atrium. (Negative atrial pressure is generated by expansion of the chest during inspiration.)

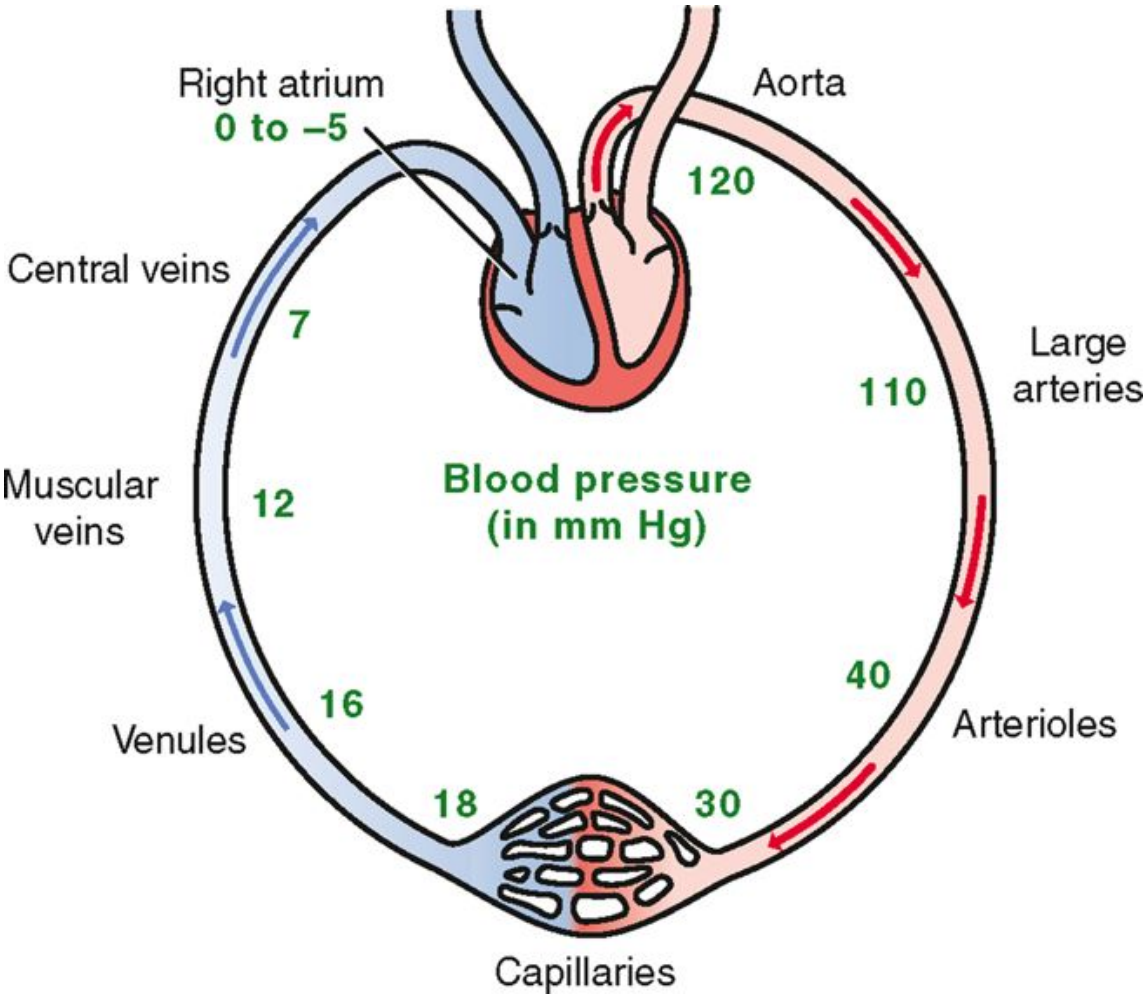


Figure 42-3 Distribution of pressure within the systemic circulation. Note that pressure is highest when blood leaves the left ventricle, falls to only 18 mm Hg as blood exits capillaries, and reaches negative values within the right atrium.

Given that pressure is only 18 mm Hg when blood leaves capillaries, we must ask, "How does blood get back to the heart? After all, a pressure of 18 mm Hg does not seem adequate to move blood from the feet all the way up to the thorax." The answer is that, in addition to the small pressure head in venules, three mechanisms help ensure venous return. First, negative pressure in the right atrium helps "suck" blood toward the heart. Second, constriction of smooth muscle in the venous wall increases venous pressure, which helps drive blood toward the heart. Third, and most important, the combination of venous valves and skeletal muscle contraction constitutes an auxiliary "venous pump." As indicated in Figure 42-4A, the veins are equipped with a system of one-way valves. When skeletal muscles contract (Fig. 42-4B), venous blood is squeezed toward the heart—the only direction the valves will permit.

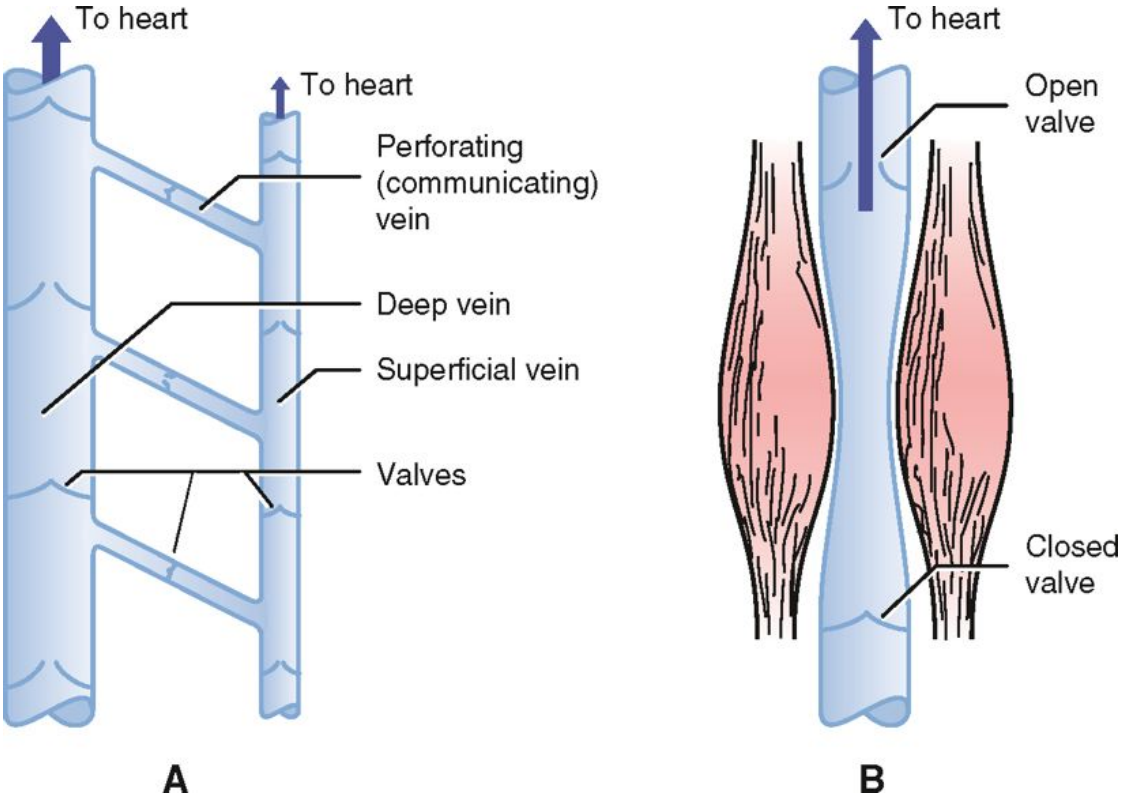


Figure 42-4 Venous valves and the auxiliary venous "pump. "A, Veins and their one-way valves in the leg. Note that the arrangement of valves ensures that blood will move toward the heart. B,

Contraction of skeletal muscle pumps venous blood toward the heart.

REGULATION OF CARDIAC OUTPUT

In the average adult, cardiac output is about 5 L/min. Hence, every minute the heart pumps the equivalent of all the blood in the body. In this section, we consider the major factors that determine how much blood the heart pumps.

Determinants of Cardiac Output

The basic equation for cardiac output is

$CO = HR \times SV$ where CO is cardiac output, HR is heart rate, and SV is stroke volume. According to the equation, an increase in HR or SV will increase CO, whereas a decrease in HR or SV will decrease CO. For the average person, heart rate is about 70 beats/min and stroke volume is about 70 mL. Multiplying these, we get 4.9 L/min—the average value for CO.

Heart Rate.

Heart rate is controlled primarily by the autonomic nervous system (ANS). Rate is increased by the sympathetic branch acting through beta***1***-adrenergic receptors in the sinoatrial (SA) node. Rate is decreased by the parasympathetic branch acting through muscarinic receptors in the SA node. Parasympathetic impulses reach the heart via the vagus nerve.

Stroke Volume.

Stroke volume is determined largely by three factors: (1) myocardial contractility, (2) cardiac afterload, and (3) cardiac preload. *Myocardial contractility* is defined as the force with which the ventricles contract. Contractility is determined primarily by the degree of cardiac dilation, which in turn is determined by the amount of venous return. The importance of venous return in regulating contractility and stroke volume is discussed separately below. In addition to regulation by venous return, contractility can be increased by the sympathetic nervous system, acting through beta***1***adrenergic receptors in the myocardium.

Preload.

Preload is formally defined as the amount of tension (stretch) applied to a muscle prior to contraction. In the heart, stretch is determined by ventricular filling pressure, that is, the *force of venous return:* the greater filling pressure is, the more the ventricles will stretch. Cardiac preload can be expressed as either *end-diastolic volume* or *end-diastolic pressure*. As discussed below, an increase in preload will increase stroke volume, whereas a decrease in preload will reduce stroke volume. Frequently, the terms *preload* and *force of venous return* are used interchangeably—although they are not truly equivalent.

Afterload.

Afterload is formally defined as the load against which a muscle exerts its force (ie, the load a muscle must overcome in order to contract). For the heart, afterload is the *arterial pressure* that the left ventricle must overcome to eject blood. Common sense tells us that, if afterload increases, stroke volume will decrease. Conversely, if afterload falls, stroke volume will rise. Cardiac afterload is determined primarily by the degree of peripheral resistance, which in turn is determined by constriction and dilation of arterioles. That is, when arterioles constrict, peripheral resistance rises, causing AP (afterload) to rise as well. Conversely, when arterioles dilate, peripheral resistance falls, causing AP to decline.

Control of Stroke Volume by Venous Return

Q: How much blood does the heart pump with each stroke?

A: Exactly the amount delivered to it by the veins!

Starling's Law of the Heart

Starling's law states that the force of ventricular contraction is proportional to muscle fiber length (up to a point). Accordingly, as fiber length (ventricular diameter) increases, there is a corresponding increase in contractile force (Fig. 42-5). Because of this built-in mechanism, when more blood enters the heart, more is pumped out. As a result, the healthy heart is able to precisely match its output with the volume of blood delivered by the veins. That is, when venous return increases, cardiac output increases correspondingly. Conversely, when venous return declines, cardiac output declines to precisely the same extent.

Hence, under normal, nonstressed conditions, stroke volume is determined by factors that regulate venous return.

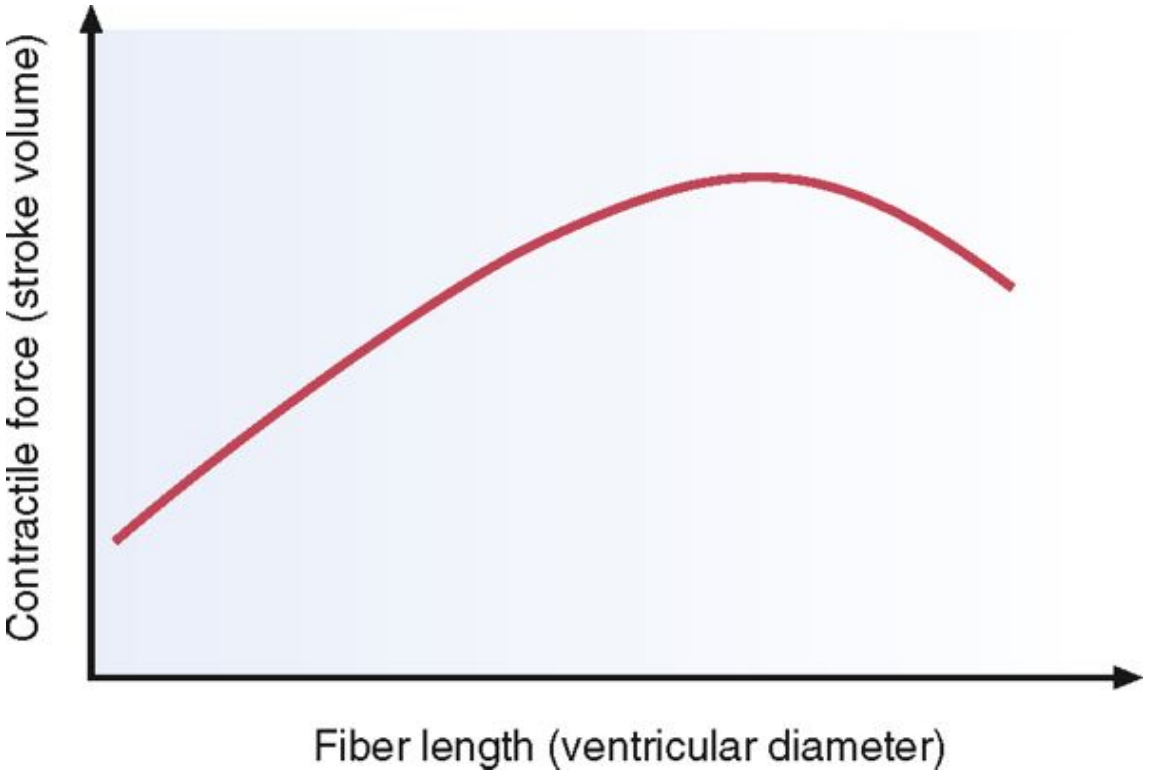


Figure 42-5 The Starling relationship between myocardial fiber length and contractile force. Note that an increase in fiber length produces a corresponding increase in contractile force. Fiber length increases as the ventricles enlarge during filling. Increased contractile force is reflected by increased stroke volume.

Why does contractile force change as a function of fiber length (ventricular diameter)? Recall that muscle contraction results from the interaction of two proteins: actin and myosin. As the heart stretches in response to increased ventricular filling, actin and myosin are brought into a more optimal alignment with each other, which allows them to interact with greater force.

Factors That Determine Venous Return

Having established that venous return is the primary determinant of stroke volume (and hence cardiac output), we need to understand the factors that determine venous return. With regard to pharmacology, the most important factor is *systemic filling pressure* (ie, the force that returns blood to the heart). The normal value for filling pressure is 7 mm Hg. This value can be raised to 17 mm Hg by constriction of veins. Filling pressure can also be raised by an increase in blood volume. Conversely, filling pressure, and hence venous return, can be lowered by venodilation or by reducing blood volume. Blood volume and venous tone can both be altered with drugs.

In addition to systemic filling pressure, three other factors influence venous return: (1) the auxiliary muscle pumps discussed above, (2) resistance to flow between peripheral vessels and the right atrium, and (3) right atrial pressure, elevation of which will impede venous return. None of these factors can be directly influenced with drugs.

Starling's Law and Maintenance of Systemic-Pulmonary Balance

Because the myocardium operates in accord with Starling's law, the right and left ventricles always pump exactly the same amount of blood. When venous return increases, stroke volume of the right ventricle increases, thereby increasing delivery of blood to the pulmonary circulation, which in turn delivers more blood to the left ventricle; this increases filling of the left ventricle, which causes *its* stroke volume to increase. Because an increase in venous return causes the output of *both* ventricles to increase, blood flow through the systemic and pulmonary circulations is always in balance, as long as the heart is healthy.

In the failing heart, Starling's law breaks down. That is, force of contraction no longer increases in proportion to increased ventricular filling. As a result, blood backs up behind the failing ventricle. The deadly consequence is illustrated in Figure 42-6. In this example, output of the left ventricle is 1% less than the output of the right ventricle, which causes blood to back up in the pulmonary circulation. In only 20 minutes, this small imbalance between left and right ventricular output shifts a liter of blood from the systemic circulation to the pulmonary circulation. In less than 40 minutes, death from pulmonary congestion would ensue. This example underscores the importance of

systemic-pulmonary balance, and the critical role of Starling's mechanism in maintaining it.

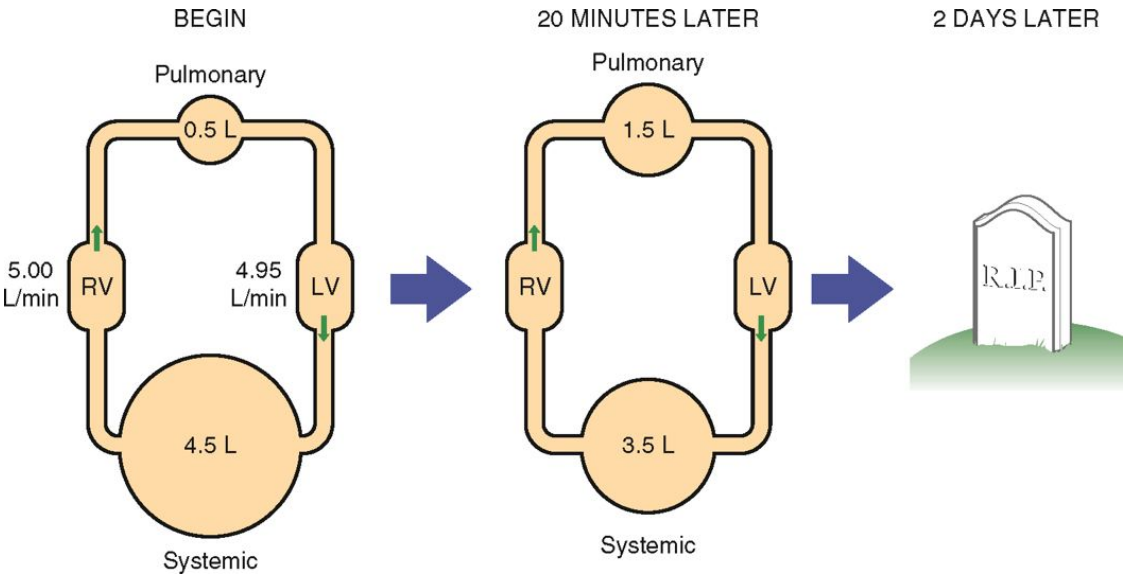


Figure 42-6 Systemic-pulmonary imbalance that develops when the output of the left and right ventricles is not identical. In this example, the output of the left ventricle is 1% less than the output of the right ventricle. Hence, while the right ventricle pumps 5000 mL/min, the left pumps only 4950 mL/min—50 mL/min less than the right side. This causes blood to back up in the pulmonary circulation. After 20 minutes, 1000 mL of blood has shifted from the systemic circulation to the pulmonary circulation. Death would ensue in less than 40 minutes. (The 2 days are an allowance for the undertaker and clergy.) Numbers in the pulmonary and systemic circulations indicate volume of blood in liters.

REGULATION OF ARTERIAL PRESSURE

AP is the driving force that moves blood through the arterial side of the systemic circulation. The general formula for AP is $AP = PR \times CO$ where AP is arterial pressure, PR is peripheral resistance, and CO is cardiac output. Accordingly, an increase in PR or CO will increase AP, whereas a decrease in PR or CO will decrease AP. Peripheral resistance is regulated primarily through con-

striction and dilation of arterioles. Cardiac output is regulated by the mechanisms discussed above. Regulation of AP through processes that alter PR and CO is discussed below.

Overview of Control Systems

Under normal circumstances, AP is regulated primarily by three systems: the ANS, the renin-angiotensin-aldosterone system (RAAS), and the kidneys. These systems differ greatly with regard to time frame of response. The ANS acts in two ways: (1) it responds rapidly (in seconds or minutes) to acute changes in blood pressure, and (2) it provides steady-state control. The RAAS responds more slowly, taking hours or days to influence AP. The kidneys are responsible for long-term control, and hence may take days or weeks to adjust AP.

Arterial pressure is also regulated by a fourth system: a family of natriuretic peptides. These peptides come into play primarily under conditions of volume overload.

Steady-State Control by the ANS

The ANS regulates AP by adjusting CO and peripheral resistance. Sympathetic tone to the heart increases heart rate and contractility, thereby increasing CO. In contrast, parasympathetic tone slows the heart, and thereby reduces CO. As discussed in Chapter 13, constriction of blood vessels is regulated exclusively by the sympathetic branch of the ANS; blood vessels have no parasympathetic innervation. Steady-state sympathetic tone provides a moderate level of vasoconstriction. The resultant resistance to blood flow maintains AP. Complete elimination of sympathetic tone would cause AP to fall by 50%.

Rapid Control by the ANS: The Baroreceptor Reflex

The baroreceptor reflex serves to maintain AP at a predetermined level. When AP changes, the reflex immediately attempts to restore AP to the preset value.

The reflex works as follows. Baroreceptors in the aortic arch and carotid sinus sense AP and relay this information to the vasoconstrictor center of the medulla. When AP changes, the vasoconstrictor center compensates by sending appropriate instructions to arterioles, veins, and the heart. For example,

when AP drops, the vasoconstrictor center causes (1) constriction of nearly all arterioles, thereby increasing peripheral resistance; (2) constriction of veins, thereby increasing venous return; and (3) acceleration of heart rate (by increasing sympathetic impulses to the heart and decreasing parasympathetic impulses). The combined effect of these responses is to restore AP to the preset level. When AP rises too high, opposite responses occur: The reflex dilates arterioles and veins, and slows the heart.

The baroreceptor reflex is poised for rapid action—but not for sustained action. When AP falls or rises, the reflex acts within seconds to restore the preset pressure. However, when AP *remains* elevated or lowered, the system resets to the new pressure within 1 to 2 days. After this, the system perceives the new (elevated or reduced) pressure as "normal," and hence ceases to respond.

Drugs that lower AP will trigger the baroreceptor reflex. For example, if we administer a drug that dilates arterioles, the resultant drop in peripheral resistance will reduce AP, causing the baroreceptor reflex to activate. The most noticeable response is *reflex tachycardia*. The baroreceptor reflex can temporarily negate efforts to lower AP with drugs.

The Renin-Angiotensin-Aldosterone System

The RAAS supports AP by causing (1) constriction of arterioles and veins, and (2) retention of water by the kidney. Vasoconstriction is mediated by a hormone named *angiotensin II*. Water retention is mediated in part by *aldosterone*. Responses develop in hours (vasoconstriction) to days (water retention). The RAAS and its role in controlling blood pressure are discussed at length in Chapter 43.

Renal Retention of Water

When AP remains low for a long time, the kidney responds by retaining water, which in turn causes AP to rise. Pressure rises because fluid retention increases blood volume, which increases venous pressure, which increases venous return, which increases CO, which increases AP. Water retention is a mechanism for maintaining AP over long periods (weeks, months, years).

Why does a reduction in AP cause the kidney to retain water? First, low AP reduces renal blood flow (RBF), which in turn reduces glomerular filtration

rate (GFR). Because less fluid is filtered, less urine is produced, and therefore more water is retained. Second, low AP activates the RAAS, causing levels of angiotensin II and aldosterone to rise. Angiotensin II causes constriction of renal blood vessels, and thereby further decreases RBF and GFR. Aldosterone promotes renal retention of sodium, which causes water to be retained along with it.

Postural Hypotension

Postural hypotension, also known as *orthostatic hypotension,* is a reduction in AP that can occur when we move from a supine or seated position to an upright position. The cause of hypotension is pooling of blood in veins, which decreases venous return, which in turn decreases CO. Between 300 and 800 mL of blood can pool in veins when we stand, causing CO to drop by as much as 2 L/min. Why does blood collect in veins? When we stand, gravity increases the pressure that blood exerts on veins. Since veins are not very muscular, they are unable to retain their shape when pressure increases, and hence they stretch. The resultant increase in venous volume allows blood to pool.

Two mechanisms help overcome postural hypotension. One is the system of auxiliary venous pumps, which promote venous return. In fact, in healthy individuals, these auxiliary pumps usually prevent postural hypotension from occurring in the first place. When postural hypotension does occur, the baroreceptor reflex can restore AP by (1) constricting veins and arterioles and (2) increasing heart rate.

What would happen if we gave a drug that promoted dilation of veins (or prevented them from constricting)? In patients taking drugs that interfere with venoconstriction, postural hypotension is more intense and more prolonged. Hypotension is more intense because venous pooling is greater. Hypotension is more prolonged because there is no venoconstriction to help reverse venous pooling. As with drugs that reduce AP by dilating arterioles, drugs that reduce AP by relaxing veins can trigger the baroreceptor reflex, and can thereby cause reflex tachycardia.

Natriuretic Peptides

Natriuretic peptides serve to protect the cardiovascular system in the event of volume overload, a condition that increases preload, and thereby increases CO and AP. Volume overload is caused by excessive retention of sodium and water. Natriuretic peptides work primarily by (1) reducing blood volume and (2) promoting dilation of arterioles and veins. Both actions lower AP.

The family of natriuretic peptides has three principal members: *atrial natriuretic peptide* (ANP), *B-* or *brain natriuretic peptide* (BNP), and *C-natriuretic peptide* (CNP). ANP is produced by myocytes of the atria; BNP is produced by myocytes of the ventricles (and to a lesser extent by cells in the brain, where BNP was discovered); and CNP is produced by cells of the vascular endothelium. When blood volume is excessive, all three peptides are released. (Release of ANP and BNP is triggered by stretching of the atria and ventricles, which occurs because of increased preload.)

ANP and BNP have similar actions. Both peptides reduce blood volume and increase venous capacitance, and thereby reduce cardiac preload. Three processes are involved. First, ANP and BNP shift fluid from the vascular system to the extravascular compartment; the underlying mechanism is increased vascular permeability. Second, they act on the kidney to cause diuresis (loss of water) and natriuresis (loss of sodium). Third, they promote dilation of arterioles and veins, in part by suppressing sympathetic outflow from the central nervous system. In addition to these actions, ANP and BNP help protect the heart during the early phase of heart failure. How? By suppressing both the RAAS and sympathetic outflow, and by inhibiting proliferation of myocytes. Although CNP shares some actions of ANP and BNP, its primary action is to promote vasodilation.

KEY POINTS*

- Arterioles serve as control valves to regulate local blood flow.
- Veins are a reservoir for blood.
- Arteries are not very distensible. As a result, large increases in AP cause only small increases in arterial diameter.

- Veins are highly distensible. As a result, small increases in venous pressure cause large increases in venous diameter.
- The adult circulatory system contains 5 L of blood, 64% of which is in systemic veins.
- Vasodilation reduces resistance to blood flow, whereas vasoconstriction increases resistance to flow.
- In addition to the small pressure head in venules, three mechanisms help ensure venous return: (1) negative pressure in the right atrium sucks blood toward the heart; (2) constriction of veins increases venous pressure, and thereby drives blood toward the heart; and (3) contraction of skeletal muscles, in conjunction with one-way venous valves, pumps blood toward the heart.
- Heart rate is increased by sympathetic nerve impulses and decreased by parasympathetic impulses.
- Stroke volume is determined by myocardial contractility, cardiac preload, and cardiac afterload.
- Preload is defined as the amount of tension (stretch) applied to a muscle prior to contraction. In the heart, preload is determined by the force of venous return.
- Afterload is defined as the load against which a muscle exerts its force. For the heart, afterload is the arterial pressure (AP) that the left ventricle must overcome to eject blood.
- Cardiac afterload is determined primarily by peripheral resistance, which in turn is determined by the degree of constriction in arterioles.
- Starling's law states that the force of ventricular contraction is proportional to myocardial fiber length. Because of this relationship, when more blood enters the heart, more is pumped out. As a result, the healthy heart is able to precisely match output with venous return.
- The most important determinant of venous return is systemic filling pressure, which can be raised by constricting veins and increasing blood volume.
- Because cardiac muscle operates under Starling's law, the right and left ventricles always pump exactly the same amount of blood (assuming the heart is

healthy). Hence, balance between the pulmonary and systemic circulations is maintained.

- Arterial pressure is regulated by the ANS, the RAAS, the kidneys, and natriuretic peptides.
- The ANS regulates AP (1) through tonic control of heart rate and peripheral resistance and (2) through the baroreceptor reflex.
- The baroreceptor reflex is only useful for short-term control of AP. When pressure remains elevated or lowered, the system resets to the new pressure within 1 to 2 days, and hence ceases to respond.
- Drugs that lower AP trigger the baroreceptor reflex, and thereby cause reflex tachycardia. Hence, the baroreceptor reflex can temporarily negate efforts to lower AP with drugs.
- The RAAS supports AP by causing (1) constriction of arterioles and veins and (2) retention of water by the kidneys. Vasoconstriction is mediated by angiotensin II; water retention is mediated in part by aldosterone.
- The kidneys provide long-term control of blood pressure by regulating blood volume.
- Postural (orthostatic) hypotension is caused by decreased venous return secondary to pooling of blood in veins, which can occur when we assume an erect posture.
- Drugs that dilate veins intensify and prolong postural hypotension. As with other drugs that reduce AP, venodilators can trigger the baroreceptor reflex, and can thereby cause reflex tachycardia.
- Natriuretic peptides defend the cardiovascular system from volume overload—primarily by reducing blood volume and promoting vasodilation.

* Key points are limited to concepts that might not have been stressed when you studied physiology (eg, veins serve as a blood reservoir). Important but obvious concepts (eg, the heart is a pump; arteries deliver blood to tissues under pressure) are not included in this summary.

43 Drugs Acting on the Renin-Angiotensin-Aldosterone System

In this chapter we consider four families of drugs: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), direct renin inhibitors (DRIs), and aldosterone antagonists. With all four groups, effects result from interfering with the renin-angiotensin-aldosterone system (RAAS). The ACE inhibitors, available for more than two decades, have established roles in the treatment of hypertension, heart failure, and diabetic nephropathy; in addition, these drugs are indicated for myocardial infarction and prevention of cardiovascular events in patients at risk. Indications for ARBs are limited to hypertension, heart failure, and diabetic nephropathy. The aldosterone antagonists have only two indications: hypertension and heart failure. Current indications for DRIs are limited to hypertension. We begin the chapter by reviewing the physiology of the RAAS, after which we discuss the drugs that affect it.

PHYSIOLOGY OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The RAAS plays an important role in regulating blood pressure, blood volume, and fluid and electrolyte balance. In addition, the system appears to mediate certain pathophysiologic changes associated with hypertension, heart failure, and myocardial infarction. The RAAS exerts its effects through angiotensin II and aldosterone.

Types of Angiotensin

Before considering the physiology of the RAAS, we need to introduce the angiotensin family, which consists of angiotensin I, angiotensin II, and angiotensin III. All three compounds are small polypeptides. Angiotensin I is the precursor of angiotensin II (Fig. 43-1) and has only weak biologic activity. In contrast, angiotensin II has strong biologic activity. Angiotensin III, which is formed by degradation of angiotensin II, has moderate biologic activity.

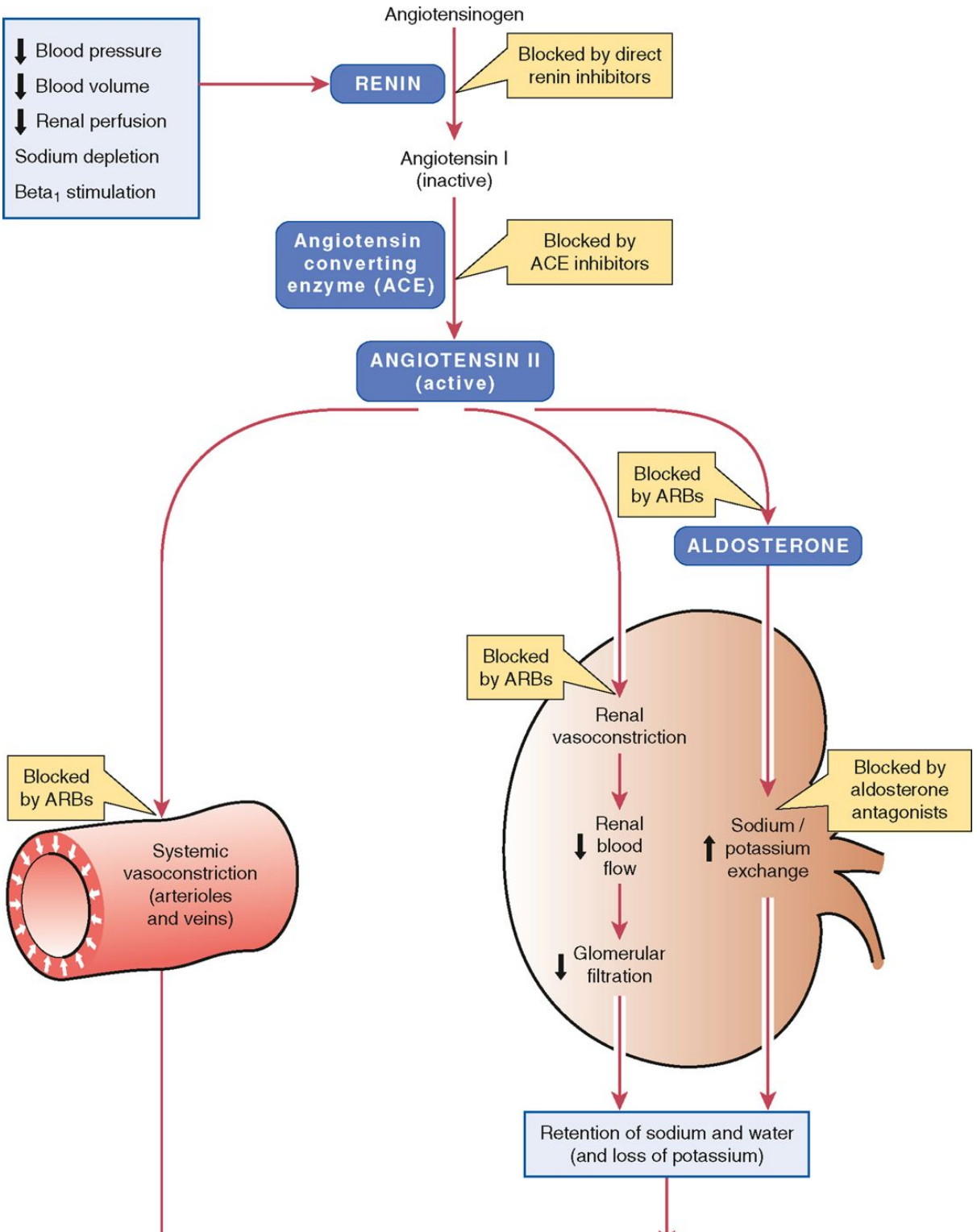

Angiotensinogen
Blood pressure
Blood volume
Renal perfusion
Sodium depletion
Beta1 stimulation
RENIN
Blocked by direct renin inhibitors
Angiotensin I (inactive)
Angiotensin converting enzyme (ACE)
Blocked by ACE inhibitors
ANGIOTENSIN II (active)
Blocked by ARBs
ALDOSTERONE
Blocked by ARBs
Renal vasoconstriction
Blocked by ARBs
Systemic vasoconstriction (arterioles and veins)
Renal blood flow
Sodium / potassium exchange
Blocked by aldosterone antagonists
Glomerular filtration
Retention of sodium and water (and loss of potassium)

Figure 43-1 Regulation of blood pressure by the renin-angiotensin-aldosterone system. In addition to the mechanisms depicted, angiotensin II can raise blood pressure by (1) acting on the distal nephron to promote reabsorption of sodium and (2) increasing vasoconstriction by three mechanisms: promoting release of norepinephrine from sympathetic nerves; promoting release of epinephrine from the adrenal medulla; and acting in the central nervous system to increase sympathetic outflow to blood vessels. (ARBs = angiotensin-receptor blockers.)

Actions of Angiotensin II

Angiotensin II participates in all processes regulated by the RAAS. The most prominent actions of angiotensin II are vasoconstriction and stimulation of aldosterone release. Both actions serve to raise blood pressure. In addition, angiotensin II (as well as aldosterone) can act on the heart and blood vessels to cause pathologic changes in their structure and function.

Vasoconstriction.

Angiotensin II is a powerful vasoconstrictor. The compound acts directly on vascular smooth muscle (VSM) to cause contraction. Vasoconstriction is prominent in arterioles and less so in veins. As a result of angiotensin-induced vasoconstriction, blood pressure rises. In addition to its direct action on blood vessels, angiotensin II can cause vasoconstriction indirectly by acting on (1) sympathetic neurons to promote norepinephrine release, (2) the adrenal medulla to promote epinephrine release, and (3) the central nervous system to increase sympathetic outflow to blood vessels.

Release of Aldosterone.

Angiotensin II acts on the adrenal cortex to promote synthesis and secretion of aldosterone, whose actions are discussed below. The adrenal cortex is highly sensitive to angiotensin II, and hence angiotensin II can stimulate aldosterone release even when angiotensin II levels are too low to induce vasoconstriction. Aldosterone secretion is enhanced when sodium levels are low and when potassium levels are high.

Alteration of Cardiac and Vascular Structure.

Angiotensin II may cause pathologic structural changes in the heart and blood vessels. In the heart, the compound may cause *hypertrophy* (increased cardiac mass) and *remodeling* (redistribution of mass within the heart). In hypertension, angiotensin II may be responsible for increasing the thickness of blood vessel walls; in atherosclerosis, it may be responsible for thickening the intimal surface of blood vessels; and in heart failure and myocardial infarction, it may be responsible for causing cardiac hypertrophy and fibrosis.

Known effects of angiotensin II that could underlie these pathologic changes include

- Increased migration, proliferation, and hypertrophy of VSM cells
- Increased production of extracellular matrix by VSM cells
- Hypertrophy of cardiac myocytes
- Increased production of extracellular matrix by cardiac fibroblasts

Actions of Aldosterone

Regulation of Blood Volume and Blood Pressure.

After being released from the adrenal cortex, aldosterone acts on distal tubules of the kidney to cause retention of sodium and excretion of potassium and hydrogen. Because retention of sodium causes water to be retained as well, aldosterone increases blood volume, which causes blood pressure to rise.

Pathologic Cardiovascular Effects.

Until recently, knowledge of aldosterone's actions was limited to effects on the kidney. Now, however, we know that aldosterone can cause more harmful effects. Like angiotensin II, aldosterone can promote cardiac remodeling and fibrosis. In addition, aldosterone can activate the sympathetic nervous system and suppress uptake of norepinephrine in the heart, thereby predisposing the heart to dysrhythmias. Aldosterone can also promote vascular fibrosis (which decreases arterial compliance) and disrupt the baroreceptor reflex. These adverse effects appear to be limited to states such as heart failure, in which levels of aldosterone can be extremely high.

Formation of Angiotensin II by Renin and Angiotensin-Converting Enzyme

As indicated in Figure 43-1, angiotensin II is formed through two sequential reactions. The first is catalyzed by renin, the second by ACE.

Renin

Renin (pronounced "reenin") catalyzes the formation of *angiotensin I* from *angiotensinogen*. This reaction is the rate-limiting step in angiotensin II formation. Renin is produced by juxtaglomerular cells of the kidney and undergoes controlled release into the bloodstream, where it cleaves angiotensinogen into angiotensin I.

Regulation of Renin Release.

Since renin catalyzes the rate-limiting step in angiotensin II formation, and since renin must be released into the blood in order to act, the factors that regulate renin release regulate the rate of angiotensin II formation.

As indicated in Figure 43-1, release of renin can be triggered by multiple factors. Release *increases* in response to a *decline* in blood pressure, blood volume, plasma sodium content, or renal perfusion pressure. Reduced renal perfusion pressure is an especially important stimulus for renin release, and can occur in response to (1) stenosis of the renal arteries, (2) reduced systemic blood pressure, and (3) reduced plasma volume (brought on by dehydration, hemorrhage, or chronic sodium depletion). For the most part, these factors increase renin release through effects exerted locally in the kidney. However, some of these factors may also promote renin release through activation of the sympathetic nervous system. (Sympathetic nerves increase secretion of renin by causing stimulation of beta***1***-adrenergic receptors on juxtaglomerular cells.)

Release of renin is *suppressed* by factors opposite to those that cause release. That is, renin secretion is inhibited by elevation of blood pressure, blood volume, and plasma sodium content. Hence, as blood pressure, blood volume, and plasma sodium content increase in response to renin release, further release of renin is suppressed. In this regard, we can view release of renin as being regulated by a classic negative feedback loop.

Angiotensin-Converting Enzyme (Kinase II)

ACE catalyzes the conversion of angiotensin I (inactive) into angiotensin II (highly active). ACE is located on the luminal surface of all blood vessels, the vasculature of the lungs being especially rich in the enzyme. Because ACE is abundant, conversion of angiotensin I into angiotensin II occurs almost instantaneously after angiotensin I has been formed. ACE is a relatively nonspecific enzyme that can act on a variety of substrates in addition to angiotensin I.

Nomenclature regarding ACE can be confusing and requires comment. As just noted, ACE can act on several substrates. When the substrate is angiotensin I, we refer to the enzyme as ACE. However, when the enzyme is acting on other substrates, we refer to it by different names. Of importance to us, when the substrate is a hormone known as *bradykinin,* we refer to the enzyme as *kinase II*. So, please remember, whether we call it ACE or kinase II, we're talking about the same enzyme.

Regulation of Blood Pressure by the Renin-Angiotensin-Aldosterone System

The RAAS is poised to help regulate blood pressure: factors that lower blood pressure turn the system on; factors that raise blood pressure turn it off. However, although the RAAS does indeed contribute to blood pressure control, its role in *normovolemic, sodium-replete* individuals is only modest. In contrast, the system can be a major factor in maintaining blood pressure in the presence of *hemorrhage, dehydration*, or *sodium depletion*.

As depicted in Figure 43-1, the RAAS, acting through angiotensin II, raises blood pressure through two basic processes: vasoconstriction and renal retention of water and sodium. Vasoconstriction raises blood pressure by increasing total peripheral resistance; retention of water and sodium raises blood pressure by increasing blood volume. Vasoconstriction occurs within minutes to hours of activating the system, and hence can raise blood pressure quickly. In contrast, days, weeks, or even months are required for the kidney to raise blood pressure by increasing blood volume.

As suggested by Figure 43-1, angiotensin II acts in two ways to promote renal retention of water. First, by constricting renal blood vessels, angiotensin II re-

duces renal blood flow, and thereby reduces glomerular filtration. Second, angiotensin II stimulates release of aldosterone from the adrenal cortex. Aldosterone then acts on renal tubules to promote retention of sodium and water and excretion of potassium.

Tissue (Local) Angiotensin II Production

In addition to the traditional RAAS that we've been discussing, in which angiotensin II is produced in the blood and then carried to target tissues, angiotensin II can be produced in individual tissues. This permits discrete, local effects of angiotensin II independent of the main system. Interference with local production of angiotensin II may underlie some effects of the ACE inhibitors.

It is important to note that some angiotensin II is produced by pathways that *do not involve* ACE. As a result, drugs that inhibit ACE cannot completely block angiotensin II production.

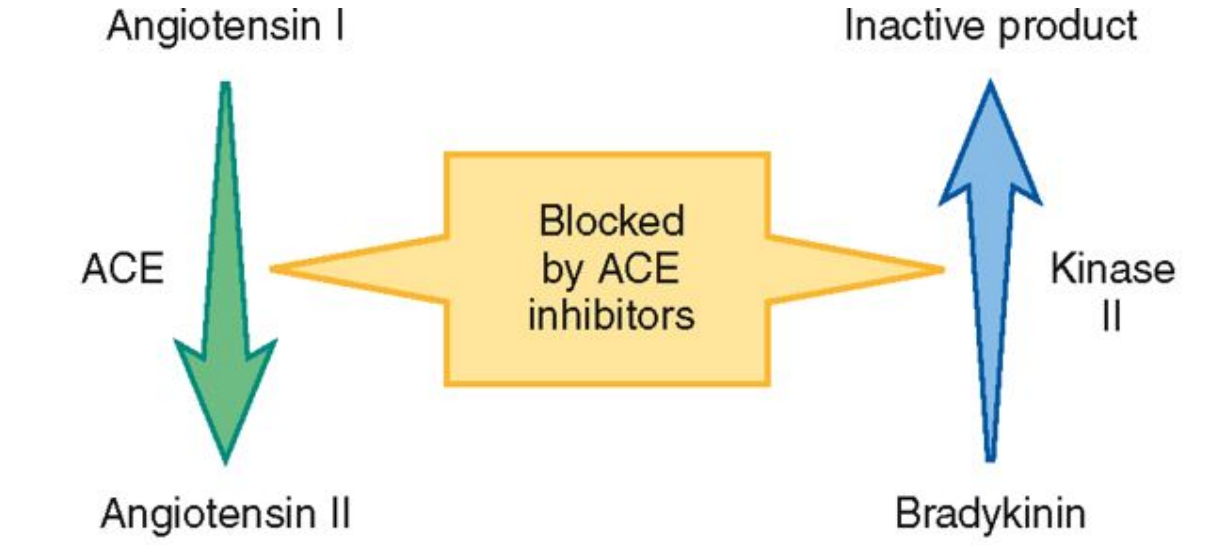
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The ACE inhibitors are important drugs for *treating* hypertension, heart failure, diabetic nephropathy, and myocardial infarction (MI). In addition, they are used to *prevent* adverse cardiovascular events in patients at risk. Their most prominent adverse effects are cough, angioedema, first-dose hypotension, and hyperkalemia. For all of these agents, beneficial effects result largely from suppressing formation of angiotensin II. Because the similarities among ACE inhibitors are much more striking than their differences, we will discuss these drugs as a group, rather than selecting a prototype to represent them.

Mechanism of Action and Overview of Pharmacologic Effects

As indicated in Figure 43-2, ACE inhibitors produce their beneficial and adverse effects by (1) reducing levels of angiotensin II (through inhibition of ACE) and (2) increasing levels of bradykinin (through inhibition of kinase II). By reducing levels of angiotensin II, ACE inhibitors can dilate blood vessels (primarily arterioles and to a lesser extent veins), reduce blood volume (through effects on the kidney), and, importantly, prevent or reverse pathologic changes in the heart and blood vessels mediated by angiotensin II and

aldosterone. Inhibition of ACE can also cause hyperkalemia and fetal injury. Elevation of bradykinin causes vasodilation (secondary to increased production of prostaglandins and nitric oxide), and can also lead to cough and angioedema.



↓ Angiotensin II results in

- Vasodilation
- ↓ Blood volume
- ↓ Cardiac and vascular remodeling
- Potassium retention
- Fetal injury

↑ Bradykinin results in

- Vasodilation
- Cough
- Angioedema (rarely)

Figure 43-2 Overview of ACE inhibitor actions and pharmacologic effects. Angiotensin-converting enzyme (ACE) and kinase II are two names for the same enzyme. When angiotensin II is the substrate, we call the enzyme ACE; when bradykinin is the substrate, we call it kinase II. Inhibition of this enzyme decreases production of angiotensin II (thereby reducing angiotensin II levels), and decreases breakdown of bradykinin (thereby increasing bradykinin levels).

Pharmacokinetics

Regarding pharmacokinetics, the following generalizations apply:

- Nearly all ACE inhibitors are administered *orally*. The only exception is enalaprilat (the active form of enalapril), which is given IV.
- Except for captopril and moexipril, all oral ACE inhibitors can be administered with food.
- With the exception of captopril, all ACE inhibitors have prolonged half-lives, and hence can be administered just once or twice a day. Captopril is administered 2 or 3 times a day.
- With the exception of lisinopril, all ACE inhibitors are *prodrugs* that must undergo conversion to their active form in the small intestine and liver. Lisinopril is active as given.
- All ACE inhibitors are *excreted by the kidneys*. As a result, nearly all can accumulate to dangerous levels in patients with kidney disease, and hence *dosages must be reduced in these patients*. Only one agent—fosinopril—does not require a dosage reduction.

Therapeutic Uses

When the ACE inhibitors were introduced (over 25 years ago), their only indication was hypertension. Since then, we have learned that their benefits are much broader: In addition to their use in hypertension, these drugs are now used for patients with heart failure, acute MI, left ventricular dysfunction, and diabetic and nondiabetic nephropathy. In addition, they can help prevent MI, stroke, and death in patients at high risk for cardiovascular events. It should be

noted that no single ACE inhibitor is approved for all of these conditions (Table 43-1). However, given that all ACE inhibitors are very similar, it seems likely that all may produce similar benefits.

Generic Name	Trade Name	Approved Indications*	Starting Dosage†	Usual Maintenance Dosage†
Benazepril	Lotensin	Hypertension	10 mg once/day	20–40 mg/day in 1 or 2 doses
Captopril	Capoten	Hypertension	25 mg 2 or 3 times/day	25–50 mg 2 or 3 times/day
		Heart failure	6.25 mg 3 times/day	50–100 mg 3 times/day
		LVD after MI	12.5 mg 3 times/day	50 mg 3 times/day
		Diabetic nephropathy	25 mg 3 times/day	25 mg 3 times/day
Enalapril	Vasotec	Hypertension	5 mg once/day	10–40 mg/day in 1 or 2 doses
		Heart failure	2.5 mg twice/day	10–20 mg twice/day
		Asymptomatic LVD	2.5 mg twice/day	10 mg twice/day
Enalaprilat	Vasotec	Hypertension	1.25 mg every 6 hr	
Fosinopril	Monopril	Hypertension	10 mg once/day	20–40 mg/day in 1 or 2 doses
		Heart failure	5–10 mg once/day	20–40 mg once/day
Lisinopril	Prinivil, Zestril	Hypertension	10 mg once/day	20–40 mg once/day
		Heart failure	2.5–5 mg once/day	20–40 mg once/day
		Acute MI	5 mg once/day	10 mg once/day
Moexipril	Univasc	Hypertension	7.5 mg once/day	7.5–30 mg/day in 1 or 2 doses
Perindopril	Aceon	Hypertension	4 mg once/day	4–8 mg/day in 1 or 2 doses
		Stable CAD	4 mg once/day	8 mg once/day
Quinapril	Accupril	Hypertension	10–20 mg/day	20–80 mg/day in 1 or 2 doses
		Heart failure	5 mg twice/day	20–40 mg twice/day
Ramipril	Altace	Hypertension	2.5 mg once/day	2.5–20 mg/day in 1 or 2 doses
		Heart failure after MI	1.25–2.5 mg twice/day	5 mg twice/day
		Prevention of MI, stroke, and death in people at high risk for CVD	2.5 mg/day for 1 wk	5 mg once/day for 3 wk
Trandolapril	Mavik	Hypertension	1 mg once/day	2–4 mg once/day
		Heart failure after MI	1 mg once/day	4 mg once/day
		LVD after MI	1 mg once/day	4 mg once/day

TABLE 43-1 ACE Inhibitors: Approved Indications and Adult Dosages

* CAD = coronary artery disease; CVD = cardiovascular disease; LVD = left ventricular dysfunction; MI = myocardial infarction.

† For all ACE inhibitors except fosinopril, dosage must be reduced in patients with significant renal impairment.

Hypertension.

All ACE inhibitors are approved for hypertension. These drugs are especially effective against malignant hypertension and hypertension secondary to renal arterial stenosis. They are also useful against essential hypertension of mild to moderate intensity—although maximal benefits may take several weeks to develop.

In patients with essential hypertension, the mechanism underlying blood pressure reduction is not fully understood. *Initial* responses are proportional to circulating angiotensin II levels and are clearly related to reduced formation of that compound. (By lowering angiotensin II levels, ACE inhibitors dilate blood vessels and reduce blood volume; both actions help lower blood pressure.) However, with *prolonged* therapy, blood pressure often undergoes additional decline. During this second phase, there is no correspondence between reductions in blood pressure and reductions in *circulating* angiotensin II. It may be that the delayed response is due to reductions in *local* angiotensin II levels—reductions that would not be revealed by measuring angiotensin II in the blood.

ACE inhibitors offer several advantages over most other antihypertensive drugs. In contrast to the sympatholytic agents, ACE inhibitors do not interfere with cardiovascular reflexes. Hence, exercise capacity is not impaired and orthostatic hypotension is minimal. In addition, these drugs can be used safely in patients with bronchial asthma, a condition that precludes the use of beta2-adrenergic antagonists. ACE inhibitors do not promote hypokalemia, hyperuricemia, or hyperglycemia—side effects seen with thiazide diuretics. Furthermore, they do not induce lethargy, weakness, or sexual dysfunction—responses that are common with other antihypertensive agents. Most importantly, *ACE inhibitors reduce the risk of cardiovascular mortality caused by hypertension*. The

only other drugs proved to reduce hypertension-associated mortality are beta blockers and diuretics (see Chapter 46).

Heart Failure.

ACE inhibitors produce multiple benefits in heart failure. By lowering arteriolar tone, these drugs improve regional blood flow, and, by reducing cardiac afterload, they increase cardiac output. By causing venous dilation, they reduce pulmonary congestion and peripheral edema. By dilating blood vessels in the kidney, they increase renal blood flow, and thereby promote excretion of sodium and water. This loss of fluid has two beneficial effects: (1) it helps reduce edema and (2) by lowering blood volume, it decreases venous return to the heart, and thereby reduces right-heart size. Lastly, by suppressing aldosterone and by reducing local production of angiotensin II in the heart, ACE inhibitors may prevent or reverse pathologic changes in cardiac structure. Although only seven ACE inhibitors are approved for heart failure (see Table 43-1), both the American Heart Association and the American College of Cardiology have concluded that the ability to improve symptoms and prolong survival is a class effect. The use of ACE inhibitors in heart failure is discussed further in Chapter 47.

Myocardial Infarction.

ACE inhibitors can reduce mortality following acute MI (heart attack). In addition, they decrease the chance of developing overt heart failure. Treatment should begin as soon as possible after infarction and should continue for at least 6 weeks. In patients who develop overt heart failure, treatment should continue long term. As for patients who do not develop heart failure, there are no data to indicate whether continued treatment would be beneficial or not. At this time, only three ACE inhibitors—captopril, lisinopril, and trandolapril—are approved for patients with MI.

Diabetic and Nondiabetic Nephropathy.

ACE inhibitors can benefit patients with diabetic nephropathy, the leading cause of end-stage renal disease in the United States. In patients with overt nephropathy, as indicated by proteinuria of more than 500 mg/day, ACE inhibitors can slow progression of renal disease. In patients with less advanced

nephropathy (30 to 300 mg proteinuria/day), ACE inhibitors can delay onset of overt nephropathy. These benefits were first demonstrated in patients with type 1 diabetes (insulin-dependent diabetes mellitus) and were later demonstrated in patients with type 2 diabetes (non–insulin-dependent diabetes mellitus). More recently, ACE inhibitors have been shown to provide similar protection in patients with nephropathy unrelated to diabetes.

The principal protective mechanism appears to be reduction of glomerular filtration pressure. ACE inhibitors lower filtration pressure by reducing levels of angiotensin II, a compound that can raise filtration pressure by two mechanisms. First, angiotensin II raises systemic blood pressure, which raises pressure in the afferent arteriole of the glomerulus (Fig. 43-3). Second, it constricts the efferent arteriole, thereby generating back-pressure in the glomerulus. The resultant increase in filtration pressure promotes injury. By reducing levels of angiotensin II, ACE inhibitors lower glomerular filtration pressure, and thereby slow development of renal injury.

At this time, the only ACE inhibitor approved for nephropathy is captopril. However, the American Diabetes Association considers benefits in diabetic nephropathy to be a class effect, and hence recommends choosing an ACE inhibitor based on its cost and likelihood of patient adherence.

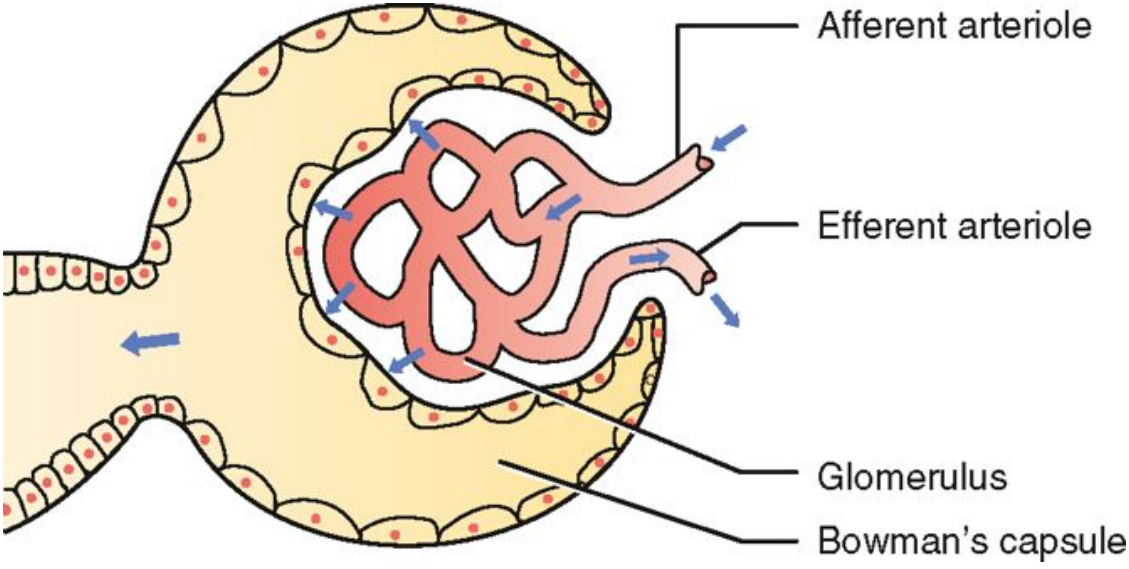


Figure 43-3 Elevation of glomerular filtration pressure by angiotensin II. Angiotensin II increases filtration pressure by (1) increasing pressure in the afferent arteriole (secondary to increasing systemic arterial pressure), and by (2) constricting the efferent arteriole, thereby generating back-pressure in the glomerulus.

Prevention of MI, Stroke, and Death in Patients at High Cardiovascular Risk.

One ACE inhibitor—*ramipril* [Altace]—is approved for reducing the risk of MI, stroke, and death (from cardiovascular causes) in patients at *high* risk for a major cardiovascular event—high risk being defined by (1) a history of stroke, coronary artery disease, peripheral vascular disease, or diabetes, combined with (2) at least one other risk factor, such as hypertension, high LDL cholesterol, low HDL cholesterol, or cigarette smoking. Ramipril was approved for this use based on results of the *Heart Outcomes Prevention Evaluation* (HOPE) trial, a large study in which patients at high

cardiovascular risk took either ramipril (10 mg/day) or placebo. Follow-up time was 5 years. The result? The combined endpoint of MI, stroke, or death from cardiovascular causes was significantly lower in the ramipril group (14% vs. 18%)—a 22% reduction in risk. Possible mechanisms underlying benefits include reduced vascular resistance and protection of the heart, blood vessels, and kidneys from the damage that angiotensin II and aldosterone can cause over time.

Like ramipril, *perindopril* [Aceon] can reduce morbidity and mortality in patients at risk for major cardiovascular events. However, the drug is not yet approved for this use. Benefits were demonstrated in the *EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease* (EUROPA). Patients in EUROPA were at lower risk than those in HOPE.

Can ACE inhibitors other than ramipril and perindopril also reduce cardiovascular risk? Possibly. However, at this time there is insufficient evidence to say for sure.

Adverse Effects

ACE inhibitors are generally well tolerated. Some adverse effects (eg, first-dose hypotension, hyperkalemia) are due to a reduction in angiotensin II, whereas others (cough, angioedema) are due to elevation of bradykinin.

First-Dose Hypotension.

A precipitous drop in blood pressure may occur following the first dose of an ACE inhibitor. This reaction is caused by widespread vasodilation secondary to abrupt lowering of angiotensin II levels. First-dose hypotension is most likely in patients with severe hypertension, in patients taking diuretics, and in patients who are sodium depleted or volume depleted. To minimize the first-dose effect, initial doses should be low. Also, diuretics should be temporarily discontinued, starting 2 to 3 days before starting an ACE inhibitor. Blood pressure should be monitored for several hours following the first dose of an ACE inhibitor. If hypotension develops, the patient should assume a supine position. If necessary, blood pressure can be raised with an infusion of normal saline.

Cough.

Persistent, dry, irritating, nonproductive cough can develop with all ACE inhibitors. The underlying cause is accumulation of bradykinin secondary to inhibition of kinase II (another name for ACE). Cough occurs in 5% to 10% of patients and is the most common reason for discontinuing therapy. Factors that increase the risk of cough include advanced age, female sex, and non-black race. Cough begins to subside 3 days after discontinuing an ACE inhibitor and is gone within 10 days.

Hyperkalemia.

Inhibition of aldosterone release (secondary to inhibition of angiotensin II production) can cause potassium retention by the kidney. As a rule, significant potassium accumulation is limited to patients taking potassium supplements, salt substitutes (which contain potassium), or a potassium-sparing diuretic. For most other patients, hyperkalemia is rare. Patients should be instructed to avoid potassium supplements and potassium-containing salt substitutes unless they are prescribed.

Renal Failure.

ACE inhibitors can cause severe renal insufficiency in patients with *bilateral renal artery stenosis or stenosis in the artery to a single remaining kidney*. In patients with renal artery stenosis, the kidneys release large amounts of renin. The resulting high levels of angiotensin II serve to maintain glomerular filtration by two mechanisms: elevation of blood pressure and constriction of efferent glomerular arterioles (see Fig. 43-3). When ACE is inhibited, causing angiotensin II levels to fall, the mechanisms that had been supporting glomerular filtration fail, causing urine production to drop precipitously. Not surprisingly, *ACE inhibitors are contraindicated for patients with bilateral renal artery stenosis (or stenosis in the artery to a single remaining kidney)*.

Fetal Injury.

For a long time, we have known that use of ACE inhibitors during the *second* and *third* trimesters of pregnancy can injure the developing fetus. Specific effects include hypotension, hyperkalemia, skull hypoplasia, pulmonary hypoplasia, anuria, renal failure (reversible and irreversible), and death. Women who become pregnant while using ACE inhibitors should discontinue treatment as soon as possible. Infants who have been exposed to ACE inhibitors during the second or third trimester should be closely monitored for hypotension, oliguria, and hyperkalemia.

Are ACE inhibitors safe *early* in pregnancy? Maybe. Maybe not. Until recently, there were no data indicating risk, and hence first-trimester exposure was considered safe. However, in 2006, an article in the *New England Journal of Medicine* reported that, among 209 children exposed to ACE inhibitors during the first trimester, 18 (8.7%) had major congenital malformations, compared with 3.2% of controls. These data contrast with animal studies, which suggest that such malformations are not likely. Furthermore, no mechanism by which ACE inhibitors might disrupt early embryogenesis is known. Nonetheless, given the new human data, it would seem that early exposure to ACE inhibitors can no longer be considered safe, and hence should be avoided.

Angioedema.

Angioedema is a potentially fatal reaction that develops in up to 1% of patients. Symptoms, which result from increased capillary permeability, include giant wheals and edema of the tongue, glottis, and pharynx. Severe reactions should be treated with subcutaneous epinephrine. If angioedema develops, ACE inhibitors should be discontinued and never used again. Angioedema is caused by accumulation of bradykinin secondary to inhibition of kinase II.

Dysgeusia and Rash.

Dysgeusia (impaired or distorted sense of taste) and rash are relatively common with captopril, but can occur with other ACE inhibitors as well. For some patients, dysgeusia may result in anorexia and weight loss. If these complications arise, the ACE inhibitor should be withdrawn. Both reactions resolve following cessation of treatment. At one time, researchers believed rash and dysgeusia were related to the sulfhydryl group found in the structure of captopril and some other ACE inhibitors. However, this appears to be untrue. Why? Because ACE inhibitors that lack a sulfhydryl group also cause these reactions.

Neutropenia.

Neutropenia, with its associated risk of infection, is a rare but serious complication. Neutropenia is most likely in patients with renal impairment and in those with collagen vascular diseases (eg, systemic lupus erythematosus, scleroderma). These patients should be followed closely. Fortunately, neutropenia is reversible when detected early. To promote early detection, a white blood cell count with differential should be obtained every 2 weeks during the first 3 months of therapy and periodically thereafter. If neutropenia develops, ACE inhibitors should be withdrawn immediately. Neutrophil counts should normalize in approximately 2 weeks. In the absence of early detection, neutropenia may progress to fatal agranulocytosis. Patients should be informed about early signs of infection (eg, fever, sore throat) and instructed to report them immediately. As with dysgeusia and rash, neutropenia is more common with captopril than with other ACE inhibitors.

Drug Interactions

Diuretics.

Diuretics may intensify first-dose hypotension. To prevent this interaction, diuretics should be withdrawn 1 week prior to initiating ACE inhibitor treatment. Diuretic therapy can be resumed later if needed.

Antihypertensive Agents.

The hypotensive effects of ACE inhibitors are often additive with those of other antihypertensive drugs (eg, diuretics, sympatholytics, vasodilators, calcium channel blockers). When an ACE inhibitor is added to an antihypertensive regimen, dosages of other drugs may require reduction.

Drugs That Raise Potassium Levels.

ACE inhibitors increase the risk of hyperkalemia caused by *potassium supplements* and *potassium-sparing diuretics*. The risk of hyperkalemia is increased because, by suppressing aldosterone secretion, ACE inhibitors can reduce excretion of potassium. To minimize the risk of hyperkalemia, potassium supplements and potassium-sparing diuretics should be employed only when clearly indicated.

Lithium.

ACE inhibitors can make lithium accumulate to toxic levels. Lithium levels should be monitored frequently.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).

Aspirin, ibuprofen, and other NSAIDs may reduce the antihypertensive effects of ACE inhibitors.

Preparations, Dosage, and Administration

Except for enalaprilat, all ACE inhibitors are administered orally. Of the oral products, all are available in single-drug formulations, and most are also available in fixed-dose combinations with hydrochlorothiazide, a thiazide diuretic. Except for captopril and moexipril, all oral formulations may be administered without regard to meals; captopril and moexipril should be administered 1 hour before meals. Dosages for all ACE inhibitors (except fosinopril) should be reduced in patients with renal impairment. Dosages for specific indications are summarized in Table 43-1. Formulations are described below.

- Benazepril is available alone (5-, 10-, 20-, and 40-mg tablets) as *Lotensin,* and combined with hydrochlorothiazide as *Lotensin HCT*.
- Captopril is available alone (12.5-, 25-, 50-, and 100-mg tablets) as *Capoten,* and combined with hydrochlorothiazide as *Capozide*.
- Enalapril is available alone (2.5-, 5-, 10-, and 20-mg tablets) as *Vasotec,* and combined with hydrochlorothiazide as *Vaseretic*.
- Enalaprilat [Vasotec], the active form of enalapril, is available in solution (1.25 mg/mL) for IV therapy of severe hypertension. Enalaprilat is the only ACE inhibitor that is not given PO.
- Fosinopril is available alone (10-, 20-, and 40-mg tablets) as *Monopril,* and combined with hydrochlorothiazide as *Monopril-HCT*.
- Lisinopril is available alone (2.5-, 5-, 10-, 20-, 30-, and 40-mg tablets) as *Prinivil* and *Zestril,* and combined with hydrochlorothiazide as *Prinzide*.
- Moexipril is available alone (7.5- and 15-mg tablets) as *Univasc,* and combined with hydrochlorothiazide as *Uniretic*.
- Perindopril is available in tablets (2, 4, and 8 mg) as *Aceon*. The drug is not available in combination with hydrochlorothiazide.
- Quinapril is available alone (5-, 10-, 20-, and 40-mg tablets) as *Accupril,* and combined with hydrochlorothiazide as *Accuretic*.
- Ramipril is available in capsules (1.25, 2.5, 5, and 10 mg) as *Altace*. The drug is not available in combination with hydrochlorothiazide.
- Trandolapril is available in tablets (1, 2, and 4 mg) as *Mavik*. The drug is not available in combination with hydrochlorothiazide.

ANGIOTENSIN II RECEPTOR BLOCKERS

The angiotensin II receptor blockers (ARBs) are a relatively new family of drugs whose indications are evolving. Initially, ARBs were approved only for hypertension. Today, they also are approved for heart failure, diabetic nephropathy, myocardial infarction, and stroke prevention.

Like the ACE inhibitors, ARBs decrease the influence of angiotensin II. However, the mechanisms involved differ: Whereas ACE inhibitors block *production* of angiotensin II, ARBs block the *actions* of angiotensin II. Because both

groups interfere with angiotensin II, they both have similar effects. They differ primarily in that ARBs do not cause cough or hyperkalemia.

Given that ACE inhibitors and ARBs have very similar effects, are these drugs considered clinically interchangeable? No. We have clear and extensive evidence that ACE inhibitors decrease cardiovascular morbidity and mortality. The evidence for ARBs is less convincing. Accordingly, until more is known, ACE inhibitors are preferred. For patients who cannot tolerate ACE inhibitors, ARBs are an appropriate second choice.

Seven ARBs are available. They are all very similar, and hence we will discuss them as a group, rather than choosing one as a prototype.

Mechanism of Action and Overview of Pharmacologic Effects

ARBs block access of angiotensin II to its receptors in blood vessels, the adrenals, and all other tissues. As a result, ARBs have effects much like those of the ACE inhibitors. By blocking angiotensin II receptors on blood vessels, ARBs cause dilation of arterioles and veins. By blocking angiotensin II receptors in the heart, ARBs can prevent angiotensin II from inducing pathologic changes in cardiac structure. By blocking angiotensin II receptors in the adrenals, ARBs decrease release of aldosterone, and can thereby increase renal excretion of sodium and water. Sodium and water excretion is further increased through dilation of renal blood vessels.

In contrast to the ACE inhibitors, ARBs do *not* inhibit kinase II, and hence do not increase levels of bradykinin in the lung. As a result, ARBs do not promote cough, the most common reason for stopping ACE inhibitors.

Therapeutic Uses

Hypertension.

All ARBs are approved for hypertension. Reductions in blood pressure equal those seen with ACE inhibitors. Whether ARBs share the ability of ACE inhibitors to reduce mortality has not been established.

Heart Failure.

Currently, only two ARBs—*valsartan* [Diovan] and *candesartan* [Atacand]—are approved for heart failure. In clinical trials, these drugs reduced symptoms, decreased hospitalizations, improved functional capacity, and increased left ventricular (LV) ejection fraction. More importantly, they prolonged survival. Because experience with these drugs is limited, they should be reserved for patients who cannot tolerate ACE inhibitors (because of cough). Although the other ARBs are not yet approved for heart failure, most authorities believe they are effective.

Diabetic Nephropathy.

Two ARBs—*irbesartan* [Avapro] and *losartan* [Cozaar]—are approved for managing nephropathy in hypertensive patients with type 2 diabetes. In clinical trials, these drugs delayed development of overt nephropathy, and slowed progression of established renal disease. Benefits are due in part to reductions in blood pressure, and in part to mechanisms that have not been determined. How do ARBs compare with ACE inhibitors? Although both groups of drugs can delay development of renal complications, only the ACE inhibitors have been shown to reduce mortality.

Myocardial Infarction.

In 2005, *valsartan* [Diovan] was approved for reducing cardiovascular mortality in post-MI patients with heart failure or LV dysfunction. Approval was based on the results of a major trial—the *Valsartan in Acute Myocardial Infarction Trial* (VALIANT)—that showed that valsartan was as effective as captopril at reducing short-term and long-term mortality in these patients.

Stroke Prevention.

One ARB—*losartan* [Cozaar]—is approved for reducing the risk of stroke in patients with hypertension and LV hypertrophy. In clinical studies, stroke prevention with losartan was better than with atenolol (a beta blocker), even though both drugs produced an equivalent decrease in blood pressure. This observation indicates that the benefits of losartan cannot be explained on the basis of reduced blood pressure alone.

Migraine Headache.

As discussed in Chapter 30, prophylactic therapy with candesartan [Atacand] can reduce the incidence and duration of migraine attacks.

Adverse Effects

All of the ARBs are well tolerated. In contrast to ACE inhibitors, ARBs do not cause clinically significant hyperkalemia. Furthermore, because ARBs do not promote accumulation of bradykinin in the lung, they do not induce cough.

Angioedema.

Like the ACE inhibitors, ARBs can cause angioedema, although the incidence may be lower with ARBs. If angioedema occurs, ARBs should be withdrawn immediately and never used again. Severe reactions are treated with subcutaneous epinephrine.

How do ARBs cause angioedema? Possibly by increasing bradykinin. Unlike ACE inhibitors, ARBs do not inhibit bradykinin breakdown. However, through an indirect mechanism, ARBs may be able to increase local bradykinin synthesis.

Is it reasonable to give an ARB to a patient who developed angioedema with an ACE inhibitor? Sometimes. About 8% of patients who experience angioedema with an ACE inhibitor will also get angioedema if given an ARB. Nonetheless, switching to an ARB may be worth the risk for specific patients, namely, those with a disorder for which ARBs are known to improve outcomes (ie, heart failure, diabetes, and myocardial infarction).

Fetal Harm.

Like the ACE inhibitors, ARBs can injure the developing fetus if taken during the second or third trimester of pregnancy, and hence are contraindicated during this period. Also, there is concern that ARBs and ACE inhibitors may harm the fetus earlier in pregnancy, and hence should be discontinued as soon as pregnancy is discovered.

Renal Failure.

Like the ACE inhibitors, ARBs can cause renal failure in patients with bilateral renal artery stenosis or stenosis in the artery to a single remaining kidney. Accordingly, ARBs are contraindicated for patients with these conditions.

Drug Interactions

The hypotensive effects of ARBs are additive with those of other antihypertensive drugs. When an ARB is added to an antihypertensive regimen, dosages of the other drugs may require reduction.

Preparations, Dosage, and Administration

All ARBs are administered PO, and all may be taken with or without food. In addition, all are available alone and in fixed-dose combinations with hydrochlorothiazide, a thiazide diuretic. Dosages for specific indications are summarized in Table 43-2. Formulations are described below.

- Candesartan is available alone (4-, 8-, 16-, and 32-mg tablets) as *Atacand,* and combined with hydrochlorothiazide as *Atacand HCT*.
- Eprosartan is available alone (400- and 600-mg tablets) as *Teveten,* and combined with hydrochlorothiazide as *Teveten HCT*.
- Irbesartan is available alone (75-, 150-, and 300-mg tablets) as *Avapro,* and combined with hydrochlorothiazide as *Avalide*.
- Losartan is available alone (25-, 50-, and 100-mg tablets) as *Cozaar,* and combined with hydrochlorothiazide as *Hyzaar*.
- Olmesartan is available alone (5-, 20-, and 40-mg tablets) as *Benicar,* and combined with hydrochlorothiazide as *Benicar HCT*.
- Telmisartan is available alone (20-, 40-, and 80-mg tablets) as *Micardis,* and combined with hydrochlorothiazide as *Micardis HCT*.
- Valsartan is available alone (40-, 80-, 160-, and 320-mg tablets) as *Diovan,* and combined with hydrochlorothiazide as *Diovan HCT*.

Generic Name	Trade Name	Approved Indications	Initial Dosage	Dosage Range
Candesartan	Atacand	Hypertension	16 mg once/day	8–32 mg/day in 1 or 2 doses
		Heart failure	4 mg once/day	4–32 mg once/day
Eprosartan	Teveten	Hypertension	600 mg once/day	400–800 mg/day in 1 or 2 doses
Irbesartan	Avapro	Hypertension	150 mg once/day	150–300 mg once/day
		Diabetic nephropathy*	300 mg once/day	300 mg once/day
Losartan	Cozaar	Hypertension	25–50 mg once/day	25–100 mg/day in 1 or 2 doses
		Stroke prevention†	50 mg once/day	50–100 mg once/day
		Diabetic nephropathy*	50 mg once/day	50–100 mg once/day
Olmesartan	Benicar	Hypertension	20 mg once/day	20–40 mg once/day
Telmisartan	Micardis	Hypertension	40 mg once/day	20–80 mg once/day
Valsartan	Diovan	Hypertension	80–160 mg once/day	80–320 mg once/day
		Heart failure	40 mg twice/day	80–160 mg twice/day
		Myocardial infarction	20 mg twice/day	80–160 mg twice/day

TABLE 43-2 Angiotensin II Receptor Blockers: Approved Indications and Adult Dosages

* In patients with type 2 diabetes.

† In patients with hypertension and left ventricular hypertrophy.

ALISKIREN, A DIRECT RENIN INHIBITOR

Direct renin inhibitors (DRIs) are drugs that act on renin to inhibit the conversion of angiotensinogen into angiotensin I. By decreasing production of angiotensin I, DRIs can suppress the entire RAAS. Currently, only one DRI is available.

Aliskiren [Tekturna], approved for hypertension in 2007, was the first DRI on the market. Blood pressure reduction equals that seen with ACE inhibitors. Aliskiren causes less cough and angioedema than the ACE inhibitors, but poses similar risks to the developing fetus.

Mechanism of Action

Aliskiren binds tightly with renin, and thereby inhibits the cleavage of angiotensinogen into angiotensin I. Since this reaction is the first and rate-limiting step in the production of angiotensin II and aldosterone, aliskiren can reduce the influence of the entire RAAS. In clinical trials, the drug decreased plasma renin activity by 50% to 80%. Although aliskiren works at an earlier step than either the ACE inhibitors or ARBs, there is no proof that doing so results in superior clinical outcomes.

Therapeutic Use

Aliskiren is approved only for treatment of *hypertension*. It may be used alone or in combination with other antihypertensives. In clinical trials, aliskiren reduced blood pressure to the same extent as did ACE inhibitors, ARBs, or calcium channel blockers. Maximal effects developed within 2 weeks. Although aliskiren can reduce blood pressure in hypertensive patients, we don't know if the drug also reduces negative outcomes (ie, blindness, stroke, kidney disease, death). In contrast, the ability of ACE inhibitors and ARBs to improve outcomes is well established. Until the long-term benefits and safety of aliskiren are known, older antihypertensives should be considered first. In addition to

its use in hypertension, aliskiren is under investigation for treating heart failure and renal failure associated with diabetes.

Pharmacokinetics

Aliskiren is administered orally, and bioavailability is low (only 2.5%). Dosing with a *high-fat meal* makes availability much lower (about 0.8%). Aliskiren undergoes some metabolism by CYP3A4 (the 3A4 isozyme of cytochrome P450), but the extent of metabolism is not known. About 25% of the drug is eliminated unchanged in the urine. The half-life is about 24 hours.

Adverse Effects

Aliskiren is generally well tolerated. At usual doses, the risk of angioedema, cough, or hyperkalemia is low. At high therapeutic doses, some patients experience diarrhea. Like other drugs that affect the RAAS, aliskiren should be avoided during pregnancy.

Angioedema and Cough.

With ACE inhibitors, angioedema and cough result from inhibition of kinase II. Since aliskiren does not inhibit kinase II, the risk of these effects is low. In clinical trials, the incidence of cough was 1.1% with aliskiren, versus 5% to 10% with an ACE inhibitor. Similarly, the incidence of angioedema was 0.06% with aliskiren, versus 1% with an ACE inhibitor. If angioedema does occur, aliskiren should be discontinued immediately.

Gastrointestinal Effects.

Aliskiren causes dose-dependent *diarrhea,* seen in 2.3% of patients taking 300 mg/day. Women and the elderly are most susceptible. Excessive doses (600 mg/day) are associated with abdominal pain and dyspepsia.

Hyperkalemia.

Like the ACE inhibitors, aliskiren rarely causes hyperkalemia when used alone. However, hyperkalemia might be expected if aliskiren were combined use with an ACE inhibitor, potassium-sparing diuretic, or potassium supplements.

Fetal Injury and Death.

Although aliskiren has not been studied in pregnant women, the drug is likely to pose a risk of major congenital malformations and fetal death. Why? Because the risk of these events is well established with other drugs that suppress the RAAS. Therefore, like the ACE inhibitors and ARBs, aliskiren is contraindicated during the second and third trimesters, and should be discontinued as soon as possible when pregnancy occurs.

Drug Interactions

Aliskiren undergoes some metabolism by CYP3A4, but it neither induces nor inhibits the P450 system. In clinical trials, aliskiren had no significant interactions with atenolol, digoxin, amlodipine, valsartan, ramipril, or hydrochlorothiazide. However, levels of aliskiren were significantly raised by atorvastatin and ketoconazole (a P450 inhibitor), and significantly lowered by irbesartan. Levels of furosemide were lowered by aliskiren.

Preparations, Dosage, and Administration

Aliskiren is available alone under the trade name *Tekturna,* and in combination with hydrochlorothiazide under the trade name *Tekturna HCT*. Both formulations are indicated for hypertension.

Aliskiren alone [Tekturna] is available in tablets (150 and 30 mg) for oral dosing. The initial dosage is 150 mg once a day. If control of blood pressure is inadequate, dosage may be increased to 300 mg once a day. Daily doses above 300 mg will not increase benefits, but will increase the risk of diarrhea. Since high-fat meals decrease absorption substantially, each daily dose should be taken at the same time with respect to meals (eg, 1 hour before dinner), so as to achieve a consistent response.

Aliskiren/hydrochlorothiazide [Tekturna HCT] is available in four strengths—150 mg/12.5 mg, 150 mg/25 mg, 300 mg/12.5 mg, and 300 mg/25 mg—for once-daily dosing. As with Tekturna, each daily dose should be taken at the same time with respect to meals.

ALDOSTERONE ANTAGONISTS

Aldosterone antagonists are drugs that block receptors for aldosterone. Two such agents are available: eplerenone and spironolactone. Both drugs have

similar structures and actions, and both are used for the same disorders: hypertension and heart failure. They differ, however, in that spironolactone is less selective than eplerenone. As a result, spironolactone causes more side effects.

Eplerenone

Eplerenone [Inspra], approved in September 2002, is the first representative of a new class of agents: *selective aldosterone receptor blockers*. The drug is used for hypertension and heart failure, and has one significant side effect: hyperkalemia.

Mechanism of Action

Eplerenone produces selective blockade of aldosterone receptors, having little or no effect on receptors for other steroid hormones (eg, glucocorticoids, progesterone, androgens). In the kidney, activation of aldosterone receptors promotes excretion of potassium and retention of sodium and water. Receptor blockade has the opposite effect: retention of potassium and increased excretion of sodium and water. Loss of sodium and water reduces blood volume and blood pressure. Blockade of aldosterone receptors at nonrenal sites may prevent or reverse pathologic effects of aldosterone on cardiovascular structure and function.

Therapeutic Use

Hypertension.

For treatment of hypertension, eplerenone may be used alone or in combination with other antihypertensive agents. Maximal reductions in blood pressure take about 4 weeks to develop. In clinical trials, reductions in blood pressure were equivalent to those produced by spironolactone, and superior to those produced by losartan (an ARB). In patients already using an ACE inhibitor or an ARB, adding eplerenone produced a further reduction in blood pressure.

Although it is clear that eplerenone can lower blood pressure, we have no information on what really matters: the drug's ability to reduce morbidity and

mortality. Until more is known, eplerenone should be reserved for patients who have not responded to traditional antihypertensive drugs.

Heart Failure.

In patients with heart failure, eplerenone can improve symptoms, reduce hospitalizations, and prolong life. Benefits appear to derive from blocking the adverse effects of aldosterone on cardiovascular structure and function. Use of eplerenone in heart failure is discussed in Chapter 47.

Pharmacokinetics

Eplerenone is administered orally. Absorption is not affected by food. Plasma levels peak about 1.5 hours after dosing. Absolute bioavailability is unknown. Eplerenone undergoes metabolism by CYP3A4 (the 3A4 isozyme of cytochrome P450), followed by excretion in the urine (67%) and feces (32%). The elimination half-life is 4 to 6 hours.

Adverse Effects

Eplerenone is generally well tolerated. The incidence of adverse effects is nearly identical to that of placebo. A few adverse effects—diarrhea, abdominal pain, cough, fatigue, gynecomastia, flu-like syndrome—occur slightly (1% to 2%) more often with eplerenone than with placebo.

Hyperkalemia.

The greatest risk is hyperkalemia, which can occur secondary to potassium retention. Because of this risk, combined use with potassium supplements, salt substitutes, or potassium-sparing diuretics (eg, spironolactone, triamterene) is contraindicated. Combined use with ACE inhibitors or ARBs is permissible, but should be done with caution. Eplerenone is contraindicated for patients with high serum potassium (above 5.5 mEq/L), and for patients with impaired renal function or type 2 diabetes with microalbuminuria, both of which can promote hyperkalemia. Monitoring potassium levels is recommended for patients at risk (eg, those taking ACE inhibitors or ARBs).

Drug Interactions

Inhibitors of CYP3A4 can increase levels of eplerenone, thereby posing a risk of toxicity. Weak inhibitors (eg, erythromycin, saquinavir, verapamil, fluconazole) can double eplerenone levels. Strong inhibitors (eg, ketoconazole, itraconazole) can increase levels fivefold. If eplerenone is combined with a weak inhibitor, eplerenone dosage should be reduced. Eplerenone should not be combined with strong inhibitors.

Drugs that raise potassium levels can increase the risk of hyperkalemia. Eplerenone should not be combined with potassium supplements, salt substitutes, or potassium-sparing diuretics. Combining the drug with ACE inhibitors or ARBs should be done with caution.

Drugs similar to eplerenone (eg, ACE inhibitors and diuretics) are known to increase levels of *lithium*. Although the combination of eplerenone and lithium has not been studied, caution is nonetheless advised. Lithium levels should be measured frequently.

Preparations, Dosage, and Administration

Eplerenone [Inspra] is available in 25- and 50-mg tablets. The usual starting dosage is 50 mg once a day, taken with or without food. After 4 weeks, dosage can be increased to 50 mg twice daily (if the hypotensive response has been inadequate). Raising the dosage above 100 mg/day is not recommended. Why? Because doing so is unlikely to increase the therapeutic response, but *will* increase the risk of hyperkalemia. In patients taking weak inhibitors of CYP3A4, the initial dosage should be reduced by 50% (to 25 mg once a day).

Spironolactone

Spironolactone [Aldactone], a much older drug than eplerenone, blocks receptors for aldosterone, but also binds with receptors for other steroid hormones (eg, glucocorticoids, progesterone, androgens). Blockade of aldosterone receptors underlies beneficial effects in hypertension and heart failure, as well as the drug's major adverse effect: hyperkalemia. Binding with receptors for other steroid hormones underlies additional adverse effects: gynecomastia, menstrual irregularities, impotence, hirsutism, and deepening of the voice. The basic pharmacology of spironolactone and its use in heart failure are discussed in Chapters 40 and 47, respectively.

KEY POINTS

- The RAAS helps regulate blood pressure, blood volume, and fluid and electrolyte balance. The system can mediate cardiovascular pathology.
- The RAAS acts through production of angiotensin II and aldosterone.
- Angiotensin II has much greater biologic activity than angiotensin I or angiotensin III.
- Angiotensin II is formed by the actions of two enzymes: renin and ACE.
- Angiotensin II causes vasoconstriction (primarily in arterioles) and release of aldosterone. In addition, angiotensin II can promote pathologic changes in the heart and blood vessels.
- Aldosterone acts on the kidneys to promote retention of sodium and water. In addition, aldosterone can also mediate pathologic changes in cardiovascular function.
- The RAAS raises blood pressure by causing vasoconstriction and by increasing blood volume (secondary to aldosterone-mediated retention of sodium and water).
- In addition to the traditional RAAS, in which angiotensin II is produced in the blood and then carried to target tissues, angiotensin II can be produced locally by individual tissues.
- Beneficial effects of ACE inhibitors result largely from inhibition of ACE and partly from inhibition of kinase II (the name for ACE when the substrate is bradykinin).
- By inhibiting ACE, ACE inhibitors decrease production of angiotensin II. The result is vasodilation, decreased blood volume, and prevention or reversal of pathologic changes in the heart and blood vessels mediated by angiotensin II and aldosterone.
- ACE inhibitors are used to treat patients with hypertension, heart failure, myocardial infarction (MI), and nephropathy, both diabetic and nondiabetic. In addition, they are used to prevent MI, stroke, and death (from cardiovascular causes) in patients at high risk for a cardiovascular event.

- ACE inhibitors can produce serious first-dose hypotension by causing a sharp drop in circulating angiotensin II.
- Cough, secondary to accumulation of bradykinin, is the most common reason for discontinuing ACE inhibitors.
- By suppressing aldosterone release, ACE inhibitors can cause hyperkalemia. Exercise caution in patients taking potassium supplements, salt substitutes, or potassium-sparing diuretics.
- ACE inhibitors can cause major fetal malformations, and should be avoided during pregnancy. Until recently, we thought that risk was limited to exposure during the second and third trimesters. However, new data indicate that exposure during the first trimester may also be dangerous as well.
- ACE inhibitors can cause a precipitous drop in blood pressure in patients with bilateral renal artery stenosis (or stenosis in the artery to a single remaining kidney).
- Angiotensin II receptor blockers (ARBs) block the actions of angiotensin II in blood vessels, the adrenals, and all other tissues.
- ARBs are similar to ACE inhibitors in that they cause vasodilation, suppress aldosterone release, promote excretion of sodium and water, reduce blood pressure, and cause birth defects and angioedema.
- ARBs differ from ACE inhibitors in that they do not cause hyperkalemia or cough.
- Aliskiren, a DRI, binds tightly with renin and thereby inhibits cleavage of angiotensinogen into angiotensin I. As a result, the drug suppresses the entire RAAS.
- Like the ACE inhibitors and ARBs, aliskiren causes vasodilation, suppresses aldosterone release, promotes excretion of sodium and water, reduces blood pressure, and causes birth defects and angioedema.
- Despite their similarities, aliskiren, ARBs, and ACE inhibitors are not clinically interchangeable.
- Aldosterone antagonists (spironolactone, eplerenone) block receptors for aldosterone.

- By blocking aldosterone receptors, aldosterone antagonists can (1) promote renal excretion of sodium and water (and can thereby reduce blood volume and blood pressure) and (2) prevent or reverse pathologic effects of aldosterone on cardiovascular structure and function.

Summary of Major Nursing Implications*

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Benazepril

Captopril

Enalapril

Enalaprilat

Fosinopril

Lisinopril

Moexipril

Perindopril

Quinapril

Ramipril

Trandolapril

Unless indicated otherwise, the implications summarized below pertain to all of the ACE inhibitors.

Preadministration Assessment

Therapeutic Goal

Reduction of blood pressure in patients with hypertension *(all ACE inhibitors)*.

Hemodynamic improvement in patients with heart failure *(captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril)*.

Slowed progression of diabetic nephropathy *(captopril)*.

Reduction of mortality following acute MI *(lisinopril)*.

Treatment of heart failure after MI *(ramipril, trandolapril)*.

Reduction of risk of MI, stroke, or death from cardiovascular causes in patients at high risk *(ramipril)*.

Reduction of cardiovascular mortality or nonfatal MI in patients with stable coronary artery disease *(perindopril)*.

Baseline Data

Determine blood pressure and obtain a white blood cell count and differential.

Identifying High-Risk Patients

ACE inhibitors are *contraindicated* during the second and third trimesters of pregnancy and for patients with (1) bilateral renal artery stenosis (or stenosis in the artery to a single remaining kidney) or (2) a history of hypersensitivity reactions (especially angioedema) to ACE inhibitors.

Exercise *caution* in patients with salt or volume depletion, renal impairment, or collagen vascular disease, and in those taking potassium supplements, salt substitutes, potassium-sparing diuretics, aliskiren, or lithium.

Implementation: Administration

Routes

Oral. *All* ACE inhibitors (except enalaprilat).

Intravenous. *Enalaprilat*.

Dosage and Administration

Begin therapy with low doses and then gradually increase the dosage.

Instruct patients to administer captopril and moexipril at least 1 hour before meals. All other oral ACE inhibitors can be administered with food.

Ongoing Evaluation and Interventions

Monitoring Summary

Monitor blood pressure closely for 2 hours after the first dose and periodically thereafter. Obtain a white blood cell count and differential every 2 weeks for the first 3 months of therapy and periodically thereafter.

Evaluating Therapeutic Effects

Hypertension.

Monitor for reduced blood pressure. The usual target pressure is systolic/diastolic of 140/90 mm Hg.

Heart Failure.

Monitor for lessening of signs and symptoms (eg, dyspnea, cyanosis, jugular vein distention, edema).

Diabetic Nephropathy.

Monitor for proteinuria.

Minimizing Adverse Effects

First-Dose Hypotension.

Severe hypotension can occur with the first dose. Minimize hypotension by (1) withdrawing diuretics 1 week before initiating ACE inhibitors and (2) using low initial doses. Monitor blood pressure for 2 hours following the first dose. **Instruct patients to lie down if hypotension develops.** If necessary, infuse normal saline to restore pressure.

Cough.

Warn patients about the possibility of persistent, dry, irritating, nonproductive cough. Instruct them to consult the prescriber if cough is bothersome. It may be necessary to discontinue the ACE inhibitor.

Hyperkalemia.

ACE inhibitors may increase potassium levels. **Instruct patients to avoid potassium supplements and potassium-containing salt substitutes unless**

they are prescribed by the provider. Potassium-sparing diuretics must also be avoided.

Fetal Injury.

Warn women of child-bearing age that taking ACE inhibitors during the *second* and *third* trimesters of pregnancy can cause major fetal injury (hypotension, hyperkalemia, skull hypoplasia, anuria, reversible and irreversible renal failure, death), and that taking these drugs earlier in pregnancy may pose a risk as well. If the patient becomes pregnant, withdraw ACE inhibitors as soon as possible. Closely monitor infants who have been exposed to ACE inhibitors during the second or third trimester for hypotension, oliguria, and hyperkalemia. **Reassure women who took ACE inhibitors during the *first* trimester that risk to the fetus is probably low.**

Angioedema.

This rare and potentially fatal reaction is characterized by giant wheals and edema of the tongue, glottis, and pharynx. **Instruct patients to seek immediate medical attention if these symptoms develop.** If angioedema is diagnosed, ACE inhibitors should be discontinued and never used again. Treat severe reactions with subcutaneous epinephrine.

Renal Failure.

Renal failure is a risk for patients with bilateral renal artery stenosis or stenosis in the artery to a single remaining kidney. ACE inhibitors are contraindicated for these people.

Dysgeusia and Rash (Mainly with Captopril).

Minimize these reactions by avoiding high doses. **Instruct patients to notify the prescriber if rash or dysgeusia persists.** If dysgeusia results in anorexia and weight loss, withdraw the drug. Rash and dysgeusia resolve with cessation of treatment.

Neutropenia (Mainly with Captopril).

Neutropenia poses a high risk of infection. **Inform patients about early signs of infection (fever, sore throat, mouth sores) and instruct them to noti-**

fy the prescriber if these occur. Obtain white blood cell counts and differentials every 2 weeks during the first 3 months of therapy and periodically thereafter. If neutropenia develops, withdraw the drug immediately; neutrophil counts should normalize in approximately 2 weeks. Neutropenia is most likely in patients with renal impairment and collagen vascular diseases (eg, systemic lupus erythematosus, scleroderma); monitor these patients closely.

Minimizing Adverse Interactions

Diuretics.

Diuretics may intensify first-dose hypotension. Withdraw diuretics 1 week prior to beginning an ACE inhibitor. Diuretics may be resumed later if needed.

Antihypertensive Agents.

The antihypertensive effects of ACE inhibitors are additive with those of other antihypertensive drugs (eg, diuretics, sympatholytics, vasodilators, calcium channel blockers). When an ACE inhibitor is added to an antihypertensive regimen, dosages of the other drugs may require reduction.

Drugs That Elevate Potassium Levels.

ACE inhibitors increase the risk of hyperkalemia associated with *potassium supplements, potassium-sparing diuretics,* and possibly *aliskiren*. Risk can be minimized by avoiding potassium supplements and potassium-sparing diuretics except when they are clearly indicated.

Lithium.

ACE inhibitors can increase serum levels of lithium, causing toxicity. Monitor lithium levels frequently.

Nonsteroidal Anti-inflammatory Drugs.

NSAIDs (eg, aspirin, ibuprofen) can interfere with the antihypertensive effects of ACE inhibitors. **Advise patients to minimize NSAID use.**

ANGIOTENSIN II RECEPTOR BLOCKERS

Candesartan

Eprosartan

Irbesartan

Losartan

Olmesartan

Telmisartan

Valsartan

Unless indicated otherwise, the implications summarized below pertain to all of the ARBs.

Preadministration Assessment

Therapeutic Goal

Reduction of blood pressure in patients with hypertension *(all ARBs)*.

Treatment of heart failure *(candesartan, valsartan)*.

Slowed progression of diabetic nephropathy *(irbesartan, losartan)*.

Stroke prevention in patients with hypertension and LV hypertrophy *(losartan)*.

Baseline Data

Determine blood pressure.

Identifying High-Risk Patients

ARBs are *contraindicated* during the second and third trimesters of pregnancy and for patients with either (1) bilateral renal artery stenosis (or stenosis in the artery to a single remaining kidney) or (2) a history of hypersensitivity reactions (especially angioedema) to ARBs.

Implementation: Administration

Route

Oral.

Dosage and Administration

Inform patients that ARBs may be taken with or without food.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Hypertension.

Monitor for reduced blood pressure. The usual target pressure is systolic/diastolic of 140/90 mm Hg.

Heart Failure.

Monitor for lessening of signs and symptoms (eg, dyspnea, cyanosis, jugular vein distention, edema).

Diabetic Nephropathy.

Monitor for proteinuria.

Minimizing Adverse Effects

Angioedema.

This rare and potentially fatal reaction is characterized by giant wheals and edema of the tongue, glottis, and pharynx. **Instruct patients to seek immediate medical attention if these symptoms develop.** If angioedema is diagnosed, ARBs should be discontinued and never used again. Treat severe reactions with subcutaneous epinephrine.

Fetal Injury.

Warn women of child-bearing age that ARBs can cause fetal injury during the *second* and *third* trimesters of pregnancy, and may pose a risk earlier in pregnancy as well. If the patient becomes pregnant, withdraw ARBs as soon as possible. Closely monitor infants who have been exposed to ARBs during the second or third trimester for hypotension, oliguria, and hyperkalemia. **Reassure women who took ARBs during the *first* trimester that risk to the fetus is low.**

Renal Failure.

Renal failure is a risk for patients with bilateral renal artery stenosis or stenosis in the artery to a single remaining kidney. ARBs inhibitors are contraindicated for these people.

Minimizing Adverse Interactions

Antihypertensive Agents.

The antihypertensive effects of ARBs are additive with those of other antihypertensive drugs (eg, diuretics, sympatholytics, vasodilators, calcium channel blockers). When an ARB is added to an antihypertensive regimen, dosages of the other drugs may require reduction.

ALISKIREN, A DIRECT RENIN INHIBITOR

Preadministration Assessment

Therapeutic Goal

Reduction of blood pressure in patients with hypertension.

Baseline Data

Determine blood pressure.

Identifying High-Risk Patients

Aliskiren is *contraindicated* during the second and third trimesters of pregnancy.

Exercise *caution* in patients taking potassium supplements, salt substitutes, potassium-sparing diuretics, or ACE inhibitors.

Implementation: Administration

Route

Oral.

Dosage and Administration

Advise patients to take each daily dose at the same time with respect to meals (eg, 1 hour before dinner). Dosage should be low (150 mg/day) initially, and increased to a maximum of 300 mg/day, if needed.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Hyperkalemia.

Aliskiren may increase potassium levels. **Instruct patients to avoid potassium supplements and potassium-containing salt substitutes unless they are prescribed by the provider.** Potassium-sparing diuretics must also be avoided.

Fetal Injury.

Warn women of child-bearing age that aliskiren taken during the *second* and *third* trimesters of pregnancy can cause fetal injury (hypotension, hyperkalemia, skull hypoplasia, anuria, reversible and irreversible renal failure, death). If the patient becomes pregnant, withdraw ACE inhibitors as soon as possible. Closely monitor infants who have been exposed to aliskiren during the second or third trimester for hypotension, oliguria, and hyperkalemia. **Reassure women who took aliskiren during the *first* trimester that this does not represent a risk to the fetus.**

Angioedema.

This rare and potentially fatal reaction is characterized by giant wheals and edema of the tongue, glottis, and pharynx. **Instruct patients to seek immediate medical attention if these symptoms develop.** If angioedema is diagnosed, aliskiren should be discontinued and never used again. Treat severe reactions with subcutaneous epinephrine.

Minimizing Adverse Interactions

Drugs That Elevate Potassium Levels.

Aliskiren increases the risk of hyperkalemia associated with *ACE inhibitors, potassium supplements,* and *potassium-sparing diuretics*. Risk can be minimized by avoiding ACE inhibitors, potassium supplements, and potassium-sparing diuretics except when they are clearly indicated.

Antihypertensive Agents.

The antihypertensive effects of aliskiren are additive with those of other antihypertensive drugs (eg, diuretics, sympatholytics, vasodilators, calcium channel blockers). When aliskiren is added to an antihypertensive regimen, dosages of the other drugs may require reduction.

44 Calcium Channel Blockers

Calcium channel blockers (CCBs) are drugs that prevent calcium ions from entering cells. These agents have their greatest effects on the heart and blood vessels. CCBs are used widely to treat hypertension, angina pectoris, and cardiac dysrhythmias. Since 1995, there has been controversy about the safety of CCBs, especially in patients with hypertension and diabetes. Alternative names for CCBs are *calcium antagonists* and *slow channel blockers*.

CALCIUM CHANNELS: PHYSIOLOGIC FUNCTIONS AND CONSEQUENCES OF BLOCKADE

Calcium channels are gated pores in the cytoplasmic membrane that regulate entry of calcium ions into cells. Calcium entry plays a critical role in the function of vascular smooth muscle (VSM) and the heart.

Vascular Smooth Muscle

In VSM, calcium channels regulate contraction. When an action potential travels down the surface of a smooth muscle cell, calcium channels open and calcium ions flow inward, thereby initiating the contractile process. If calcium channels are blocked, contraction will be prevented and vasodilation will result.

At therapeutic doses, CCBs act selectively on *peripheral arterioles* and *arteries and arterioles of the heart*. CCBs have no significant effect on veins.

Heart

In the heart, calcium channels help regulate function of the myocardium, the sinoatrial (SA) node, and the atrioventricular (AV) node. Calcium channels at all three sites are coupled to beta***1***-adrenergic receptors.

Myocardium.

In cardiac muscle, calcium entry has a positive inotropic effect. That is, calcium increases force of contraction. If calcium channels in atrial and ventricular muscle are blocked, contractile force will diminish.

SA Node.

Pacemaker activity of the SA node is regulated by calcium influx. When calcium channels are open, spontaneous discharge of the SA node increases. Conversely, when calcium channels close, pacemaker activity declines. Hence, the effect of calcium channel blockade is to reduce heart rate.

AV Node.

Impulses that originate in the SA node must pass through the AV node on their way to the ventricles. Because of this arrangement, regulation of AV conduction plays a critical role in coordinating contraction of the ventricles with contraction of the atria.

The excitability of AV nodal cells is regulated by calcium entry. When calcium channels are open, calcium entry increases and cells of the AV node discharge more readily. Conversely, when calcium channels are closed, discharge of AV nodal cells is suppressed. Hence, the effect of calcium channel blockade is to decrease velocity of conduction through the AV node.

Coupling of Cardiac Calcium Channels to Beta*1*Adrenergic Receptors.

In the heart, calcium channels are coupled to beta*1*-adrenergic receptors (Fig. 44-1). As a result, when cardiac beta*1* receptors are activated, calcium influx is enhanced. Conversely, when beta*1* receptors are blocked, calcium influx is suppressed. Because of this relationship, CCBs and beta blockers have identical effects on the heart. That is, they both reduce force of contraction, slow heart rate, and suppress conduction through the AV node.

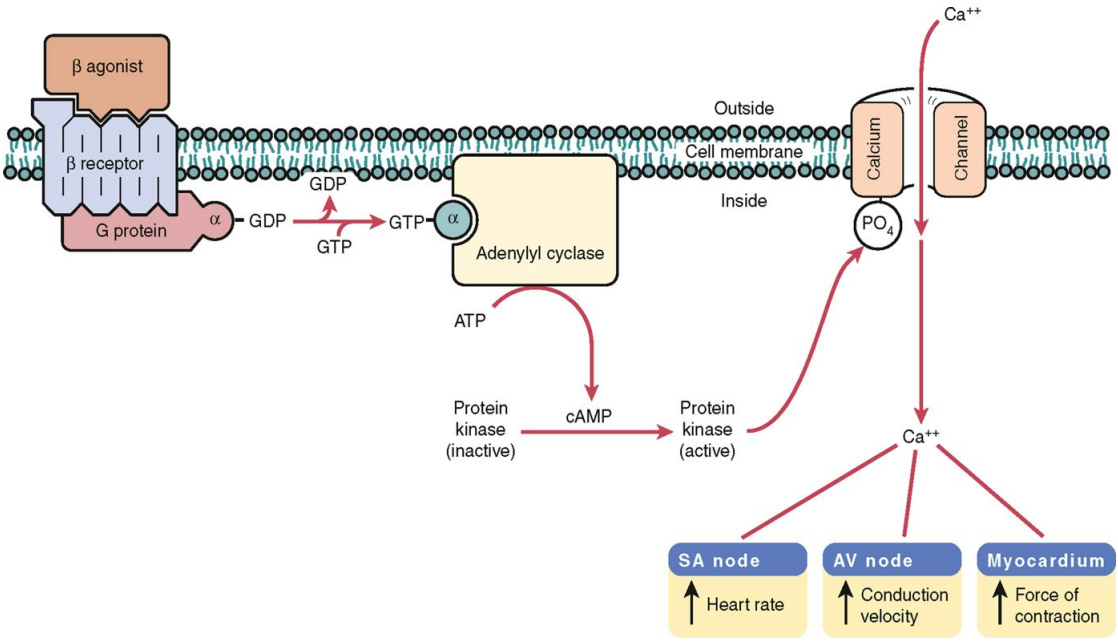


Figure 44-1 Coupling of cardiac calcium channels with beta1-adrenergic receptors. In the heart, beta1 receptors are coupled to calcium channels. As a result, when cardiac beta1 receptors are activated, calcium influx is enhanced. The process works as follows. Binding of an agonist (eg, norepinephrine) causes a conformational change in the beta receptor, which in turn causes a change in G protein, converting it from an inactive state (in which GDP is bound to the alpha subunit) to an active state (in which GTP is bound to the alpha subunit). (G protein is so named because it binds guanine nucleotides: GDP and GTP.) Following activation, the alpha subunit dissociates from the rest of G protein and activates adenylyl cyclase, an enzyme that converts ATP to cyclic AMP (cAMP). cAMP then activates protein kinase, an enzyme that phosphorylates proteins—in this case, the calcium channel. Phosphorylation changes the channel such that calcium entry is enhanced when the channel opens. (Opening of the channel is triggered by a change in membrane voltage [ie, by passage of an action potential].)The effect of calcium entry on cardiac function is determined by the type of cell in-

volved. If the cell is in the SA node, heart rate increases; if the cell is in the AV node, impulse conduction through the node accelerates; and if the cell is part of the myocardium, force of contraction is increased. Because binding of a single agonist molecule to a single beta receptor stimulates the synthesis of many cAMP molecules, with the subsequent activation of many protein kinase molecules, causing the phosphorylation of many calcium channels, this system can greatly amplify the signal initiated by the agonist.

CALCIUM CHANNEL BLOCKERS: CLASSIFICATION AND SITES OF ACTION

Classification

The CCBs used in the United States belong to three chemical families (Table 44-1). The largest family is the *dihydropyridines,* for which *nifedipine* is the prototype. This family name is encountered frequently and hence is worth remembering. The other two families consist of orphans: *verapamil* is the only *phenylalkylamine,* and *diltiazem* is the only *benzothiazepine*. The drug names are important; the family names are not.

		Indications			
Classification	**Sites of Action**	**Hypertension**	**Angina**	**Dysrhythmias**	**Others**
Dihydropyridines					
Nifedipine [Adalat, Nifediac, Nifedical, Procardia]	Arterioles	✓	✓		§
Amlodipine [Norvasc]	Arterioles	✓	✓		
Clevidipine [Cleviprex]	Arterioles				§
Felodipine [Plendil]	Arterioles	✓			
Isradipine [DynaCirc]	Arterioles	✓			
Nicardipine [Cardene]	Arterioles	✓	✓		
Nimodipine [Nimotop]	Arterioles				‡
Nisoldipine [Sular]	Arterioles	✓			§
Phenylalkylamines					
Verapamil [Calan, Covera-HS, Isoptin SR, Verelan]	Arterioles/heart	✓	✓	✓	§
Benzothiazepines					
Diltiazem [Cardizem, Dilacor-XR,	Arterioles/heart	✓	✓	✓	

TABLE 44-1 Calcium Channel Blockers: Classification, Sites of Action, and Indications

‡ Prophylaxis of neurologic injury after rupture of an intracranial aneurysm.

§ MigrainDe headache (investigational use).

Sites of Action

At therapeutic doses, the dihydropyridines act primarily on arterioles; in contrast, verapamil and diltiazem act on arterioles *and* the heart (see Table 44-1). However, although dihydropyridines don't affect the heart at *therapeutic* doses, *toxic* doses can produce dangerous cardiac suppression (just like verapamil and diltiazem can). The differences in selectivity among CCBs are based on structural differences among the drugs themselves and structural differences among calcium channels.

VERAPAMIL AND DILTIAZEM: AGENTS THAT ACT ON VASCULAR SMOOTH MUSCLE AND THE HEART

Verapamil

Verapamil [Calan, Covera-HS, Isoptin SR, Verelan] blocks calcium channels in blood vessels and in the heart. Major indications are angina pectoris, essential hypertension, and cardiac dysrhythmias. Verapamil was the first CCB available and will serve as our prototype for the group.

Hemodynamic Effects

The overall hemodynamic response to verapamil is the net result of (1) direct effects on the heart and blood vessels and (2) reflex responses.

Direct Effects.

By blocking calcium channels in the heart and blood vessels, verapamil has five direct effects:

- Blockade at peripheral arterioles causes dilation, and thereby reduces arterial pressure.
- Blockade at arteries and arterioles of the heart increases coronary perfusion.

- Blockade at the SA node reduces heart rate.
- Blockade at the AV node decreases AV nodal conduction.
- Blockade in the myocardium decreases force of contraction.

Of the direct effects on the heart, reduced AV conduction is the most important.

Indirect (Reflex) Effects.

Verapamil-induced lowering of blood pressure activates the baroreceptor reflex, causing increased firing of sympathetic nerves to the heart. Norepinephrine released from these nerves acts to increase heart rate, AV conduction, and force of contraction. However, since these same three parameters are suppressed by the direct actions of verapamil, the direct and indirect effects tend to neutralize each other.

Net Effect.

Because the direct effects of verapamil on the heart are counterbalanced by indirect effects, the drug has little or no net effect on cardiac performance: For most patients, heart rate, AV conduction, and contractility are not noticeably altered. Consequently, the overall cardiovascular effect of verapamil is simply vasodilation accompanied by reduced arterial pressure and increased coronary perfusion.

Pharmacokinetics

Verapamil may be administered orally and IV. The drug is well absorbed following oral administration, but undergoes extensive metabolism on its first pass through the liver. Consequently, only about 20% of an oral dose reaches the systemic circulation. Effects begin in 30 minutes and peak within 5 hours. Elimination is primarily by hepatic metabolism. Because the drug is eliminated by the liver, doses must be reduced substantially in patients with hepatic impairment.

Therapeutic Uses

Angina Pectoris.

Verapamil is used widely to treat angina pectoris. The drug is approved for vasospastic angina and angina of effort. Benefits in both disorders derive from vasodilation. The role of verapamil in antianginal therapy is discussed further in Chapter 50.

Essential Hypertension.

Verapamil is a first-line agent for chronic hypertension. The drug lowers blood pressure by promoting dilation of arterioles. The role of verapamil and other CCBs in hypertension is discussed in Chapter 46.

Cardiac Dysrhythmias.

Verapamil, administered IV, is used to slow ventricular rate in patients with atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia. Benefits derive from suppressing impulse conduction through the AV node, thereby preventing the atria from driving the ventricles at an excessive rate. Antidysrhythmic applications are discussed in Chapter 48.

Migraine.

Verapamil can help prevent migraine headache. This investigational use is discussed in Chapter 30.

Adverse Effects

Common Effects.

Verapamil is generally well tolerated. *Constipation* occurs frequently and is the most common complaint. This problem, which can be especially severe in the elderly, can be minimized by increasing dietary fluids and fiber. Constipation results from blockade of calcium channels in smooth muscle of the intestine. Other common effects—*dizziness, facial flushing, headache,* and *edema of the ankles and feet*—occur secondary to vasodilation.

Cardiac Effects.

Blockade of calcium channels in the heart can compromise cardiac function. In the SA node, calcium channel blockade can cause bradycardia; in the AV node, blockade can cause partial or complete AV block; and in the myocardi-

um, blockade can decrease contractility. When the heart is healthy, these effects are rarely of clinical significance. However, in patients with certain cardiac diseases, verapamil can seriously exacerbate dysfunction. Accordingly, the drug must be used with special caution in patients with cardiac failure, and must not be used at all in patients with sick sinus syndrome or second-degree or third-degree AV block.

Other Effects.

In older patients, CCBs have been associated with *chronic eczematous eruptions*. Although a causal relationship has not been proved, it might be wise to withdraw CCBs from older patients who develop an unexplained eczematous rash.

Gingival hyperplasia (overgrowth of gum tissue) has been reported.

Drug Interactions

Digoxin.

Like verapamil, digoxin suppresses impulse conduction through the AV node. Accordingly, when these drugs are used concurrently, the risk of AV block is increased. Patients receiving the combination should be monitored closely.

Verapamil increases plasma levels of digoxin by about 60%, thereby increasing the risk of digoxin toxicity. If signs of toxicity appear, digoxin dosage should be reduced.

Beta-Adrenergic Blocking Agents.

Beta blockers and verapamil have the same effects on the heart: they decrease heart rate, AV conduction, and contractility. Hence, when a beta blocker and verapamil are used together, there is a risk of excessive cardiosuppression. To minimize risk, beta blockers and IV verapamil should be administered several hours apart.

Toxicity

Clinical Manifestations.

Overdose can produce severe hypotension and cardiotoxicity (bradycardia, AV block, ventricular tachydysrhythmias).

Treatment.

General Measures.

Verapamil can be removed from the GI tract with gastric lavage followed by a cathartic. Intravenous calcium gluconate can counteract both vasodilation and negative inotropic effects, but will not reverse AV block.

Hypotension.

Hypotension can be treated with IV norepinephrine, which promotes vasoconstriction (by activating alpha*1* receptors on blood vessels) and increases cardiac output (by activating beta*1* receptors in the heart). Placing the patient in modified Trendelenburg's position (legs elevated) and administering IV fluids may also help.

Bradycardia and AV Block.

Bradycardia and AV block can be treated with isoproterenol (a beta-adrenergic agonist) and with atropine (an anticholinergic drug that blocks parasympathetic influences on the heart). If pharmacologic measures are inadequate, electronic pacing may be required.

Ventricular Tachydysrhythmias.

The preferred treatment is direct-current (DC) cardioversion. Antidysrhythmic drugs (procainamide, lidocaine) may also be tried.

Preparations, Dosage, and Administration

Oral.

Verapamil is available in standard tablets (40, 80, and 120 mg) as Calan; sustained-release tablets (120, 180, and 240 mg) as Calan SR, Covera-HS, and Isoptin SR; and sustained-release capsules (120, 180, 240, and 360 mg) as Verelan. In addition, verapamil is available as Verelan PM (100-, 200-, and 300-mg capsules), a timed-release formulation that, when administered at bedtime,

produces maximum verapamil levels in the morning. The sustained-, timed-, and extended-release formulations are approved only for hypertension. Instruct patients to swallow these products intact, without crushing or chewing. A fixed-dose combination with trandolapril (an angiotensin-converting enzyme [ACE] inhibitor) is available under the trade name *Tarka*.

The usual initial dosage for *angina pectoris* is 80 to 120 mg 3 times a day. The usual initial dosage for *essential hypertension* is 80 mg 3 times a day (using standard tablets), 240 mg of a sustained-release formulation (administered once a day in the morning with food), or 200 mg of Verelan PM (administered once a day at bedtime). Dosages should be reduced for elderly patients and for patients with advanced renal or liver disease. Dosages for dysrhythmias are presented in Chapter 48.

Intravenous.

Intravenous verapamil is used for dysrhythmias. Because IV verapamil can cause severe adverse cardiovascular effects, blood pressure and the electrocardiogram (ECG) should be monitored and equipment for resuscitation should be immediately available. Intravenous dosages for dysrhythmias are presented in Chapter 48.

Diltiazem

Actions and Uses.

Like verapamil, diltiazem [Cardizem, Dilacor-XR, others] blocks calcium channels in the heart and blood vessels. As a result, the actions and applications of the two drugs are very similar. Diltiazem has the same effects on cardiovascular function as verapamil. Both drugs lower blood pressure through arteriolar dilation and, because their direct suppressant actions are balanced by reflex cardiac stimulation, both have little *net* effect on the heart. Like verapamil, diltiazem is used for angina pectoris, essential hypertension, and cardiac dysrhythmias (atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia).

Pharmacokinetics.

Oral diltiazem is well absorbed and then extensively metabolized on its first pass through the liver. As a result, bioavailability is only about 50%. Effects begin rapidly (within a few minutes) and peak within half an hour. The drug undergoes nearly complete metabolism prior to elimination in the urine and feces.

Adverse Effects.

Adverse effects are like those of verapamil, except that diltiazem causes less constipation. The most common effects are dizziness, flushing, headache, and edema of the ankles and feet. Like verapamil, diltiazem can exacerbate cardiac dysfunction in patients with bradycardia, sick sinus syndrome, heart failure, or second-degree or third-degree AV block. Like other CCBs, diltiazem may cause chronic eczematous rash in the elderly.

Drug Interactions.

Like verapamil, diltiazem can exacerbate digoxin-induced suppression of AV conduction, and can intensify the cardiosuppressant effects of beta blockers. Patients receiving diltiazem concurrently with digoxin or a beta blocker should be monitored closely for cardiac status.

Preparations, Dosage, and Administration.

Oral diltiazem is available in standard tablets (30, 60, 90, and 120 mg) as Cardizem, extended-release tablets (120, 180, 240, 300, 360, and 420 mg) as Cardizem LA, and sustained-release capsules (60, 90, 120, 180, 240, 300, 360, and 420 mg) as Cardizem CD, Cartia XT, Dilacor XR, Dilt-CD, Dilt-XR, Diltia XT, Taztia XT and Tiazac. The drug is also available in solution (5 mg/mL) for IV administration under the trade name Cardizem. The usual initial dosage for hypertension is 180 mg once a day with Cardizem CD, 60 to 120 mg twice a day with Cardizem CD or Dilacor XR, and 180 to 240 mg once a day with Cardizem LA. Angina pectoris can be treated with standard tablets (30 mg 4 times a day initially and 60 mg 4 times a day for maintenance). Intravenous diltiazem is reserved for dysrhythmias.

DIHYDROPYRIDINES: AGENTS THAT ACT MAINLY ON VASCULAR SMOOTH MUSCLE

All of the drugs discussed in this section belong to the *dihydropyridine* family. At therapeutic doses, these drugs produce significant blockade of calcium channels in blood vessels and minimal blockade of calcium channels in the heart. The dihydropyridines are similar to verapamil in some respects but quite different in others.

Nifedipine

Nifedipine [Adalat, Nifedical, Nifediac, Procardia] was the first dihydropyridine available and will serve as our prototype for the group. Like verapamil, nifedipine blocks calcium channels in VSM and thereby promotes vasodilation. However, in contrast to verapamil, nifedipine produces very little blockade of calcium channels in the heart. As a result, nifedipine cannot be used to treat dysrhythmias, does not cause cardiac suppression, and is less likely than verapamil to exacerbate pre-existing cardiac disorders. Nifedipine also differs from verapamil in that nifedipine is more likely to cause reflex tachycardia. Contrasts between nifedipine and verapamil are summarized in Table 44-2.

Property	Drug	
	Nifedipine	Verapamil
Direct Effects on the Heart and Arterioles		
Arteriolar dilation	Yes	Yes
Effects on the heart		
Reduced automaticity	No	Yes
Reduced AV conduction	No	Yes
Reduced contractile force	No	Yes
Major Indications		
Hypertension	Yes	Yes
Angina pectoris (classic and variant)	Yes	Yes
Dysrhythmias	No	Yes
Adverse Effects		
Exacerbation of		
AV block	No	Yes
Sick sinus syndrome	No	Yes
Heart failure	No	Yes
Effects secondary to vasodilation		
Edema (ankles and feet)	Yes	Yes
Flushing	Yes	Yes
Headaches	Yes	Yes
Dizziness	Yes	Yes
Reflex tachycardia	Yes	No
Constipation	No	Yes
Drug Interactions		

TABLE 44-2 Comparisons and Contrasts Between Nifedipine and Verapamil

Hemodynamic Effects

Direct Effects.

The direct effects of nifedipine on the cardiovascular system are limited to blockade of calcium channels in VSM. Blockade of calcium channels in peripheral arterioles causes vasodilation, and thereby lowers arterial pressure. Channel blockade in arteries and arterioles of the heart increases coronary perfusion. Because nifedipine does not block cardiac calcium channels at usual therapeutic doses, the drug has no *direct* suppressant effects on automaticity, AV conduction, or contractile force.

Indirect (Reflex) Effects.

By lowering blood pressure, nifedipine activates the baroreceptor reflex, thereby causing sympathetic stimulation of the heart. Because nifedipine lacks direct cardiosuppressant actions, cardiac stimulation is unopposed, and hence heart rate and contractile force increase.

It is important to note that reflex effects occur primarily with the *fast-acting* formulation of nifedipine, not with the sustained-release formulation. Why? Because the baroreceptor reflex is turned on only by a *rapid* fall in blood pressure; a gradual decline will not activate the reflex. With the fast-acting formulation, blood levels of nifedipine rise quickly, and hence blood pressure drops quickly and the reflex is turned on. Conversely, with the sustained-release formulation, blood levels of nifedipine rise slowly, and hence blood pressure falls slowly and the reflex is blunted.

Net Effect.

The overall hemodynamic response to nifedipine is simply the sum of its direct effect (vasodilation) and indirect effect (reflex cardiac stimulation). Accordingly, nifedipine (1) lowers blood pressure, (2) increases heart rate, and (3) increases contractile force. Please note, however, that the reflex increases in heart rate and contractile force are transient and occur primarily with the rapid-acting formulation.

Pharmacokinetics

Nifedipine is well absorbed following oral administration, but undergoes extensive first-pass metabolism. As a result, only about 50% of an oral dose reaches the systemic circulation. With the fast-acting formulation, effects begin rapidly and peak in 30 minutes; with the sustained-release formulation, effects begin in 20 minutes and peak in 6 hours. Nifedipine is fully metabolized prior to excretion in the urine.

Therapeutic Uses

Angina Pectoris.

Nifedipine is indicated for vasospastic angina and angina of effort. The drug is usually combined with a beta blocker to prevent reflex stimulation of the heart, which could intensify anginal pain. Long-term use reduces the rates of overt heart failure, coronary angiography, and coronary bypass surgery—but not rates of stroke, myocardial infarction, or death. The role of nifedipine in angina is discussed further in Chapter 50.

Hypertension.

Nifedipine is used widely to treat *essential hypertension*. Only the sustained-release formulation should be used. In the past, nifedipine was used for *hypertensive emergencies,* but has largely been replaced by drugs that are safer. The use of CCBs in essential hypertension is discussed further in Chapter 46.

Investigational Uses.

Nifedipine has been used on an investigational basis to *suppress preterm labor* (see Chapter 63).

Adverse Effects

Some adverse effects are like those of verapamil; others are quite different. Like verapamil, nifedipine can cause *flushing, dizziness, headache, peripheral edema,* and *gingival hyperplasia,* and may pose a risk of *chronic eczematous rash* in older patients. In contrast to verapamil, nifedipine causes very little constipation. Also, since nifedipine causes minimal blockade of calcium channels in the heart, the drug is not likely to exacerbate AV block, heart failure, bradycardia,

or sick sinus syndrome. Accordingly, nifedipine is preferred to verapamil for patients with these disorders.

A response that occurs with nifedipine that does not occur with verapamil is *reflex tachycardia*. This response is problematic in that it increases cardiac oxygen demand and can thereby increase pain in patients with angina. To prevent reflex tachycardia, nifedipine can be combined with a beta blocker (eg, propranolol).

Rapid-acting nifedipine has been associated with increased mortality in patients with myocardial infarction and unstable angina. Other rapid-acting CCBs have been associated with an increased risk of myocardial infarction in patients with hypertension. However, in both cases, a cause-and-effect relationship has not been established. Nonetheless, the National Heart, Lung, and Blood Institute has recommended that rapid-acting nifedipine, especially in higher doses, be used with great caution, if at all. It is important to note that these adverse effects have not been associated with *sustained-release* nifedipine or with any other long-acting CCB.

Drug Interactions

Beta-Adrenergic Blockers.

Beta blockers are combined with nifedipine to prevent reflex tachycardia. It is important to note that, whereas beta blockers can *decrease* the adverse cardiac effects of *nifedipine,* they can *intensify* the adverse cardiac effects of *verapamil* and *diltiazem*.

Toxicity

When taken in excessive dosage, nifedipine loses selectivity. Hence, toxic doses affect the heart in addition to blood vessels. Consequently, the manifestations and treatment of nifedipine overdose are the same as described above for verapamil.

Preparations, Dosage, and Administration

Nifedipine is available in capsules (10 and 20 mg) as Adalat and Procardia and sustained-release tablets (30, 60, and 90 mg) as Adalat CC, Nifedical XL, Nifedi-

ac CC, and Procardia XL. Instruct patients to swallow sustained-release tablets whole, without crushing or chewing.

For treatment of *angina pectoris,* the usual initial dosage is 10 mg 3 times a day. The usual maintenance dosage is 10 to 20 mg 3 times a day. The maximum recommended dosage is 180 mg/day.

For *essential hypertension,* only the sustained-release tablets are approved. The usual initial dosage is 30 mg once a day.

Other Dihydropyridines

In addition to nifedipine, seven other dihydropyridines are available. All are similar to nifedipine. Like nifedipine, these drugs produce greater blockade of calcium channels in VSM than in the heart.

Nicardipine.

At therapeutic doses, nicardipine [Cardene, Cardene SR, Cardene I.V.] produces selective blockade of calcium channels in blood vessels and has minimal direct effects on the heart. The drug has two indications: essential hypertension and effort-induced angina pectoris. The most common adverse effects are flushing, headache, asthenia (weakness), dizziness, palpitations, and edema of the ankles and feet. As with other CCBs, eczematous rash may develop in older patients. Gingival hyperplasia (overgrowth of gum tissue) has been reported. Like nifedipine, nicardipine can be combined with a beta blocker to promote therapeutic effects and suppress reflex tachycardia. Nicardipine is available in standard capsules (20 and 30 mg) as Cardene, sustained-release capsules (30, 45, and 60 mg) as Cardene SR, and an IV formulation (2.5 mg/mL) as Cardene I.V. The usual initial dosage for *angina pectoris* is 20 mg 3 times a day using the standard capsules. The usual initial dosage for *essential hypertension* is 20 mg 3 times a day (using standard capsules) or 30 mg twice a day (using sustained-release capsules).

Amlodipine.

At therapeutic doses, amlodipine [Norvasc] produces selective blockade of calcium channels in blood vessels, having minimal direct effects on the heart. Approved indications are essential hypertension and angina pectoris (effort

induced and vasospastic). Amlodipine is administered orally and absorbed slowly; peak levels develop in 6 to 12 hours. The drug has a long half-life (30 to 50 hours) and therefore is effective with once-a-day dosing. Principal adverse effects are peripheral and facial edema. Flushing, dizziness, and headache may also occur, as may eczematous rash in older patients. In contrast to other dihydropyridines, amlodipine causes little reflex tachycardia. Amlodipine is available in 2.5-, 5-, and 10-mg tablets. The usual initial dosage for hypertension or angina pectoris is 5 mg once a day. A fixed-dose combination with benazepril (an ACE inhibitor) is available under the trade name *Lotrel*.

Isradipine.

Like nifedipine, isradipine [DynaCirc, DynaCirc CR] produces relatively selective blockade of calcium channels in blood vessels. In the United States, the drug is approved only for hypertension. Isradipine is rapidly absorbed following oral administration, but undergoes extensive first-pass metabolism. Parent drug and metabolites are excreted in the urine. The most common side effects are facial flushing (11%), headache (14%), dizziness (7%), and ankle edema (7%). Eczematous rash may develop in older patients. In contrast to nifedipine, isradipine causes minimal reflex tachycardia. The drug is available in capsules (2.5 and 5 mg) and controlled-release tablets (5 and 10 mg). The usual antihypertensive dosage is 2.5 to 5 mg twice a day.

Felodipine.

Felodipine [Plendil] produces selective blockade of calcium channels in blood vessels. In the United States, the drug is approved only for hypertension. Felodipine is well absorbed following oral administration but undergoes extensive first-pass metabolism. As a result, bioavailability is low—only 20%. Plasma levels peak in 2.5 to 5 hours and then decay with a half-life of 24 hours. Because of its prolonged half-life, felodipine is effective with once-a-day dosing. Characteristic adverse effects are reflex tachycardia, peripheral edema, headache, facial flushing, and dizziness. Eczematous rash may develop in older patients. Gingival hyperplasia has been reported. Felodipine is available in extended-release tablets (2.5, 5, and 10 mg). The usual dosage for hypertension is 5 to 10 mg once a day. A fixed-dose combination with enalapril (an ACE inhibitor) is available under the trade name *Lexxel*.

Nimodipine.

Nimodipine [Nimotop] produces selective blockade of calcium channels in *cerebral blood vessels*. The only approved application is prophylaxis of neurologic injury following rupture of an intracranial aneurysm. Benefits derive from preventing the cerebral arterial spasm that follows subarachnoid hemorrhage (SAH) and can result in ischemic neurologic injury. Dosing (60 mg every 4 hours) should begin within 96 hours of SAH and continue for 21 days. Nimodipine is available in 30-mg liquid-filled capsules for oral administration only. *Nimodipine must never be given parenterally* (eg, IM, IV) owing to a risk of potentially fatal cardiovascular events.

Nisoldipine.

Like nifedipine, nisoldipine [Sular] produces selective blockade of calcium channels in blood vessels; the drug has minimal direct effects on the heart. The only approved indication is hypertension. Nisoldipine is well absorbed following oral administration, but the first-pass effect limits bioavailability to 5%. Plasma levels peak 6 hours after administration. The most common side effects are dizziness, headache, and peripheral edema. Reflex tachycardia may also occur. As with other CCBs, eczematous rash may develop in older patients. Nisoldipine is available in extended-release tablets (10, 20, 30, and 40 mg). The dosage for hypertension is 20 to 60 mg once a day.

Clevidipine.

Clevidipine [Cleviprex], approved in 2008, is indicated only for *intravenous* therapy of *severe* hypertension, defined as systolic blood pressure above 180 mm Hg or diastolic pressure above 115 mm Hg. The drug has an ultrashort half-life (about 1 minute), owing to rapid inactivation by plasma esterases. Effects are not altered by impairment of liver or kidney function. Because of IV dosing and rapid inactivation, blood pressure falls quickly and then rises quickly when the infusion is slowed or stopped. As a result, responses can be easily titrated. Clevidipine is formulated in a lipid emulsion made from soybean oil and egg yolk phospholipids, and hence is contraindicated for patients allergic to soy beans or eggs. Clevidipine is supplied in single-dose vials (50 or 100 mL) at a concentration of 0.5 mg/mL. For patients with severe hypertension, the infusion rate is 1 to 2 mg/hr initially, and can be doubled every

3 minutes up to a maximum of 32 mg/hr. In clinical trials, the average time to reach the target blood pressure was 10.9 minutes. The most common side effects are headache, nausea, and vomiting. Like other dihydropyridines, clevidipine can cause hypotension and reflex tachycardia.

KEY POINTS

- Calcium channels are gated pores in the cytoplasmic membrane that regulate calcium entry into cells.
- In blood vessels, calcium entry causes vasoconstriction, and hence calcium channel blockade causes vasodilation.
- In the heart, calcium entry increases heart rate, AV conduction, and myocardial contractility, and hence calcium channel blockade has the opposite effects.
- In the heart, calcium channels are coupled to beta***1*** receptors, activation of which enhances calcium entry. As a result, calcium channel blockade and beta blockade have identical effects on cardiac function.
- At therapeutic doses, nifedipine and the other dihydropyridines act primarily on VSM; in contrast, verapamil and diltiazem act on VSM *and* on the heart.
- All CCBs promote vasodilation, and hence are useful in hypertension and angina pectoris.
- Because they suppress AV conduction, verapamil and diltiazem are useful for treating cardiac dysrhythmias (in addition to hypertension and angina pectoris).
- Because of their cardiosuppressant effects, verapamil and diltiazem can cause bradycardia, partial or complete AV block, and exacerbation of heart failure.
- Beta blockers intensify cardiosuppression caused by verapamil and diltiazem.

- Nifedipine and other dihydropyridines can cause reflex tachycardia. Tachycardia is most intense with rapid-acting formulations, and much less intense with sustained-release formulations.
- Beta blockers can be used to suppress reflex tachycardia caused by nifedipine and other dihydropyridines.
- Because they cause vasodilation, all CCBs can cause dizziness, headache, and peripheral edema.
- In toxic doses, nifedipine and other dihydropyridines can cause cardiosuppression, just like verapamil and diltiazem.
- Rapid-acting nifedipine has been associated with increased mortality in patients with myocardial infarction and unstable angina, although a cause-and-effect relationship has not been established. The National Heart, Lung, and Blood Institute has recommended that rapid-acting nifedipine, especially in higher doses, be used with great caution, if at all.

Summary of Major Nursing Implications*

VERAPAMIL AND DILTIAZEM

Preadministration Assessment

Therapeutic Goal

Verapamil and diltiazem are indicated for *hypertension, angina pectoris,* and *cardiac dysrhythmias* (atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia).

Baseline Data

For *all patients,* determine blood pressure and pulse rate, and obtain laboratory evaluations of liver and kidney function. For patients with *angina pectoris,* obtain baseline data on the frequency and severity of anginal attacks. For baseline data relevant to *hypertension,* see Chapter 46.

Identifying High-Risk Patients

Verapamil and diltiazem are *contraindicated* for patients with severe hypotension, sick sinus syndrome (in the absence of electronic pacing), and second-degree or third-degree AV block. Use with *caution* in patients with heart failure or liver impairment and in patients taking digoxin or beta blockers.

Implementation: Administration

Routes

Oral, IV.

Administration

Oral.

Verapamil and *diltiazem* may be used for angina pectoris and essential hypertension. *Verapamil* may be used with digoxin to control ventricular rate in patients with atrial fibrillation and atrial flutter.

Sustained-release formulations are reserved for essential hypertension. **Instruct patients to swallow sustained-release formulations whole, without crushing or chewing.**

Prior to administration, measure blood pressure and pulse rate. If hypotension or bradycardia is detected, withhold medication and notify the prescriber.

Intravenous.

Intravenous therapy (with verapamil or diltiazem) is reserved for cardiac dysrhythmias. Perform injections slowly (over 2 to 3 minutes). Monitor the ECG for AV block, sudden reduction in heart rate, and prolongation of the PR or QT interval. Have facilities for cardioversion and cardiac pacing immediately available.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Angina Pectoris.

Keep an ongoing record of anginal attacks, noting the time and intensity of each attack and the likely precipitating event. **Teach outpatients to chart the time, intensity, and circumstances of their attacks, and to notify the prescriber if attacks increase.**

Essential Hypertension.

Monitor blood pressure periodically. For most patients, the goal is to reduce systolic/diastolic pressure to a value below 140/90 mm Hg. **Teach patients to self-monitor their blood pressure and to maintain a blood pressure record.**

Minimizing Adverse Effects

Cardiosuppression.

Verapamil and diltiazem can cause bradycardia, AV block, and heart failure. **Inform patients about manifestations of cardiac effects (eg, slow heartbeat, shortness of breath, weight gain) and instruct them to notify the prescriber if these occur.** If cardiac impairment is severe, drug use should stop.

Peripheral Edema.

Inform patients about signs of edema (swelling in ankles or feet) and instruct them to notify the prescriber if these occur. If necessary, edema can be reduced with a diuretic.

Constipation.

Constipation occurs primarily with *verapamil*. **Advise patients that constipation can be minimized by increasing dietary fluid and fiber.**

Minimizing Adverse Interactions

Digoxin.

The combination of digoxin with verapamil or diltiazem increases the risk of partial or complete AV block. Monitor for indications of impaired AV conduction (missed beats, slowed ventricular rate).

Verapamil (and possibly diltiazem) can increase plasma levels of digoxin. Digoxin dosage should be reduced.

Beta Blockers.

Concurrent use of a beta blocker with verapamil or diltiazem can cause bradycardia, AV block, or heart failure. Monitor closely for cardiac suppression. Administer *intravenous verapamil* and beta blockers several hours apart.

Managing Acute Toxicity

Remove unabsorbed drug with gastric lavage followed by a cathartic. Give intravenous calcium to help counteract excessive vasodilation and reduced myocardial contractility.

To raise blood pressure, give IV norepinephrine. Intravenous fluids and placing the patient in modified Trendelenburg's position can also help.

Bradycardia and AV block can be reversed with isoproterenol and atropine. If these are inadequate, electronic pacing may be required.

Ventricular tachydysrhythmias can be treated with DC cardioversion. Antidysrhythmic drugs (lidocaine or procainamide) may also be used.

DIHYDROPYRIDINES

Amlodipine

Clevidipine

Felodipine

Isradipine

Nicardipine

Nifedipine

Nimodipine

Nisoldipine

Preadministration Assessment

Therapeutic Goal

Amlodipine, nifedipine, and *nicardipine* are approved for essential hypertension and angina pectoris.

Isradipine, felodipine, and *nisoldipine* are approved for hypertension only.

Nimodipine is used only for subarachnoid hemorrhage.

Clevidipine is used only for *severe* hypertension.

Baseline Data

See nursing implications for *Verapamil and Diltiazem*.

Identifying High-Risk Patients

Use dihydropyridines with *caution* in patients with hypotension, sick sinus syndrome (in the absence of electronic pacing), angina pectoris (because of reflex tachycardia), heart failure, and second-degree or third-degree AV block.

Implementation: Administration

Route

Oral. All dihydropyridines except clevidipine.

Intravenous. Nicardipine, clevidipine.

Administration

Instruct patients to swallow sustained-release formulations whole, without crushing or chewing.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

See nursing implications for *Verapamil and Diltiazem*.

Minimizing Adverse Effects

Reflex Tachycardia.

Reflex tachycardia can be suppressed with a beta blocker.

Peripheral Edema.

Inform patients about signs of edema (swelling in ankles or feet) and instruct them to notify the prescriber if these occur. If necessary, edema can be reduced with a diuretic.

Managing Acute Toxicity

See nursing implications for *Verapamil and Diltiazem*.

45 Vasodilators

Vasodilation can be produced with a variety of drugs. The major classes of vasodilators, along with representative agents, are listed in Table 45-1. Some of these drugs act primarily on arterioles, some act primarily on veins, and some act on both types of vessel. The vasodilators are widely used, with indications ranging from hypertension to angina pectoris to heart failure. Many of the vasodilators have been discussed in previous chapters. Four agents—hydralazine, minoxidil, diazoxide, and nitroprusside—are introduced here.

In approaching the vasodilators, we begin by considering concepts that apply to the vasodilators as a group. After that we discuss the pharmacology of individual agents.

Category	Examples
Drugs Acting on the Renin-Angiotensin-Aldosterone System	
Angiotensin-Converting Enzyme Inhibitors	Captopril
	Enalapril
Angiotensin II Receptor Blockers	Losartan
	Valsartan
Direct Renin Inhibitors	Aliskiren
Organic Nitrates	Nitroglycerin
	Isosorbide dinitrate
Calcium Channel Blockers	Diltiazem
	Verapamil
	Nifedipine
Sympatholytic Drugs	
Alpha-Adrenergic Blockers	Phentolamine
	Phenoxybenzamine
	Prazosin
	Terazosin
Ganglionic Blockers	Mecamylamine
Adrenergic Neuron Blockers	Reserpine
	Guanadrel
Centrally Acting Agents	Clonidine
	Methyldopa
Drugs for Pulmonary Arterial	Bosentan
Hypertension	Epoprostenol
Other Important Vasodilators	Hydralazine

TABLE 45-1 Types of Vasodilators

BASIC CONCEPTS IN VASODILATOR PHARMACOLOGY

Selectivity of Vasodilatory Effects

Vasodilators differ from one another with respect to the types of blood vessels they affect. Some agents (eg, hydralazine) produce selective dilation of arterioles. Others (eg, nitroglycerin) produce selective dilation of veins. Still others (eg, prazosin) dilate arterioles *and* veins. The selectivity of some important vasodilators is summarized in Table 45-2.

	Site of Vasodilation	
Vasodilator	**Arterioles**	**Veins**
Hydralazine	+	
Minoxidil	+	
Diltiazem	+	
Nifedipine	+	
Verapamil	+	
Diazoxide	+	
Prazosin	+	+
Terazosin	+	+
Phentolamine	+	+
Nitroprusside	+	+
Captopril	+	+
Enalapril	+	+
Losartan	+	+

TABLE 45-2 Vasodilator Selectivity

The selectivity of a vasodilator determines its hemodynamic effects. For example, drugs that dilate *resistance vessels* (arterioles) cause a decrease in cardiac *afterload* (the force the heart works against to pump blood). By decreasing afterload, arteriolar dilators reduce cardiac work while causing cardiac output and tissue perfusion to increase. In contrast, drugs that dilate *capacitance vessels* (veins) reduce the force with which blood is returned to the heart, which reduces ventricular filling. This reduction in filling decreases cardiac *preload* (the degree of stretch of the ventricular muscle prior to contraction), which in turn decreases the force of ventricular contraction. Hence, by decreasing preload, venous dilators cause a decrease in cardiac work, along with a decrease in cardiac output and tissue perfusion.

Because hemodynamic responses to dilation of arterioles and veins differ, the selectivity of a vasodilator is a major determinant of its effects, both therapeutic and undesired. Undesired effects related to selective dilation of arterioles and veins are discussed below. Therapeutic implications of selective dilation are discussed in Chapters 46, 47, 50, 52, and 106—the chapters in which the primary uses of the vasodilators are presented.

Overview of Therapeutic Uses

The vasodilators, as a group, have a broad spectrum of uses. Principal indications are *essential hypertension, hypertensive crisis, angina pectoris, heart failure,* and *myocardial infarction*. Additional indications include *pheochromocytoma, peripheral vascular disease, pulmonary arterial hypertension,* and *production of controlled hypotension during surgery*. The specific applications of any particular agent are determined by its pharmacologic profile. Important facets of that profile are route of administration, site of vasodilation (arterioles, veins, or both), and intensity and duration of effects.

Adverse Effects Related to Vasodilation

Postural Hypotension

Postural (orthostatic) hypotension is defined as a fall in blood pressure brought on by moving from a supine or seated position to an upright position. The underlying cause is relaxation of smooth muscle in *veins*. Because of venous re-

laxation, gravity causes blood to "pool" in veins, thereby decreasing venous return to the heart. Reduced venous return causes a decrease in cardiac output and a corresponding drop in blood pressure. Hypotension from venous dilation is minimal in recumbent subjects because, when we are lying down, the impact of gravity on venous return is small.

Patients receiving vasodilators should be informed about symptoms of hypotension (lightheadedness, dizziness) and advised to sit or lie down if these occur. Failure to follow this advice may result in fainting. Patients should also be informed that they can minimize hypotension by avoiding abrupt transitions from a supine or seated position to an upright position.

Reflex Tachycardia

Reflex tachycardia can be produced by dilation of arterioles *or* veins. The mechanism is this: (1a) *arteriolar* dilation causes a direct decrease in arterial pressure or (1b) *venous* dilation reduces cardiac output, which in turn reduces arterial pressure; (2) baroreceptors in the aortic arch and carotid sinus sense the drop in pressure and relay this information to the vasomotor center of the medulla; and (3) in an attempt to bring blood pressure back up, the medulla sends impulses along sympathetic nerves instructing the heart to beat faster.

Reflex tachycardia is undesirable for two reasons. First, tachycardia can put an unacceptable burden on the heart. Second, if the vasodilator was given to reduce blood pressure, tachycardia would raise pressure and thereby counteract the desired effect.

To help prevent vasodilator-induced reflex tachycardia, patients can be pretreated with a beta blocker (eg, propranolol), which will block sympathetic stimulation of the heart.

Expansion of Blood Volume

Prolonged use of *arteriolar* or *venous* dilators can cause an increase in blood volume (secondary to prolonged reduction of blood pressure). The increase in volume represents an attempt by the body to restore blood pressure to pretreatment levels.

Why does blood volume increase? First, reduced blood pressure triggers secretion of aldosterone by the adrenal glands. Aldosterone then acts on the kidney

to promote retention of sodium and water, thereby increasing blood volume. Second, by reducing arterial pressure, vasodilators decrease both renal blood flow and glomerular filtration rate; because filtrate volume is decreased, the kidney is able to reabsorb an increased fraction of filtered sodium and water, which causes blood volume to expand.

Increased blood volume can negate the beneficial effects of the vasodilator. For example, if volume increases during the treatment of hypertension, blood pressure will rise and the benefits of therapy will be canceled. To prevent the kidney from neutralizing the beneficial effects of vasodilation, patients often receive concurrent therapy with a diuretic, which prevents fluid retention and volume expansion.

PHARMACOLOGY OF INDIVIDUAL VASODILATORS

In this section we focus on four drugs: hydralazine, minoxidil, diazoxide, and sodium nitroprusside. All of the other vasodilators are discussed at length in other chapters, and hence discussion of them here is brief.

Hydralazine

Cardiovascular Effects

Hydralazine [Apresoline] causes selective dilation of arterioles. The drug has little or no effect on veins. Arteriolar dilation results from a direct action on vascular smooth muscle (VSM). The exact mechanism is unknown. In response to arteriolar dilation, peripheral resistance and arterial blood pressure fall. In addition, heart rate and myocardial contractility increase, largely by reflex mechanisms. Because hydralazine acts selectively on arterioles, postural hypotension is minimal.

Pharmacokinetics

Absorption and Time Course of Action.

Hydralazine is readily absorbed following oral administration. Effects begin within 45 minutes and persist for 6 hours or more. With parenteral administration, effects begin fast (within 10 minutes) and last 2 to 4 hours.

Metabolism.

Hydralazine is inactivated by a metabolic process known as *acetylation*. The ability to acetylate drugs is genetically determined. Some people are rapid acetylators; some are slow acetylators. The distinction between rapid and slow acetylators can be clinically significant. Why? Because individuals who acetylate hydralazine slowly are likely to have higher blood levels of the drug, which can result in excessive vasodilation and other undesired effects. To avoid hydralazine accumulation, dosage should be reduced in slow acetylators.

Therapeutic Uses

Essential Hypertension.

Oral hydralazine can be used to lower blood pressure in patients with essential hypertension. The regimen almost always includes a beta blocker, and may also include a diuretic. Although commonly employed in the past, hydralazine has been largely replaced by newer antihypertensive agents (see Chapter 46).

Hypertensive Crisis.

Parenteral hydralazine is used to lower blood pressure rapidly in severe hypertensive episodes. The drug should be administered in small, incremental doses. If dosage is excessive, severe hypotension may replace the hypertension. Treatment of hypertensive emergencies is discussed in Chapter 46.

Heart Failure.

As discussed in Chapter 47, hydralazine (usually in combination with isosorbide dinitrate) can be used short term to reduce afterload in patients with heart failure. With prolonged therapy, tolerance to hydralazine develops.

Adverse Effects

Reflex Tachycardia.

By lowering arterial blood pressure, hydralazine can trigger reflex stimulation of the heart, thereby causing cardiac work and myocardial oxygen demand to

increase. Because hydralazine-induced reflex tachycardia is frequently severe, the drug is usually combined with a beta blocker.

Increased Blood Volume.

Hydralazine-induced hypotension can cause sodium and water retention and a corresponding increase in blood volume. A diuretic can prevent volume expansion.

Systemic Lupus Erythematosus–like Syndrome.

Hydralazine can cause an acute rheumatoid syndrome that closely resembles systemic lupus erythematosus (SLE). Symptoms include muscle pain, joint pain, fever, nephritis, pericarditis, and the presence of antinuclear antibodies. The syndrome occurs most frequently in slow acetylators and is rare when dosage is kept below 200 mg/day. If an SLE–like reaction occurs, hydralazine should be discontinued. Symptoms are usually reversible but may take 6 or more months to resolve. In some cases, rheumatoid symptoms persist for years.

Other Adverse Effects.

Common responses include *headache, dizziness, weakness,* and *fatigue*. These reactions are related to hydralazine-induced hypotension.

Drug Interactions

Hydralazine is combined with a *beta blocker* to protect against reflex tachycardia, and with *diuretics* to prevent sodium and water retention and expansion of blood volume. Drugs that lower blood pressure will intensify hypotensive responses to hydralazine. Accordingly, if hydralazine is used with other *antihypertensive agents,* care is needed to avoid excessive hypotension. In the treatment of heart failure, hydralazine is usually combined with *isosorbide dinitrate,* a drug that dilates veins.

Preparations, Dosage, and Administration

Preparations.

Hydralazine [Apresoline] is available in tablets (10, 25, 50, and 100 mg) for oral use and in solution (20 mg/mL in 1-mL ampules) for parenteral administration. Hydralazine is also available in fixed-dose combination with (1) hydrochlorothiazide (a diuretic) under the trade name *Apresazide* and (2) isosorbide dinitrate (a vasodilator) under the trade name *BiDil*. As discussed in Chapters 8 and 47, BiDil is the first drug product approved for treating a specific ethnic group—namely, African Americans.

Oral Therapy.

Dosage should be low initially (10 mg 4 times a day) and then gradually increased. Rapid increases may produce excessive hypotension. Usual maintenance dosages for adults range from 25 to 100 mg twice a day. Daily doses greater than 200 mg are associated with an increased incidence of adverse effects and should be avoided.

Parenteral Therapy.

Parenteral administration (IV and IM) is reserved for hypertensive crises. The usual dose is 20 to 40 mg, repeated as needed. Blood pressure should be monitored frequently to minimize excessive hypotension. In most cases, patients can be switched from parenteral hydralazine to oral therapy within 48 hours.

Minoxidil

Minoxidil, formerly available as Loniten, produces more intense vasodilation than hydralazine but also causes more severe adverse reactions. Because it is both very effective and very dangerous, minoxidil is reserved for patients with severe hypertension unresponsive to safer drugs.

Cardiovascular Effects

Like hydralazine, minoxidil produces selective dilation of *arterioles*. Little or no venous dilation occurs. Arteriolar dilation decreases peripheral resistance and arterial blood pressure. In response, reflex mechanisms increase heart rate and myocardial contractility. Both responses can increase cardiac oxygen demand, and can thereby exacerbate angina pectoris.

Vasodilation results from a direct action on VSM. In order to relax VSM, minoxidil must first be metabolized to minoxidil sulfate. This metabolite then

causes potassium channels in VSM to open. The resultant efflux of potassium hyperpolarizes VSM cells, thereby reducing their ability to contract.

Pharmacokinetics

Minoxidil is rapidly and completely absorbed following oral administration. Vasodilation is maximal within 2 to 3 hours and then gradually declines. Residual effects may persist for 2 days or more. Minoxidil is extensively metabolized. Metabolites and parent drug are eliminated in the urine. The drug's half-life is 4.2 hours.

Therapeutic Uses

The only cardiovascular indication for minoxidil is *severe hypertension*. Because of its serious adverse effects, minoxidil is reserved for patients who have not responded to safer drugs. To minimize adverse responses (reflex tachycardia, expansion of blood volume, pericardial effusion), minoxidil should be used with a beta blocker plus intensive diuretic therapy.

Topical minoxidil [Rogaine, others] is used to promote hair growth in balding men and women (see Chapter 104).

Adverse Effects

Reflex Tachycardia.

Blood pressure reduction triggers reflex tachycardia, a serious effect that can be minimized by giving a beta blocker.

Sodium and Water Retention.

Fluid retention is both common and serious. Volume expansion may be so severe as to cause cardiac decompensation. Management of fluid retention requires a high-ceiling diuretic (eg, furosemide) used alone or in combination with a thiazide diuretic. If diuretics are inadequate, dialysis must be employed, or minoxidil must be withdrawn.

Hypertrichosis.

About 80% of patients taking minoxidil for 4 weeks or more develop hypertrichosis (excessive growth of hair). Hair growth begins on the face and later develops on the arms, legs, and back. Hypertrichosis appears to result from proliferation of epithelial cells at the base of the hair follicle; vasodilation may also be involved. Hairiness is a cosmetic problem that can be controlled by shaving or using a depilatory. However, many patients, primarily women, find hypertrichosis both unmanageable and intolerable and refuse to continue treatment.

Pericardial Effusion.

Rarely, minoxidil-induced fluid retention results in pericardial effusion (fluid accumulation beneath the pericardium). In most cases, pericardial effusion is asymptomatic. However, in some cases, fluid accumulation becomes so great as to cause cardiac tamponade (compression of the heart with a resultant decrease in cardiac performance). If tamponade occurs, it must be treated by pericardiocentesis or surgical drainage.

Other Adverse Effects.

Minoxidil may cause *nausea, headache, fatigue, breast tenderness, glucose intolerance, thrombocytopenia,* and *skin reactions* (rashes, Stevens-Johnson syndrome). In addition, the drug has caused *hemorrhagic cardiac lesions* in experimental animals.

Preparations, Dosage, and Administration

Minoxidil is supplied in 2.5- and 10-mg tablets. The initial dosage is 5 mg once a day. The maximum dosage is 100 mg/day. The usual adult dosage is 10 to 40 mg/day administered in single or divided doses. When a rapid response is needed, a loading dose of 5 to 20 mg is given followed by doses of 2.5 to 10 mg every 4 hours.

A topical formulation [Rogaine, others] is available for treating baldness (see Chapter 104).

Diazoxide

Diazoxide [Hyperstat IV] is a close relative of the thiazide diuretics but lacks diuretic effects. The drug is indicated for hypertensive emergencies.

Cardiovascular Effects

Like hydralazine and minoxidil, diazoxide produces selective dilation of *arterioles;* the drug does not dilate veins. Intravenous diazoxide causes a rapid drop in diastolic and systolic pressure. Reduced arterial pressure triggers reflex tachycardia along with an increase in myocardial contractility; these effects combine to increase cardiac output. Arteriolar dilation also promotes substantial salt and water retention.

Vasodilation results from a direct effect on VSM. Diazoxide activates potassium channels in VSM, which results in hyperpolarization and a reduced ability to contract.

Pharmacokinetics

Diazoxide is administered IV, either as a bolus injection or by infusion. Bolus injection is generally preferred. Effects begin within minutes and may persist for hours. Most of the drug is eliminated unchanged in the urine.

Therapeutic Uses

Parenteral diazoxide is reserved for acute treatment of hypertensive emergencies (eg, malignant hypertension, hypertensive encephalopathy). Oral antihypertensive agents should be instituted as soon as possible. In most cases, diazoxide can be discontinued in 4 to 5 days.

Adverse Effects

Reflex Tachycardia.

Reflex tachycardia occurs in response to lowering blood pressure. Tachycardia can be blunted with a beta blocker.

Salt and Water Retention.

Diazoxide causes substantial retention of salt and water. The primary cause is reduced glomerular filtration. If fluid retention is severe, edema and even congestive heart failure can result. Edema and expansion of blood volume can be prevented with a diuretic, preferably a high-ceiling agent (eg, furosemide).

Hyperglycemia.

Like the thiazide diuretics, diazoxide can suppress release of insulin, and can thereby cause blood glucose to rise. For most patients, the degree of hyperglycemia is insignificant. However, for patients with diabetes, hyperglycemia may be substantial. If hyperglycemia develops, insulin dosage should be increased.

Hyperuricemia.

Like the thiazide diuretics, diazoxide can decrease renal excretion of uric acid, thereby raising uric acid levels in blood. For most patients, hyperuricemia is asymptomatic. However, in gout-prone individuals, uric acid retention may precipitate a gouty attack.

Other Adverse Effects.

Diazoxide may cause *GI effects* (nausea, vomiting, anorexia), *headache, flushing, hypotension,* and *temporary interruption of labor*. Rapid injection of large doses may produce *severe hypotension, anginal symptoms,* and *myocardial infarction*.

Drug Interactions

Diuretics.

High-ceiling diuretics are used to counteract diazoxide-induced retention of salt and water. Because *thiazide diuretics* might potentiate the hyperglycemic and hyperuricemic effects of diazoxide, these agents should be avoided.

Antihypertensive Drugs.

With the exception of high-ceiling diuretics, antihypertensive drugs should generally be avoided. Why? Because an excessive reduction of blood pressure could result.

Preparations, Dosage, and Administration

Diazoxide [Hyperstat IV] is available in solution (15 mg/mL) for IV administration. In the past, it was common to administer diazoxide as a single, large (300-mg) IV bolus. This is no longer recommended. Experts now consider it

safer and more effective to use a series of "minibolus" injections, rather than one large injection. Accordingly, treatment should begin with a dose of 1 to 3 mg/kg injected by rapid IV push (30 seconds or less). Dosing is then repeated every 5 to 15 minutes until the desired drop in blood pressure has been achieved. Once hypertension has been controlled, injections can be made every 4 to 24 hours. Blood pressure should be monitored closely until an acceptable and stable level has been produced; hourly monitoring should be performed thereafter. The patient should remain recumbent for at least 30 minutes after diazoxide injection. After 4 or 5 days, the patient can usually be switched to oral antihypertensive therapy.

Sodium Nitroprusside

Sodium nitroprusside [Nitropress] is a potent and efficacious vasodilator. It is also the fastest acting antihypertensive agent available. Because of these qualities, nitroprusside is a drug of choice for hypertensive emergencies.

Cardiovascular Effects

In contrast to hydralazine, minoxidil, and diazoxide, nitroprusside causes *venous* dilation in addition to *arteriolar* dilation. Curiously, although nitroprusside is an effective arteriolar dilator, reflex tachycardia is minimal. Administration is by IV infusion, and effects begin at once. By adjusting the infusion rate, blood pressure can be depressed to almost any level desired. When the infusion is stopped, blood pressure returns to pretreatment levels in minutes. Nitroprusside can trigger retention of sodium and water; furosemide can help offset this effect.

Mechanism of Action

Once in the body, nitroprusside breaks down to release *nitric oxide* (Fig. 45-1), which then activates *guanylate cyclase,* an enzyme present in VSM. Guanylate cyclase catalyzes the production of *cyclic GMP,* which, through a series of reactions, causes vasodilation. This mechanism is similar to that of nitroglycerin.

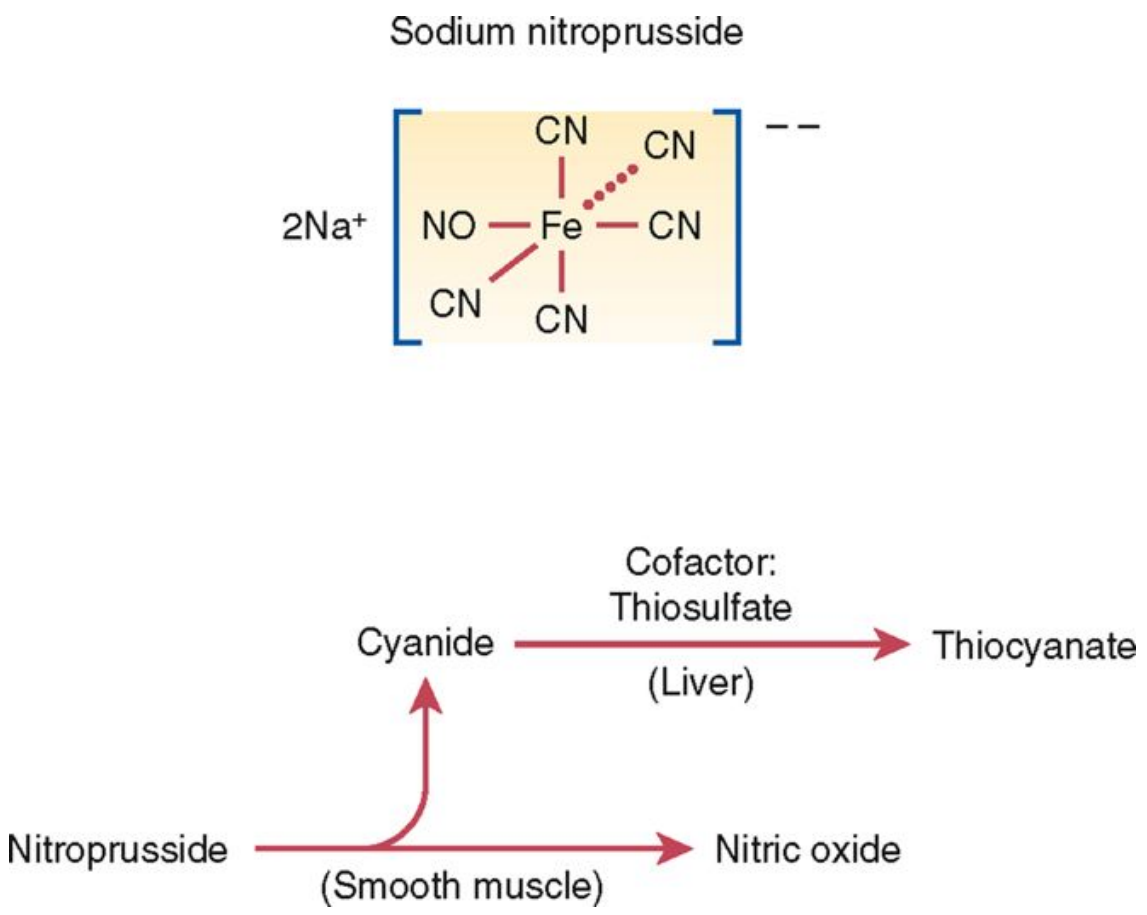


Figure 45-1 Structure and metabolism of sodium nitroprusside. Note the five cyanide (CN) groups in nitroprusside and their liberation during metabolism. Note also the release of nitric oxide (NO), the active component of nitroprusside.

Metabolism

As shown in Figure 45-1, nitroprusside contains five *cyanide groups,* which are split free in the first step of nitroprusside metabolism. *Nitric oxide,* the active component, is released next. Both reactions take place in smooth muscle. Once freed, the cyanide groups are converted to *thiocyanate* by the liver, using *thiosulfate* as a cofactor. Thiocyanate is eliminated by the kidneys over several days.

Therapeutic Uses

Hypertensive Emergencies.

Nitroprusside is used to lower blood pressure rapidly in hypertensive emergencies. Oral antihypertensive medication should be initiated simultaneously. During nitroprusside treatment, furosemide may be needed to prevent excessive retention of fluid.

Other Uses.

Nitroprusside is approved for producing controlled hypotension during surgery (to reduce bleeding in the surgical field). In addition, the drug has been employed investigationally to treat severe, refractory congestive heart failure and myocardial infarction.

Adverse Effects

Excessive Hypotension.

If administered too rapidly, nitroprusside can cause a precipitous drop in blood pressure, resulting in headache, palpitations, nausea, vomiting, and sweating. Blood pressure should be monitored continuously.

Cyanide Poisoning.

Rarely, lethal amounts of cyanide have accumulated. Cyanide buildup is most likely in patients with liver disease and in those with low stores of thiosulfate, the cofactor needed for cyanide detoxification. The chances of cyanide poisoning can be minimized by avoiding rapid infusion (faster than 5 mcg/kg/min) and by coadministering thiosulfate. If cyanide toxicity occurs, nitroprusside should be withdrawn.

Thiocyanate Toxicity.

When nitroprusside is given for several days, thiocyanate may accumulate. Although much less hazardous than cyanide, thiocyanate can also cause adverse effects. These effects, which involve the central nervous system (CNS), include disorientation, psychotic behavior, and delirium. To minimize toxicity, patients receiving nitroprusside for more than 3 days should undergo monitoring of plasma thiocyanate, which must be kept below 0.1 mg/mL.

Preparations, Dosage, and Administration

Sodium nitroprusside [Nitropress] is available in powdered form (50 mg) to be dissolved and then diluted for IV infusion. Fresh solutions may have a faint brown coloration. Solutions that are deeply colored (blue, green, dark red) should be discarded. Nitroprusside in solution can be degraded by light, and hence should be protected with an opaque material.

Blood pressure can be adjusted to practically any level by increasing or decreasing the rate of infusion. The initial infusion rate is 0.3 mcg/kg/min. The maximal rate is 10 mcg/kg/min. If infusion at the maximal rate for 10 minutes fails to produce an adequate drop in blood pressure, administration should stop. During the infusion, blood pressure should be monitored continuously, with either an arterial line or an electronic monitoring device. No other drugs should be mixed with the nitroprusside solution.

Drugs Acting on the Renin-Angiotensin-Aldosterone System

As discussed in Chapter 43, the renin-angiotensin-aldosterone system (RAAS) plays an important role in the regulation of blood pressure, blood volume, and fluid and electrolyte balance. A key component of the system—angiotensin II—is a powerful vasoconstrictor that acts on arterioles and veins. Hence, by blocking either the formation or actions of angiotensin II, we can promote dilation of arterioles and veins.

Angiotensin-Converting Enzyme (ACE) Inhibitors.

Inhibitors of ACE promote vasodilation by blocking the conversion of angiotensin I (a weak vasoconstrictor) into angiotensin II (a powerful vasoconstrictor). The result is dilation of arterioles and veins. The primary indications for ACE inhibitors are essential hypertension and heart failure. In addition, these drugs can help preserve renal function in people with diabetes. The basic pharmacology of the ACE inhibitors is presented in Chapter 43. Their use in hypertension and heart failure is discussed in Chapters 46 and 47, respectively.

Angiotensin II Receptor Blockers (ARBs).

These drugs have effects much like those of the ACE inhibitors. However, instead of preventing formation of angiotensin II, these drugs block receptors for angiotensin II. Like the ACE inhibitors, ARBs dilate arterioles and veins. Currently, ARBs have three indications: hypertension, heart failure, and diabetic nephropathy. The basic pharmacology of the ARBs is discussed in Chapter 43.

Direct Renin Inhibitors (DRIs).

Like ACE inhibitors, the DRIs prevent formation of angiotensin II. However, the mechanism is different: Rather than inhibiting ACE, the DRIs inhibit renin, the enzyme that forms angiotensin I; in the absence of angiotensin I, angiotensin II cannot be made. Like the ACE inhibitors and ARBs, the DRIs promote dilation of arterioles and veins. The only DRI currently available—aliskiren—is approved only for hypertension. The basic pharmacology of aliskiren is discussed in Chapter 43.

Organic Nitrates

The organic nitrates (eg, nitroglycerin, isosorbide dinitrate) produce selective dilation of veins; dilation of arterioles is minimal. The primary indication for these drugs is angina pectoris. In addition, nitroglycerin is given to treat heart failure and myocardial infarction, and to provide controlled hypotension during surgery. The pharmacology of the organic nitrates is discussed in Chapter 50.

Calcium Channel Blockers

The calcium channel blockers (eg, verapamil, nifedipine) produce vasodilation by preventing calcium entry into VSM. At therapeutic doses, these drugs produce selective dilation of arterioles. Primary indications are hypertension and angina pectoris. The calcium channel blockers are the subject of Chapter 44.

Sympatholytic Drugs

Sympatholytic drugs promote vasodilation by preventing the sympathetic nervous system from causing vasoconstriction. Some of these drugs act by direct blockade of vascular adrenergic receptors. Others act on sympathetic ganglia, adrenergic neurons, or the CNS.

Alpha-Adrenergic Blocking Agents.

The alpha blockers (eg, phentolamine, prazosin) promote vasodilation by preventing activation of alpha adrenergic receptors on veins and arterioles. In their capacity as vasodilators, these drugs have multiple therapeutic applications, including hypertension, peripheral vascular disease, and pheochromocytoma. The alpha blockers are discussed in Chapter 18.

Ganglionic Blocking Agents.

Ganglionic blocking agents interrupt impulse transmission through all ganglia of the autonomic nervous system. By doing so, they prevent sympathetic stimulation of arterioles and veins, and thereby cause vasodilation. Ganglionic blockers can be used for hypertensive emergencies and severe cases of essential hypertension. In addition, they can be given to produce hypotension during surgery. Prominent side effects—dry mouth, blurred vision, urinary retention, and paresis of the bowel—result from parasympathetic blockade. At this time, only one ganglionic blocker—mecamylamine—is available (see Chapter 16).

Adrenergic Neuron Blocking Agents.

Adrenergic neuron blockers (eg, reserpine) act within terminals of adrenergic neurons to reduce norepinephrine release. Vasodilation results from their effect on sympathetic nerves that innervate blood vessels. The adrenergic neuron blockers, which are used for hypertension, are discussed in Chapter 19.

Centrally Acting Agents.

The centrally acting sympatholytics (eg, clonidine, methyldopa) act within the CNS to inhibit impulse outflow along sympathetic nerves. These agents are used primarily for hypertension. Their pharmacology is discussed in Chapter 19.

Nesiritide

Nesiritide [Natrecor] is a synthetic form of B-natriuretic peptide. The drug dilates arterioles *and* veins. Three mechanisms are involved: suppression of the RAAS, suppression of CNS sympathetic outflow, and a direct effect on VSM.

Nesiritide is indicated only for short-term therapy of acutely decompensated heart failure (see Chapter 47).

Drugs for Pulmonary Arterial Hypertension

Four vasodilators—ambrisentan [Letairis], bosentan [Tracleer], epoprostenol [Flolan], and treprostinil [Remodulin]—are used to dilate pulmonary blood vessels in patients with pulmonary arterial hypertension. Ambrisentan and bosentan block vascular receptors for endothelin-1, a powerful vasoconstrictor. Epoprostenol and treprostinil stimulate production of cyclic AMP in vascular smooth muscle. All four drugs are discussed in Chapter 106.

KEY POINTS

- Some vasodilators are selective for arterioles, some are selective for veins, and some dilate both types of vessel.
- Drugs that dilate arterioles reduce cardiac afterload, and can thereby reduce cardiac work while increasing cardiac output and tissue perfusion.
- Drugs that dilate veins reduce cardiac preload, and can thereby reduce cardiac work, cardiac output, and tissue perfusion.
- Principal indications for vasodilators are essential hypertension, hypertensive crisis, angina pectoris, heart failure, and myocardial infarction.
- Drugs that dilate veins can cause orthostatic hypotension.
- Drugs that dilate arterioles or veins can cause reflex tachycardia, which increases cardiac work and elevates blood pressure. Reflex tachycardia can be blunted with a beta blocker.
- Drugs that dilate arterioles or veins can cause fluid retention, a response that can be blunted with a diuretic.
- Hydralazine causes selective dilation of arterioles.
- Hydralazine can cause a syndrome that resembles SLE.
- Minoxidil causes selective and profound dilation of arterioles.
- Minoxidil can cause hypertrichosis.

- Sodium nitroprusside dilates arterioles and veins.
- Prolonged infusion of nitroprusside can result in toxic accumulation of cyanide and thiocyanate.

46 Drugs for Hypertension*

Hypertension (elevated blood pressure [BP]) is a common, chronic disorder that affects 65 million Americans and over 1 billion people worldwide. Left untreated, hypertension can lead to heart disease, kidney disease, and stroke. Conversely, a treatment program of lifestyle modifications and drug therapy can reduce both BP and the risk of long-term complications. However, it is important to appreciate that we cannot cure hypertension; we can only reduce symptoms. As a result, treatment must continue lifelong, making nonadherence a significant problem. Despite advances in management, hypertension remains underdiagnosed and undertreated: Among Americans with the disease, 70% have been diagnosed, 59% undergo treatment, and only 34% take sufficient medicine to bring their BP under control.

Fourteen drug classes are used for treatment. All have been introduced in previous chapters. Hence, in this chapter, rather than struggling with a huge array of new drugs, we simply discuss the antihypertensive applications of drugs you already know about.

In 2003, the National Heart, Lung, and Blood Institute issued revised clinical guidelines on hypertension. This document—*The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,* known simply as *JNC 7*—was prepared by a special committee of the National High Blood Pressure Education Program. Recommendations in JNC 7 update and simplify those of JNC 6, released in 1997. Important changes include a new BP classification scheme, increased emphasis on controlling systolic BP, and the recommendation to use thiazide diuretics as initial therapy for most patients. Throughout this chapter, clinical practice recommendations reflect those in JNC 7.*

BASIC CONSIDERATIONS IN HYPERTENSION

In this section, we consider three issues: (1) classification of BP based on values for systolic and diastolic pressure, (2) types of hypertension, and (3) the damaging effects of chronic hypertension.

* Be aware that, although JNC 7 is the most influential guideline in the United States, it is not the only authoritative guideline available. Since the publication of JNC 7, updated treatment guidelines have been released by several organizations, including the American Society of Hypertension, the Canadian Hypertension Education Program, the European Society of Hypertension in conjunction with the European Society of Cardiology, and the World Health Organization in conjunction with the International Society of Hypertension. Recommendations in these guidelines generally parallel those in JNC 7. However, important differences do exist.

CLASSIFICATION OF BLOOD PRESSURE

JNC 7 defines four BP categories: normal, prehypertension, stage 1 hypertension, and stage 2 hypertension (Table 46-1). This scheme differs from that of JNC 6 in three ways:

- The cutoff values for normal BP have been reduced.
- A new category—prehypertension—has been added.
- Two classes of hypertension—stages 2 and 3 from JNC 6—have been combined into one—stage 2 in JNC 7—because management of both is much the same.

Classification*	Systolic (mm Hg)		Diastolic (mm Hg)
Normal	<120	*and*	<80
Prehypertension	120–139	*or*	80–89
Stage 1 Hypertension	140–159	*or*	90–99
Stage 2 Hypertension	≥160	*or*	≥100

Data from The Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 289:2560–2572, 2003.

TABLE 46-1 Classification of Blood Pressure for Adults Age 18 and Older

* Not taking any antihypertensive drugs and not acutely ill. When systolic and diastolic pressures fall into different categories, the higher category should be selected to classify BP status. For example, 160/92 mm Hg should be classified as stage 2 hypertension. Isolated systolic hypertension is defined as systolic BP of 140 mm Hg or higher and diastolic BP below

90 mm Hg and staged appropriately (eg, 170/82 is defined as stage 2 isolated systolic hypertension).

Normal.

In JNC 7, normal BP is defined as systolic BP below 120 mm Hg and diastolic BP below 80 mm Hg, compared with 130/85 in JNC 6. Why were the cutoff values reduced? Because the values from JNC 6 are not as safe as previously believed.

Prehypertension.

Prehypertension is defined as systolic BP of 120 to 139 mm Hg or diastolic BP of 80 to 89 mm Hg. BP in this range carries an increased risk of cardiovascular disease, even though outright hypertension has not yet developed. Data from the Framingham Heart Study show that, relative to people with normal BP, those with BP in the prehypertension range have a 2- to 3-fold increased risk of cardiovascular events. To reduce risk, these people should adopt certain health-promoting lifestyle changes (see below). Prehypertension affects about 30% of American adults (about 60 million people).

Hypertension.

Hypertension is defined as systolic BP above 140 mm Hg or diastolic BP above 90 mm Hg. If systolic BP is above 140 mm Hg and diastolic BP is below 90 mm Hg, a diagnosis of *isolated systolic hypertension* (ISH) applies. When systolic BP and diastolic BP fall in different categories, BP classification is based on the higher category. For example, a reading of 160/92 mm Hg indicates stage 2 hypertension, and a reading of 170/82 indicates stage 2 ISH.

Diagnosis of hypertension should be based on several BP readings, not just one. If an initial screen shows that BP is elevated (but does not represent an immediate danger), measurement should be repeated on two subsequent visits. At each visit, two measurements should be made, at least 5 minutes apart. The patient should be seated in a chair—not on an examination table—with his or her feet on the floor. High readings should be confirmed in the contralateral arm. If the mean of all readings shows that systolic BP is indeed greater than 140 mm Hg or that diastolic BP is greater than 90 mm Hg, a diagnosis of hypertension can be made.

TYPES OF HYPERTENSION

There are two broad categories of hypertension: *primary hypertension* and *secondary hypertension*. As indicated in Table 46-2, primary hypertension is by far the most common form of hypertensive disease. Less than 10% of people with hypertension have a secondary form.

Type of Hypertension	Frequency (%)
Primary (Essential) Hypertension	92
Secondary Hypertension	
Chronic renal disease	4
Renovascular disease	2
Oral contraceptive–induced	1
Coarctation of the aorta	0.3
Primary aldosteronism	0.2
Cushing's syndrome	0.1
Pheochromocytoma	0.1
Sleep apnea	?
Thyroid or parathyroid disease	?

TABLE 46-2 Types of Hypertension and Their Frequency

Primary (Essential) Hypertension

Primary hypertension is defined as hypertension that has no identifiable cause. A diagnosis of primary hypertension is made by ruling out probable specific causes of BP elevation. Primary hypertension is a chronic, progressive disorder. In the absence of treatment, patients will experience a continuous, gradual rise in BP over the rest of their lives.

In the United States, primary hypertension affects about 30% of adults. However, not all groups are at equal risk: older people are at higher risk than younger people; African Americans and Hispanic Americans are at higher risk than white Americans; postmenopausal women are at higher risk than premenopausal women; and obese people are at higher risk than lean people.

Although the cause of primary hypertension is unknown, the condition can be successfully treated. It should be understood, however, that treatment is not curative: Drugs can lower BP, but they can't eliminate the underlying pathology. Consequently, treatment must continue lifelong.

Primary hypertension is also referred to as *essential hypertension*. This alternative name preceded the term *primary hypertension* and reflects our ignorance about the cause of the problem. Historically, it had been noted that, as people grew older, their BP rose. Why older people had elevated BP was (and remains) unknown. One hypothesis noted that, as people aged, their vascular systems offered greater resistance to blood flow. In order to move blood against this increased resistance, a compensatory increase in BP was required. Therefore, the hypertension that occurred with age was seen as being "essential" for providing adequate perfusion of tissues—hence, the term *essential hypertension*. Over time, the term came to be applied to all cases of hypertension for which an underlying cause could not be found.

Secondary Hypertension

Secondary hypertension is defined as an elevation of BP brought on by an identifiable primary cause. The most common are listed in Table 46-2.

Because secondary hypertension results from an identifiable cause, it may be possible to treat that cause directly, rather than relying on antihypertensive drugs for symptomatic relief. As a result, some individuals can actually be cured. For example, if hypertension occurs secondary to pheochromocytoma (a catecholamine-secreting tumor), surgical removal of the tumor may produce permanent cure. When cure is not possible, secondary hypertension can be managed with the same drugs used for primary hypertension.

BOX 46-1 ISOLATED SYSTOLIC HYPERTENSION: THE REAL KILLER OF AGING AMERICANS

Over the past 15 years, several large randomized clinical trials involving older hypertensive patients have produced unequivocal evidence that, compared with elevated *diastolic* BP, elevated *systolic* BP is the stronger predictor of cardiovascular disease, kidney disease, stroke, and death. Additional studies have shown that, when elevated systolic BP is reduced, there is a corresponding reduction in the incidence of kidney failure, heart failure, MI, stroke, and death. Accordingly, in 2000, the Coordinating Committee of the National High Blood Pressure Education Program issued a clinical advisory recommending that systolic BP—rather than diastolic BP—be used as the major clinical endpoint for the detection, evaluation, and treatment of hypertension, especially in middle-aged and older Americans. The importance of elevated systolic pressure is reflected in the recommendations of JNC 7, released in 2003.

Some readers may be asking, "What's new here? I mean, hasn't elevated systolic BP always been a concern?" Well, no, it hasn't. In fact, until recently, isolated systolic hypertension (ISH)—defined as systolic BP above 140 mm Hg and diastolic BP below 90 mm Hg—was considered a relatively benign condition that did not merit treatment. After all, most experts agreed that, in people with hypertension, elevated diastolic BP—not elevated systolic BP—was the principal cause of morbidity and mortality. Of course, this view has been proven dead wrong.

ISH is primarily a disease of the elderly. As we grow older, systolic BP gradually rises. The underlying cause is increased stiffness (reduced compliance) in large arteries—owing to progressive replacement of elastin with collagen in the arterial wall. Among older Americans, ISH is the most common form of hypertension: According to the National Health and Nutrition Examination Survey (NHANES), of all hypertensive individuals over the age of 60, fully 65% have ISH. Because of their ISH, older people are at increased risk, as demonstrated in the Multiple Risk Factor Intervention Trial (MRFIT), which evaluated over 316,000 men and found a nearly linear relationship between increased systolic BP and increased risk of adverse cardiovascular events.

Does lowering elevated systolic BP reduce cardiovascular risk? Yes indeed! The benefits of treating ISH have been documented in several large, randomized controlled trials. Important among these are the Systolic Hypertension in the Elderly Program (SHEP) and the Systolic Hypertension in Europe (Syst-

Eur) trial. An analysis of the results of these trials indicated that lowering systolic BP decreased overall mortality by 13%, cardiovascular mortality by 18%, cardiovascular complications by 26%, coronary events by 23%, and stroke by 30%.

Unfortunately, among people with ISH, control of BP is generally poor. For most hypertensive people, the target BP is 140/90 mm Hg. However, among elderly African Americans, only 25% achieve this goal. And among white Americans, the success rate is even worse: Only 18% achieve the goal. This low success rate is both sad and troubling, in that it means many people will experience unnecessary morbidity and mortality.

The low rate of BP control in the elderly, coupled with our heightened appreciation of the dangers of ISH, led the Coordinating Committee to issue its advisory. As noted, the Committee recommended that systolic BP, rather than diastolic BP, be the major consideration in the detection, evaluation, and treatment of hypertension—especially in older Americans. The Committee recommended using either a low-dose thiazide diuretic (with or without a beta blocker) or a long-acting dihydropyridine CCB for initial treatment. These recommendations were based in part on the successful use of these drugs in the SHEP and Syst-Eur trials. Although ACE inhibitors were not recommended by the Committee, recent evidence indicates that these drugs too can reduce the risk of stroke, MI, heart failure, and death in older hypertensive people.

CONSEQUENCES OF HYPERTENSION

Chronic hypertension is associated with increased morbidity and mortality. Left untreated, prolonged elevation of BP can lead to heart disease (myocardial infarction [MI], heart failure, angina pectoris), kidney disease, and stroke. The degree of injury is directly related to the degree of pressure elevation: the higher the pressure, the greater the risk. Among people 40 to 70 years old, the risk of cardiovascular disease is doubled for each 20 mm Hg increase in systolic BP or each 10 mm Hg increase in diastolic BP—beginning at 115/75 mm Hg and continuing through 185/155 mm Hg. For people over the age of 50, elevated *systolic* BP poses a greater risk than elevated diastolic BP (Box 46-1). For patients of all ages, hypertension-related deaths result largely from cerebral hemorrhage, renal failure, heart failure, and MI.

Unfortunately, despite its potential for serious harm, hypertension usually remains asymptomatic until long after injury has begun to develop. As a result, the disease can exist for years before overt pathology is evident. Because injury develops slowly and progressively, and because hypertension rarely causes discomfort, many people who have the disease don't know it. Furthermore, many who do know it forgo treatment, largely because hypertension doesn't make them feel bad—that is, until it's too late.

MANAGEMENT OF CHRONIC HYPERTENSION

In this section we consider treatments for chronic hypertension. We begin by addressing patient evaluation and other basic issues, after which we discuss the two modes of management: lifestyle modifications and drug therapy.

BASIC CONSIDERATIONS

Benefits of Lowering Blood Pressure

Multiple clinical trials have demonstrated unequivocally that, when the BP of hypertensive individuals is lowered, morbidity is decreased and life is prolonged. Treatment reduces the incidence of stroke by 35% to 40%, MI by 20% to 25%, and heart failure by more than 50%. Although reductions in morbidity are not as dramatic, they are nonetheless significant: Among patients with stage 1 hypertension plus additional cardiovascular risk factors, one death would be prevented for every 11 patients who reduced systolic pressure by 12 mm Hg for a period of 10 years—and among those with hypertension plus cardiovascular disease or target-organ damage, one death would be prevented for every 9 patients who achieved a sustained 12 mm Hg reduction in pressure.

Patient Evaluation

Evaluation of patients with hypertension has two major objectives. Specifically, we must assess for (1) identifiable causes of hypertension, and (2) factors that increase cardiovascular risk. To aid evaluation, diagnostic tests are required.

Hypertension with a Treatable Cause.

As discussed above, some forms of hypertension result from a treatable cause, such as Cushing's syndrome, pheochromocytoma, and oral contraceptive use (see Table 46-2). Patients should be evaluated for these causes and managed appropriately. In many cases, direct treatment of the underlying cause can control BP, thereby eliminating the need for further antihypertensive therapy.

Factors That Increase Cardiovascular Risk.

Two types of factors—existing target-organ damage and major cardiovascular risk factors—increase the risk of cardiovascular events in patients with hypertension. When these factors are present, aggressive therapy is indicated. Accordingly, in order to select appropriate interventions, we must identify patients with the following types of *target-organ damage:*

- Heart disease
- Left ventricular hypertrophy
- Angina pectoris
- Prior MI
- Prior coronary revascularization
- Heart failure
- Stroke or transient ischemic attack
- Chronic kidney disease
- Peripheral arterial disease
- Retinopathy

as well as patients with the following *major cardiovascular risk factors* (other than hypertension):

- Cigarette smoking
- Obesity
- Inadequate exercise
- Dyslipidemia
- Diabetes

- Microalbuminuria
- Advancing age (above 55 years for men, above 65 years for women)
- Family history of premature cardiovascular disease

Diagnostic Tests.

The following tests should be done in all patients: electrocardiogram; complete urinalysis; hemoglobin and hematocrit; and blood levels of sodium, potassium, calcium, creatinine, glucose, uric acid, triglycerides, and cholesterol (total, LDL, and HDL cholesterol).

Treatment Goals

The ultimate goal in treating hypertension is to reduce cardiovascular and renal morbidity and mortality. Hopefully, this can be accomplished without decreasing quality of life with the drugs employed. For most patients with stage 1 or stage 2 hypertension, the goal is to maintain systolic BP below 140 mm Hg and diastolic BP below 90 mm Hg. For patients with diabetes or chronic kidney disease, the target BP is lower: 130/80 mm Hg. For patients over the age of 50, reducing *systolic* pressure is the primary goal. However, although treatment focuses on systolic pressure, interventions that achieve the systolic goal will likely achieve the diastolic goal too.

Therapeutic Interventions

We can reduce BP in two ways: We can implement healthy lifestyle changes and we can treat with antihypertensive drugs. As shown in Table 46-3, for people with *prehypertension,* lifestyle changes are all that is needed. In contrast, for those with *hypertension*—either stage 1 or stage 2—a *combination* of lifestyle changes and drugs is indicated. Lifestyle changes and drug therapy are discussed in detail below.

Blood Pressure Classification	Therapeutic Interventions	Blood Pressure Goal	
		Patients Without Diabetes or Chronic Kidney Disease	Patients With Diabetes or Chronic Kidney Disease
Normal	Encourage lifestyle changes	Prevent increase	Prevent increase
Prehypertension	Initiate lifestyle changes	Prevent increase/ promote decrease	Prevent increase/ promote decrease
Stage 1 hypertension	Initiate or continue lifestyle changes and begin antihypertensive drug therapy	<140/<90 mm Hg	<130/<80 mm Hg
Stage 2 hypertension	Initiate or continue lifestyle changes and begin or intensify antihypertensive drug therapy	<140/<90 mm Hg	<130/<80 mm Hg

Recommendations from The Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 289:2560–2572, 2003.

TABLE 46-3 Overview of Blood Pressure Management in Adults 18 Years and Older

LIFESTYLE MODIFICATIONS

Lifestyle changes offer multiple cardiovascular benefits—and they do so with little cost and minimal risk. When implemented before hypertension develops, they may actually prevent hypertension. When implemented after hypertension has developed, they can lower BP, thereby decreasing or eliminating the need for drugs. Lastly, lifestyle modifications can decrease other cardiovascular risk factors. Accordingly, all patients should be strongly encouraged to adopt a healthy lifestyle. Key components are discussed below.

Weight Loss.

There is a direct relationship between obesity and elevation of BP. Studies indicate that weight loss can reduce BP in 60% to 80% of overweight hypertensive individuals. In addition, weight loss can enhance responses to antihypertensive drugs. Consequently, a program of calorie restriction and exercise is recommended for all patients who are overweight. The goal is to achieve a body mass index in the normal range (18.5 to 24.9).*

* The definition and calculation of body mass index are presented in Chapter 81 (Drugs for Obesity).

Sodium Restriction.

Reducing sodium chloride (salt) intake can lower BP in people with hypertension, and can help prevent overt hypertension in those with prehypertension. In addition, salt restriction can enhance the hypotensive effects of drugs. However, the benefits of sodium restriction are short lasting: Over time, BP returns to its original level, despite continued salt restriction. Nonetheless, JNC 7 recommends that all people with hypertension consume no more than 6 gm of sodium chloride (2.4 gm of sodium) a day. The Institute of Medicine recommends even lower salt consumption: 3.8 gm/day for adults age 50 and younger, 3.2 gm/day for adults age 51 to 70, and 2.9 gm/day for adults age 71 and older. To facilitate salt restriction, patients should be given information on the salt content of foods.

Experts disagree about the relationship between salt intake and BP in *normotensive* patients. In particular, they disagree as to whether a high-salt diet *causes* hypertension. Hence, for people with normal BP, a low-salt diet may be considered healthy or unnecessary, depending on the expert you consult.

The DASH Eating Plan.

Two studies have shown that we can reduce BP by adopting a healthy diet, known as the Dietary Approaches to Stop Hypertension (DASH) eating plan. This diet is rich in fruits, vegetables, and low-fat dairy products, and low in total fat, saturated fats, and cholesterol. In addition, the plan encourages intake of whole-grain products, fish, poultry, and nuts, and recommends minimal intake of red meat and sweets. Details are available online at www.nhlbi.nih.gov/health/public/heart/hbp/dash.

Alcohol Restriction.

Excessive alcohol consumption can raise BP and create resistance to antihypertensive drugs. Accordingly, patients should limit alcohol intake: Most men should consume no more than 1 ounce/day; women and lighter weight men should consume no more than 0.5 ounce/day. (One ounce of ethanol is equivalent to about two mixed drinks, two glasses of wine, or two cans of beer.)

Aerobic Exercise.

Regular aerobic exercise (eg, jogging, walking, swimming, bicycling) can reduce BP by about 10 mm Hg. In addition, exercise facilitates weight loss, reduces the risk of cardiovascular disease, and reduces all-cause mortality. In normotensive people, exercise decreases the risk of developing hypertension. Accordingly, all people with a sedentary lifestyle should be encouraged to develop an exercise program. An activity as simple as brisk walking 30 to 45 minutes most days of the week is beneficial.

Smoking Cessation.

Smoking is a major risk factor for cardiovascular disease. Each time a cigarette is smoked, BP rises. In patients with hypertension, smoking can reduce the effects of antihypertensive drugs. Clearly, all patients who smoke should be strongly encouraged to quit. (Pharmacologic aids to smoking cessation are discussed in Chapter 39.) As a rule, use of nicotine replacement products (eg, nicotine gum, nicotine patch) does not elevate BP. The cardiovascular benefits of quitting become evident within 1 year.

Maintenance of Potassium and Calcium Intake.

Potassium has a beneficial effect on BP. In patients with hypertension, potassium can lower BP. In normotensive people, high potassium intake helps protect against hypertension, whereas low intake elevates BP. For optimal cardiovascular effects, all people should take in 50 to 90 mmol of potassium a day. Preferred sources are fresh fruits and vegetables. If hypokalemia develops secondary to diuretic therapy, dietary intake may be insufficient to correct the problem. In this case, the patient may need to use a potassium supplement, a potassium-sparing diuretic, or a potassium-containing salt substitute.

Although adequate calcium is needed for overall good health, the impact of calcium on BP is only modest. In epidemiologic studies, high calcium intake is associated with a reduced incidence of hypertension. Among patients with hypertension, a few may be helped by increasing calcium intake. To maintain good health, calcium intake should be 1000 mg/day for adults under the age of 50, and 1200 mg/day for those 51 and older.

DRUG THERAPY

Drug therapy, together with lifestyle modifications, can control BP in all patients with chronic hypertension. The decision to use drugs should be the result of collaboration between prescriber and patient. A wide range of antihypertensive drugs is available, permitting versatility in the regimen. Consequently, for the majority of patients, it should be possible to establish a program that is effective and yet devoid of objectionable side effects.

Review of Blood Pressure Control

Before discussing the antihypertensive drugs, we need to review the major mechanisms by which BP is controlled. This information will help us understand the mechanisms by which drugs lower BP.

Principal Determinants of Blood Pressure

The principal determinants of BP are summarized in Figure 46-1. As indicated, arterial pressure is the product of cardiac output and peripheral resistance. An increase in either will increase BP.

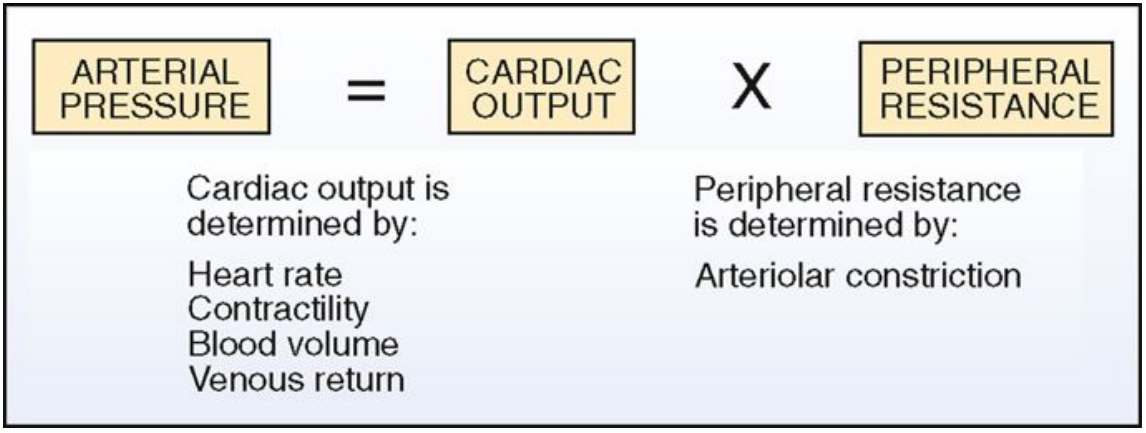


Figure 46-1 Primary determinants of arterial blood pressure.

As shown in the figure, *cardiac output* is influenced by four factors: (1) heart rate, (2) myocardial contractility (force of contraction), (3) blood volume, and (4) venous return of blood to the heart. An increase in any of these will increase cardiac output, thereby causing BP to rise. Conversely, by reducing these factors, we can make BP fall. Drugs that affect these factors are (1) beta blockers, verapamil, and diltiazem and other drugs that decrease heart rate and contractile force; (2) diuretics and other drugs that decrease blood volume; and (3) venodilators, which reduce venous return.

Peripheral vascular resistance is regulated by arteriolar constriction. Accordingly, we can reduce BP with drugs that promote arteriolar dilation.

Systems That Help Regulate Blood Pressure

Having established that BP is determined by heart rate, myocardial contractility, blood volume, venous return, and arteriolar constriction, we can now examine how these factors are regulated. Three regulatory systems are of particular significance: (1) the sympathetic nervous system, (2) the renin-angiotensin-aldosterone system (RAAS), and (3) the kidney.

Sympathetic Baroreceptor Reflex.

The sympathetic nervous system employs a reflex circuit—the baroreceptor reflex—to keep BP at a preset level. This circuit operates as follows: (1) Baroreceptors in the aortic arch and carotid sinus sense BP and relay this information to the brainstem. (2) When BP is perceived as too low, the brainstem sends impulses along sympathetic nerves to stimulate the heart and blood vessels. (3) BP is then elevated by (a) activation of beta***1*** receptors in the heart, resulting in increased cardiac output; and (b) activation of vascular alpha***1*** receptors, resulting in vasoconstriction. (4) When BP has been restored to an acceptable level, sympathetic stimulation of the heart and vascular smooth muscle subsides.

The baroreceptor reflex frequently opposes our attempts to reduce BP with drugs. Opposition occurs because the “set point” of the baroreceptors is high in people with hypertension. That is, the baroreceptors are set to perceive excessively high BP as “normal” (ie, appropriate). As a result, the system operates to maintain BP at pathologic levels. Consequently, when we attempt to lower BP using drugs, the reduced (healthier) pressure is interpreted by the

baroreceptors as below what it should be, and, in response, signals are sent along sympathetic nerves to "correct" the reduction. These signals produce reflex tachycardia and vasoconstriction—responses that can counteract the hypotensive effects of drugs. Clearly, if treatment is to succeed, the regimen must compensate for the resistance offered by this reflex. Taking a *beta blocker,* which will block reflex tachycardia, can be an effective method of compensation. Fortunately, when BP has been suppressed with drugs for an extended time, the baroreceptors become reset at a lower level. Consequently, as therapy proceeds, sympathetic reflexes offer progressively less resistance to the hypotensive effects of medication.

Renin-Angiotensin-Aldosterone System.

The RAAS can elevate BP, thereby negating the hypotensive effects of drugs. The RAAS is discussed at length in Chapter 43 and reviewed briefly here.

How does the RAAS elevate BP? The process begins with the release of renin from juxtaglomerular cells of the kidney. These cells release renin in response to reduced renal blood flow, reduced blood volume, reduced BP, and activation of beta***1***-adrenergic receptors on the cell surface. Following its release, *renin* catalyzes the conversion of angiotensinogen into angiotensin I, a weak vasoconstrictor. After this, *angiotensin-converting enzyme* (ACE) acts on angiotensin I to form *angiotensin II,* a compound that constricts systemic and renal blood vessels. Constriction of systemic blood vessels elevates BP by increasing peripheral resistance. Constriction of renal blood vessels elevates BP by reducing glomerular filtration, which causes retention of salt and water, which in turn increases blood volume and BP. In addition to causing vasoconstriction, angiotensin II causes release of *aldosterone* from the adrenal cortex. Aldosterone acts on the kidney to further increase retention of sodium and water.

Since drug-induced reductions in BP can activate the RAAS, this system can counteract the effect we are trying to achieve. We have five ways to cope with this problem. First, we can suppress renin release with *beta blockers*. Second, we can prevent conversion of angiotensinogen to angiotensin I with a *direct renin inhibitor*. Third, we can prevent the conversion of angiotensin I into angiotensin II with an *ACE inhibitor*. Fourth, we can block receptors for angiotensin II with an *angiotensin II receptor blocker*. And fifth, we can block receptors for aldosterone with an *aldosterone antagonist*.

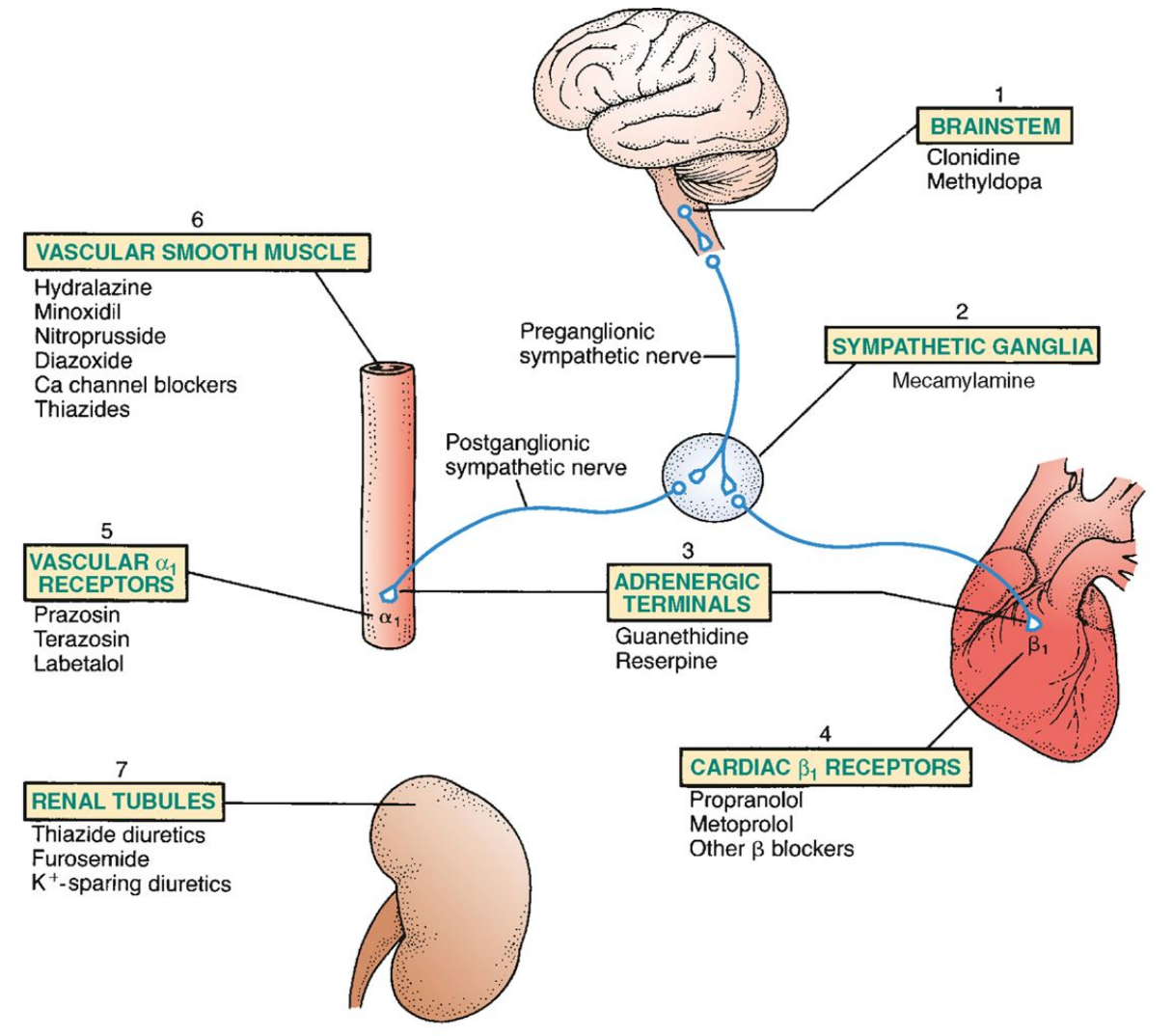
Renal Regulation of Blood Pressure.

As discussed in Chapter 42, the kidney plays a central role in long-term regulation of BP. When BP falls, glomerular filtration rate (GFR) falls as well, thereby promoting retention of sodium, chloride, and water. The resultant increase in blood volume increases venous return to the heart, causing an increase in cardiac output, which in turn increases arterial pressure. We can neutralize renal effects on BP with *diuretics*.

Antihypertensive Mechanisms: Sites of Drug Action and Effects Produced

As discussed above, drugs can lower BP by reducing heart rate, myocardial contractility, blood volume, venous return, and the tone of arteriolar smooth muscle. In this section we survey the principal mechanisms by which drugs produce these effects.

The major mechanisms for lowering BP are summarized in Figure 46-2 and Table 46-4. The figure depicts the principal sites at which antihypertensive drugs act. The table summarizes the effects elicited when drugs act at these sites. The numbering system used below corresponds with the system used in Figure 46-2 and Table 46-4.



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COMPONENTS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

8a	8b	8c	8d	8e
β_1 RECEPTORS ON JUXTAGLOMERULAR CELLS	RENIN	ANGIOTENSIN-CONVERTING ENZYME	ANGIOTENSIN II RECEPTORS	ALDOSTERONE RECEPTORS
Propranolol Metoprolol Other β blockers	Aliskiren	Captopril Enalapril Other ACE inhibitors	Losartan Valsartan Other ARBs	Eplerenone Spironolactone

Figure 46-2 Sites of action of antihypertensive drugs. Note that some antihypertensive agents act at more than one site: beta blockers act at sites 4 and 8a, and thiazides act at sites 6 and 7. The hemodynamic consequences of drug actions at the sites depicted are summarized in Table 46-4. (ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker.)

1—Brainstem.

Antihypertensive drugs acting in the brainstem suppress sympathetic outflow to the heart and blood vessels, resulting in decreased heart rate, decreased myocardial contractility, and vasodilation. Vasodilation contributes the most to reducing BP. Dilation of arterioles reduces BP by decreasing vascular resistance. Dilation of veins reduces BP by decreasing venous return to the heart.

2—Sympathetic Ganglia.

Ganglionic blockade reduces sympathetic stimulation of the heart and blood vessels. Antihypertensive effects result primarily from dilation of arterioles and veins. Ganglionic blocking agents (eg, mecamylamine) produce such a profound reduction in BP that they are used rarely, and then only for hypertensive emergencies.

3—Terminals of Adrenergic Nerves.

Antihypertensive agents that act at adrenergic nerve terminals decrease the release of norepinephrine, resulting in decreased sympathetic stimulation of the heart and blood vessels.

4—Beta*1*-Adrenergic Receptors on the Heart.

Blockade of cardiac beta*1* receptors prevents sympathetic stimulation of the heart. As a result, heart rate and myocardial contractility decline.

5—Alpha*1*-Adrenergic Receptors on Blood Vessels.

Blockade of vascular alpha*1* receptors promotes dilation of arterioles and veins. Arteriolar dilation reduces peripheral resistance. Venous dilation reduces venous return to the heart.

6—Vascular Smooth Muscle.

Several antihypertensive drugs (see Fig. 46-2) act directly on vascular smooth muscle to cause relaxation. Two of these agents—sodium nitroprusside and diazoxide—are used only for hypertensive emergencies. The rest are used for chronic hypertension.

7—Renal Tubules.

Diuretics act on renal tubules to promote salt and water excretion. As a result, blood volume declines, causing BP to fall.

Components of the Renin-Angiotensin-Aldosterone System (8a to 8e)

8a—Beta*1* Receptors on Juxtaglomerular Cells.

Blockade of beta*1* receptors on juxtaglomerular cells suppresses release of renin. The resultant decrease in angiotensin II levels has three effects: peripheral vasodilation, renal vasodilation, and suppression of aldosterone-mediated volume expansion.

8b—Renin.

Inhibition of renin decreases conversion of angiotensinogen into angiotensin I, and thereby suppresses the entire RAAS. The result is peripheral vasodilation, renal vasodilation, and suppression of aldosterone-mediated volume expansion.

8c—Angiotensin-Converting Enzyme.

Inhibitors of ACE suppress formation of angiotensin II. The result is peripheral vasodilation, renal vasodilation, and suppression of aldosterone-mediated volume expansion.

8d—Angiotensin II Receptors.

Blockade of angiotensin II receptors prevents the actions of angiotensin II. Hence blockade results in peripheral vasodilation, renal vasodilation, and suppression of aldosterone-mediated volume expansion.

8e—Aldosterone Receptors.

Blockade of aldosterone receptors in the kidney promotes excretion of sodium and water, and thereby reduces blood volume.

Site of Drug Action*	Representative Drug	Drug Effects
1. Brainstem	Clonidine	Suppression of sympathetic outflow decreases sympathetic stimulation of the heart and blood vessels.
2. Sympathetic ganglia	Mecamylamine	Ganglionic blockade reduces sympathetic stimulation of the heart and blood vessels.
3. Adrenergic nerve terminals	Guanethidine	Reduced norepinephrine release decreases sympathetic stimulation of the heart and blood vessels.
4. Cardiac $beta_1$ receptors	Propranolol	$Beta_1$ blockade decreases heart rate and myocardial contractility.
5. Vascular $alpha_1$ receptors	Prazosin	$Alpha_1$ blockade causes vasodilation.
6. Vascular smooth muscle	Hydralazine	Relaxation of vascular smooth muscle causes vasodilation.
7. Renal tubules	Chlorothiazide	Promotion of diuresis results in decreased blood volume.
Components of the renin-angiotensin-aldosterone system (8a to 8e)		
8a. $Beta_1$ receptors on juxtaglomerular cells	Propranolol	$Beta_1$ blockade suppresses renin release, resulting in (1) vasodilation secondary to reduced production of angiotensin II, and (2) prevention of aldosterone-mediated volume expansion.
8b. Renin	Aliskiren	Inhibition of renin suppresses formation angiotensin I, which in turn decreases formation of angiotensin II, and thereby reduces (1) vasoconstriction and (2) aldosterone-mediated volume expansion.

TABLE 46-4 Summary of Antihypertensive Effects Elicited by Drug Actions at Specific Sites

* Site numbers in this table correspond with site numbers in Figure 46-2.

Classes of Antihypertensive Drugs

In this section we consider the principal drugs employed to treat *chronic* hypertension. Drugs for hypertensive emergencies and hypertensive disorders of pregnancy are considered separately.

Individual antihypertensive drugs and their classes are summarized in Table 46-5. Combination products are summarized in Table 46-6. All of these drugs have been discussed in previous chapters. Accordingly, discussion here is limited to their use in hypertension. Of primary interest are mechanisms of antihypertensive action and major adverse effects.

Diuretics

Diuretics are a mainstay of antihypertensive therapy. These drugs reduce BP when used alone, and they can enhance the effects of other hypotensive drugs. The basic pharmacology of the diuretics is discussed in Chapter 40.

Thiazide Diuretics.

The thiazide diuretics (eg, hydrochlorothiazide, chlorthalidone) are among the most commonly used antihypertensive drugs. Thiazides reduce BP by two mechanisms: reduction of blood volume and reduction of arterial resistance. Reduced blood volume is responsible for initial antihypertensive effects. Reduced vascular resistance develops over time and is responsible for long-term antihypertensive effects. The mechanism by which thiazides reduce vascular resistance has not been determined.

The principal adverse effect of thiazides is *hypokalemia*. This can be minimized by consuming potassium-rich foods (eg, bananas, citrus fruits) and using potassium supplements or a potassium-sparing diuretic. Other side effects include *dehydration, hyperglycemia,* and *hyperuricemia*.

As discussed in Box 46-2, thiazides are superior to calcium channel blockers and ACE inhibitors, and hence are preferred to these more expensive drugs.

High-Ceiling (Loop) Diuretics.

High-ceiling diuretics (eg, furosemide) produce much greater diuresis than the thiazides. For most individuals with chronic hypertension, the amount of fluid loss that loop diuretics can produce is greater than needed or desirable. Consequently, loop diuretics are not used routinely. Rather, they are reserved for (1) patients who need greater diuresis than can be achieved with thiazides and (2) patients with a low GFR (because thiazides won't work when GFR is low). Like the thiazides, the loop diuretics lower BP by reducing blood volume and promoting vasodilation.

Most adverse effects are like those of the thiazides: *hypokalemia, dehydration, hyperglycemia,* and *hyperuricemia*. In addition, high-ceiling agents can cause *hearing loss*.

Potassium-Sparing Diuretics.

The degree of diuresis induced by the potassium-sparing agents (eg, spironolactone) is small. Consequently, these drugs have only modest hypotensive effects. However, because of their ability to conserve potassium, these drugs can play an important role in an antihypertensive regimen. Specifically, they can balance potassium loss caused by thiazides or loop diuretics. The most significant adverse effect of the potassium-sparing agents is *hyperkalemia*. Because of the risk of hyperkalemia, potassium-sparing diuretics must not be used in combination with one another or with potassium supplements. Also, they should not be used routinely with ACE inhibitors, angiotensin II receptor blockers, or aldosterone antagonists, all of which promote significant hyperkalemia.

Sympatholytics (Antiadrenergic Drugs)

Sympatholytic drugs suppress the influence of the sympathetic nervous system on the heart, blood vessels, and other structures. These drugs are used widely for hypertension.

As indicated in Table 46-5, there are five subcategories of sympatholytic drugs: (1) beta blockers, (2) alpha***1*** blockers, (3) alpha/beta blockers, (4) centrally acting alpha***2*** agonists, and (5) adrenergic neuron blockers.

Diuretics	Sympatholytics	RAAS Suppressants	Others
Thiazides and Related Diuretics	**Beta Blockers**	**ACE Inhibitors**	**Direct-Acting Vasodilators**
Bendroflumethiazide	Acebutolol (has ISA)	Benazepril	Hydralazine
Benzthiazide	Atenolol	Captopril	Minoxidil
Chlorothiazide	Betaxolol	Enalapril	**Calcium Channel Blockers**
Chlorthalidone	Bisoprolol	Fosinopril	Amlodipine
Cyclothiazide	Carteolol (has (ISA)	Lisinopril	Diltiazem (non-DHP)
Hydrochlorothiazide	Metoprolol	Moexipril	Felodipine
Hydroflumethiazide	Nadolol	Quinapril	Isradipine
Indapamide	Nebivolol	Ramipril	Nicardipine
Methyclothiazide	Penbutolol (has ISA)	Trandolapril	Nifedipine
Metolazone	Pindolol (has ISA)	**Angiotensin II Receptor Blockers**	Nimodipine
Polythiazide	Propranolol	Candesartan	Nisoldipine
Quinethazone	Timolol	Eprosartan	Verapamil (non-DHP)
Trichlormethiazide	**Alpha$_1$ Blockers**	Irbesartan	
Loop Diuretics	Doxazosin	Losartan	
Bumetanide	Prazosin	Olmesartan	
Ethacrynic acid	Terazosin	Telmisartan	
Furosemide	**Alpha/Beta Blockers**	Valsartan	
Torsemide	Carvedilol	**Direct Renin Inhibitor**	
Potassium-Sparing			

TABLE 46-5 Drugs for Chronic Hypertension

Beta-Adrenergic Blockers.

The beta blockers (eg, propranolol, metoprolol) are among the most widely used antihypertensive drugs. However, despite their efficacy and frequent use, the exact mechanism by which they reduce BP is somewhat uncertain. Beta blockers are less effective in African Americans than in whites.

The beta blockers have at least four useful actions in hypertension. First, blockade of cardiac beta***1*** receptors decreases heart rate and contractility, thereby causing cardiac output to decline. Second, beta blockers can suppress reflex tachycardia caused by vasodilators. Third, blockade of beta***1*** receptors on juxtaglomerular cells of the kidney reduces release of renin, thereby reducing angiotensin II–mediated vasoconstriction and aldosterone-mediated volume expansion. Fourth, long-term use of beta blockers reduces peripheral vascular resistance—by a mechanism that is unknown. This action could readily account for most of their antihypertensive effects.

Four beta blockers have *intrinsic sympathomimetic activity* (see Table 46-5). That is, they can produce mild activation of beta receptors while blocking receptor activation by strong agonists (eg, norepinephrine). As a result, heart rate at rest is slowed less than with other beta blockers. Accordingly, if a patient develops symptomatic bradycardia with another beta blocker, switching to one of these may help.

Beta blockers can produce a variety of adverse effects. Blockade of cardiac beta***1*** receptors can produce *bradycardia, decreased atrioventricular (AV) conduction,* and *reduced contractility*. Consequently, beta blockers should not be used by patients with sick sinus syndrome or second- or third-degree AV block—and must be used with care in patients with heart failure. Blockade of beta***2*** receptors in the lung can promote *bronchoconstriction*. Accordingly, beta blockers should be avoided by patients with asthma. If an asthmatic individual absolutely must use a beta blocker, a beta***1***-selective agent (eg, metoprolol) should be employed. Beta blockers can mask signs of hypoglycemia, and therefore must be used with caution in patients with diabetes. Although conventional wisdom has it that beta blockers can cause depression, insomnia, bizarre

dreams, and sexual dysfunction, a review of older clinical trials indicated that the risk is small or nonexistent.

Generic Name	Trade Name
Combinations with a Thiazide Diuretic	
Thiazide Plus a Beta Blocker	
Hydrochlorothiazide + propranolol	Inderide
Hydrochlorothiazide + metoprolol	Lopressor HCT
Hydrochlorothiazide + timolol	Timolide
Hydrochlorothiazide + bisoprolol	Ziac
Bendroflumethiazide + nadolol	Corzide
Chlorthalidone + atenolol	Tenoretic
Thiazide Plus an ACE Inhibitor	
Hydrochlorothiazide + captopril	Capozide
Hydrochlorothiazide + benazepril	Lotensin HCT
Hydrochlorothiazide + enalapril	Vaseretic
Hydrochlorothiazide + fosinopril	Monopril HCT
Hydrochlorothiazide + lisinopril	Prinzide, Zestoretic
Hydrochlorothiazide + moexipril	Uniretic
Hydrochlorothiazide + quinapril	Accuretic, Quinaretic
Thiazide Plus an ARB	
Hydrochlorothiazide + losartan	Hyzaar
Hydrochlorothiazide + valsartan	Diovan HCT
Hydrochlorothiazide + candesartan	Atacand HCT
Hydrochlorothiazide + eprosartan	Teveten HCT
Hydrochlorothiazide + irbesartan	Avalide
Hydrochlorothiazide + telmisartan	Micardis HCT
Hydrochlorothiazide + olmesartan	Benicar HCT
Thiazide Plus a Direct Renin Inhibitor	

TABLE 46-6 Combination Products for Chronic Hypertension

BOX 46-2 AND THE BEST DRUG IS … THE CHEAP ONE!

Results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),*1* published in 2002, show unequivocally that the least expensive drugs for hypertension, the thiazide diuretics, are also the most effective—a welcome revelation in these cost-conscious times. ALLHAT is an important trial that should have a profound impact on clinical practice.

ALLHAT was a large, double-blind trial that compared the impact of four antihypertensive drugs—chlorthalidone (a thiazide diuretic), amlodipine (a CCB), lisinopril (an ACE inhibitor), and doxazosin (an alpha blocker)—on the incidence of adverse cardiovascular (CV) events. The study enrolled 33,357 patients, including more women (47%), blacks (32%), and Hispanics (19%) than most earlier trials. All participants had stage 1 or stage 2 hypertension plus at least one additional risk factor for coronary heart disease (CHD). The mean follow-up time was 4.9 years.

The results? With one drug—doxazosin—the incidence of adverse CV events was substantially higher than with the others, and hence this arm of the study was terminated early. Effects of the remaining three drugs—chlorthalidone, amlodipine, and lisinopril—were similar in some respects but significantly different in others. With all three, rates of (1) fatal CHD or nonfatal heart attacks and (2) all-cause mortality were identical. However, in other ways, chlorthalidone was clearly superior. Specifically, chlorthalidone was slightly better at reducing systolic BP. More importantly, chlorthalidone was associated with fewer adverse CV events: Compared with patients taking chlorthalidone, those taking amlodipine experienced a higher 6-year rate of heart failure (10.2% vs. 7.7%), and those taking lisinopril experienced higher 6-year rates of stroke (6.3% vs. 5.6%), heart failure (8.7% vs. 7.7%), and combined CV disease (33.3% vs. 30.9%).

You might ask "Can the results seen with chlorthalidone, lisinopril, and amlodipine be extended to other members of the drug families they represent?" The answer is a qualified "Yes." All thiazide diuretics are very similar, and hence the results seen with chlorthalidone are likely to be seen with other

thiazides. Similarly, all ACE inhibitors are much the same, and hence the results seen with lisinopril are probably representative. The story with amlodipine is different. Amlodipine belongs to a subclass of CCBs known as dihydropyridines (DHPs), which differ significantly from CCBs in other subclasses. Accordingly, extrapolation of the results seen with amlodipine should probably be limited to CCBs in the DHP subclass.

How do thiazides compare with beta blockers? Unfortunately, beta blockers were not included in ALLHAT. However, data from other large studies indicate that beta blockers are certainly no more effective than thiazides, and may well be less effective.

The message from ALLHAT is both clear and compelling: Thiazide diuretics should be the initial drugs of choice for most patients with hypertension. These drugs are at least as effective as the alternatives, and they cost *much* less. Hydrochlorothiazide, for example, costs about 10 cents a day, compared with about $1 a day for amlodipine. Clearly, if most patients were to switch from amlodipine (and other expensive drugs) to the thiazides, the savings for our health system would be huge—and would quickly offset the $120 million that taxpayers invested on ALLHAT. Wouldn't it be great if more clinical studies led to the same good news: The best drug for what ails you is also the cheapest.

Postscript

Do the results of the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA)[2] refute the results of ALLHAT? Not really. Although ASCOT-BPLA is an important clinical trial that may well lead to changes in hypertension treatment, the trial does not directly challenge the superiority of thiazides—at least when thiazides are used alone. ASCOT-BPLA enrolled 19,257 patients, most of whom were treated with either (1) a *combination* of amlodipine plus perindopril (nearly identical to the CCB/ACE inhibitor combination used in ALLHAT) or (2) a *combination* of atenolol (a beta blocker) plus bendroflumethiazide (a thiazide diuretic). The result? After a median follow-up of 5.5 years, patients taking the CCB/ACE inhibitor combination experienced significantly fewer adverse CV events than did patients taking the beta blocker/thiazide combination, indicating that one *combination* is better than the other. The results do not say, however, that the CCB *alone* or the

ACE inhibitor *alone* is superior to the thiazide *alone*. Hence we cannot compare these results directly with those of ALLHAT (which showed that, when used alone, a thiazide *is* better than a CCB or an ACE inhibitor). What ASCOT-BPLA *does* suggest is that a CCB/ACE inhibitor combination would be better as first-line therapy of hypertension than the currently recommended beta blocker/thiazide combination. Whether a thiazide/CCB combination or a thiazide/ACE inhibitor combination would be better still has yet to be determined.

1 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker versus diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 288:2981–2997, 2002.

2 Dahlof B, Sever PS, Poulter NR, for the ASCOT Investigators: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA): A multicenter randomized controlled trial. Lancet 366:895–906, 2005.

The basic pharmacology of the beta blockers is discussed in Chapter 18.

Alpha*1* Blockers.

The alpha*1* blockers (eg, doxazosin, terazosin) prevent stimulation of alpha*1* receptors on arterioles and veins, thereby preventing sympathetically mediated vasoconstriction. The resultant vasodilation reduces both peripheral resistance and venous return to the heart.

The most disturbing side effect of alpha blockers is *orthostatic hypotension*. Hypotension can be especially severe with the initial dose. Significant hypotension continues with subsequent doses but is less profound.

The American College of Cardiology recommends that alpha blockers *not* be used as first-line therapy for hypertension. Why? Because in a huge clinical trial known as ALLHAT, in which doxazosin was compared with chlorthalidone (a thiazide diuretic), patients taking doxazosin experienced 25% more cardiovascular events and were twice as likely to be hospitalized for heart failure. It is not clear whether doxazosin *increased* cardiovascular risk or chlorthalidone *decreased* risk. Either way, the diuretic is clearly preferred to the alpha blocker.

The basic pharmacology of the alpha blockers is discussed in Chapter 18.

Alpha/Beta Blockers: Carvedilol and Labetalol.

Carvedilol and labetalol are unusual in that they can block alpha*1* receptors as well as beta receptors. Blood pressure reduction results from a combination of actions: (1) alpha*1* blockade promotes dilation of arterioles and veins, (2) blockade of cardiac beta*1* receptors reduces heart rate and contractility, and (3) blockade of beta*1* receptors on juxtaglomerular cells suppresses release of renin. Presumably, these drugs also share the ability of other beta blockers to reduce peripheral vascular resistance. Like other nonselective beta blockers, labetalol and carvedilol can exacerbate bradycardia, AV heart block, and asthma. Blockade of venous alpha*1* receptors can produce postural hypotension.

Centrally Acting Alpha*2* Agonists.

As discussed in Chapter 19, these drugs (eg, clonidine, methyldopa) act within the brainstem to suppress sympathetic outflow to the heart and blood vessels. The result is vasodilation and reduced cardiac output, both of which help lower BP. All central alpha*2* agonists can cause *dry mouth* and *sedation*. In addition, clonidine can cause severe *rebound hypertension* if treatment is abruptly discontinued. Additional adverse effects of methyldopa are *hemolytic anemia* (accompanied by a positive direct Coombs' test) and *liver disorders*.

Adrenergic Neuron Blockers.

This group consists of three drugs: guanethidine, guanadrel, and reserpine. All three drugs decrease BP through actions in the terminals of postganglionic sympathetic neurons. Guanethidine and guanadrel inhibit release of norepinephrine, whereas reserpine causes norepinephrine depletion. Both actions result in decreased sympathetic stimulation of the heart and blood vessels.

The major adverse effect of *guanethidine* and *guanadrel* is *severe orthostatic hypotension* resulting from decreased sympathetic tone to veins. Because of this risk, these drugs are last-choice agents for chronic hypertension.

The major adverse effect of *reserpine* is *depression*. Accordingly, reserpine is absolutely contraindicated for patients with a history of depressive illness.

The basic pharmacology of reserpine, guanethidine, and guanadrel is discussed in Chapter 19.

Direct-Acting Vasodilators: Hydralazine and Minoxidil

Hydralazine and minoxidil reduce BP by promoting dilation of *arterioles*. Neither drug causes significant dilation of veins. Because venous dilation is minimal, the risk of orthostatic hypotension is low. With both drugs, lowering of BP may be followed by reflex tachycardia, renin release, and fluid retention. Reflex tachycardia and release of renin can be prevented with a beta blocker. Fluid retention can be prevented with a diuretic.

The most disturbing adverse effect of *hydralazine* is a syndrome resembling *systemic lupus erythematosus* (SLE). Fortunately, this reaction is rare at recommended doses. If an SLE–like reaction occurs, hydralazine should be withdrawn. Hydralazine is considered a third-choice drug for chronic hypertension.

Minoxidil is substantially more dangerous than hydralazine. By causing fluid retention, minoxidil can promote *pericardial effusion* (accumulation of fluid beneath the myocardium) that in some cases progresses to *cardiac tamponade* (compression of the heart). A less serious effect is *hypertrichosis* (excessive hair growth). Because of its capacity for significant harm, minoxidil is not used routinely for chronic hypertension. Instead, the drug is reserved for patients with severe hypertension that has not responded to safer drugs.

The basic pharmacology of hydralazine and minoxidil is discussed in Chapter 45.

Calcium Channel Blockers

The calcium channel blockers (CCBs) fall into two groups: dihydropyridines (eg, nifedipine) and nondihydropyridines (verapamil and diltiazem). Drugs in both groups promote dilation of arterioles. In addition, verapamil and diltiazem have direct suppressant effects on the heart.

Like other vasodilators, CCBs can cause *reflex tachycardia*. This reaction is greatest with the dihydropyridines and minimal with verapamil and diltiazem. Reflex tachycardia is low with verapamil and diltiazem because of cardiosuppression. Since dihydropyridines do not block cardiac calcium channels, reflex tachycardia with these drugs can be substantial.

Because of their ability to compromise cardiac performance, verapamil and diltiazem must be used cautiously in patients with bradycardia, heart failure, or AV heart block. These precautions do not apply to dihydropyridines.

The *rapid-acting* formulation of *nifedipine* has been associated with increased mortality in patients with MI and unstable angina. As a result, the National Heart, Lung, and Blood Institute has recommended that rapid-acting nifedipine be used with great caution, if at all.

The basic pharmacology of the CCBs is discussed in Chapter 44.

Drugs that Suppress the RAAS

Because the RAAS plays an important role in controlling BP, drugs that suppress the system—especially the ACE inhibitors—have a significant role in controlling hypertension. The basic pharmacology of these drugs is discussed in Chapter 43.

ACE Inhibitors.

The ACE inhibitors (eg, captopril, enalapril) lower BP by preventing formation of angiotensin II, and thereby prevent angiotensin II–mediated vasoconstriction and aldosterone-mediated volume expansion. In hypertensive diabetic patients with renal damage, these actions slow progression of kidney injury. Like the beta blockers, ACE inhibitors are less effective in African Americans than in white patients. Principal adverse effects are *persistent cough, first-dose hypotension, angioedema,* and *hyperkalemia* (secondary to suppression of aldosterone release). Because of the risk of hyperkalemia, combined use with potassium supplements or potassium-sparing diuretics is generally avoided. ACE inhibitors can cause serious *fetal harm,* especially during the second and third trimesters of pregnancy, and hence must not be given to pregnant women. ACE inhibitors—along with angiotensin receptor blockers (ARBs) and direct renin inhibitors (DRIs)—are the only antihypertensive drugs specifically contraindicated during pregnancy.

Angiotensin II Receptors Blockers.

ARBs lower BP in much the same way as do ACE inhibitors. Like the ACE inhibitors, ARBs prevent angiotensin II–mediated vasoconstriction and release

of aldosterone. The only difference is that ARBs do so by blocking the *actions* of angiotensin II, whereas ACE inhibitors block the *formation* of angiotensin II. Both groups lower BP to the same extent. Like the ACE inhibitors, ARBs can cause *fetal harm* and must not be used during pregnancy. In contrast to ACE inhibitors, ARBs do not induce cough or significant hyperkalemia but they do cause angioedema.

Direct Renin Inhibitors.

DRIs act directly on renin to inhibit conversion of angiotensinogen into angiotensin II. As a result, DRIs can suppress the entire RAAS. At this time, only one DRI—*aliskiren* [Tekturna]—is available. Antihypertensive effects equal those of ACE inhibitors, ARBs, and CCBs. Compared with ACE inhibitors, aliskiren causes less hyperkalemia, cough, or angioedema—but poses a similar risk of *fetal harm*. In addition, aliskiren causes *diarrhea* in 2.3% of patients. Although we know that aliskiren can lower BP, we don't yet know if it reduces adverse outcomes (eg, stroke, kidney failure, MI). Accordingly, until experience with the drug is more extensive, other antihypertensives should be considered first.

Aldosterone Antagonists.

Aldosterone antagonists lower BP by promoting renal excretion of sodium and water. Only two agents are available: *eplerenone* and *spirolactone*. (In case you're confused about spironolactone, yes, it's the same drug we discussed above under *potassium-sparing diuretics*. We're discussing it here because it produces diuresis through aldosterone receptor blockade.) Both spironolactone and eplerenone promote renal retention of potassium, and hence pose a risk of *hyperkalemia*. Accordingly, they should not be given to patients with existing hyperkalemia, and should not be combined with potassium-sparing diuretics or potassium supplements. Combined use with ACE inhibitors, ARBs, and DRIs is permissible, but must be done with caution. Spironolactone is discussed in Chapter 40 (Diuretics), eplerenone is discussed in Chapter 43 (Drugs Acting on the Renin-Angiotensin-Aldosterone System), and both are discussed again in Chapter 47 (Drugs for Heart Failure).

Fundamentals of Hypertension Drug Therapy

Treatment Algorithm

The basic approach to treating hypertension is outlined in Figure 46-3. As shown, lifestyle changes should be instituted first. If these fail to lower BP enough, drug therapy should be started—and the lifestyle changes should continue. Treatment often begins with a single drug. If needed, another drug may be *added* (if the initial drug was well tolerated but inadequate) or *substituted* (if the initial drug was poorly tolerated). However, before another drug is considered, possible reasons for failure of the initial drug should be assessed. Among these are insufficient dosage, poor adherence, excessive salt intake, and the presence of secondary hypertension. If treatment with two drugs is unsuccessful, a third and even fourth may be added.

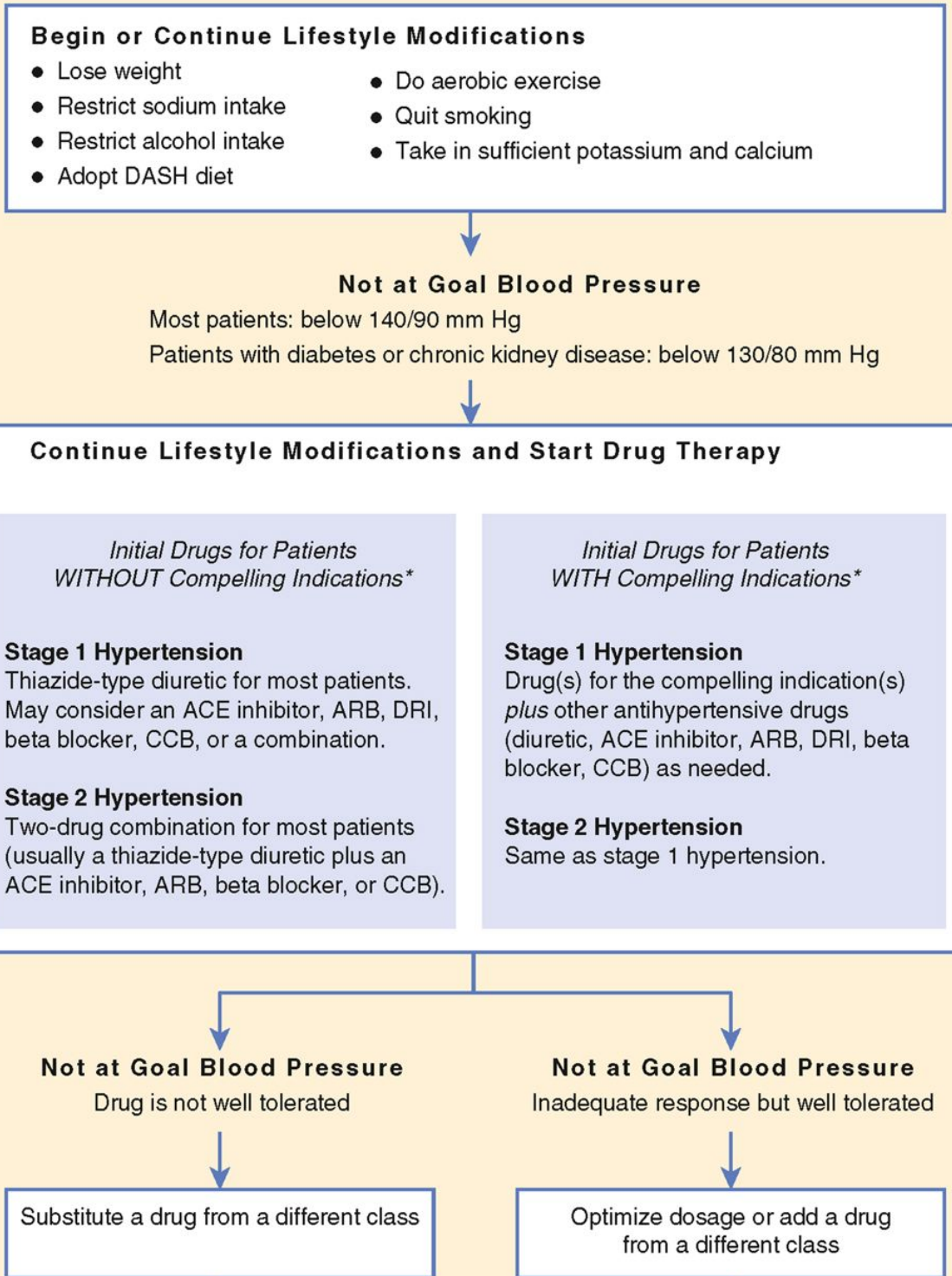
Begin or Continue Lifestyle Modifications
Lose weight
Restrict sodium intake
Restrict alcohol intake
Adopt DASH diet
Do aerobic exercise
Quit smoking
Take in sufficient potassium and calcium
Not at Goal Blood Pressure
Most patients: below 140/90 mm Hg
Patients with diabetes or chronic kidney disease: below 130/80 mm Hg
Continue Lifestyle Modifications and Start Drug Therapy
Initial Drugs for Patients WITHOUT Compelling Indications*
Stage 1 Hypertension
Thiazide-type diuretic for most patients. May consider an ACE inhibitor, ARB, DRI, beta blocker, CCB, or a combination.
Stage 2 Hypertension
Two-drug combination for most patients (usually a thiazide-type diuretic plus an ACE inhibitor, ARB, beta blocker, or CCB).
Initial Drugs for Patients WITH Compelling Indications*
Stage 1 Hypertension
Drug(s) for the compelling indication(s) plus other antihypertensive drugs (diuretic, ACE inhibitor, ARB, DRI, beta blocker, CCB) as needed.
Stage 2 Hypertension
Same as stage 1 hypertension.
Not at Goal Blood Pressure
Drug is not well tolerated
Substitute a drug from a different class
Not at Goal Blood Pressure
Inadequate response but well tolerated
Optimize dosage or add a drug from a different class

Figure 46-3 Algorithm for treating hypertension.(ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; DASH = Dietary Approaches to Stop Hypertension; DRI = direct renin inhibitor.)*A "compelling indication" is a comorbid condition (eg, heart failure, diabetes) for which a specific class of antihypertensive drugs has been shown to improve outcomes. See text for details.

Initial Drug Selection

Initial drug selection is determined by the presence or absence of a *compelling indication,* defined as a comorbid condition for which a specific class of antihypertensive drugs has been shown to improve outcomes. Initial drugs for patients with and without compelling indications are discussed below.

Patients WITHOUT Compelling Indications.

For initial therapy in the absence of a compelling indication, a *thiazide diuretic* is recommended for most patients. This preference is based on long-term controlled trials showing conclusively that thiazides can reduce morbidity and mortality in hypertensive patients, and are well tolerated and inexpensive too (see Box 46-2). Other options for initial therapy—*ACE inhibitors, ARBs, DRIs, CCBs,* and *alpha/beta blockers*—equal diuretics in their ability to lower BP. However, they may not be as effective at reducing morbidity and mortality. Accordingly, these drugs should be reserved for special indications and for patients who have not responded to thiazides. Certain other alternatives—*centrally acting sympatholytics, adrenergic neuron blockers,* and *direct-acting vasodilators*—are associated with a high incidence of undesirable effects, and hence are not well suited for initial monotherapy. One last alternative—*alpha1 blockers*—is no longer recommended as first-line therapy. As noted above, when the alpha blocker doxazosin was compared with the diuretic chlorthalidone, doxazosin was associated with a much higher incidence of adverse cardiovascular events.

Beta blockers require special comment. In JNC 7, these drugs are recommended as first-line alternatives to thiazides for initial therapy of uncomplicated hypertension. However, several studies have shown that newer drugs—ACE inhibitors, ARBs, and CCBs—are superior to beta blockers at preventing stroke and cardiac events in this population. Accordingly, the American Heart Associ-

ation now recommends against using beta blockers as first-line therapy in patients without compelling indications. On the other hand, if a patient already *has* heart disease (eg, angina pectoris, systolic heart failure, tachydysrhythmias, prior myocardial infarction), beta blockers clearly improve outcomes, and hence remain first-choice drugs for these patients.

How many drugs should be used for initial therapy? The answer depends on the hypertension stage. For patients with stage 1 hypertension, treatment with just one drug—usually a thiazide diuretic—is recommended. For patients with stage 2 hypertension, initial therapy should consist of two drugs—typically a thiazide combined with either an ACE inhibitor, ARB, or CCB.

Patients WITH Compelling Indications.

For patients with hypertension plus certain comorbid conditions (eg, heart failure, diabetes), there is strong evidence that specific antihypertensive drugs can reduce morbidity and mortality. Drugs shown to improve outcomes for six comorbid conditions are indicated in Table 46-7. Clearly, these drugs should be used for initial therapy. If needed, other antihypertensive agents can be added to the regimen. Management of hypertension in patients with diabetes and renal disease—two specific comorbid conditions—is discussed further under *Individualizing Therapy*.

High-Risk Comorbid Conditions That Constitute Compelling Indications for the Drugs Checked	Drug Classes Recommended for Initial Therapy of Hypertension*					
	Diuretic	Beta Blocker	ACE Inhibitor	ARB	CCB	Aldosterone Antagonist
Heart failure	✓	✓	✓	✓		✓
Post–myocardial infarction		✓	✓			✓
High coronary disease risk	✓	✓	✓		✓	
Diabetes	✓	✓	✓	✓	✓	
Chronic kidney disease			✓	✓		
Recurrent stroke prevention	✓		✓			

Adapted from The Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 289:2560–2572, 2003.

TABLE 46-7 Classes of Antihypertensive Drugs Recommended for Initial Therapy of Hypertension in Patients with Certain High-Risk Comorbid Conditions

* ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker.

Adding Drugs to the Regimen

Rationale for Drug Selection.

When using two or more drugs to treat hypertension, each drug should come from a different class. That is, each drug should have a different mechanism of action. In accord with this guideline, it would be appropriate to combine a beta blocker, a diuretic, and a vasodilator, since each lowers BP by a different mechanism. In contrast, it would be inappropriate to combine two thiazide diuretics or two beta blockers or two vasodilators.

Benefits of Multidrug Therapy.

Treatment with multiple drugs offers significant benefits. First, by employing drugs that have different mechanisms, we can increase the chance of success: Attacking BP control at several sites is likely to be more effective than attacking at one site. Second, when drugs are used in combination, each can be administered in a lower dosage than would be possible if it were used alone. As a result, both the frequency and the intensity of side effects are reduced. Third, when proper combinations are selected, one agent can offset the adverse effects of another. For example, if a vasodilator is used alone, reflex tachycardia is likely. However, if a vasodilator is combined with a beta blocker, reflex tachycardia will be minimal.

Dosing

For each drug in the regimen, *dosage should be low initially and then gradually increased*. There are several reasons for this approach. First, for most people with chronic hypertension, the disease poses no immediate threat. Hence, there is no need to lower BP rapidly using large doses. Second, when BP is reduced slowly, baroreceptors gradually reset to the new, lower pressure. As a result, sympathetic reflexes offer less resistance to the hypotensive effects of therapy. Third, since there is no need to drop BP rapidly, and since higher doses carry a higher risk of adverse effects, use of high initial doses would needlessly increase the risk of unpleasant responses.

Step-Down Therapy

After BP has been controlled for at least 1 year, an attempt should be made to reduce dosages and the number of drugs in the regimen. Of course, lifestyle modifications should continue. When reductions are made slowly and progressively, many patients are able to maintain BP control with less medication—and some can be maintained with no medication at all. If drugs are discontinued, regular follow-up is essential, because BP usually returns to hypertensive levels—although it may take years to do so.

Individualizing Therapy

Patients with Comorbid Conditions

Comorbid conditions complicate treatment. Two conditions that are especially problematic—renal disease and diabetes—are discussed below. Preferred drugs for patients with these and other comorbid conditions are summarized in Table 46-7. Drugs to avoid in patients with specific comorbid conditions are summarized in Table 46-8.

Comorbid Condition	Drugs to Be Avoided or Used with Caution	Reason for Concern
Cardiovascular Disorders		
Heart failure	Verapamil Diltiazem	These drugs act on the heart to decrease myocardial contractility and can thereby further reduce cardiac output.
AV heart block	Beta blockers Labetalol Verapamil Diltiazem	These drugs act on the heart to suppress AV conduction and can thereby intensify AV block.
Coronary artery disease	Guanethidine Hydralazine	Reflex tachycardia induced by these drugs can precipitate an anginal attack.
Post–myocardial infarction	Guanethidine Hydralazine	Reflex tachycardia induced by these drugs can increase cardiac work and oxygen demand.
Other Disorders		
Dyslipidemia	Beta blockers Diuretics	These drugs may exacerbate dyslipidemia.
Renal insufficiency	K^+-sparing diuretics K^+ supplements	Use of these agents can lead to dangerous accumulations of potassium.
Asthma	Beta blockers Labetalol	$Beta_2$ blockade promotes bronchoconstriction.
Depression	Reserpine	These drugs can cause depression.

TABLE 46-8 Comorbid Conditions That Require Cautious Use or Complete Avoidance of Certain Antihypertensive Drugs

Renal Disease.

Nephrosclerosis (hardening of the kidney) secondary to hypertension is among the most common causes of progressive renal disease. Pathophysiologic changes include degeneration of renal tubules and fibrotic thickening of the glomeruli, both of which contribute to renal insufficiency. Nephrosclerosis sets the stage for a downward spiral: Renal insufficiency causes water retention, which in turn causes BP to rise higher, which in turn promotes even more renal injury, and so forth. Accordingly, early detection and treatment are essential. To retard progression of renal damage, the most important action is to lower BP. The target BP is 130/80 mm Hg or lower. Achieving this goal often requires three or more drugs. Although all classes of antihypertensive agents are effective in nephrosclerosis, ACE inhibitors and ARBs work best. Hence, in the absence of contraindications, all patients should get one of these drugs. As a rule, a diuretic is used too. In patients with advanced renal insufficiency, thiazide diuretics are ineffective, hence a loop diuretic should be employed. Potassium-sparing diuretics should be avoided.

Diabetes.

In patients with diabetes, the target BP is 130/80 mm Hg or less. Preferred antihypertensive drugs are ACE inhibitors, ARBs, CCBs, and diuretics (in low doses). In patients with diabetic nephropathy, ACE inhibitors and ARBs can slow progression of renal damage and reduce albuminuria. In diabetic patients, as in nondiabetics, beta blockers and diuretics can decrease morbidity and mortality. Keep in mind, however, that beta blockers can suppress glycogenolysis and mask early signs of hypoglycemia, and therefore must be used with caution. Thiazides and high-ceiling diuretics promote hyperglycemia, and hence should be used with care.

How do ACE inhibitors compare with CCBs in patients with hypertension and diabetes? In one large study, patients taking nisoldipine (a CCB) had a higher incidence of MI than did patients taking enalapril (an ACE inhibitor). Because the study was not placebo controlled, it was impossible to distinguish between two possible interpretations: (1) the CCB increased the risk of MI or (2) the ACE

inhibitor protected against MI. Either way, it seems clear that ACE inhibitors are better than CCBs for patients with hypertension and diabetes.

Patients in Special Populations

African Americans.

Hypertension is a major health problem for African American adults. Hypertension develops earlier in blacks than in whites, has a much higher incidence, and is likely to be more severe. As a result, African Americans face a greater risk of heart disease, end-stage renal disease, and stroke. Compared with the general population, African Americans experience a 50% higher rate of death from heart disease, an 80% higher rate of death from stroke, and a 320% higher rate of hypertension-related end-stage renal disease.

With timely treatment, the disparity between blacks and nonblacks can be greatly reduced, if not eliminated. We know that blacks and whites respond equally to treatment (although not always to the same drugs). The problem is that, among blacks, hypertension often goes untreated until after significant organ damage has developed. If hypertension were diagnosed and treated earlier, the prognosis would be greatly improved. Accordingly, it is important that African Americans undergo routine monitoring of BP. If hypertension is diagnosed, treatment should begin at once. Because African Americans have a high incidence of salt sensitivity, obesity, and cigarette use, lifestyle modifications are an important component of treatment.

African Americans respond better to some antihypertensive drugs than to others. Controlled trials have shown that *diuretics* can decrease morbidity and mortality in blacks. Accordingly, diuretics are drugs of first choice. *CCBs* and *alpha/beta blockers* are also effective. In contrast, monotherapy with *beta blockers* or *ACE inhibitors* is less effective in blacks than in whites. Nonetheless, beta blockers and ACE inhibitors should be used if they are strongly indicated for a comorbid condition. For example, ACE inhibitors should be used in black patients who have type 1 diabetes with proteinuria. Also, ACE inhibitors should be used in patients with hypertensive nephrosclerosis, a condition for which ACE inhibitors are superior to CCBs.

Children and Adolescents.

The incidence of secondary hypertension in children is much higher than in adults. Accordingly, efforts to diagnose and treat an underlying cause should be especially diligent. For children with primary hypertension, treatment is the same as for adults—although doses are lower and should be adjusted with care. Because ACE inhibitors and ARBs can cause fetal harm, they should be avoided in girls who are sexually active or pregnant.

The Elderly.

The incidence of hypertension in people over age 60 is about 65%, and the prevalence of isolated systolic hypertension is greater than in younger adults. In clinical trials, antihypertensive treatment has reduced the incidence of stroke by 36% and MI by 27%. Although all antihypertensive drugs are effective in older adults, only *beta blockers* and *diuretics* have been shown in controlled trials to reduce morbidity and mortality. Hence, these drugs are generally preferred. In patients with isolated systolic hypertension, diuretics are preferred. Because cardiovascular reflexes are blunted in the elderly, treatment carries a significant risk of orthostatic hypotension. Accordingly, initial doses should be low—about one-half those used for younger adults. Drugs that are especially likely to cause orthostatic hypotension (eg, guanethidine, alpha***1*** blockers, alpha/beta blockers) should be used with caution, as should clonidine and methyldopa (central alpha***2*** agonists), both of which can impair cognitive function.

Minimizing Adverse Effects

Antihypertensive drugs can produce many unwanted effects, including hypotension, sedation, and sexual dysfunction. (Although not stressed previously, practically all antihypertensive drugs can interfere with sexual feelings or performance.)

The fundamental strategy for decreasing side effects is to tailor the regimen to the sensitivities of the patient. Simply put, if one drug causes effects that are objectionable, a more acceptable drug should be substituted. The best way to identify unacceptable responses is to encourage patients to report them.

Adverse effects caused by exacerbation of comorbid diseases are both predictable and avoidable. We know, for example, that beta blockers can intensify

asthma and AV block, and hence should not be taken by people with these disorders. Other conditions that can be aggravated by antihypertensive drugs are listed in Table 46-8. To help avoid drug-disease mismatches, the medical history should identify all comorbid conditions. With this information, the prescriber can choose drugs that are least likely to make the comorbid condition worse.

High initial doses and rapid dosage escalation can increase the incidence and severity of adverse effects. Accordingly, doses should be low at first and then gradually increased. Remember, there is usually no need to reduce BP rapidly. Hence, it makes no sense to give large initial doses that can produce a rapid fall in BP but that also produce intense undesired responses.

Promoting Adherence

The major cause of treatment failure in patients with chronic hypertension is lack of adherence to the prescribed regimen. In this section we consider the causes of nonadherence and discuss some solutions.

Why Adherence Is Often Hard to Achieve

Much of the difficulty in promoting adherence stems from the nature of hypertension itself. Hypertension is a chronic, slowly progressing disease that, through much of its course, is devoid of overt symptoms. Because symptoms are absent, it can be difficult to convince patients that they are ill and need treatment. In addition, since there are no symptoms to relieve, drugs cannot produce an obvious therapeutic response. In the absence of such a response, it can be difficult for patients to believe that their medication is doing anything useful.

Because hypertension progresses very slowly, the disease tends to encourage procrastination. For most people, the adverse effects of hypertension will not become manifest for many years. Realizing this, patients may reason (incorrectly) that they can postpone therapy without significantly increasing risk.

The negative aspects of treatment also contribute to nonadherence. Antihypertensive regimens can be complex and expensive. In addition, treatment must continue lifelong. Lastly, antihypertensive drugs can cause a number of adverse effects, ranging from sedation to hypotension to impaired sexual

function. It is difficult to convince people who are feeling good to take drugs that may make them feel worse. Some people may decide that exposing themselves to the negative effects of therapy today is paying too high a price to avoid the adverse consequences of hypertension at some indefinite time in the future.

Ways to Promote Adherence

Patient Education.

Adherence requires motivation, and patient education can help provide it. Patients should be taught about the consequences of hypertension and the benefits of treatment. Because hypertension does not cause discomfort, it may not be clear to patients that their condition is indeed serious. Patients must be made to understand that, left untreated, hypertension can cause heart disease, kidney disease, and stroke. In addition, patients should appreciate that, with proper therapy, the risks of these long-term complications can be minimized, resulting in a longer and healthier life. Lastly, patients must understand that drugs do not cure hypertension—they only control symptoms. Hence, for treatment to be effective, medication must be taken lifelong.

Teach Self-Monitoring.

Patients should be taught the goal of treatment (usually maintenance of BP below 140/90 mm Hg), and they should be taught to monitor and record their BP daily. This increases patient involvement and provides positive feedback that can help promote adherence.

Minimize Side Effects.

Common sense dictates that, if we expect patients to comply with long-term treatment, we must keep undesired effects to a minimum. As discussed above, adverse effects can be minimized by (1) encouraging patients to report side effects, (2) discontinuing objectionable drugs and substituting more acceptable ones, (3) avoiding drugs that can exacerbate comorbid conditions, and (4) using doses that are low initially and then gradually increased.

Establish a Collaborative Relationship.

The patient who feels like a collaborative partner in the treatment program is more likely to comply than is the patient who feels that treatment is being imposed. Collaboration allows the patient to help set treatment goals, create the treatment program, and evaluate progress. In addition, a collaborative relationship facilitates communication about side effects. This is especially important with respect to drug-induced sexual dysfunction, which patients may be reluctant to disclose.

Simplify the Regimen.

Antihypertensive regimens may consist of several drugs taken multiple times a day. Such complex regimens deter adherence. Therefore, in order to promote adherence, the dosing schedule should be as simple as possible. Once an effective regimen has been established, dosing just once or twice daily should be tried. If an appropriate combination product is available (eg, a fixed-dose combination of a thiazide diuretic plus an ACE inhibitor), the combination product may be substituted for its components.

Other Measures.

Adherence can be promoted by giving positive reinforcement when therapeutic goals are achieved. Involvement of family members can be helpful. Also, adherence can be promoted by scheduling office visits at convenient times and by following up when appointments are missed. For many patients, antihypertensive therapy represents a significant economic burden; devising a regimen that is effective but inexpensive will help.

DRUGS FOR HYPERTENSIVE EMERGENCIES

A hypertensive emergency exists when diastolic BP exceeds 120 mm Hg. The severity of the emergency is determined by the likelihood of organ damage. When excessive BP is associated with papilledema (edema of the retina), intracranial hemorrhage, MI, or acute congestive heart failure, a severe emergency exists—and BP must be lowered rapidly (within 1 hour). If severe hypertension is present but does not yet pose an immediate threat of organ damage, it is preferable to reduce BP more slowly (over 24 to 48 hours). Why? Because rapid reductions can cause cerebral ischemia, MI, and renal failure. Hence, pressure should be reduced gradually whenever possible.

The major drugs used for hypertensive emergencies are discussed below. All reduce BP by causing vasodilation, and all are administered IV.

Sodium Nitroprusside.

When acute, severe hypertension demands a rapid but controlled reduction in BP, IV nitroprusside [Nitropress] is usually the drug of first choice. Nitroprusside is a direct-acting vasodilator that relaxes smooth muscle of arterioles and veins. Effects begin in seconds and then fade rapidly when administration ceases. Nitroprusside is administered by continuous IV infusion using a pump to control the rate. The usual rate is 0.5 to 8 mcg/kg/min. To avoid overshoot, continuous BP monitoring is required. Because nitroprusside has an extremely short duration of action, overshoot can be corrected quickly by reducing the rate of the infusion. Prolonged infusion (longer than 72 hours) can produce toxic accumulation of thiocyanate and should be avoided. The basic pharmacology of nitroprusside is discussed in Chapter 45.

Fenoldopam.

Fenoldopam [Corlopam] is an IV drug indicated for short-term management of hypertensive emergencies. Benefits equal those of nitroprusside. Fenoldopam lowers BP by activating dopamine***1*** receptors on arterioles, and thereby promotes vasodilation. In animal models, the drug dilates renal, coronary, mesenteric, and peripheral vessels.

Fenoldopam differs from other antihypertensives in that it helps maintain (or even improve) renal function. Two mechanisms are involved. First, the drug dilates renal blood vessels, and thereby increases renal blood flow (despite reducing arterial pressure). Second, fenoldopam promotes sodium and water excretion through direct effects on renal tubules.

Fenoldopam has a rapid onset and short duration. Effects begin in less than 5 minutes. The drug undergoes rapid hepatic metabolism followed by renal excretion. Its plasma half-life is only 5 minutes.

Fenoldopam is generally well tolerated. The most common side effects are hypotension, headache, flushing, dizziness, and reflex tachycardia—all of which occur secondary to vasodilation. Tachycardia may cause ischemia in patients with angina. Combined use with a beta blocker can minimize tachycardia, but

may also result in excessive lowering of BP. Fenoldopam can elevate intraocular pressure, and hence should be used with caution in patients with glaucoma.

Fenoldopam is administered by continuous IV infusion. To minimize tachycardia, the initial dosage should be low. The typical infusion rate is 0.1 to 0.3 mcg/kg/min. With continuous 24-hour infusion, no tolerance develops to antihypertensive effects, and there is no rebound increase in BP when the infusion is stopped. With a 48-hour infusion, some tolerance may develop. Oral antihypertensive therapy can be added as soon as BP has stabilized.

Labetalol.

Labetalol [Trandate] blocks alpha- and beta-adrenergic receptors. BP is reduced by arteriolar dilation secondary to alpha blockade. Beta blockade prevents reflex tachycardia in response to reduced arterial pressure, and hence the drug is probably safe for patients with angina or MI. Beta blockade can aggravate bronchial asthma, heart failure, AV block, cardiogenic shock, and bradycardia. Accordingly, labetalol should not be given to patients with these disorders. Administration is by slow IV injection.

Diazoxide.

Diazoxide [Hyperstat IV] causes selective dilation of arterioles. Effects begin within minutes and may persist for hours. The drug can be administered by IV bolus or slow IV infusion (over 15 to 30 minutes). Diazoxide can cause reflex tachycardia and hence should be avoided in patients with angina. Reflex tachycardia can be reduced with a beta blocker. Fluid retention may occur and can be controlled with a diuretic. Hyperglycemia may be a complication for patients with diabetes. The basic pharmacology of diazoxide is discussed in Chapter 45.

Clevidipine.

Clevidipine [Cleviprex], approved in 2008, is a dihydropyridine CCB with an ultrashort half-life (about 1 minute). Administration is by IV infusion. As with nitroprusside, effects begin rapidly and then fade rapidly when the infusion is slowed or stopped. As a result, BP can be easily titrated. For patients with severe hypertension, the infusion rate is 1 to 2 mg/hr initially, and can be

doubled every 3 minutes up to a maximum of 32 mg/hr. In clinical trials, the average time to reach the target BP was 10.9 minutes. The most common side effects are headache, nausea, and vomiting. The basic pharmacology of clevidipine is discussed in Chapter 44.

DRUGS FOR HYPERTENSIVE DISORDERS OF PREGNANCY

Hypertension is the most common complication of pregnancy, with an incidence of about 10%. When hypertension develops, it is essential to distinguish between chronic hypertension and preeclampsia. Why? Because chronic hypertension is relatively benign, whereas preeclampsia can lead to life-threatening complications for the mother and fetus.

CHRONIC HYPERTENSION

Chronic hypertension, which occurs in 5% of pregnancies, is defined as hypertension that was present before pregnancy or that developed prior to the 20th week of gestation. Persistent *severe* hypertension carries a risk to both the mother and fetus. Potential adverse outcomes include placental abruption, maternal cardiac decompensation, premature birth, fetal growth retardation, central nervous system hemorrhage, and renal failure. The goal of treatment is to minimize the risk of hypertension to the mother and fetus while avoiding drug-induced harm to the fetus. With the exception of ACE inhibitors, ARBs, and DRIs, antihypertensive drugs that were being taken before pregnancy can be continued. *ACE inhibitors, ARBs, and DRIs are contraindicated because of their potential for harm* (fetal growth retardation, congenital malformations, neonatal renal failure, neonatal death). When drug therapy is initiated *during* pregnancy, *methyldopa* is the traditional agent of choice. The drug has limited effects on uteroplacental and fetal hemodynamics, and does not adversely affect the fetus or neonate. Regardless of the drug selected, treatment should not be too aggressive. Why? Because an excessive drop in BP could compromise uteroplacental blood flow.

How high can BP rise before drug therapy is indicated? According to guidelines issued in 2001 by the American College of Obstetricians and Gynecologists (ACOG), "severe" hypertension requires treatment, whereas "mild" hypertension generally does not. (The ACOG defines severe hypertension as systolic BP above 180 mm Hg or diastolic BP above 110 mm Hg, and

mild hypertension as systolic BP 140 to 179 mm Hg or diastolic BP 90 to 109 mm Hg.) There is good evidence that treating severe hypertension reduces risk. In contrast, there is little evidence that treating mild hypertension offers significant benefit.

Women who have chronic hypertension during pregnancy are at increased risk of developing preeclampsia (see below). Unfortunately, reducing BP does *not* lower this risk.

PREECLAMPSIA AND ECLAMPSIA

Preeclampsia is a multisystem disorder characterized by the combination of elevated BP (above 140/90 mm Hg) and proteinuria (300 mg or more in 24 hours) that develop after the 20th week of gestation. The disorder occurs in about 5% of pregnancies. Rarely, women with preeclampsia develop seizures. If seizures do develop, the condition is then termed *eclampsia*. Risk factors for preeclampsia include obesity, black race, chronic hypertension, diabetes, collagen vascular disorders, and previous preeclampsia. The etiology of preeclampsia is complex and incompletely understood.

Preeclampsia poses serious risks for the fetus and mother. Risks for the fetus include intrauterine growth restriction, premature birth, and even death. The mother is at risk for seizures (eclampsia), renal failure, pulmonary edema, stroke, and death.

Management of preeclampsia is based on the severity of the disease, the status of mother and fetus, and the length of gestation. The objective is to preserve the health of the mother and deliver an infant that will not require intensive and prolonged neonatal care. Success requires close maternal and fetal monitoring. Although drugs can help reduce BP, delivery is the only cure.

Management of *mild* preeclampsia is controversial and depends on the duration of gestation. If preeclampsia develops near term, and if fetal maturity is certain, induction of labor is advised. However, if mild preeclampsia develops earlier in gestation, experts disagree about what to do. Suggested measures include bed rest, prolonged hospitalization, treatment with antihypertensive drugs, and prophylaxis with an anticonvulsant. Studies to evaluate these strategies have generally failed to demonstrate benefits from any of them, including treatment with antihypertensive drugs.

The definitive intervention for *severe* preeclampsia is delivery. However, making the choice to induce labor presents a dilemma. Since preeclampsia can deteriorate rapidly, with grave consequences for mother and fetus, immediate delivery is recommended. However, if the fetus is not sufficiently mature, immediate delivery could threaten its life. Hence the dilemma: Do we deliver the fetus immediately, which would eliminate risk for the mother but present a serious risk for the fetus—or do we postpone delivery, which would reduce risk for the fetus but greatly increase risk for the mother? If the woman elects to postpone delivery, then BP can be lowered with drugs. Because severe preeclampsia can be life threatening, treatment must be done in a tertiary care center to permit close monitoring of mother and fetus. The major objective is to prevent maternal cerebral complications (eg, hemorrhage, encephalopathy). The drug of choice for lowering BP is *hydralazine* (5 mg by IV bolus); dosing may be repeated 3 times at 20-minute intervals.

Because preeclampsia can (rarely) evolve into eclampsia, an anticonvulsant may be given for prophylaxis. *Magnesium sulfate* is the drug of choice. In one study, prophylaxis with magnesium sulfate reduced the risk of eclampsia by 58% and the risk of death by 45%. Dosing consists of a 10-gm IM loading dose followed by 5 gm IM every 4 hours for maintenance.

If eclampsia develops, magnesium sulfate is the preferred drug for seizure control. Dosing consists of a 4-gm IV loading dose followed by 5 gm IM injected into alternate buttocks every 4 hours for maintenance. To ensure therapeutic effects and prevent toxicity, blood levels of magnesium should be monitored. The target range is 4 to 7 mEq/L (the normal range for magnesium is 1.5 to 2 mEq/L).

Efforts to prevent preeclampsia with drugs have been disappointing. Low-dose aspirin may offer modest protection. Several other preparations—magnesium, zinc, vitamin C, vitamin E, fish oil, and diuretics—appear to offer no protection at all.

KEY POINTS

- Hypertension is defined as systolic BP greater than 140 mm Hg or diastolic BP greater than 90 mm Hg.
- Primary hypertension (essential hypertension), defined as hypertension with no identifiable cause, is the most common form of hypertension.
- Untreated hypertension can lead to heart disease, kidney disease, and stroke.
- In patients older than 50, elevated *systolic* BP represents a greater cardiovascular risk than elevated *diastolic* BP.
- The goal of antihypertensive therapy is to decrease morbidity and mortality without decreasing quality of life. For most patients, this goal is achieved by maintaining BP below 140/90 mm Hg, or below 130/80 mm Hg for those with diabetes or chronic kidney disease.
- To reduce BP, two kinds of treatment may be used: drug therapy and lifestyle modification (weight reduction, smoking cessation, reduction of salt and alcohol intake, following the DASH diet, and increasing aerobic exercise).
- The baroreceptor reflex, the kidneys, and the RAAS can oppose our attempts to lower BP with drugs. We can counteract the baroreceptor reflex with a beta blocker, the kidneys with a diuretic, and the RAAS with an ACE inhibitor, ARB, DRI, or aldosterone antagonist.
- Thiazide diuretics (eg, hydrochlorothiazide) and loop diuretics (eg, furosemide) reduce BP in two ways: they reduce blood volume (by promoting diuresis) and they reduce arterial resistance (by an unknown mechanism).
- Loop diuretics should be reserved for (1) patients who need greater diuresis than can be achieved with thiazides and (2) patients with a low GFR (because thiazides don't work when GFR is low).
- Beta blockers (eg, propranolol) appear to lower BP primarily by reducing peripheral vascular resistance; the mechanism is unknown. They may also lower BP by decreasing myocardial contractility and suppressing reflex tachycardia (through beta***1*** blockade in the heart), and by decreasing renin release (through beta***1*** blockade in the kidney).
- Calcium channel blockers (eg, diltiazem, nifedipine) reduce BP by promoting dilation of arterioles.

- ACE inhibitors, ARBs, and DRIs lower BP by preventing angiotensin II–mediated vasoconstriction and aldosterone-mediated volume expansion. ACE inhibitors work by blocking the formation of angiotensin II, whereas ARBs block the actions of angiotensin II. DRIs prevent formation of angiotensin I, and thereby shut down the entire RAAS.
- Aldosterone antagonists lower BP by preventing aldosterone-mediated retention of sodium and water in the kidney.
- Patients with stage 1 hypertension can often be treated with one drug, whereas those with stage 2 hypertension usually require two or more drugs.
- Thiazide diuretics are preferred drugs for initial therapy of uncomplicated hypertension.
- When a combination of drugs is used for hypertension, each drug should have a different mechanism of action.
- Dosages of antihypertensive drugs should be low initially and then gradually increased. This approach minimizes adverse effects and permits baroreceptors to reset to a lower pressure.
- Lack of patient adherence is the major cause of treatment failure in antihypertensive therapy.
- Adherence is difficult to achieve because (1) hypertension has no symptoms (so drug benefits aren't obvious); (2) hypertension progresses slowly (so patients think they can postpone treatment); and (3) treatment is complex and expensive, continues lifelong, and can cause adverse effects.
- A severe hypertensive emergency exists when diastolic BP exceeds 120 mm Hg and there is ongoing end-organ damage.
- Nitroprusside (IV) is a drug of choice for hypertensive emergencies.
- Hypertension is the most common complication of pregnancy.
- Methyldopa is a drug of choice for treating chronic hypertension of pregnancy.

Summary of Major Nursing Implications*

ANTIHYPERTENSIVE DRUGS

Preadministration Assessment

Therapeutic Goal

The goal of antihypertensive therapy is to prevent the long-term sequelae of hypertension (heart disease, kidney disease, stroke) while minimizing drug effects that can reduce quality of life. For most patients, BP should be reduced to less than 140/90 mm Hg or less than 130/80 mm Hg for those with diabetes or chronic kidney disease.

Baseline Data

The following tests should be done in all patients: BP; electrocardiogram; complete urinalysis; hemoglobin and hematocrit; and blood levels of sodium, potassium, calcium, creatinine, glucose, uric acid, triglycerides, and cholesterol (total, LDL, and HDL cholesterol).

Identifying High-Risk Patients

When taking the patient's drug history, attempt to identify drugs that can raise BP or that can interfere with the effects of antihypertensive drugs. Some drugs of concern are listed below under *Minimizing Adverse Interactions*.

The patient history should identify comorbid conditions that either contraindicate use of specific agents (eg, asthma and AV block contraindicate use of beta blockers) or require that drugs be used with special caution (eg, thiazide diuretics must be used with caution in patients with gout or diabetes). For risk factors that pertain to specific antihypertensive drugs, refer to the chapters in which those drugs are discussed.

Implementation: Administration

Routes

All drugs for chronic hypertension are administered orally. None is injected.

Dosage

To minimize adverse effects, dosages should be low initially and then gradually increased. It is counterproductive to employ high initial dosages that produce a rapid fall in pressure while also producing intense undesired responses that can discourage adherence. After 12 months of successful treatment, dosage reductions should be tried.

Implementation: Measures to Enhance Therapeutic Effects

Lifestyle Modifications

In hypertensive patients, lifestyle changes can reduce BP and increase responsiveness to antihypertensive drugs. These changes should be tried for 6 to 12 months before implementing drug therapy and should continue even if drug therapy is required.

Weight Reduction.

Help overweight patients develop an exercise program and a restricted-calorie diet. The goal is a body mass index in the normal range (18.5 to 24.9).

Sodium Restriction.

Encourage patients to consume no more than 6 gm of salt (2.4 gm of sodium) daily and provide them with information on the salt content of foods.

DASH Diet.

Encourage patients to adopt a diet rich in fruits, vegetables, and low-fat dairy products, and low in total fat, unsaturated fat, and cholesterol.

Alcohol Restriction.

Encourage patients to limit alcohol consumption to 1 ounce/day (for most men) and 0.5 ounce/day (for women and lighter weight men). One ounce of ethanol is equivalent to about two mixed drinks, two glasses of wine, or two cans of beer.

Exercise.

Encourage patients with a sedentary lifestyle to perform 30 to 45 minutes of aerobic exercise (eg, walking, jogging, swimming, bicycling) most days of the week.

Smoking Cessation.

Strongly encourage patients to quit smoking. Teach patients about aids for smoking cessation (eg, nicotine patch, bupropion, varenicline).

Promoting Adherence

Nonadherence is the major cause of treatment failure. Achieving adherence is difficult for several reasons: hypertension is devoid of overt symptoms; drugs do not make people feel better—and may make them feel worse; regimens can be complex and expensive; complications of hypertension take years to develop, thereby providing a misguided rationale for postponing treatment; and treatment usually lasts lifelong.

Provide Patient Education.

Educate patients about the long-term consequences of hypertension and the ability of lifestyle changes and drug therapy to decrease morbidity and prolong life. Inform patients that drugs do not cure hypertension, and therefore must usually be taken lifelong.

Encourage Self-Monitoring.

Make certain that patients know the treatment goal (usually reduction of BP to less than 140/90 mm Hg) and teach them to monitor and chart their own BP. This will increase their involvement and help them see the benefits of treatment.

Minimize Adverse Effects.

Adverse drug effects are an obvious deterrent to adherence. Measures to reduce undesired effects are discussed below, under *Minimizing Adverse Effects*.

Establish a Collaborative Relationship.

Encourage patients to be active partners in setting treatment goals, creating a treatment program, and evaluating progress.

Simplify the Regimen.

An antihypertensive regimen can consist of several drugs taken multiple times a day. Once an effective regimen has been established, attempt to switch to once-a-day or Twice-A-Day dosing. If an appropriate combination product is available (eg, a fixed-dose combination of a thiazide diuretic plus an ACE inhibitor), substitute the combination product for its components.

Other Measures.

Additional measures to promote adherence include providing positive reinforcement when treatment goals are achieved, involving family members in the treatment program, scheduling office visits at convenient times, following up on patients who miss an appointment, and devising a program that is effective but keeps costs low.

Ongoing Evaluation and Interventions

Evaluating Treatment

Monitor BP periodically. The usual goal is to reduce it to less than 140/90 mm Hg. **Teach patients to self-monitor their BP and to maintain a BP record.**

Minimizing Adverse Effects

General Considerations.

The fundamental strategy for decreasing adverse effects is to tailor the regimen to the sensitivities of the patient. If a drug causes objectionable effects, a more acceptable drug should be substituted.

Inform patients about the potential side effects of treatment and encourage them to report objectionable responses.

Avoid drugs that can exacerbate comorbid conditions. For example, don't give beta blockers to patients who have bradycardia, AV block, or asthma. Table 46-8 lists drugs to avoid in patients with specific disorders.

Initiate therapy with low doses and increase them gradually.

Adverse Effects of Specific Drugs.

For measures to minimize adverse effects of specific antihypertensive drugs (eg, beta blockers, diuretics, ACE inhibitors), refer to the chapters in which those drugs are discussed.

Minimizing Adverse Interactions

When taking the patient history, identify drugs that can raise BP or interfere with the effects of antihypertensive drugs. Drugs of concern include oral contraceptives, nasal decongestants and other cold remedies, nonsteroidal anti-inflammatory drugs, glucocorticoids, appetite suppressants, tricyclic antidepressants, monoamine oxidase inhibitors, cyclosporine, erythropoietin, and alcohol (in large quantities).

Antihypertensive regimens frequently contain two or more drugs, thereby posing a potential risk of adverse interactions (eg, ACE inhibitors can increase the risk of hyperkalemia caused by potassium-sparing diuretics). For interactions that pertain to specific antihypertensive drugs, refer to the chapters in which those drugs are discussed.

47 Drugs for Heart Failure

Heart failure is a disease with two major forms: (1) heart failure with left ventricular (LV) systolic dysfunction, and (2) diastolic heart failure, also known as heart failure with preserved LV ejection fraction. In this chapter, discussion is limited to the first form. Accordingly, from this point in the chapter on, the term *heart failure* (HF) will be used to denote the first form only.

Heart failure is a progressive, often fatal disorder characterized by ventricular dysfunction, reduced cardiac output, insufficient tissue perfusion, and signs of fluid retention (eg, peripheral edema, shortness of breath). The disease affects nearly 5 million Americans and, every year, is responsible for 12 to 15 million office visits, 6.5 million hospital days, and about 300,000 deaths. Of those who have HF, 24% are likely to die within 1 year, and 65% within 5 years. Heart failure is primarily a disease of the elderly, affecting 2% to 3% of those at age 65 and more than 80% of those over 80. In 2008, direct and indirect healthcare costs of HF were estimated at more than $35 billion. With improved evaluation and care, many hospitalizations could be prevented, quality of life could be improved, and life expectancy could be extended.

In the past, HF was commonly referred to as *congestive heart failure*. This term was used because HF frequently causes fluid accumulation (congestion) in the lungs and peripheral tissues. However, because many patients do not have signs of pulmonary or systemic congestion, the term *heart failure* is now preferred.

Drugs recommended for treatment include diuretics, inhibitors of the renin-angiotensin-aldosterone system (RAAS), beta blockers, and digoxin. In this chapter, only digoxin is discussed at length. The other drugs are presented at length in previous chapters, and hence discussion here is limited to their use in heart failure.

In order to understand HF and its treatment, you need a basic understanding of hemodynamics. In particular, you need to understand the role of venous pressure, afterload, and Starling's mechanism in determining cardiac output. You also need to understand the roles of the baroreceptor reflex, the RAAS, and the kidneys in regulating arterial pressure. If your understanding of these concepts

is a little hazy, you can refresh your memory by reading Chapter 42 (Review of Hemodynamics).

PATHOPHYSIOLOGY OF HEART FAILURE

Heart failure is a syndrome in which the heart is unable to pump sufficient blood to meet the metabolic needs of tissues. The syndrome is characterized by signs of *inadequate tissue perfusion* (fatigue, shortness of breath, exercise intolerance) and/or signs of *volume overload* (venous distention, peripheral and pulmonary edema). The major underlying causes of HF are chronic hypertension and myocardial infarction. Other causes include valvular heart disease, coronary artery disease, congenital heart disease, dysrhythmias, and aging of the myocardium. In its earliest stage, HF is asymptomatic. As failure progresses, fatigue and shortness of breath develop. As cardiac performance declines further, blood backs up behind the failing ventricles, causing venous distention, peripheral edema, and pulmonary edema. Heart failure is a chronic disorder that requires continuous treatment with drugs.

Cardiac Remodeling

In the initial phase of failure, the heart undergoes remodeling, a process in which the ventricles dilate (grow larger), hypertrophy (increase in wall thickness), and become more spherical (less cylindrical). These alterations in cardiac geometry increase wall stress and reduce LV ejection fraction. Remodeling occurs in response to cardiac injury, brought on by infarction and other causes. The remodeling process is driven primarily by neurohormonal systems, including the sympathetic nervous system (SNS) and the RAAS. In addition to promoting remodeling, neurohormonal factors promote cardiac fibrosis and myocyte death. The net result of these pathologic changes—remodeling, fibrosis, and cell death—is progressive decline in cardiac output. As a rule, cardiac remodeling precedes development of symptoms, and continues after they appear. As a result, cardiac performance continues to decline.

Physiologic Adaptations to Reduced Cardiac Output

In response to reductions in cardiac pumping ability, the body undergoes several adaptive changes. Some of these help improve tissue perfusion; others compound existing problems.

Cardiac Dilation.

Dilation of the heart is characteristic of HF. Cardiac dilation results from a combination of increased venous pressure (see below) and reduced contractile force. Reduced contractility lowers the amount of blood ejected during systole, causing end-systolic volume to rise. The increase in venous pressure increases diastolic filling, which causes the heart to expand even further.

Because of Starling's mechanism, the increase in heart size that occurs in HF helps improve cardiac output. That is, as the heart fails and its volume expands, contractile force increases, causing a corresponding increase in stroke volume. However, please note that the maximal contractile force that can be developed by the failing heart is considerably lower than the maximal force of the healthy heart. This limitation is reflected in the curve for the failing heart shown in Figure 47-1.

If cardiac dilation is insufficient to maintain cardiac output, other factors come into play. As discussed below, these are not always beneficial.

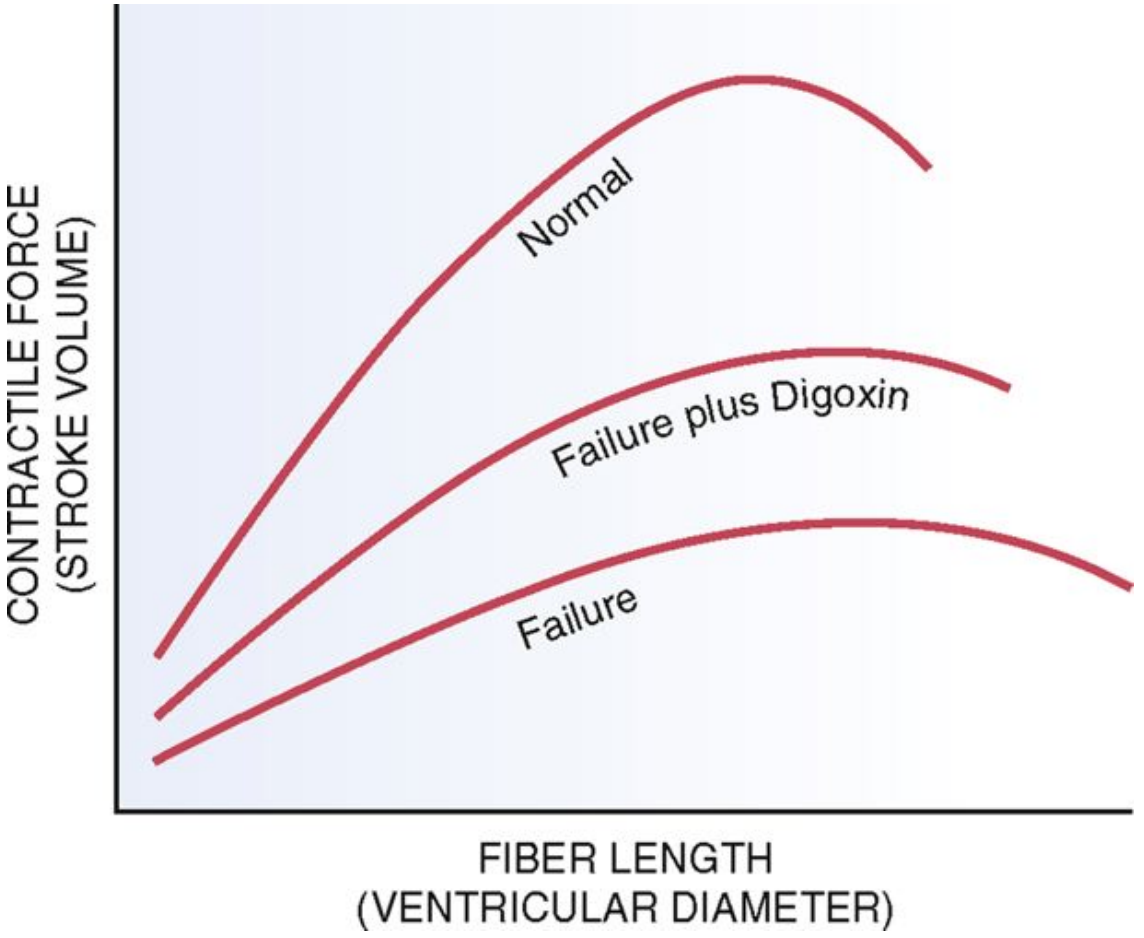

Figure 47-1 Relationship of ventricular diameter to contractile force. In the normal heart and the failing heart, increased fiber length produces increased contractile force. However, for any given fiber length, contractile force in the failing heart is much less than in the healthy heart. By increasing cardiac contractility, digoxin shifts the relationship between fiber length and stroke volume in the failing heart toward that in the normal heart.

Increased Sympathetic Tone.

Heart failure causes arterial pressure to fall. In response, the baroreceptor reflex increases sympathetic output to the heart, veins, and arterioles. At

the same time, parasympathetic effects on the heart are reduced. The consequences of increased sympathetic tone are summarized below.

- *Increased heart rate*. Acceleration of heart rate increases cardiac output, thereby helping improve tissue perfusion. However, if heart rate increases too much, there will be insufficient time for complete ventricular filling, and hence cardiac output will fall.
- *Increased contractility*. Increased myocardial contractility has the obvious benefit of increasing cardiac output. The only detriment is an increase in cardiac oxygen demand.
- *Increased venous tone*. Elevation of venous tone increases venous pressure, and thereby increases ventricular filling. Because of Starling's mechanism, increased filling increases stroke volume. Unfortunately, if venous pressure is excessive, blood will back up behind the failing ventricles, thereby aggravating pulmonary and peripheral edema. Furthermore, excessive filling pressure can dilate the heart so much that stroke volume will begin to decline (see Fig. 47-1).
- *Increased arteriolar tone*. Elevation of arteriolar tone increases arterial pressure, thereby increasing perfusion of vital organs. Unfortunately, increased arterial pressure also means the heart must pump against greater resistance. Since cardiac reserve is minimal in HF, the heart may be unable to meet this challenge, and output may fall.

Water Retention and Increased Blood Volume.

Mechanisms.

Water retention results from two mechanisms. First, reduced cardiac output causes a reduction in renal blood flow, which in turn decreases glomerular filtration rate (GFR). As a result, urine production is decreased and water is retained. Retention of water increases blood volume.

Second, HF activates the RAAS. Activation occurs in response to reduced blood pressure and reduced renal blood flow. Once activated, the RAAS promotes water retention by increasing circulating levels of *aldosterone* and *angiotensin II*. Aldosterone acts directly on the kidneys to promote retention of sodium and water. Angiotensin II causes constriction of renal blood vessels, which de-

creases renal blood flow, and thereby further decreases urine production. In addition, angiotensin II causes constriction of systemic arterioles and veins, and thereby increases venous and arterial pressure.

Consequences.

As with other adaptive responses to HF, increased blood volume can be beneficial or harmful. Increased blood volume increases venous pressure, and thereby increases venous return. As a result, ventricular filling and stroke volume are increased. The resultant increase in cardiac output can improve tissue perfusion. However, as noted, if venous pressure is too high, edema of the lungs and periphery may result. More importantly, *if the increase in cardiac output is insufficient to maintain adequate kidney function, renal retention of water will progress unabated. The resultant accumulation of fluid will cause severe cardiac, pulmonary, and peripheral edema—and, ultimately, death*.

Natriuretic Peptides.

In response to stretching of the atria and dilation of the ventricles, the heart releases two natriuretic peptides: atrial natriuretic peptide (ANP) and B-natriuretic peptide (BNP). As discussed in Chapter 42, these hormones promote dilation of arterioles and veins, and also promote loss of sodium and water through the kidneys. Hence, they tend to counterbalance vasoconstriction caused by the SNS and angiotensin II, as well as retention of sodium and water caused by the RAAS. However, as HF progresses, the effects of ANP and BNP eventually become overwhelmed by the effects of the SNS and RAAS.

The Vicious Cycle of "Compensatory" Physiologic Responses

As discussed above, reduced cardiac output leads to compensatory responses: (1) cardiac dilation, (2) activation of the SNS, (3) activation of the RAAS, and (4) retention of water and expansion of blood volume. Although these responses represent the body's attempt to compensate for reduced cardiac output, they can actually make matters worse:

excessive heart rate can reduce ventricular filling; excessive arterial pressure can lower cardiac output; and excessive venous pressure can cause pulmonary and peripheral edema. Hence, as depicted in Figure 47-2, the "compensatory" responses can create a self-sustaining cycle of maladaptation that further im-

pairs cardiac output and tissue perfusion. If cardiac output becomes too low to maintain sufficient production of urine, the resultant accumulation of water will eventually be fatal. The actual cause of death is complete cardiac failure secondary to excessive cardiac dilation and cardiac edema.

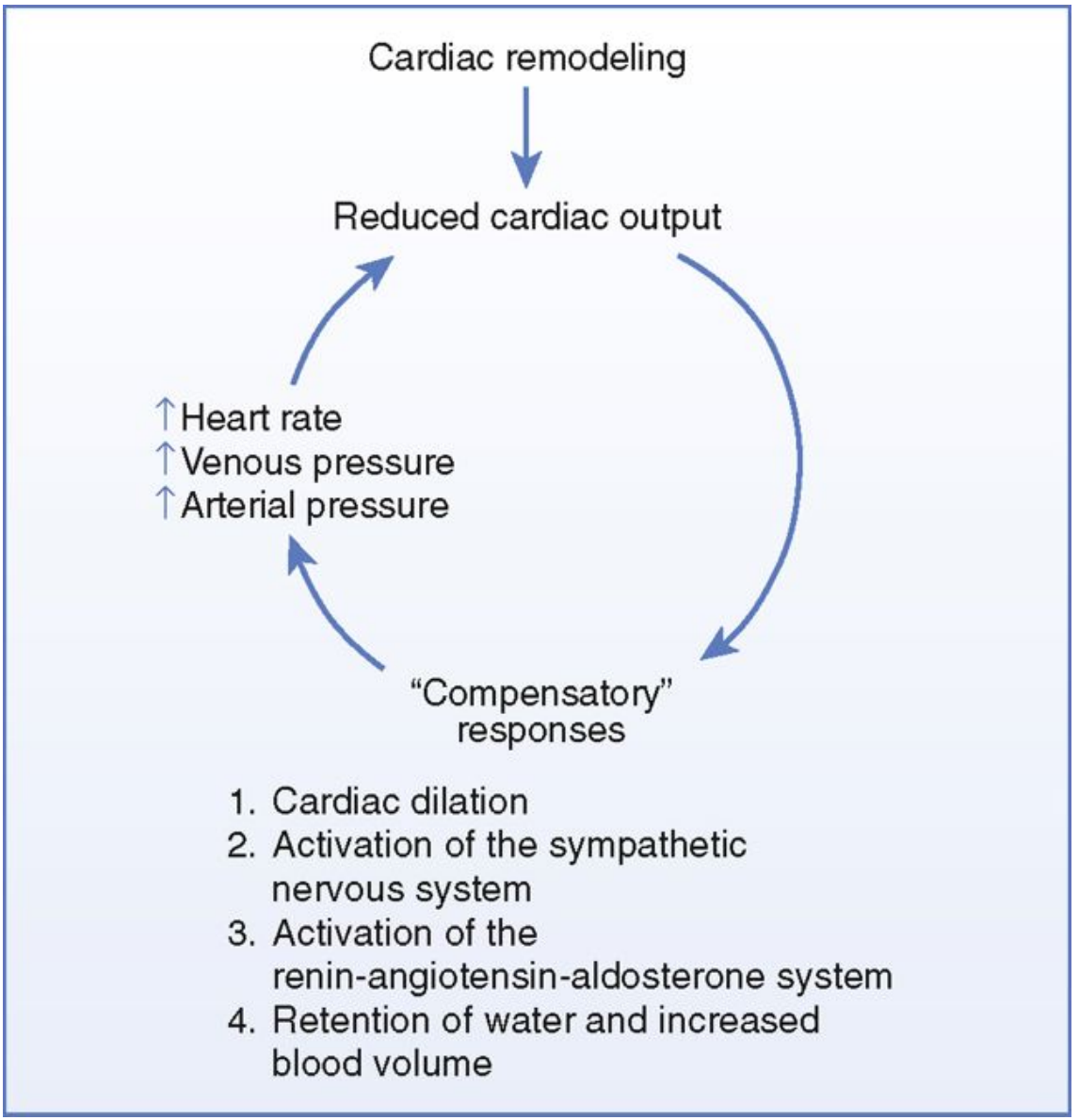

Figure 47-2 The vicious cycle of maladaptive compensatory responses to a failing heart.

Signs and Symptoms of Heart Failure

The prominent signs and symptoms of HF are a direct consequence of the pathophysiology just described. Decreased tissue perfusion results in reduced exercise tolerance, fatigue, and shortness of breath; shortness of breath may also reflect pulmonary edema. Increased sympathetic tone produces tachycardia. Increased ventricular filling, reduced systolic ejection, and myocardial hypertrophy result in cardiomegaly (increased heart size). The combination of increased venous tone plus increased blood volume helps cause pulmonary edema, peripheral edema, hepatomegaly (increased liver size), and distention of the jugular veins. Weight gain results from fluid retention.

Classification of Heart Failure Severity

There are two major schemes for classifying HF severity. One scheme, established by the New York Heart Association (NYHA), classifies HF based on the functional limitations it causes. A newer scheme, proposed jointly by the American College of Cardiology (ACC) and the American Heart Association (AHA), is based on the observation that HF is a progressive disease that moves through stages of increasing severity.

The NYHA scheme, which has four classes, can be summarized as follows:

- Class I—No limitation of ordinary physical activity
- Class II—Slight limitation of physical activity: normal activity produces fatigue, dyspnea, palpitations, or angina
- Class III—Marked limitation of physical activity: even mild activity produces symptoms
- Class IV—Symptoms occur at rest

The ACC/AHA scheme, which also has four stages, can be summarized as follows:

- Stage A—At high risk for HF but without structural heart disease or symptoms of HF
- Stage B—Structural heart disease but without symptoms of HF
- Stage C—Structural heart disease with prior or current symptoms of HF

- Stage D—Advanced structural heart disease with marked symptoms of HF at rest, and requiring specialized interventions (eg, heart transplant, mechanical assist device)

The ACC/AHA scheme was unveiled in treatment guidelines issued in 2001. The 2005 version of that document—*ACC/AHA 2005 Guideline Update for the Evaluation and Management of Chronic Heart Failure in the Adult*—and its 2009 focused update are discussed below under *Management of Heart Failure*.

Please note that the ACC/AHA scheme is intended to complement the NYHA scheme, not replace it. The relationship between the two is shown graphically in Figure 47-3.

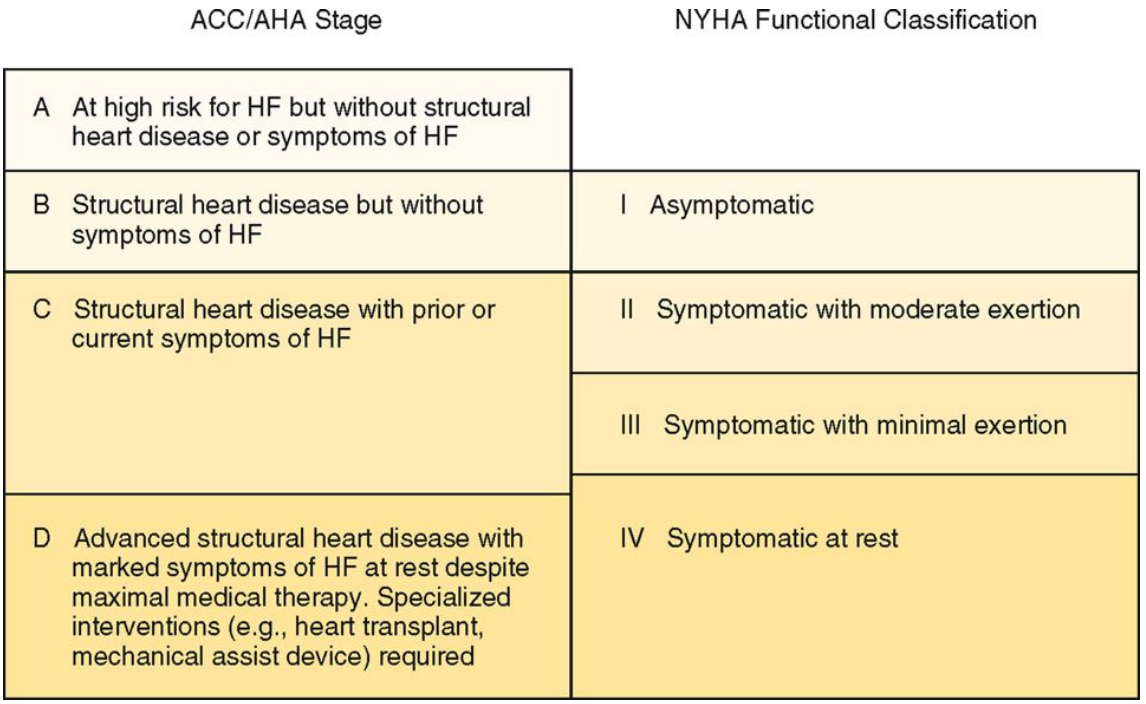

Figure 47-3 American College of Cardiology/American Heart Association (ACC/AHA) Stage and New York Heart Association (NYHA) Classification of Heart Failure.

OVERVIEW OF DRUGS USED TO TREAT HEART FAILURE

For routine therapy, heart failure is treated with three types of drugs: (1) diuretics, (2) agents that inhibit the RAAS, and (3) beta blockers. Other agents (eg, digoxin, dopamine, hydralazine, nesiritide) may be used as well.

Diuretics

Diuretics are first-line drugs for all patients with signs of volume overload or with a history of volume overload. By reducing blood volume, these drugs can decrease venous pressure, arterial pressure (afterload), pulmonary edema, peripheral edema, and cardiac dilation. However, excessive diuresis must be avoided: If blood volume drops too low, cardiac output and blood pressure may fall precipitously, thereby further compromising tissue perfusion. For the most part, benefits of diuretics are limited to symptom reduction. As a rule, these drugs do not prolong survival. The basic pharmacology of the diuretics is discussed in Chapter 40.

Thiazide Diuretics.

The thiazide diuretics (eg, hydrochlorothiazide) produce moderate diuresis. These oral agents are used for long-term therapy of HF when edema is not too great. Since thiazides are ineffective when GFR is low, these drugs cannot be used if cardiac output is greatly reduced. The principal adverse effect of the thiazides is *hypokalemia,* which increases the risk of *digoxin-induced dysrhythmias* (see below).

High-Ceiling (Loop) Diuretics.

The loop diuretics (eg, furosemide) produce profound diuresis. In contrast to the thiazides, these drugs can promote fluid loss even when GFR is low. Hence, loop diuretics are preferred to thiazides when cardiac output is greatly reduced. Administration may be oral or IV. Because they can mobilize large volumes of water, and because they work when GFR is low, loop diuretics are drugs of choice for patients with severe HF. Like the thiazides, these drugs can cause *hypokalemia,* thereby increasing the risk of *digoxin toxicity*. In addition, loop diuretics can cause severe *hypotension* secondary to excessive volume reduction.

Potassium-Sparing Diuretics.

In contrast to the thiazides and loop diuretics, the potassium-sparing diuretics (eg, spironolactone, triamterene) promote only scant diuresis. In patients with HF, these drugs are employed to counteract potassium loss caused by thiazide and loop diuretics, thereby lowering the risk of digoxin-induced dysrhythmias. Not surprisingly, the principal adverse effect of the potassium-sparing drugs is *hyperkalemia*. Because *angiotensin-converting enzyme (ACE) inhibitors* and *angiotensin II receptor blockers (ARBs)* also carry a risk of hyperkalemia, caution is needed if these drugs are combined with a potassium-sparing diuretic. Accordingly, when therapy with an ACE inhibitor or ARB is initiated, the potassium-sparing diuretic should be discontinued. It can be resumed later if needed.

One potassium-sparing diuretic—spironolactone—prolongs survival in patients with HF primarily by blocking receptors for aldosterone, not by causing diuresis. This drug and a related agent—eplerenone—are discussed below under *Aldosterone Antagonists*.

Drugs That Inhibit the RAAS

The RAAS plays an important role both in cardiac remodeling and in the hemodynamic changes that occur in response to reduced cardiac output. Accordingly, agents that inhibit the RAAS can be highly beneficial. Four groups of drugs are available: ACE inhibitors, ARBs, direct renin inhibitors (DRIs), and aldosterone antagonists. Of the four, the ACE inhibitors have been studied most thoroughly in HF. The basic pharmacology of the RAAS inhibitors is presented in Chapter 43.

ACE Inhibitors

ACE inhibitors (eg, captopril, enalapril) are a cornerstone of HF therapy. These drugs can improve functional status and prolong life. In one trial, the 2-year mortality rate for patients taking enalapril was 47% lower than the rate for patients taking placebo. Other large, controlled trials have shown similar benefits. Accordingly, in the absence of specific contraindications, all patients with HF should receive one of these drugs. Although ACE inhibitors can be used alone, they are usually combined with a beta blocker and a diuretic.

How do ACE inhibitors help? They block production of angiotensin II, decrease release of aldosterone, and suppress degradation of kinins. As a result, they improve hemodynamics and favorably alter cardiac remodeling.

Hemodynamic Benefits.

By suppressing production of angiotensin II, ACE inhibitors cause dilation of arterioles and veins and they decrease release of aldosterone. Resulting benefits in HF are as follows:

- *Arteriolar dilation* improves regional blood flow in the kidneys and other tissues and, by reducing afterload, it increases stroke volume and cardiac output. Increased renal blood flow promotes excretion of sodium and water.
- *Venous dilation* reduces venous pressure, and thereby reduces pulmonary congestion, peripheral edema, preload, and cardiac dilation.
- *Suppression of aldosterone release* enhances excretion of sodium and water, while causing retention of potassium.

Interestingly, suppression of angiotensin II production diminishes over time, suggesting that long-term benefits are the result of some other action.

Impact on Cardiac Remodeling.

With continued use, ACE inhibitors have a favorable impact on cardiac remodeling. Elevation of kinins is largely responsible. This statement is based in part on the observation that, in experimental models, giving a kinin receptor blocker decreases beneficial effects on remodeling. Also, we know that suppression of angiotensin II production diminishes over time, and hence reduced angiotensin II cannot fully explain long-term benefits.

Adverse Effects.

The principal adverse effects of the ACE inhibitors are *hypotension* (secondary to arteriolar dilation), *hyperkalemia* (secondary to decreased aldosterone release), *intractable cough*, and *angioedema*. In addition, these drugs can cause *renal failure in patients with bilateral renal artery stenosis*. If taken during pregnancy—especially the second and third trimesters—ACE inhibitors can cause *fetal injury*. Accordingly, if pregnancy occurs, these drugs should be discontinued. Because of their ability to elevate potassium levels, ACE inhibitors

should be used with caution in patients taking potassium supplements or a potassium-sparing diuretic (eg, spironolactone, triamterene).

Dosage.

Adequate dosage is critical: Higher dosages are associated with increased survival. Results of the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial indicate that the doses needed to increase survival are higher than those needed to produce hemodynamic changes. Unfortunately, in everyday practice, dosages are often too low: Providers frequently prescribe dosages that are large enough to produce hemodynamic benefits, but are still too low to prolong life. Target dosages associated with increased survival are summarized in Table 47-1. These dosages should be used unless side effects make them intolerable.

Drug	Initial Daily Dose	Maximum Daily Dose
ACE Inhibitors		
Captopril [Capoten]	6.25 mg 3 times	50 mg 3 times
Enalapril [Vasotec]	2.5 mg twice	10–20 mg twice
Fosinopril [Monopril]	5–10 mg once	40 mg once
Lisinopril [Zestril, Prinvil]	2.5–5 mg once	20–40 mg once
Perindopril [Aceon]	2 mg once	8–16 mg once
Quinapril [Accupril]	5 mg twice	20 mg twice
Ramipril [Altace]	1.25–2.5 mg once	10 mg once
Trandolapril [Mavik]	1 mg once	4 mg once
Angiotensin II Receptor Blockers		
Candesartan [Benicar]	4–8 mg once	32 mg once
Losartan [Cozaar]	25–50 mg once	50–100 mg once
Valsartan [Diovan]	20–40 mg twice	160 mg twice
Aldosterone Antagonists		
Eplerenone [Inspra]	25 mg once	50 mg once
Spironolactone [Aldactone]	12.5–25 mg once	25 mg once or twice

TABLE 47-1 Inhibitors of the Renin-Angiotensin-Aldosterone System Used in Heart Failure

Angiotensin II Receptor Blockers

In patients with HF, the effects of ARBs are similar to those of ACE inhibitors—but not identical. Hemodynamic effects of both groups are much the same. Clinical trials have shown that ARBs improve LV ejection fraction, reduce HF symptoms, increase exercise tolerance, decrease hospitalization, enhance quality of life, and, most importantly, reduce mortality. However, because ARBs do not increase levels of kinins, their effects on cardiac remodeling are less favorable than those of ACE inhibitors. For this reason, and because

clinical experience with ACE inhibitors is much greater than with ARBs, ACE inhibitors are generally preferred. For now, ARBs should be reserved for HF patients who cannot tolerate ACE inhibitors, usually owing to intractable cough. (Because ARBs do not increase bradykinin levels, they do not cause cough.)

Aldosterone Antagonists

In patients with HF, aldosterone antagonists—*spironolactone* [Aldactone] and *eplerenone* [Inspra]—can reduce symptoms, decrease hospitalizations, and prolong life. These benefits were first demonstrated with spironolactone in the Randomized Aldactone Evaluation Study (RALES). Similar results were subsequently obtained with eplerenone. Current guidelines recommend adding an aldosterone antagonist to standard HF therapy (ie, a diuretic, an ACE inhibitor or ARB, and a beta blocker), but only in patients with moderately severe or severe symptoms.

How do aldosterone antagonists help? Primarily by blocking aldosterone receptors in the heart and blood vessels. To understand these effects, we need to review the role of aldosterone in HF. In the past, researchers believed that all aldosterone did was promote renal retention of sodium (and water) in exchange for excretion of potassium. However, we now know that aldosterone has additional—and more harmful—effects. Among these are

- Promotion of myocardial remodeling (which impairs pumping)
- Promotion of myocardial fibrosis (which increases the risk of dysrhythmias)
- Activation of the SNS and suppression of norepinephrine uptake in the heart (both of which can promote dysrhythmias and ischemia)
- Promotion of vascular fibrosis (which decreases arterial compliance)
- Promotion of baroreceptor dysfunction

During HF, activation of the RAAS causes levels of aldosterone to rise. In some patients, levels reach 20 times normal. As aldosterone levels grow higher, harmful effects increase, and prognosis becomes progressively worse.

Drugs can reduce the impact of aldosterone by either decreasing aldosterone production or blocking aldosterone receptors. ACE inhibitors, ARBs, and DRIs decrease aldosterone production; spironolactone and eplerenone block aldos-

terone receptors. Although ACE inhibitors and ARBs can reduce aldosterone production, they do not block it entirely. Furthermore, production is suppressed only for a relatively short time. Hence, when ACE inhibitors or ARBs are used alone, detrimental effects of aldosterone can persist. However, when an aldosterone antagonist is added to the regimen, any residual effects are eliminated. As a result, symptoms of HF are improved and life is prolonged.

Aldosterone antagonists have one major adverse effect: *hyperkalemia*. The underlying cause is renal retention of potassium. Risk is increased by renal impairment and by using an ACE inhibitor or ARB. To minimize risk, potassium levels and renal function should be measured at baseline and periodically thereafter. Potassium supplements should be discontinued.

Spironolactone—but not eplerenone—poses a significant risk of *gynecomastia* (breast enlargement) in men, a condition that can be both cosmetically troublesome and painful. In the RALES trial, 10% of males experienced painful breast enlargement.

Direct Renin Inhibitors

As discussed in Chapter 43, DRIs can shut down the entire RAAS. In theory, their benefits in HF should equal those of the ACE inhibitors and ARBs. At this time, only one DRI is available. This drug—*aliskiren* [Tekturna]—is being tested in HF, but is not yet approved for the disorder.

Beta Blockers

The role of beta blockers in HF continues to evolve. Until the mid-1990s, HF was considered an absolute contraindication to these drugs. After all, blockade of cardiac beta***1***-adrenergic receptors *reduces* contractility—an effect that is clearly detrimental, given that contractility is already compromised in the failing heart. However, it is now clear that, with careful control of dosage, beta blockers can improve patient status. Controlled trials have shown that three beta blockers—*carvedilol* [Coreg], *bisoprolol* [Zebeta], and *sustained-release metoprolol* [Toprol XL]—when added to conventional therapy, can improve LV ejection fraction, increase exercise tolerance, slow progression of HF, reduce the need for hospitalization, and, most importantly, prolong survival. Accordingly, beta blockers are now recommended for most patients. These drugs can

even be used in patients with severe disease (NYHA Class IV), provided the patient is euvolemic and hemodynamically stable. Although the mechanism underlying benefits is uncertain, likely possibilities include protecting the heart from excessive sympathetic stimulation and protecting against dysrhythmias. Because excessive beta blockade can reduce contractility, doses must be very low initially and then gradually increased. Full benefits may not be seen for 1 to 3 months. Among patients with HF, the principal adverse effects are (1) fluid retention and worsening of HF, (2) fatigue, (3) hypotension, and (4) bradycardia or heart block. The basic pharmacology of the beta blockers is discussed in Chapter 18.

Digoxin and Other Cardiac Glycosides

Digoxin and the other cardiac glycosides are best known for their *positive inotropic actions,* that is, their ability to increase myocardial contractile force. By increasing contractile force, these drugs can increase cardiac output. In addition, cardiac glycosides can alter the electrical activity of the heart, and they can favorably affect neurohormonal systems. Unfortunately, although these drugs can reduce symptoms of HF, they do not prolong life. Used widely in the past, cardiac glycosides are considered second-line agents today. The pharmacology of these drugs is discussed at length later.

Inotropic Agents (Other Than Cardiac Glycosides)

In addition to the cardiac glycosides, we have two other groups of inotropic drugs: sympathomimetics and phosphodiesterase (PDE) inhibitors. Unlike the cardiac glycosides, which can be taken orally, these other inotropics must be given by IV infusion. Accordingly, their use is restricted to acute care of hospitalized patients. Because the cardiac glycosides can be given PO, they are the only inotropics suited for long-term therapy.

Sympathomimetic Drugs: Dopamine and Dobutamine

The basic pharmacology of dopamine and dobutamine is presented in Chapter 17. Discussion here is limited to their use in HF. Both drugs are administered by IV infusion.

Dopamine.

Dopamine (formerly available as Intropin) is a catecholamine that can activate (1) beta***1***-adrenergic receptors in the heart, (2) dopamine receptors in the kidney, and (3) at high doses, alpha***1***-adrenergic receptors in blood vessels. Activation of beta***1*** receptors increases myocardial contractility, thereby improving cardiac performance. Beta***1*** activation also increases heart rate, creating a risk of tachycardia. Activation of dopamine receptors dilates renal blood vessels, thereby increasing renal blood flow and urine output. Activation of alpha***1*** receptors increases vascular resistance (afterload), and can thereby reduce cardiac output. Dopamine is administered by continuous infusion. Constant monitoring of blood pressure, the electrocardiogram (ECG), and urine output is required. Dopamine is employed as a short-term rescue measure for patients with severe, acute cardiac failure.

Dobutamine.

Dobutamine (formerly available as Dobutrex) is a synthetic catecholamine that causes selective activation of beta***1***-adrenergic receptors. By doing so, the drug can increase myocardial contractility, and can thereby improve cardiac performance. Like dopamine, dobutamine can cause tachycardia. In contrast to dopamine, dobutamine does not activate alpha***1*** receptors, and therefore does not increase vascular resistance. As a result, the drug is generally preferred to dopamine for short-term treatment of acute HF. Administration is by continuous infusion.

Phosphodiesterase Inhibitors

Inamrinone.

Inamrinone, formerly known as *amrinone,* has been called an *inodilator* because it increases myocardial contractility *and* promotes vasodilation. Increased contractility results from intracellular accumulation of cyclic AMP (cAMP) secondary to inhibition of PDE3, an enzyme that degrades cAMP. The mechanism underlying vasodilation is unclear. Comparative studies indicate that improvements in cardiac function elicited by inamrinone are superior to those elicited by dopamine or dobutamine. Like dopamine and dobutamine, inamrinone is administered by IV infusion, and hence is not suited for outpatient use. Inamrinone is indicated only for short-term (2- to 3-day) treatment of

HF in patients who have not responded to RAAS inhibitors, diuretics, and digoxin. The drug should be protected from light and should not be mixed with glucose-containing solutions. Constant monitoring is required. The initial dose is 0.75 mg/kg IV administered over 2 to 3 minutes. The maintenance infusion is 5 to 10 mcg/kg/min.

Milrinone.

Like inamrinone, milrinone (formerly available as Primacor) is an inodilator. Increased contractility results from accumulation of cAMP secondary to inhibition of PDE3. Milrinone is administered by IV infusion and is indicated only for short-term therapy of severe HF. Dosing is complex.

Vasodilators (Other Than ACE Inhibitors and ARBs)

Isosorbide Dinitrate Plus Hydralazine

For treatment of HF, isosorbide dinitrate (ISDN) and hydralazine are usually combined. The combination represents an alternative to ACE inhibitors or ARBs. However, ACE inhibitors and ARBs are generally preferred.

Isosorbide dinitrate [Isordil, others] belongs to the same family as nitroglycerin. Like nitroglycerin, ISDN causes selective dilation of *veins*. In patients with severe, refractory HF, the drug can reduce congestive symptoms and improve exercise capacity. In addition to its hemodynamic actions, ISDN may inhibit abnormal myocyte growth, and hence may retard cardiac remodeling. Principal adverse effects are *orthostatic hypotension* and *reflex tachycardia*. The basic pharmacology of ISDN and other organic nitrates is discussed in Chapter 50 (Drugs for Angina Pectoris).

Hydralazine [Apresoline] causes selective dilation of *arterioles*. By doing so, the drug can improve cardiac output and renal blood flow. For treatment of HF, hydralazine is always used in combination with ISDN, since hydralazine by itself is not very effective. Principal adverse effects are *hypotension, tachycardia,* and a syndrome that resembles *systemic lupus erythematosus*. The basic pharmacology of hydralazine is discussed in Chapter 45 (Vasodilators).

In 2005, the Food and Drug Administration approved *BiDil,* a fixed-dose combination of hydralazine and isosorbide dinitrate, for treating HF—but only in

African Americans, making BiDil the first medication approved for a specific ethnic group. Can BiDil help people in other ethnic groups? Probably, but data are lacking: The manufacturer only tested the product in blacks. As discussed in Chapter 8 (under the heading *Race*), testing was limited to blacks primarily because of regulatory and market incentives, not because there were data suggesting it wouldn't work for others. Of course, now that BiDil is approved, clinicians may prescribe it for anyone they see fit. Each BiDil tablet contains 37.5 mg hydralazine and 20 mg isosorbide dinitrate. The recommended dosage is 1 or 2 tablets 3 times a day.

Intravenous Vasodilators for Acute Care

Nitroglycerin.

Intravenous nitroglycerin is a powerful *venodilator* that produces a dramatic reduction in venous pressure. Effects have been described as being equivalent to "pharmacologic phlebotomy." In HF, nitroglycerin is used to relieve acute severe pulmonary edema. Principal adverse effects are *hypotension* and resultant *reflex tachycardia*. The basic pharmacology of nitroglycerin is discussed in Chapter 50 (Drugs for Angina Pectoris).

Sodium Nitroprusside.

Sodium nitroprusside [Nitropress] acts rapidly to dilate *arterioles* and *veins*. Arteriolar dilation reduces afterload and thereby increases cardiac output. Venodilation reduces venous pressure and thereby decreases pulmonary and peripheral congestion. The drug is indicated for short-term therapy of severe refractory HF. The principal adverse effect is *profound hypotension*. Blood pressure must be monitored continuously. The basic pharmacology of nitroprusside is discussed in Chapter 45 (Vasodilators).

Nesiritide.

Nesiritide [Natrecor] is a synthetic form of human BNP indicated only for short-term, IV therapy of hospitalized patients with acutely decompensated HF, characterized by increased pulmonary capillary wedge pressure (PCWP) and dyspnea at rest. Nesiritide is produced by recombinant DNA technology and has the same amino acid sequence as naturally occurring BNP. Hemody-

namic benefits equal those of nitroglycerin. However, nesiritide costs much more than nitroglycerin, and hypotension, which can be caused by both drugs, lasts much longer.

In 2005, two meta-analyses of older data suggested that nesiritide may *increase* the risk of renal injury and death. The resulting controversy is not yet resolved. Although there is debate as to whether nesiritide actually increases mortality, one thing is nonetheless clear: There are no data to show that it *reduces* mortality. Until more is known, an expert panel, convened by the drug's manufacturer, has recommended that use of nesiritide be strictly limited to inpatients with acutely decompensated HF (and that it *not* be used for unlabeled indications, including intermittent outpatient infusions or scheduled repetitive use). The panel also noted the need for large-scale trials to assess the benefits and risks of nesiritide compared with standard therapy.

Mechanism of Action.

Nesiritide affects hemodynamics by three mechanisms: suppression of the RAAS, suppression of sympathetic outflow from the central nervous system (CNS), and direct dilation of arterioles and veins. In patients with HF, benefits derive primarily from direct vasodilation. To promote vasodilation, nesiritide binds with receptors on vascular smooth muscle (VSM), and thereby stimulates production of cyclic GMP (cGMP), a second messenger that causes VSM to relax. This mechanism is similar to that of nitroglycerin, which also stimulates cGMP production. However, whereas nitroglycerin acts primarily on veins, nesiritide dilates arterioles as well. By dilating arterioles and veins, nesiritide reduces both preload and afterload. The net result is a decrease in PCWP and increased cardiac output. Also, by dilating afferent renal arterioles, nesiritide increases GFR, and thereby increases excretion of sodium and water. The result is a reduction in blood volume, which further reduces cardiac preload.

Clinical Effects.

Nesiritide has been studied in several clinical trials, including the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial, which compared nesiritide with IV nitroglycerin and placebo. The result? Three hours after the start of treatment, nesiritide produced a significant reduction in PCWP and a significant improvement in dyspnea. The effect was equivalent

to that of IV nitroglycerin and superior to that of placebo. To date, there are no data to show that nesiritide prolongs life.

Pharmacokinetics.

With continuous infusion, nesiritide achieves steady-state levels that are 3 to 6 times greater than the level of endogenous BNP present at baseline. Nesiritide is eliminated by three mechanisms: (1) proteolytic cleavage by endopeptidases present on the luminal surface of blood vessels; (2) binding to clearance receptors on the surface of cells, followed by cellular uptake and proteolytic cleavage; and (3) renal filtration. The drug's half-life is short, about 18 minutes.

Adverse Effects.

The principal adverse effect is symptomatic *hypotension*. In the VMAC trial, hypotension developed in 4% of patients, about the same rate seen with nitroglycerin. However, because nesiritide has a longer half-life than nitroglycerin, the duration of hypotension was also longer (2.2 hours vs. 0.7 hours with nitroglycerin). The risk of hypotension is increased by high doses of nesiritide and by concurrent use of ACE inhibitors and other vasodilators. In addition to causing hypotension, nesiritide can cause ventricular tachycardia (3%), headache (8%), back pain (4%), dizziness (3%), and nausea (4%). An analysis of several clinical trials suggested that nesiritide may cause renal damage.

Preparations, Dosage, and Administration.

Nesiritide [Natrecor] is available in 1.5-mg, single-use vials. The powder must be dissolved and then diluted to a final concentration of 6 mcg/mL. Dosing consists of an initial IV bolus (2 mcg/kg) followed by continuous infusion (0.01 mcg/kg/min), typically lasting 48 hours or less. If symptomatic hypotension develops, the infusion should be slowed or stopped.

CARDIAC (DIGITALIS) GLYCOSIDES

The cardiac glycosides are naturally occurring compounds that have profound effects on the mechanical and electrical properties of the heart. In addition, they have important neurohormonal effects. Because these drugs are prepared by extraction from *Digitalis purpurea* (purple foxglove) and *Digitalis lan-*

ata (Grecian foxglove), the cardiac glycosides are also known as *digitalis glycosides*.

How do cardiac glycosides help people with HF? For many decades, benefits were ascribed solely to increased myocardial contractility. It is now clear, however, that effects on neurohormonal systems are also important.

Cardiac glycosides are dangerous drugs. Why? Because, at doses close to therapeutic, they can cause severe dysrhythmias. Because of their prodysrhythmic actions, these drugs must be used with respect, caution, and skill.

In the United States, digoxin is the only cardiac glycoside available. Glycosides available in the past include digitoxin, deslanoside, and powdered digitalis leaf. For patients with HF, cardiac glycosides are now considered second-line drugs.

Digoxin

Digoxin [Lanoxin, Lanoxicaps] is indicated for HF and control of dysrhythmias (see Chapter 48). When used for HF, digoxin can reduce symptoms, increase exercise tolerance, and decrease hospitalizations. However, the drug does not prolong life. Furthermore, when used by *women,* it may actually *shorten* life (Box 47-1).

Chemistry

Digoxin consists of three components: a steroid nucleus, a lactone ring, and three molecules of digitoxose (a sugar). It is because of the sugars that digoxin is known as a glycoside. The region of the molecule composed of the steroid nucleus plus the lactone ring (ie, the region without the sugar molecules) is responsible for the pharmacologic effects of digoxin. The sugars only increase solubility.

BOX 47-1 ATTENTION LADIES: DIGOXIN MAY BE HAZARDOUS TO YOUR HEALTH

Researchers who conducted a re-analysis of older data discovered that, for *women* with heart failure, digoxin may do more harm than good. In 1997, the Digitalis Investigation Group[1] (DIG) reported the results of a large, randomized,

placebo-controlled trial designed to assess the impact of digoxin on morbidity and mortality in patients with heart failure. The study enrolled 6801 patients (men and women) with heart failure and followed them for an average of 37 months. They all took an ACE inhibitor and a diuretic; half also received digoxin and the other half received a placebo. The result? Digoxin improved symptoms and decreased hospitalizations, but did not reduce mortality. The overall death rate was 35%, regardless of whether patients took digoxin or placebo. However, the data were not analyzed for possible gender-related effects. Accordingly, in 2002, Rathore et al.* performed a retrospective analysis of the DIG data to determine whether digoxin had different effects in men and women. What did their analysis reveal? Among men, digoxin had no significant impact on mortality, mirroring the overall mortality seen in 1997. However, among *women,* digoxin produced a small, but significant *increase* in mortality: After 37 months, the death rate was 28.9% for women taking placebo compared with 33.1% for those taking digoxin—an increase of 4.2%.

Why did digoxin increase the mortality rate in women, but not in men? The answer is unknown. Theoretical possibilities include sex-based differences in autonomic function, muscle metabolism, signal transduction, or myocardial cell growth and function. However, there may be a more simple answer: In the women who died, digoxin plasma levels may have been excessive. It is well established that digoxin can be lethal at high levels. In the DIG trial, digoxin levels were measured only in randomly selected patients, and hence Rathore et al. lacked the data needed to determine whether deaths were related to high drug levels. If high digoxin levels were indeed responsible for the observed mortality increase, then the take-home message is obvious: We must keep digoxin doses low.

The Rathore et al. study suggests that, for female patients, the benefits of digoxin therapy (primarily a small [4%] decrease in the risk of hospitalization) may not justify the risk (possible drug-induced death). Until more is known, prudence dictates using digoxin in women with increased caution. As a rule, the drug should be reserved for patients who have not responded adequately to first-line medicines: ACE inhibitors or ARBs, diuretics, and beta blockers. Furthermore, digoxin levels should be kept as low as possible (0.5 to 0.8 ng/mL is a reasonable initial target). Finally, although the re-analysis underscores the potential dangers of digoxin, we mustn't forget that the drug *can* bene-

fit many patients—especially those with heart failure combined with atrial fibrillation. Accordingly, we shouldn't withhold digoxin indiscriminately. Nor should we discontinue it without careful consideration, since doing so might lead to hemodynamic decompensation.

1 The Digitalis Investigation Group: The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 336:525–533, 1997.

* Rathore SS, Wang Y, Krumholz H: Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med 347:1403–1411, 2002.

Mechanical Effects on the Heart

Digoxin exerts a *positive inotropic action* on the heart. That is, the drug *increases the force of ventricular contraction,* and can thereby increase cardiac output.

Mechanism of Inotropic Action.

Digoxin increases myocardial contractility by inhibiting an enzyme known as *sodium, potassium-ATPase* (Na^+,K^+-ATPase). By way of an indirect process described below, inhibition of Na^+,K^+-ATPase promotes calcium accumulation within myocytes. The calcium then augments contractile force by facilitating the interaction of myocardial contractile proteins: actin and myosin.

To understand how inhibition of Na^+,K^+-ATPase causes intracellular calcium to rise, we must first understand the normal role of Na^+,K^+-ATPase in myocytes. That role is illustrated in Figure 47-4. As indicated, when an action potential passes along the myocyte membrane (sarcolemma), Na^+ ions and Ca^{++} ions enter the cell, and K^+ ions exit. Once the action potential has passed, these ion fluxes must be reversed, so that the original ionic balance of the cell can be restored. Na^+,K^+-ATPase is critical to this process. As shown in Figure 47-4, Na^+,K^+-ATPase acts as a "pump" to draw extracellular K^+ ions into the cell, while simultaneously extruding intracellular Na^+. The energy required for pumping Na^+ and K^+ is provided by the breakdown of ATP—hence the name Na^+,K^+-ATPase. To complete the normalization of cellular ionic composition, Ca^{++} ions must leave the cell. Extrusion of Ca^{++} is accomplished through an exchange process in which extracellular Na^+ ions are taken into the cell while Ca^{++} ions exit. This exchange of Na^+ for Ca^{++} is a passive (energy-independent) process.

We can now answer the question, how does inhibition of Na+,K+-ATPase increase intracellular Ca++? By inhibiting Na+,K+-ATPase, digoxin prevents the myocyte from restoring its proper ionic composition following the passage of an action potential. Inhibition of Na+,K+-ATPase blocks uptake of K+ and extrusion of Na+. Hence, with each successive action potential, intracellular K+ levels decline and intracellular Na+ levels rise. It is this rise in Na+ that leads to the rise in intracellular Ca++. In the presence of excess intracellular Na+, further Na+ entry is suppressed. Since Na+ entry is suppressed, the passive exchange of Ca++ for Na+ cannot take place, and hence Ca++ accumulates within the cell.

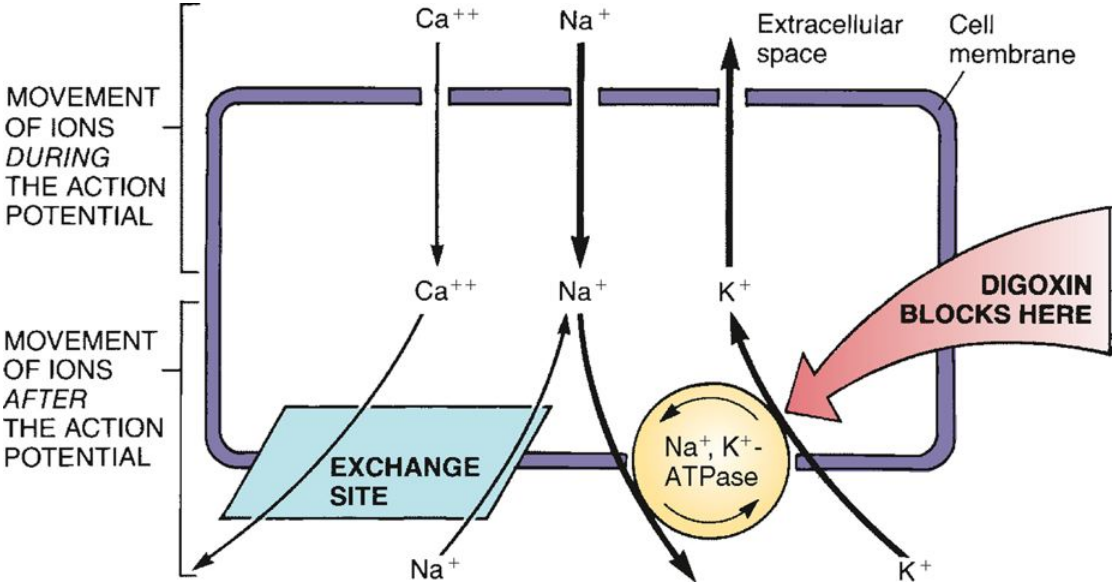

Figure 47-4 Ion fluxes across the cardiac cell membrane. During the action potential, Na+ and Ca++ enter the cardiac cell and K+ exits. Following the action potential, Na+,K+-ATPase pumps Na+ out of the cell and takes up K+. Ca++ leaves the cell in exchange for the uptake of Na+. By inhibiting Na+,K+-ATPase, digoxin prevents the extrusion of Na+, causing Na+ to accumulate inside the cell. The resulting buildup of intracellular Na+ suppresses the Na+-Ca++ exchange process, thereby causing intracellular levels of Ca++ to rise.

Relationship of Potassium to Inotropic Action.

Potassium ions compete with digoxin for binding to Na^+,K^+-ATPase. This competition is of great clinical significance. Because potassium competes with digoxin, when potassium levels are low, binding of digoxin to Na^+,K^+-ATPase increases. This increase can produce excessive inhibition of Na^+,K^+-ATPase with resultant toxicity. Conversely, when levels of potassium are high, inhibition of Na^+,K^+-ATPase by digoxin is reduced, causing a reduction in the therapeutic response. Because an increase in potassium can impair therapeutic responses, whereas a decrease in potassium can cause toxicity, it is imperative that potassium levels be kept within the normal physiologic range: 3.5 to 5 mEq/L.

Hemodynamic Benefits in Heart Failure

Increased Cardiac Output.

In patients with HF, increased myocardial contractility increases cardiac output. As shown in Figure 47-1, by increasing contractility, digoxin shifts the relationship of fiber length to stroke volume in the failing heart toward that in the healthy heart. Consequently, at any given heart size, the stroke volume of the failing heart increases, causing cardiac output to rise.

Consequences of Increased Cardiac Output.

As a result of increased cardiac output, three major secondary responses occur: (1) sympathetic tone declines, (2) urine production increases, and (3) renin release declines. These responses can reverse virtually all signs and symptoms of HF. However, they do not correct the underlying problem of cardiac remodeling.

Decreased Sympathetic Tone.

By increasing contractile force and cardiac output, digoxin increases arterial pressure. In response, sympathetic nerve traffic to the heart and blood vessels is reduced via the baroreceptor reflex. (Recall that a compensatory *increase* in sympathetic tone had taken place because of HF.)

The decrease in sympathetic tone has several beneficial effects. First, heart rate is reduced, thereby allowing more complete ventricular filling. Second, afterload is reduced (because of reduced arteriolar constriction), thereby allowing more complete ventricular emptying. Third, venous pressure is reduced (because of reduced venous constriction), thereby reducing cardiac distention, pulmonary congestion, and peripheral edema.

Increased Urine Production.

The increase in cardiac output increases renal blood flow, and thereby increases production of urine. The resultant loss of water reduces blood volume, which in turn reduces cardiac distention, pulmonary congestion, and peripheral edema.

Decreased Renin Release.

In response to increased arterial pressure, renin release declines, causing levels of aldosterone and angiotensin II to decline as well. The decrease in angiotensin II decreases vasoconstriction, thereby further reducing afterload and venous pressure. The decrease in aldosterone reduces retention of sodium and water, which reduces blood volume, which in turn further reduces venous pressure.

Summary of Hemodynamic Effects.

In summary, we can see that, through direct and indirect mechanisms, digoxin has the potential to reverse all of the overt manifestations of HF: cardiac output improves, heart rate decreases, heart size declines, constriction of arterioles and veins decreases, water retention reverses, blood volume declines, peripheral and pulmonary edema decrease, and weight is lost (owing to water loss). In addition, exercise tolerance improves and fatigue is reduced. There is, however, one important caveat: Although digoxin can produce substantial improvement in HF symptoms, it does not prolong life.

Neurohormonal Benefits in Heart Failure

At dosages below those needed for positive inotropic effects, digoxin can modulate the activity of neurohormonal systems. The underlying mechanism is inhibition of Na^+,K^+–ATPase.

In the kidney, digoxin can suppress renin release. How? By inhibiting Na^+,K^+-ATPase in renal tubules, digoxin decreases tubular absorption of sodium. As a result, less sodium is presented to the distal tubule, and hence renin release is suppressed.

Through effects on the vagus nerve, digoxin can decrease sympathetic outflow from the CNS. Specifically, by inhibiting Na^+,K^+-ATPase in vagal afferent fibers, digoxin increases the sensitivity of cardiac baroreceptors. As a result, these receptors discharge more readily, thereby signaling the CNS to reduce sympathetic traffic to the periphery.

How important are these effects on renin and sympathetic tone? No one knows for sure. However, they are probably just as important as inotropic effects, and perhaps even more important.

Electrical Effects on the Heart

The effects of digoxin on the electrical activity of the heart are of therapeutic and toxicologic importance. It is because of its electrical effects that digoxin is useful for treating dysrhythmias (see Chapter 48). Ironically, these same electrical effects are responsible for *causing* dysrhythmias, the most serious adverse effect of digoxin.

The electrical effects of digoxin can be bewildering in their complexity. Through a combination of actions, digoxin can alter the electrical activity in noncontractile tissue (sinoatrial [SA] node, atrioventricular [AV] node, Purkinje fibers) as well as in ventricular muscle. In these various regions, digoxin can alter automaticity, refractoriness, and impulse conduction. Whether these parameters are increased or decreased depends on cardiac status, digoxin dosage, and the particular region involved.

Although the electrical effects of digoxin are many and varied, only a few are clinically significant. These are discussed below.

Mechanisms for Altering Electrical Activity of the Heart.

Digoxin alters the electrical properties of the heart by *inhibiting Na^+, K^+-ATPase* and by *enhancing vagal influences on the heart*. By inhibiting Na^+,K^+-ATPase, digoxin alters the distribution of ions (Na^+, K^+, Ca^{++}) across the cardiac cell membrane. This change in ion distribution can alter the electrical responsive-

ness of the cells involved. Since hypokalemia intensifies inhibition of Na+,K+-ATPase, hypokalemia intensifies alterations in cardiac electrical properties.

Digoxin acts in two ways to enhance vagal effects on the heart. First, the drug acts in the CNS to increase the firing rate of vagal fibers that innervate the heart. Second, digoxin increases the responsiveness of the SA node to acetylcholine (the neurotransmitter released by the vagus). The net result of these vagotonic effects is (1) decreased automaticity of the SA node, and (2) decreased conduction through the AV node.

Effects on Specific Regions of the Heart.

In the SA node, digoxin decreases automaticity (by the vagotonic mechanisms just mentioned). In the AV node, digoxin decreases conduction velocity and prolongs the effective refractory period. These effects, which can promote varying degrees of AV block, result primarily from the drug's vagotonic actions. In Purkinje fibers, digoxin-induced inhibition of Na+,K+-ATPase results in increased automaticity; this increase can generate ectopic foci that, in turn, can cause ventricular dysrhythmias. In the ventricular myocardium, digoxin acts to shorten the effective refractory period and (possibly) increase automaticity.

Adverse Effects I: Cardiac Dysrhythmias

Dysrhythmias are the most serious adverse effect of digoxin. The drug causes dysrhythmias by altering the electrical properties of the heart. Fortunately, when used in the dosages recommended today, dysrhythmias are uncommon.

What kinds of dysrhythmias can occur? Digoxin can mimic practically all types of dysrhythmias. Atrioventricular block with escape beats is among the most common. Ventricular flutter and ventricular fibrillation are the most dangerous.

Because serious dysrhythmias are a potential consequence of therapy, all patients should be evaluated frequently for changes in heart rate and rhythm. If significant changes occur, digoxin should be withheld and the prescriber consulted. Outpatients should be taught to monitor their pulses and instructed to report any significant changes in rate or regularity.

Mechanism of Ventricular Dysrhythmia Generation.

Digoxin-induced ventricular dysrhythmias result from a combination of four factors:

- Decreased automaticity of the SA node
- Decreased impulse conduction through the AV node
- Spontaneous discharge of Purkinje fibers (caused in part by increased automaticity)
- Shortening of the effective refractory period in ventricular muscle

Increased Purkinje fiber discharge and shortening of the ventricular effective refractory period predispose the ventricles to developing ectopic beats. Potential ectopic beats become manifest because the effects of digoxin on the SA and AV nodes decrease the ability of the normal pacemaker to drive the ventricles, thereby allowing ventricular ectopic beats to take over.

Predisposing Factors.

Hypokalemia.

The most common cause of dysrhythmias in patients receiving digoxin is hypokalemia secondary to the use of diuretics. Less common causes include vomiting and diarrhea. Hypokalemia promotes dysrhythmias by increasing digoxin-induced inhibition of Na^+,K^+-ATPase, which in turn leads to increased automaticity of Purkinje fibers. Because low potassium can precipitate dysrhythmias, *it is imperative that serum potassium levels be kept within a normal range*. If diuretic therapy causes potassium levels to fall, a potassium-sparing diuretic (eg, spironolactone) can be prescribed to correct the problem. Potassium supplements may also be used. Patients should be taught to recognize symptoms of hypokalemia (eg, muscle weakness) and instructed to notify the prescriber if these develop.

Elevated Digoxin Levels.

Digoxin has a narrow therapeutic range: Drug levels only slightly higher than therapeutic greatly increase the risk of toxicity. Possible causes of excessive digoxin

levels include (1) intentional or accidental overdose, (2) increased digoxin absorption, and (3) decreased digoxin elimination.

If digoxin levels are kept within the optimal therapeutic range—now considered to be 0.5 to 0.8 ng/mL—the chances of a dysrhythmia will be reduced. However, it is important to note that careful control over drug levels does not eliminate the risk. As discussed above, there is only a loose relationship between digoxin levels and clinical effects. As a result, some patients may experience dysrhythmias even when drug levels are within what is normally considered the therapeutic range.

Heart Disease.

The ability of digoxin to cause dysrhythmias is greatly increased by the presence of heart disease. Doses of digoxin that have no adverse effects on healthy volunteers can precipitate serious dysrhythmias in patients with HF. The probability and severity of a dysrhythmia are directly related to the severity of the underlying disease. Since heart disease is the reason for taking digoxin, it should be no surprise that people taking the drug are at risk of dysrhythmias.

Diagnosing Digoxin-Induced Dysrhythmias.

Diagnosis is not easy. Why? Largely because the failing heart is prone to spontaneous dysrhythmias. Hence, when a dysrhythmia occurs, we cannot simply assume that digoxin is the cause: The possibility that the dysrhythmia is the direct result of heart disease must be considered. Compounding diagnostic difficulties is the poor correlation between plasma digoxin levels and dysrhythmia onset. Because of this loose association, the presence of an apparently excessive digoxin level does not necessarily indicate that digoxin is responsible for the problem. Laboratory data required for diagnosis include digoxin level, serum electrolytes, and an ECG. Ultimately, diagnosis is based on experience and clinical judgment. Resolution of the dysrhythmia following digoxin withdrawal confirms the diagnosis.

Managing Digoxin-Induced Dysrhythmias.

With proper treatment, digoxin-induced dysrhythmias can almost always be controlled. Basic management measures are as follows:

- *Withdraw digoxin and potassium-wasting diuretics.* For many patients, no additional treatment is needed. To help ensure that medication is stopped, a written order to withhold digoxin should be made.
- *Monitor serum potassium.* If the potassium level is low or nearly normal, potassium (IV or PO) should be administered. Potassium displaces digoxin from Na^+,K^+-ATPase and thereby helps reverse toxicity. However, if potassium levels are high or if AV block is present, no more potassium should be given. Under these conditions, more potassium may cause complete AV block.
- Some patients may require an antidysrhythmic drug. *Phenytoin* and *lidocaine* are most effective. Quinidine, another antidysrhythmic drug, can cause plasma levels of digoxin to rise, and hence should not be used.
- Patients who develop bradycardia or AV block can be treated with atropine. (Atropine blocks the vagal influences that underlie bradycardia and AV block.) Alternatively, electronic pacing may be employed.
- When overdose is especially severe, digoxin levels can be lowered using *Fab antibody fragments* [Digibind]. Following IV administration, these fragments bind digoxin, and thereby prevent it from acting. Treatment is expensive: A full neutralizing dose costs $2000 to $3000. *Cholestyramine* and *activated charcoal,* agents that also bind digoxin, can be administered orally to suppress absorption of digoxin from the GI tract.

Adverse Effects II: Noncardiac Adverse Effects

The principal noncardiac toxicities of digoxin concern the GI system and the CNS. Since adverse effects on these systems frequently precede development of dysrhythmias, symptoms involving the GI tract and CNS can provide advance warning of more serious toxicity. Accordingly, patients should be taught to recognize these effects and instructed to notify the prescriber if they occur.

Anorexia, nausea, and *vomiting* are the most common GI side effects. These responses result primarily from stimulation of the chemoreceptor trigger zone of the medulla. Digoxin rarely causes diarrhea.

Fatigue is the most frequent CNS effect. *Visual disturbances* (eg, blurred vision, yellow tinge to vision, appearance of halos around dark objects) are also relatively common.

Adverse Effects III: Measures to Reduce Adverse Effects

Patient education can help reduce the incidence of toxicity. Patients should be warned about digoxin-induced dysrhythmias and instructed to take their medication exactly as prescribed. In addition, they should be informed about symptoms of developing toxicity (altered heart rate or rhythm, visual or GI disturbances) and instructed to notify the prescriber if these develop. If a potassium supplement or potassium-sparing diuretic is part of the regimen, it should be taken exactly as ordered.

Drug Interactions

Digoxin is subject to a large number of significant drug interactions. Some are pharmacodynamic and some are pharmacokinetic. Several important interactions are discussed below. A summary of interactions is presented in Table 47-2.

Drug	Effect
Pharmacodynamic Interactions	
Thiazide diuretics	Promote potassium loss and thereby increase the risk of digoxin-induced dysrhythmias
Loop diuretics	
Beta blockers	Decrease contractility and heart rate
Verapamil	
Diltiazem	
Sympathomimetics	Increase contractility and heart rate
Pharmacokinetic Interactions	
Cholestyramine	Decrease digoxin levels by decreasing digoxin absorption or bioavailability
Kaolin-pectin	
Neomycin	
Sulfasalazine	
Aminoglycosides	Increase digoxin levels by increasing digoxin absorption or bioavailability
Antacids	
Colestipol	
Azithromycin	
Clarithromycin	
Erythromycin	
Omeprazole	
Tetracycline	
Alprazolam	Increase digoxin levels by decreasing excretion of digoxin, altering distribution of digoxin, or both
Amiodarone	

TABLE 47-2 Drug Interactions with Digoxin

Diuretics.

Thiazide diuretics and *loop diuretics* promote loss of potassium, and thereby increase the risk of digoxin-induced dysrhythmias. Accordingly, when digoxin and these diuretics are used concurrently, serum potassium levels must be monitored and maintained within a normal range (3.5 to 5 mEq/L). If hypokalemia develops, potassium levels can be restored with potassium supplements, a potassium-sparing diuretic, or both.

ACE Inhibitors and ARBs.

These drugs can increase potassium levels, and can thereby decrease therapeutic responses to digoxin. Exercise caution if an ACE inhibitor or ARB is combined with potassium supplements or a potassium-sparing diuretic.

Sympathomimetics.

Sympathomimetic drugs (eg, dopamine, dobutamine) act on the heart to increase the rate and force of contraction. The increase in contractile force can add to the positive inotropic effects of digoxin. These complementary actions can be beneficial. In contrast, the ability of sympathomimetics to increase heart rate may be detrimental in that the risk of a tachydysrhythmia is increased.

Quinidine.

Quinidine is an antidysrhythmic drug that can cause plasma levels of digoxin to rise. Quinidine increases digoxin levels by (1) displacing digoxin from tissue binding sites and (2) reducing the renal excretion of digoxin. By elevating levels of free digoxin, quinidine can promote digoxin toxicity. Accordingly, concurrent use of quinidine and digoxin should be avoided.

Verapamil.

Verapamil, a calcium channel blocker, can significantly increase plasma levels of digoxin. If the combination is employed, digoxin dosage must be reduced. In addition, verapamil can suppress myocardial contractility, and can thereby counteract the benefits of digoxin.

Pharmacokinetics

Absorption.

Absorption of oral digoxin can be variable. The extent of absorption is lowest and most variable with digoxin *tablets,* ranging between 60% and 80%. Absorption from digoxin capsules [Lanoxicaps]* is more complete and less variable, ranging between 90% and 100%. However, although digoxin capsules permit excellent absorption, they do have one drawback: they are much more expensive than the tablets. Hence, it may be preferable to reserve the capsules for patients in whom stable drug levels cannot be achieved with tablets.

Several factors can decrease digoxin bioavailability. For example, meals high in bran can decrease absorption significantly. Bioavailability can also be decreased by cholestyramine, kaolin-pectin, and certain other drugs (see Table 47-2). Taking digoxin with meals decreases the rate of absorption but not the extent of absorption.

In the past, there was considerable variability in the absorption of digoxin from tablets prepared by different manufacturers. This variability resulted from differences in the rate and extent of tablet dissolution. Because of this variable bioavailability, it had been recommended that patients not switch between different digoxin brands. Today, bioavailability of digoxin in tablets produced by different companies is fairly uniform, making brands of digoxin more interchangeable than in the past. However, given the narrow therapeutic range of digoxin, some authorities still recommend that patients not switch between brands of digoxin tablets—even when prescriptions are written generically—except with the approval and supervision of the prescriber.

* Digoxin capsules [Lanoxicaps] are available in Canada, but are no longer sold in the United States.

Distribution.

Digoxin is distributed widely and crosses the placenta. High levels are achieved in cardiac and skeletal muscle, owing largely to binding to Na^+,K^+-ATPase. About 23% of digoxin in plasma is bound to proteins, mainly albumin.

Elimination.

Digoxin is eliminated primarily by *renal excretion*. Hepatic metabolism is minimal. Because digoxin is eliminated by the kidneys, renal impairment can lead to toxic accumulation. Accordingly, dosage must be reduced if kidney function declines. Because digoxin is not metabolized to a significant extent, changes in liver function do not affect digoxin levels.

Half-Life and Time to Plateau.

The half-life of digoxin is about 1.5 days. Hence, in the absence of a loading dose, about 6 days (four half-lives) are required for plateau levels to be achieved. When use of the drug is discontinued, another 6 days are required for digoxin stores to be eliminated.

Single-Dose Time Course.

Effects of a single oral dose begin 30 minutes to 2 hours after administration and peak within 4 to 6 hours. Effects of IV digoxin begin rapidly (within 5 to 30 minutes) and peak in 1 to 4 hours.

A Note on Plasma Digoxin Levels.

Most hospitals are equipped to measure plasma levels of digoxin. The optimal range is 0.5 to 0.8 ng/mL. Levels above 1.0 ng/mL offer no additional benefits, but do increase the risk of toxicity. Knowledge of plasma levels can be useful for

- Establishing dosage
- Monitoring compliance
- Diagnosing toxicity
- Determining the cause of therapeutic failure

Once a stable blood level has been achieved, routine measurement of digoxin levels can be replaced with an annual measurement. Additional measurements may be useful when

- Digoxin dosage is changed
- Symptoms of HF intensify
- Kidney function deteriorates

- Signs of toxicity appear
- Drugs that can affect digoxin levels are added to or deleted from the regimen

Although knowledge of digoxin plasma levels can aid the clinician, it must be understood that the extent of this aid is limited. The correlation between plasma levels of digoxin and clinical effects—both therapeutic and adverse—is not very tight: Drug levels that are safe and effective for patient A may be subtherapeutic for patient B and toxic for patient C. Because of interpatient variability, knowledge of digoxin levels does not permit precise predictions of therapeutic effects or toxicity. Hence, information regarding drug levels must not be relied on too heavily. Rather, this information should be seen as but one factor among several to be considered when evaluating clinical responses.

Preparations, Dosage, and Administration

Preparations.

Digoxin is available in four formulations:

- Tablets—0.125 and 0.25 mg [Lanoxin]
- Pediatric elixir—0.05 mg/mL [Lanoxin]
- Solution for injection—0.1 and 0.25 mg/mL [Lanoxin]
- Capsules with digoxin in solution—0.05, 0.1, and 0.2 mg [Lanoxicaps]

Administration.

Digoxin can be administered *orally* and *intravenously. Intramuscular* administration should be avoided, owing to a risk of tissue damage and severe pain. Prior to dosing, the rate and regularity of the heartbeat should be determined. If heart rate is less than 60 beats/min or if a change in rhythm is detected, digoxin should be withheld and the prescriber notified. When digoxin is given IV, cardiac status should be monitored continuously for 1 to 2 hours.

Dosage in Heart Failure.

Most patients can be treated with initial and maintenance dosages of 0.125 mg/day. Doses above 0.25 mg/day are rarely used or needed. The target plasma drug level is 0.5 to 0.8 ng/mL.

Digitalization.

The term *digitalization* refers to the use of a loading dose to achieve high plasma levels of digoxin quickly. (As noted, 6 days are needed for drug levels to reach plateau if no loading dose is employed.) Although digitalization was common in the past, the practice is now considered both unnecessary and inappropriate.

Digitoxin

Digitoxin, no longer available in the United States, is similar to digoxin in most respects. The drugs have the same mechanism of action (inhibition of Na^+,K^+-ATPase), the same clinical applications (treatment of HF and dysrhythmias), and the same major toxicities (dysrhythmias). The principal differences between them are pharmacokinetic: Absorption of digitoxin is complete, whereas absorption of digoxin is both incomplete and variable; digitoxin is eliminated by the liver, whereas digoxin is eliminated by the kidneys; and digitoxin has a longer half-life (7 days vs. 1.6 days). Because digitoxin has a prolonged half-life, management of toxicity is much harder than with digoxin. For more information on digitoxin, refer to the fourth edition of this book.

MANAGEMENT OF HEART FAILURE

Our discussion of HF management is based on recommendations in the *ACC/AHA 2005 Guideline Update for the Evaluation and Management of Chronic Heart Failure in the Adult* and on an update—*Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults*— issued in 2009. As noted earlier, these guidelines approach HF as a progressive disease that advances through four stages of increasing severity. Management for each stage is discussed below.

These management measures are consistent with those in another guideline—*HFSA 2006 Comprehensive Heart Failure Practice Guideline*—issued by the Heart Failure Society of America. (In addition to discussing heart failure with LV systolic dysfunction [ie, the form of heart failure that we've been discussing], the HFSA guidelines address other issues, including acutely decompensated heart failure, heart failure with preserved LV ejection fraction [diastolic heart failure], and heart failure in special populations.)

Stage A

By definition, patients in ACC/AHA Stage A have no symptoms of HF and no structural or functional cardiac abnormalities—but they do have behaviors or conditions strongly associated with developing HF. Important among these are hypertension, coronary artery disease, diabetes, family history of cardiomyopathy, and a personal history of alcohol abuse, rheumatic fever, or treatment with a cardiotoxic drug (eg, doxorubicin, trastuzumab).

Management is directed at reducing risk. Hypertension, hyperlipidemia, and diabetes should be controlled, as should ventricular rate in patients with supraventricular tachycardias. An ACE inhibitor or ARB can be useful for patients with diabetes, atherosclerosis, or hypertension. Patients should cease behaviors that increase HF risk, especially smoking and alcohol abuse. (Excessive, chronic consumption of alcohol is a leading cause of cardiomyopathy. In patients with HF, acute alcohol consumption can suppress contractility.) There is no evidence that getting regular exercise can prevent development of HF, although exercise does have other health benefits. Routine use of dietary supplements to prevent structural heart disease is not recommended.

Stage B

Like patients in Stage A, those in Stage B have no signs or symptoms of HF, but they do have structural heart disease that is strongly associated with development of HF. Among these structural changes are LV hypertrophy or fibrosis, LV dilation or hypocontractility, valvular heart disease, and previous myocardial infarction.

The goal of management is to prevent development of symptomatic HF. The approach is to implement measures that can prevent further cardiac injury and thereby retard the progression of remodeling and LV dysfunction. Specific measures include all those discussed above for Stage A. In addition, treatment with an ACE inhibitor plus a beta blocker is recommended for all patients with a reduced ejection fraction, history of myocardial infarction, or both. For patients who cannot tolerate ACE inhibitors, an ARB may be used instead. As in Stage A, there is no evidence that using dietary supplements or getting regular exercise can help prevent progression to symptomatic HF.

Stage C

Patients in Stage C have symptoms of HF and also have structural heart disease. As discussed earlier, symptoms include dyspnea, fatigue, peripheral edema, and distention of the jugular veins. Treatment has four major goals: (1) relief of pulmonary and peripheral congestive symptoms, (2) improvement of functional capacity and quality of life, (3) slowing of cardiac remodeling and progression of LV dysfunction, and (4) prolongation of life. Treatment measures include those recommended for Stages A and B, plus those discussed below.

Drug Therapy

Drug therapy of HF has changed dramatically over the past 15 years. Formerly, cardiac glycosides—usually digoxin—were the mainstay of treatment. Today, their role is secondary. First-line therapy now consists of three drugs: a diuretic, an ACE inhibitor or ARB, and a beta blocker. As a rule, digoxin is added only when symptoms cannot be managed with the preferred agents.

Diuretics.

All patients with evidence of fluid retention should restrict salt intake and use a diuretic. Diuretics are the only reliable means of correcting fluid overload. Furthermore, these drugs produce symptomatic improvement faster than any other agents. If renal function is good, a thiazide diuretic will work. However, if renal function is significantly impaired, as it is in most patients, a loop diuretic will be needed. Efficacy of diuresis is best assessed by daily measurement of body weight. Once fluid overload has been corrected, diuretic therapy should continue to prevent recurrence. Diuretics should not be used alone. Rather, for most patients, they should be combined with an ACE inhibitor (or ARB) plus a beta blocker. Since aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can decrease the effects of diuretics, these agents should be avoided. As noted, although diuretics reduce symptoms, they do not prolong survival.

ACE Inhibitors and ARBs.

In the absence of specific contraindications (eg, pregnancy), all patients with Stage C HF should receive an ACE inhibitor. If fluid retention is evident, a di-

uretic should be used as well. Symptomatic improvement may take weeks or even months to develop. However, even in the absence of symptomatic improvement, ACE inhibitors may prolong life. Dosage should be sufficient to reduce mortality (see Table 47-1).

For patients who cannot tolerate ACE inhibitors (owing to intractable cough or angioedema), ARBs are considered a reasonable alternative. However, it is important to note that clinical experience with ARBs is much less than with ACE inhibitors, and that ACE inhibitors have a more favorable effect on cardiac remodeling.

Aldosterone Antagonists.

Adding an aldosterone antagonist (spironolactone or eplerenone) to standard therapy (ie, diuretic, ACE inhibitor or ARB, and a beta blocker) is reasonable in patients with moderately severe or severe symptoms of HF following a heart attack. However, aldosterone antagonists must not be used if kidney function is impaired or serum potassium is elevated. Monitoring renal function and potassium levels is imperative.

Beta Blockers.

In the absence of specific contraindications, all patients with Stage C HF should receive an approved beta blocker (eg, carvedilol). As with ACE inhibitors, symptomatic improvement may not be evident for months. Nonetheless, life may be prolonged even in the absence of clinical improvement.

Digoxin.

Digoxin may be used in combination with ACE inhibitors (or ARBs), diuretics, and beta blockers to improve clinical status. However, although digoxin can reduce symptoms, it does not prolong life. The usual dosage is 0.125 mg/day. Adjustments are based on clinical response. Digoxin may be started early to help improve symptoms, or it may be reserved for patients who have not responded adequately to a diuretic, ACE inhibitor or ARB, and beta blocker.

Isosorbide Dinitrate/Hydralazine.

Adding ISDN/hydralazine is *recommended* to improve outcomes in self- described African Americans who have moderate to severe symptoms despite

optimal therapy with ACE inhibitors, beta blockers, and diuretics. For all other patients who continue to have symptoms despite treatment with standard therapy, adding ISDN/hydralazine to the regimen is considered *reasonable*. For patients who cannot tolerate ACE inhibitors or ARBs, *substitution* of ISDN/hydralazine is considered reasonable.

Drugs to Avoid

Patients in Stage C should avoid three classes of drugs: antidysrhythmics, calcium channel blockers, and NSAIDs (eg, aspirin). Reasons for not using these drugs are:

- *Antidysrhythmic agents*—These drugs have cardiosuppressant and prodysrhythmic actions that can make HF worse. Only two agents—amiodarone [Cordarone] and dofetilide [Tikosyn]—have been proven not to reduce survival.
- *Calcium channel blockers*—These drugs can make HF worse and may increase the risk of adverse cardiovascular events. Only the vasoselective CCBs have been shown not to reduce survival.
- *NSAIDs*—These drugs promote sodium retention and peripheral vasoconstriction. Both actions can make HF worse. In addition, NSAIDs can reduce the efficacy and intensify the toxicity of diuretics and ACE inhibitors. Hence, even though aspirin has beneficial effects on coagulation, it should still be avoided.

Device Therapy

Implanted Cardioverter-Defibrillators.

Cardiac arrest and fatal ventricular dysrhythmias are relatively common complications of HF. Accordingly, implantable cardioverter-defibrillators are now recommended for primary or secondary prevention to reduce mortality in selected patients.

Cardiac Resynchronization.

When the left and right ventricles fail to contract at the same time, cardiac output is further compromised. Synchronized contractions can be restored

with a biventricular pacemaker. In clinical trials, cardiac resynchronization improved exercise tolerance and quality of life and reduced all-cause mortality.

Exercise Training

In the past, bed rest was recommended owing to concern that physical activity might accelerate progression of LV dysfunction. However, we now know that inactivity is actually detrimental: it reduces conditioning, worsens exercise intolerance, and contributes to HF symptoms. Conversely, studies have shown that exercise training can improve clinical status, increase exercise capacity, and improve quality of life. Accordingly, exercise training should be considered for all stable patients.

Evaluating Treatment

Evaluation is based on symptoms and physical findings. Reductions in dyspnea on exertion, paroxysmal nocturnal dyspnea, and orthopnea (difficulty breathing, except in the upright position) indicate success. The physical examination should assess for reductions in jugular distention, edema, and rales. Success is also indicated by increased capacity for physical activity. Accordingly, patients should be interviewed to determine improvements in the maximal activity they can perform without symptoms, the type of activity that regularly produces symptoms, and the maximal activity they can tolerate. (Activity is defined as walking, stair climbing, activities of daily living, or any other activity that is appropriate.) Successful treatment should also improve health-related quality of life in general. Hence the interview should look for improvements in sleep, sexual function, outlook on life, cognitive function (alertness, memory, concentration), and ability to participate in usual social, recreational, and work activities.

Routine measurement of ejection fraction or maximal exercise capacity is not recommended. Although the degree of reduction in ejection fraction measured at the beginning of therapy is predictive of outcome, improvement in the ejection fraction does not necessarily indicate the prognosis has changed.

Stage D

Patients in Stage D have advanced structural heart disease and marked symptoms of HF at rest, despite treatment with maximal dosages of medications used in Stage C. Repeated and prolonged hospitalization is common. For eligible candidates, the best long-term solution is a heart transplant. An implantable LV mechanical assist device can be used as a "bridge" in patients awaiting a transplant and to prolong life in those who are not transplant eligible.

Management focuses largely on control of fluid retention, which underlies most signs and symptoms. Intake and output should be monitored closely, and the patient should be weighed daily. Fluid retention can usually be treated with a loop diuretic, perhaps combined with a thiazide diuretic. If volume overload becomes severe, the patient should be hospitalized and given an IV diuretic. If needed, IV dopamine or dobutamine can be added to increase renal blood flow, thereby enhancing diuresis. Patients should not be discharged until a stable and effective oral diuretic regimen has been established.

What about beta blockers and ACE inhibitors? These agents may be tried, but doses should be low and responses monitored with care. Why? Because, in Stage D, beta blockers pose a significant risk of making HF worse, and ACE inhibitors may induce profound hypotension or renal failure.

When severe symptoms persist despite application of all recommended therapies, options for end-of-life care should be discussed with the patient and family.

KEY POINTS

- Heart failure with LV systolic dysfunction, referred to simply as *heart failure* (HF) in this chapter, is characterized by ventricular dysfunction, reduced cardiac output, signs of inadequate tissue perfusion (fatigue, shortness of breath, exercise intolerance), and signs of fluid overload (venous distention, peripheral edema, pulmonary edema).
- The initial phase of HF consists of cardiac remodeling—a process in which the ventricles dilate (grow larger), hypertrophy (increase in wall thickness), and become more spherical—coupled with cardiac fibrosis and myocyte death. As a result of these changes, cardiac output is reduced.

- Reduced cardiac output leads to compensatory responses: (1) activation of the SNS, (2) activation of the RAAS, and (3) retention of water and expansion of blood volume. As a result of volume expansion, cardiac dilation increases.
- If the compensatory responses are not sufficient to maintain adequate production of urine, body water will continue to accumulate, eventually causing death (from complete cardiac failure secondary to excessive cardiac dilation and cardiac edema).
- There are three major groups of drugs for heart failure: diuretics, ACE inhibitors or ARBs, and beta blockers. Cardiac glycosides (eg, digoxin), which had been used widely in the past, may be added as indicated.
- Diuretics are first-line drugs for all patients with fluid overload. By reducing blood volume, these drugs can decrease venous pressure, arterial pressure, pulmonary edema, peripheral edema, and cardiac dilation.
- Although diuretics can reduce symptoms of HF, they do not prolong survival.
- Thiazide diuretics are ineffective when GFR is low, and hence cannot be used if cardiac output is greatly reduced.
- Loop diuretics are effective even when GFR is low, and hence are preferred to thiazides for most patients.
- Thiazide diuretics and loop diuretics can cause hypokalemia, and can thereby increase the risk of digoxin-induced dysrhythmias.
- Potassium-sparing diuretics are used to counteract potassium loss caused by thiazide diuretics and loop diuretics.
- Potassium-sparing diuretics can cause hyperkalemia. By doing so, they can increase the risk of hyperkalemia in patients taking ACE inhibitors or ARBs.
- In patients with HF, ACE inhibitors improve functional status and reduce mortality. In the absence of specific contraindications, all patients should get one.
- ACE inhibitors block formation of angiotensin II, promote accumulation of kinins, and reduce aldosterone release. As a result, these drugs cause dilation of veins and arterioles, promote renal excretion of water, and favorably alter cardiac remodeling.

- By dilating arterioles, ACE inhibitors (1) improve regional blood flow in the kidneys and other tissues and (2) reduce cardiac afterload, which causes stroke volume and cardiac output to rise.
- By dilating veins, ACE inhibitors reduce venous pressure, which in turn reduces pulmonary congestion, peripheral edema, preload, and cardiac dilation.
- By suppressing aldosterone release, ACE inhibitors increase excretion of sodium and water, and decrease excretion of potassium.
- By increasing levels of kinins (and partly by decreasing levels of angiotensin II), ACE inhibitors can favorably alter cardiac remodeling.
- Side effects of ACE inhibitors include hypotension, hyperkalemia, cough, angioedema, and birth defects.
- ARBs share the beneficial hemodynamic effects of ACE inhibitors, but not the beneficial effects on cardiac remodeling.
- In patients with HF, ARBs should be reserved for patients intolerant of ACE inhibitors (usually owing to cough).
- In patients with HF, aldosterone antagonists (eg, spironolactone, eplerenone) reduce symptoms and prolong life. Benefits derive from blocking aldosterone receptors in the heart and blood vessels.
- Isosorbide dinitrate (which dilates veins) plus hydralazine (which dilates arterioles) can be used in place of an ACE inhibitor (or ARB) if an ACE inhibitor (or ARB) cannot be used.
- BiDil, a fixed-dose combination of hydralazine and isosorbide dinitrate, is approved specifically for treating HF in blacks.
- Beta blockers can prolong survival in patients with HF, and hence are considered first-line therapy.
- To avoid excessive cardiosuppression, beta blocker dosage must be very low initially and then gradually increased.
- Cardiac glycosides and other inotropic agents increase the force of myocardial contraction, and thereby increase cardiac output.

- Of the available inotropic agents, digoxin is the only one that is both effective and safe when used *orally,* and hence the only one suitable for long-term use.
- Digoxin increases contractility by inhibiting myocardial Na^+,K^+-ATPase, thereby (indirectly) increasing intracellular calcium, which in turn facilitates the interaction of actin and myosin.
- Potassium competes with digoxin for binding to Na^+,K^+-ATPase. Hence, if potassium levels are low, excessive inhibition of Na^+,K^+-ATPase can occur, resulting in toxicity. Conversely, if potassium levels are high, insufficient inhibition can occur, resulting in loss of therapeutic effects. Accordingly, it is imperative to keep potassium levels in the normal physiologic range: 3.5 to 5 mEq/L.
- By increasing cardiac output, digoxin can reverse all of the overt manifestations of HF: cardiac output improves, heart rate decreases, heart size declines, constriction of arterioles and veins decreases, water retention reverses, blood volume declines, peripheral and pulmonary edema decrease, weight is lost (owing to water loss), and exercise tolerance improves. Unfortunately, although digoxin can improve symptoms, it does not prolong life.
- In patients with HF, benefits of digoxin are not due solely to improved cardiac output: Neurohormonal effects are important too.
- Digoxin causes dysrhythmias by altering the electrical properties of the heart (secondary to inhibition of Na^+,K^+-ATPase).
- The most common reason for digoxin-related dysrhythmias is diuretic-induced hypokalemia.
- If a severe digoxin overdose is responsible for dysrhythmias, digoxin levels can be lowered using Fab antibody fragments [Digibind].
- In addition to dysrhythmias, digoxin can cause GI effects (anorexia, nausea, vomiting) and CNS effects (fatigue, visual disturbances). Gastrointestinal and CNS effects often precede dysrhythmias, and therefore can provide advance warning of serious toxicity.
- Digoxin has a narrow therapeutic range.
- Digoxin is eliminated by renal excretion.

- Although routine monitoring of digoxin levels is generally unnecessary, monitoring can be helpful when dosage is changed, symptoms of HF intensify, kidney function declines, signs of toxicity appear, or drugs that affect digoxin levels are added to or deleted from the regimen.
- Maintenance doses of digoxin are based primarily on observation of the patient: Doses should be large enough to minimize symptoms of HF but not so large as to cause adverse effects.
- Maintenance doses of digoxin must be reduced if renal function declines.
- Therapy of Stage C HF has four major goals: (1) relief of pulmonary and peripheral congestion, (2) improvement of functional status and quality of life, (3) retarding progression of cardiac remodeling and LV dysfunction, and (4) prolongation of life.
- For routine therapy, Stage C HF is treated with a diuretic, an ACE inhibitor or ARB, and a beta blocker

Summary of Major Nursing Implications*

DIGOXIN

Preadministration Assessment

Therapeutic Goal

Digoxin is used to treat HF and dysrhythmias. Be sure to confirm which disorder the drug has been ordered for.

Baseline Data

Assess for signs and symptoms of HF, including fatigue, weakness, cough, breathing difficulty (orthopnea, dyspnea on exertion, paroxysmal nocturnal dyspnea), jugular distention, and edema.

Determine baseline values for maximal activity without symptoms, activity that regularly causes symptoms, and maximal tolerated activity.

Laboratory tests should include an ECG, serum electrolytes, measurement of ejection fraction, and evaluation of kidney function.

Identifying High-Risk Patients

Digoxin is *contraindicated* for patients experiencing ventricular fibrillation, ventricular tachycardia, or digoxin toxicity.

Exercise *caution* in the presence of conditions that can predispose the patient to serious adverse responses to digoxin, such as hypokalemia, partial AV block, advanced HF, or renal impairment.

Implementation: Administration

Routes

Oral, slow IV injection.

Administration

Oral.

Determine heart rate and rhythm prior to administration. If heart rate is less than 60 beats/min or if a change in rhythm is detected, withhold digoxin and notify the prescriber.

Warn patients not to "double up" on doses in attempts to compensate for missed doses.

Intravenous.

Monitor cardiac status closely for 1 to 2 hours following IV injection.

Promoting Adherence

Because digoxin has a narrow therapeutic range, rigid adherence to the prescribed dosage is essential. **Inform patients that failure to take digoxin exactly as prescribed may lead to toxicity or therapeutic failure.** If poor adherence is suspected, serum drug levels may help in assessing the extent of nonadherence.

Implementation: Measures to Enhance Therapeutic Effects

Advise patients to limit salt intake to 2 gm/day, and to avoid excessive fluids. Advise patients who drink alcohol to consume no more than one drink each day. Advise obese patients to adopt a reduced-calorie diet. Help patients establish an appropriate program of regular, mild exercise (eg, walking, cycling). Precipitating factors for HF (eg, hypertension, valvular heart disease) should be corrected.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Evaluation is based on symptoms and physical findings. Assess for reductions in orthopnea, dyspnea on exertion, paroxysmal nocturnal dyspnea, neck vein distention, edema, and rales, and for increased capacity for physical activity. In addition, assess for improvements in sleep, sexual function, outlook on life, cognitive function, and ability to participate in social, recreational, and work activities.

Measurement of plasma drug levels can help determine the cause of therapeutic failure. The optimal range for digoxin is 0.5 to 0.8 ng/mL.

Minimizing Adverse Effects

Cardiotoxicity.

Dysrhythmias are the most serious adverse effect of digoxin.

Monitor hospitalized patients for alterations in heart rate or rhythm, and withhold digoxin if significant changes develop.

Inform outpatients about the danger of dysrhythmias. Teach them to monitor their pulses for rate and rhythm, and instruct them to notify the prescriber if significant changes occur. Provide the patient with an ECG rhythm strip; this can be used by providers unfamiliar with the patient (eg, when the patient is traveling) to verify suspected changes in rhythm.

Hypokalemia, usually diuretic induced, is the most frequent underlying cause of dysrhythmias. Monitor serum potassium concentrations. If hypokalemia develops, potassium levels can be raised with potassium supplements, a

potassium-sparing diuretic, or both. **Teach patients to recognize early signs of hypokalemia (eg, muscle weakness), and instruct them to notify the prescriber if these develop.** Severe vomiting and diarrhea can increase potassium loss; exercise caution if these events occur.

To treat digoxin-induced dysrhythmias: (1) withdraw digoxin and diuretics (make sure that a written order for digoxin withdrawal is made); (2) administer potassium (unless potassium levels are above normal or AV block is present); (3) administer an antidysrhythmic drug (phenytoin or lidocaine, but not quinidine) if indicated; (4) manage bradycardia with atropine or electrical pacing; and (5) treat with Fab fragments if toxicity is life threatening.

Noncardiac Effects.

Nausea, *vomiting, anorexia, fatigue,* and *visual disturbances* (blurred or yellow vision) frequently foreshadow more serious toxicity (dysrhythmias) and should be reported immediately. **Inform patients about these early indications of toxicity, and instruct them to notify the prescriber if they develop.**

Minimizing Adverse Interactions

Diuretics.

Thiazide diuretics and *loop diuretics* increase the risk of dysrhythmias by promoting potassium loss. Monitor potassium levels. If hypokalemia develops, it should be corrected with potassium supplements, a potassium-sparing diuretic, or both.

ACE Inhibitors and ARBs.

These drugs can elevate potassium levels, and can thereby decrease therapeutic responses to digoxin. Exercise caution if an ACE inhibitor or ARB is combined with potassium supplements or a potassium-sparing diuretic.

Sympathomimetic Agents.

Sympathomimetic drugs (eg, dopamine, dobutamine) stimulate the heart, thereby increasing the risk of tachydysrhythmias and ectopic pacemaker activity. When sympathomimetics are combined with digoxin, monitor closely for dysrhythmias.

Quinidine.

Quinidine can elevate plasma levels of digoxin. If quinidine is employed concurrently with digoxin, digoxin dosage must be reduced. Do not use quinidine to treat digoxin-induced dysrhythmias.

48 Antidysrhythmic Drugs

A dysrhythmia is defined as *an abnormality in the rhythm of the heartbeat*. In their mildest forms, dysrhythmias have only modest effects on cardiac output. However, in their most severe forms, dysrhythmias can so disable the heart that no blood is pumped at all. Because of their ability to compromise cardiac function, dysrhythmias are associated with a high degree of morbidity and mortality.

There are two basic types of dysrhythmias: *tachydysrhythmias* (dysrhythmias in which heart rate is increased) and *bradydysrhythmias* (dysrhythmias in which heart rate is slowed). In this chapter, we only consider the tachydysrhythmias. This is by far the largest group of dysrhythmias and the group that responds best to drugs. We do not discuss the bradydysrhythmias because they are few in number and are commonly treated with electronic pacing. When drugs are indicated, atropine (see Chapter 14) and isoproterenol (see Chapter 17) are usually the agents of choice.

It is important to appreciate that virtually all of the drugs used to treat dysrhythmias can also *cause* dysrhythmias. These drugs can create new dysrhythmias and worsen existing ones. Because of these prodysrhythmic actions, antidysrhythmic drugs should be employed only when the benefits of treatment clearly outweigh the risks.

For two reasons, use of antidysrhythmic drugs is declining. First, research has shown that some of these agents actually *increase* the risk of death. Second, nonpharmacologic therapies—especially implantable defibrillators and radiofrequency ablation—have begun to replace drugs as the preferred treatment for many dysrhythmia types.

A note on terminology: Dysrhythmias are also known as *arrhythmias*. Since the term *arrhythmia* denotes an *absence* of cardiac rhythm, whereas *dysrhythmia* denotes an *abnormal* rhythm, dysrhythmia would seem the more appropriate term.

INTRODUCTION TO CARDIAC ELECTROPHYSIOLOGY, DYSRHYTHMIAS, AND THE ANTIDYSRHYTHMIC DRUGS

In this section we discuss background information that will help you understand the actions and uses of antidysrhythmic drugs. We begin by reviewing the electrical properties of the heart and the electrocardiogram. Next, we discuss how dysrhythmias are generated. After that, we discuss classification of the antidysrhythmic drugs as well as the ability of these drugs to *cause* dysrhythmias themselves. We conclude by discussing the major dysrhythmias and the basic principles that guide antidysrhythmic therapy.

ELECTRICAL PROPERTIES OF THE HEART

Dysrhythmias result from alteration of the electrical impulses that regulate cardiac rhythm—and antidysrhythmic drugs control rhythm by correcting or compensating for these alterations. Accordingly, in order to understand both the generation and treatment of dysrhythmias, we must first understand the electrical properties of the heart. Therefore, we begin the chapter by reviewing (1) pathways and timing of impulse conduction, (2) cardiac action potentials, and (3) basic elements of the electrocardiogram (ECG).

Impulse Conduction: Pathways and Timing

For the heart to pump effectively, contraction of the atria and ventricles must be coordinated. Coordination is achieved through precise timing and routing of impulse conduction. In the healthy heart, impulses originate in the sinoatrial (SA) node, spread rapidly through the atria, pass slowly through the atrioventricular (AV) node, and then spread rapidly through the ventricles via the His-Purkinje system (Fig. 48-1).

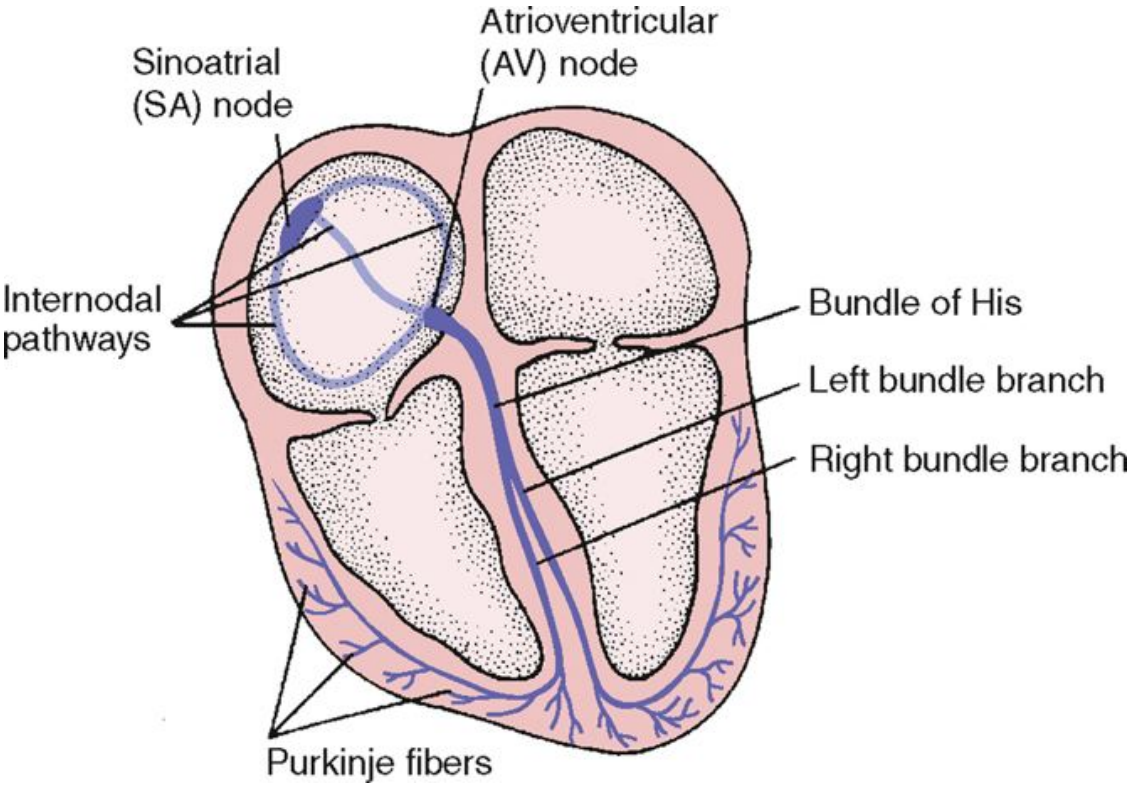

Figure 48-1 Cardiac conduction pathways.

SA Node.

Under normal circumstances, the SA node serves as the pacemaker for the heart. Pacemaker activity results from spontaneous phase 4 depolarization (see below). Because cells of the sinus node usually discharge faster than other cells that display automaticity, the SA node normally dominates all other potential pacemakers.

After the SA node discharges, impulses spread rapidly through the atria along the *internodal pathways*. This rapid conduction allows the atria to contract in unison.

AV Node.

Impulses originating in the atria must travel through the AV node to reach the ventricles. In the healthy heart, impulses arriving at the AV node are delayed

before going on to excite the ventricles. This delay provides time for blood to fill the ventricles prior to ventricular contraction.

His-Purkinje System.

The fibers of the His-Purkinje system consist of specialized conducting tissue. The function of these fibers is to conduct electrical excitation very rapidly to all parts of the ventricles. Stimulation of the His-Purkinje system is caused by impulses leaving the AV node. These impulses are conducted rapidly down the bundle of His, enter the right and left bundle branches, and then distribute to the many fine branches of the Purkinje fibers (see Fig. 48-1). Because impulses travel quickly through this system, all regions of the ventricles are stimulated almost simultaneously, producing synchronized ventricular contraction with resultant forceful ejection of blood.

Cardiac Action Potentials

Cardiac cells can initiate and conduct action potentials, consisting of self-propagating waves of depolarization followed by repolarization. As in neurons, cardiac action potentials are generated by the movement of ions into and out of cells. These ion fluxes take place by way of specific channels in the cell membrane. In the resting cardiac cell, negatively charged ions cover the inner surface of the cell membrane while positively charged ions cover the external surface. Because of this separation of charge, the cell membrane is said to be *polarized*. Under proper conditions, channels in the cell membrane open, allowing positively charged ions to rush in. This influx eliminates the charge difference across the cell membrane, and hence the cell is said to depolarize. Following depolarization, positively charged ions are extruded from the cell, causing the cell to return to its original polarized state.

In the heart, two kinds of action potentials occur: *fast potentials* and *slow potentials*. These potentials differ with respect to the mechanisms by which they are generated, the kinds of cells in which they occur, and the drugs to which they respond.

Profiles of fast and slow potentials are depicted in Figure 48-2. Please note that action potentials in this figure represent the electrical activity of *single cardiac cells*. Such single-cell recordings, which are made using experimental prepar-

ations, should not be confused with the ECG, which is made using surface electrodes, and hence reflects the electrical activity of the entire heart.

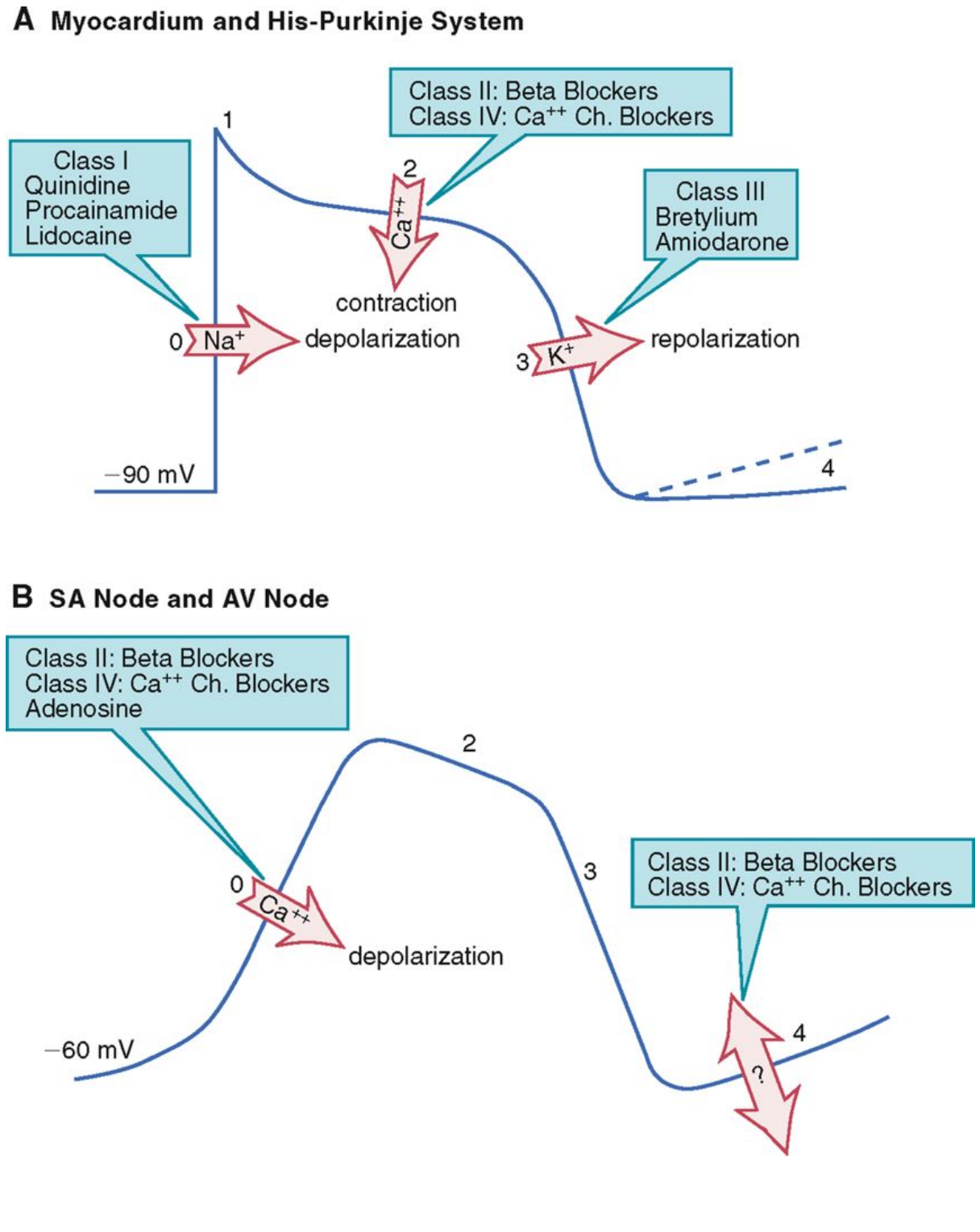
A Myocardium and His-Purkinje System
Class II: Beta Blockers
Class IV: Ca++ Ch. Blockers
Class I
Quinidine
Procainamide
Lidocaine
Class III
Bretylium
Amiodarone
1
2
Ca++
contraction
0
Na+
depolarization
3
K+
repolarization
−90 mV
4
B SA Node and AV Node
Class II: Beta Blockers
Class IV: Ca++ Ch. Blockers
Adenosine
2
0
Ca++
depolarization
3
Class II: Beta Blockers
Class IV: Ca++ Ch. Blockers
−60 mV
4
?

Figure 48-2 Ion fluxes during cardiac action potentials and effects of antidysrhythmic drugs. A, Fast potential of the His-Purkinje system and atrial and ventricular myocardium. Blockade of sodium influx by class I drugs slows conduction in the His-Purkinje system. Blockade of calcium influx by beta blockers and calcium channel blockers decreases contractility. Blockade of potassium efflux by class III drugs delays repolarization and thereby prolongs the effective refractory period. B, Slow potential of the sinoatrial (SA) node and atrioventricular (AV) node. Blockade of calcium influx by beta blockers, calcium channel blockers, and adenosine slows AV conduction. Beta blockers and calcium channel blockers decrease SA nodal automaticity (phase 4 depolarization); the ionic basis of this effect is not understood.

Fast Potentials

Fast potentials occur in fibers of the *His-Purkinje system* and in *atrial and ventricular muscle*. These responses serve to conduct electrical impulses rapidly throughout the heart.

As indicated in panel *A* of Figure 48-2, fast potentials have five distinct phases, labeled 0, 1, 2, 3, and 4. As we discuss each phase, we will focus on its ionic basis and its relationship to the actions of antidysrhythmic drugs.

Phase 0.

In phase 0, the cell undergoes *rapid depolarization* in response to *influx of sodium ions*. Phase 0 is important in that the speed of phase 0 depolarization determines the velocity of impulse conduction. Drugs that decrease the rate of phase 0 depolarization (by blocking sodium channels) slow impulse conduction though the His-Purkinje system and myocardium.

Phase 1.

During phase 1, rapid (but partial) repolarization takes place. Phase 1 has no relevance to antidysrhythmic drugs.

Phase 2.

Phase 2 consists of a prolonged plateau in which the membrane potential remains relatively stable. During this phase, *calcium* enters the cell and promotes contraction of atrial and ventricular muscle. Drugs that reduce calcium entry during phase 2 do *not* influence *cardiac rhythm*. However, since calcium influx is required for contraction, these drugs *can* reduce myocardial contractility.

Phase 3.

In phase 3, rapid repolarization takes place. This repolarization is caused by *extrusion of potassium* from the cell. Phase 3 is relevant in that delay of repolarization prolongs the action potential duration, and thereby prolongs the effective refractory period (ERP). (The ERP is the time during which a cell is unable to respond to excitation and initiate a new action potential. Hence, extending the ERP prolongs the minimum interval between two propagating responses.) Phase 3 repolarization can be delayed by drugs that block potassium channels.

Phase 4.

During phase 4, two types of electrical activity are possible: (1) the membrane potential may remain *stable* (solid line in Fig. 48-2A), or (2) the membrane may undergo *spontaneous depolarization* (dotted line). In cells undergoing spontaneous depolarization, the membrane potential gradually rises until a threshold potential is reached. At this point, rapid phase 0 depolarization takes place, setting off a new action potential. Hence, it is phase 4 depolarization that gives cardiac cells *automaticity* (ie, the ability to initiate an action potential through self-excitation). The capacity for self-excitation makes potential pacemakers of all cells that have it.

Under normal conditions, His-Purkinje cells undergo very slow spontaneous depolarization, and myocardial cells do not undergo any. However, under pathologic conditions, significant phase 4 depolarization may occur in all of these cells, and especially in Purkinje fibers. When this happens, a dysrhythmia can result.

Slow Potentials

Slow potentials occur in cells of the *SA node* and *AV node*. The profile of a slow potential is depicted in Figure 48-2*B*. Like fast potentials, slow potentials are generated by ion fluxes. However, the specific ions involved are not the same for every phase.

From a physiologic and pharmacologic perspective, slow potentials have three features of special significance: (1) phase 0 depolarization is slow and mediated by calcium influx, (2) these potentials conduct slowly, and (3) spontaneous phase 4 depolarization in the SA node normally determines heart rate.

Phase 0.

Phase 0 (depolarization phase) of slow potentials differs significantly from phase 0 of fast potentials. As we can see from Figure 48-2, whereas phase 0 of fast potentials is caused by a *rapid influx of sodium,* phase 0 of slow potentials is caused by slow *influx of calcium*. Because calcium influx is slow, the rate of depolarization is slow; and because depolarization is slow, these potentials conduct slowly. This explains why impulse conduction through the AV node is delayed. Phase 0 of the slow potential is of therapeutic significance in that drugs that suppress calcium influx during phase 0 can slow (or stop) AV conduction.

Phases 1, 2, and 3.

Slow potentials lack a phase 1 (see Fig. 48-2*B*). Phases 2 and 3 of the slow potential are not significant with respect to the actions of antidysrhythmic drugs.

Phase 4.

Cells of the SA node and AV node undergo spontaneous phase 4 depolarization. The ionic basis of this phenomenon is complex and incompletely understood.

Under normal conditions, the rate of phase 4 depolarization in cells of the SA node is faster than in all other cells of the heart. As a result, the SA node discharges first and determines heart rate. Hence, the SA node is referred to as the cardiac *pacemaker*.

As indicated in Figure 48-2*B*, two classes of drugs (beta blockers and calcium channel blockers) can suppress phase 4 depolarization. By doing so, these agents can decrease automaticity in the SA node.

The Electrocardiogram

The ECG provides a graphic representation of cardiac electrical activity. The ECG can be used to identify dysrhythmias and monitor responses to therapy. (*Note:* In referring to the electrocardiogram, two abbreviations may be used: EKG and ECG. Some people prefer EKG over ECG. Why? Because ECG sounds much like EEG [electroencephalogram] when spoken aloud.)

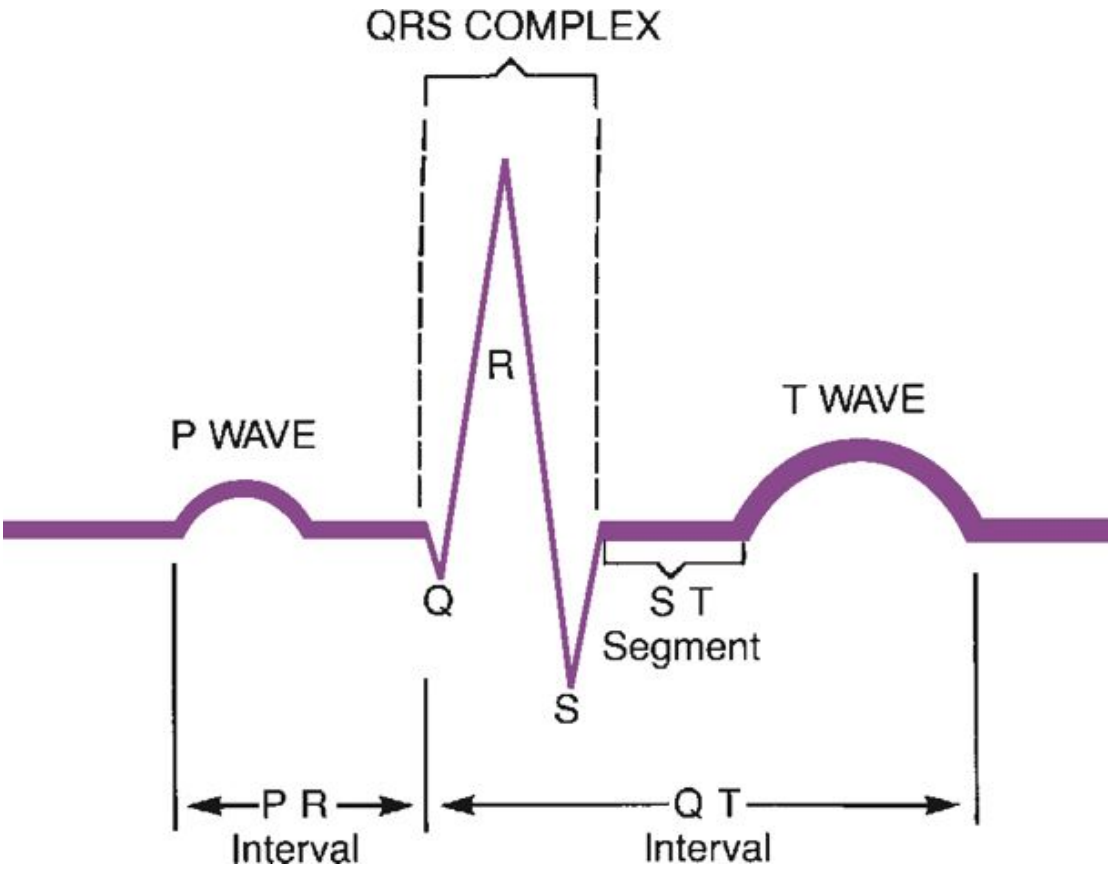

Figure 48-3 The electrocardiogram.

The major components of an ECG are illustrated in Figure 48-3. As we can see, three features are especially prominent: the P wave, the QRS complex, and the T wave. The P wave is caused by *depolarization in the atria*. Hence, the P wave corresponds to atrial contraction. The QRS complex is caused by *depolarization of the ventricles*. Hence, the QRS complex corresponds to ventricular contraction. If conduction through the ventricles is slowed, the QRS complex will

widen. The T wave is caused by *repolarization of the ventricles*. Hence, this wave is not associated with overt physical activity of the heart.

In addition to the features just described, the ECG has three other components of interest: the PR interval, the QT interval, and the ST segment. The PR interval is defined as the time between the onset of the P wave and the onset of the QRS complex. Lengthening of this interval indicates a delay in conduction through the AV node. Several drugs increase the PR interval. The QT interval is defined as the time between the onset of the QRS complex and completion of the T wave. This interval is prolonged by drugs that delay ventricular repolarization. The ST segment is the portion of the ECG that lies between the end of the QRS complex and the beginning of the T wave. Digoxin depresses the ST segment.

GENERATION OF DYSRHYTHMIAS

Dysrhythmias arise from two fundamental causes: *disturbances of impulse formation* (automaticity) and *disturbances of impulse conduction*. One or both of these disturbances underlie all dysrhythmias. Factors that may alter automaticity or conduction include hypoxia, electrolyte imbalance, cardiac surgery, reduced coronary blood flow, myocardial infarction, and antidysrhythmic drugs.

Disturbances of Automaticity

Disturbances of automaticity can occur in any area of the heart. Cells normally capable of automaticity (cells of the SA node, AV node, and His-Purkinje system) can produce dysrhythmias if their normal rate of discharge changes. In addition, dysrhythmias may be produced if tissues that do not normally express automaticity (atrial and ventricular muscle) develop spontaneous phase 4 depolarization.

Altered automaticity in the SA node can produce tachycardia or bradycardia. Excessive discharge of sympathetic neurons that innervate the SA node can augment automaticity to such a degree that sinus tachycardia results. Excessive vagal (parasympathetic) discharge can suppress automaticity to such a degree that sinus bradycardia results.

Increased automaticity of Purkinje fibers is a common cause of dysrhythmias. The increase can be brought on by injury and by excessive stimulation of Purk-

inje fibers by the sympathetic nervous system. If Purkinje fibers begin to discharge faster than the SA node, they will escape control by the SA node; potentially serious dysrhythmias may result.

Under special conditions, automaticity may develop in cells of atrial and ventricular muscle. Dysrhythmias will result if these cells begin to fire faster than the SA node.

Disturbances of Conduction

Atrioventricular Block.

Impaired conduction through the AV node produces varying degrees of AV block. If impulse conduction is delayed (but not prevented entirely), the block is termed *first degree*. If some impulses pass through the node but others do not, the block is termed *second degree*. If all traffic through the AV node stops, the block is termed *third degree*.

Reentry (Recirculating Activation).

Reentry, also referred to as recirculating activation, is a generalized mechanism by which dysrhythmias can be produced. Reentry causes dysrhythmias by establishing a localized, self-sustaining circuit capable of repetitive cardiac stimulation. Reentry results from a unique form of conduction disturbance. The mechanism of reentrant activation and the effects of drugs on this process are described below.

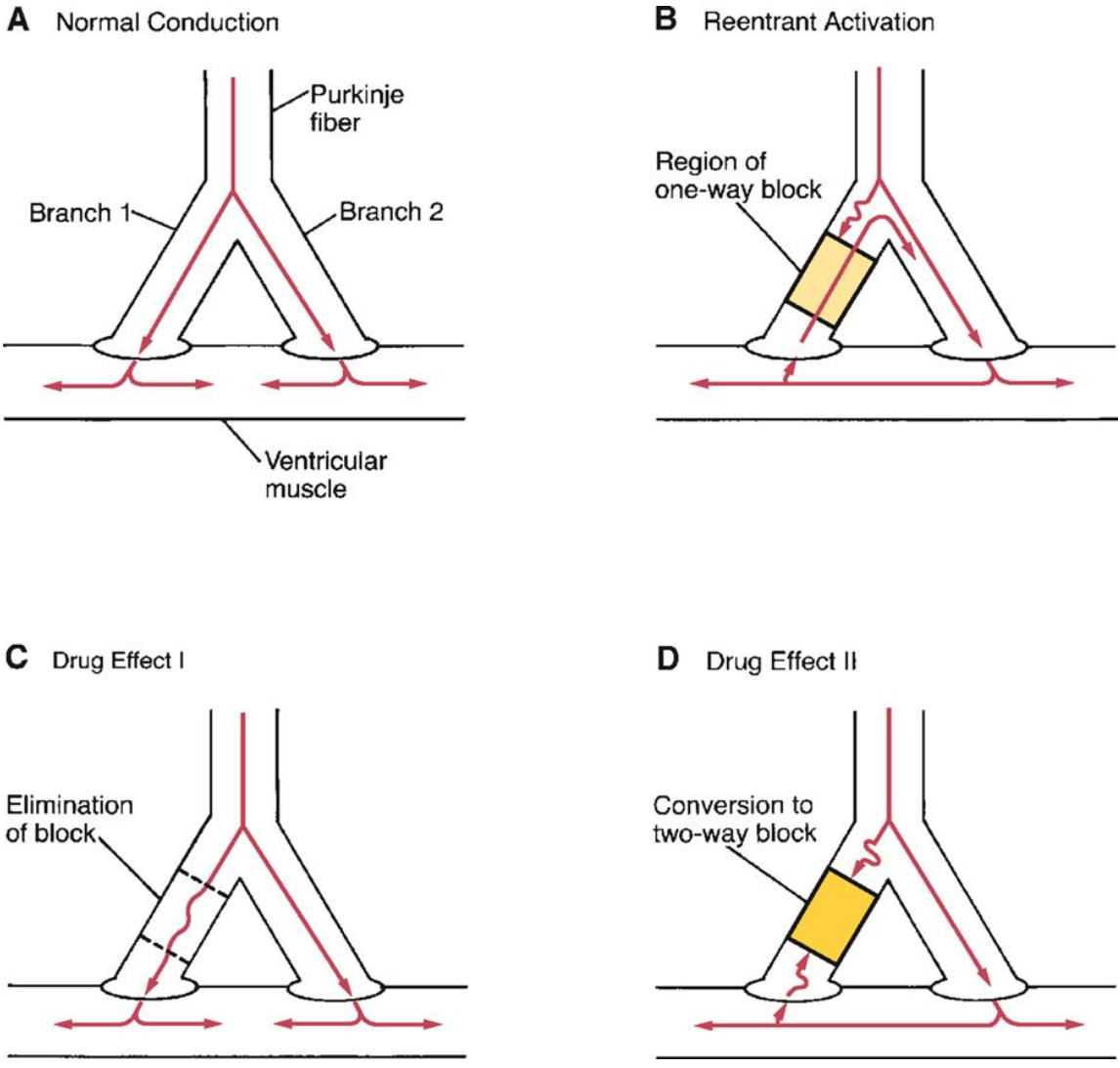

Figure 48-4 Reentrant activation: mechanism and drug effects. A, In normal conduction, impulses from the branched Purkinje fiber stimulate the strip of ventricular muscle in two places. Within the muscle, waves of excitation spread from both points of excitation, meet between the Purkinje fibers, and cease further travel. B, In the presence of one-way block, the strip of muscle is excited at only one location. Impulses spreading from this area meet no impulses coming from the left and, therefore, can travel far enough to stimulate branch 1 of the Purkinje fiber.

This stimulation passes back up the fiber, past the region of one-way block, and then stimulates branch 2, causing reentrant activation. C, Elimination of reentry by a drug that improves conduction in the sick branch of the Purkinje fiber. D, Elimination of reentry by a drug that further suppresses conduction in the sick branch, thereby converting one-way block into two-way block.

The mechanism for establishing a reentrant circuit is depicted in Figure 48-4, panels *A* and *B*. In the figure, the inverted Y-shaped structure represents a branched Purkinje fiber terminating on a strip of ventricular muscle, which appears as a horizontal bar. Normal impulse conduction is shown in Figure 48-4*A*. As indicated by the arrows, impulses travel down both branches of the Purkinje fiber to cause excitation of the muscle at two locations. Impulses created within the muscle travel in both directions (to the right and left) away from their sites of origin. Those impulses that are moving toward each other meet midway between the two branches of the Purkinje fiber. Since in the wake of both impulses the muscle is in a refractory state, neither impulse can proceed further, and hence both impulses stop.

Figure 48-4*B* depicts a reentrant circuit. The shaded area in branch 1 of the Purkinje fiber represents a region of one-way conduction block. This region prevents conduction of impulses downward (toward the muscle) but does not prevent impulses from traveling upward. (Impulses can travel back up the block because impulses in muscle are very strong, and hence are able to pass the block, whereas impulses in the Purkinje fiber are weaker, and hence are unable to pass.) A region of one-way block is essential for reentrant activation.

How does one-way block lead to reentrant activation? As an impulse travels down the Purkinje fiber, it is stopped in branch 1 but continues unimpeded in branch 2. Upon reaching the tip of branch 2, the impulse stimulates the muscle. As described above, the impulse in the muscle travels to the right and to the left away from its site of origin. However, in this new situation, as the impulse travels toward the impaired branch of the Purkinje fiber, it meets no impulse coming from the other direction, and hence continues on, resulting in stimulation of the terminal end of branch 1. This stimulation causes an impulse to travel backward up the Purkinje fiber. Since blockade of conduction is unidirectional, the impulse passes through the region of block and then back

down into branch 2, causing reentrant activation of this branch. Under proper conditions, the impulse will continue to cycle indefinitely, resulting in repetitive ectopic beats.

There are two mechanisms by which drugs can abolish a reentrant dysrhythmia. First, drugs can improve conduction in the sick branch of the Purkinje fiber, and can thereby eliminate the one-way block (Fig. 48-4*C*). Alternatively, drugs can suppress conduction in the sick branch, thereby converting one-way block into two-way block (Fig. 48-4*D*).

CLASSIFICATION OF ANTIDYSRHYTHMIC DRUGS

According to the Vaughan Williams classification scheme, the antidysrhythmic drugs fall into five groups (Table 48-1). As the table shows, there are four major classes of antidysrhythmic drugs (classes I, II, III, and IV) and a fifth group that includes adenosine and digoxin. Membership in classes I through IV is determined by effects on ion movements during slow and fast potentials (see Fig. 48-2).

Class I: Sodium Channel Blockers

Class IA

Quinidine

Procainamide [Procanbid]

Disopyramide [Norpace]

Class IB

Lidocaine [Xylocaine]

Phenytoin [Dilantin]

Mexiletine [Mexitil]

Class IC

Flecainide [Tambocor]

Propafenone [Rythmol]

Other Class I

Moricizine [Ethmozine]

Class II: Beta Blockers

Propranolol [Inderal]

Acebutolol [Sectral]

Esmolol [Brevibloc]

Class III: Potassium Channel Blockers (Drugs That Delay Repolarization)

Amiodarone [Cordarone, Pacerone]

Dofetilide [Tikosyn]

TABLE 48-1 Vaughan Williams Classification of Antidysrhythmic Drugs

Class I: Sodium Channel Blockers

Class I drugs block cardiac sodium channels (see Fig. 48-2*A*). By doing so, these drugs slow impulse conduction in the atria, ventricles, and His-Purkinje system. Class I constitutes the largest group of antidysrhythmic drugs.

Class II: Beta Blockers

Class II consists of beta-adrenergic blocking agents. As suggested by Figure 48-2, these drugs reduce calcium entry (during fast and slow potentials) and they depress phase 4 depolarization (in slow potentials only). Beta blockers have three prominent effects on the heart:

- In the SA node, they reduce automaticity.
- In the AV node, they slow conduction velocity.
- In the atria and ventricles, they reduce contractility.

Cardiac effects of the beta blockers are nearly identical to those of the calcium channel blockers.

Class III: Potassium Channel Blockers (Drugs That Delay Repolarization)

Class III drugs block potassium channels (Fig. 48-2*A*), and thereby delay repolarization of fast potentials. By delaying repolarization, these drugs prolong both the action potential duration and the effective refractory period.

Class IV: Calcium Channel Blockers

Only two calcium channel blockers—verapamil and diltiazem—are employed as antidysrhythmics. As indicated in Figure 48-2, calcium channel blockade has the same impact on cardiac action potentials as beta blockade. Accordingly, verapamil, diltiazem, and beta blockers have nearly identical effects on cardiac function—namely, reduction of automaticity in the SA node, delay of conduction through the AV node, and reduction of myocardial contractility. Antidysrhythmic benefits derive from suppressing AV nodal conduction.

Other Antidysrhythmic Drugs

Adenosine and digoxin do not fit into the four major classes of antidysrhythmic drugs. Both drugs suppress dysrhythmias by decreasing conduction through the AV node and reducing automaticity in the SA node.

PRODYSRHYTHMIC EFFECTS OF ANTIDYSRHYTHMIC DRUGS

Virtually all of the drugs used to treat dysrhythmias have prodysrhythmic (proarrhythmic) effects. That is, *all of these drugs can worsen existing dysrhythmias and generate new ones*. This ability was documented dramatically in the Cardiac Arrhythmia Suppression Trial (CAST), in which use of class IC drugs (encainide and flecainide) to prevent dysrhythmias after myocardial infarction actually *doubled the rate of mortality*. Because of their prodysrhythmic actions, antidysrhythmic drugs should be used only when dysrhythmias are symptomatically significant, and only when the potential benefits clearly outweigh the risks. Applying this guideline, it would be inappropriate to give antidysrhythmic drugs to a patient with nonsustained ventricular tachycardia, since this dysrhythmia does not significantly reduce cardiac output. Conversely, when a patient is facing death from ventricular fibrillation, any therapy that might work must be tried; in this case, the risk of prodysrhythmic effects is clearly outweighed by the potential benefits of stopping the fibrillation. Regardless of the particular circumstances of drug use, all patients must be followed closely.

Of the mechanisms by which drugs can cause dysrhythmias, one deserves special mention: prolongation of the QT interval. As discussed in Chapter 7, drugs that prolong the QT interval increase the risk of *torsades de pointes,* a dysrhythmia that can progress to fatal ventricular fibrillation. All class IA and class III agents cause QT prolongation, and hence must be used with special caution.

OVERVIEW OF COMMON DYSRHYTHMIAS AND THEIR TREATMENT

The common dysrhythmias can be divided into two major groups: *supraventricular dysrhythmias* and *ventricular dysrhythmias*. In general, ventricular dysrhythmias are more dangerous than supraventricular dysrhythmias. With

either type, intervention is required only if the dysrhythmia interferes with effective ventricular pumping. Treatment often proceeds in two phases: (1) *termination* of the dysrhythmia (with electrical countershock, drugs, or both), followed by (2) *long-term suppression* with drugs. Dysrhythmias can also be treated with an implantable cardioverter-defibrillator or by destroying small areas of cardiac tissue using radiofrequency (RF) catheter ablation.

It is important to appreciate that drug therapy of dysrhythmias is highly empiric (ie, based largely on the response of the patient and not on scientific principles). In practice, this means that, even after a dysrhythmia has been identified, we cannot predict with certainty just which drugs will be effective. Frequently, trials with several drugs are required before control of rhythm is achieved. In the discussion below, only first-choice drugs are considered.

Supraventricular Dysrhythmias

Supraventricular dysrhythmias are dysrhythmias that arise in areas of the heart above the ventricles (atria, SA node, AV node). Supraventricular dysrhythmias per se are not especially harmful. Why? Because dysrhythmic activity within the atria does not significantly reduce cardiac output (except in patients with valvular disorders and heart failure). Supraventricular tachydysrhythmias *can* be dangerous, however, in that atrial impulses are likely to traverse the AV node, resulting in excitation of the ventricles. If the atria drive the ventricles at an excessive rate, diastolic filling will be incomplete and cardiac output will decline. Hence, when treating supraventricular tachydysrhythmias, the objective is frequently one of slowing ventricular rate (by blocking impulse conduction through the AV node) and not elimination of the dysrhythmia itself. Of course, if treatment did abolish the dysrhythmia, this outcome would not be unwelcome. Acute treatment of supraventricular dysrhythmias is accomplished with vagotonic maneuvers, direct-current (DC) cardioversion, and certain drugs: class II agents, class IV agents, adenosine, and digoxin.

Atrial Fibrillation.

Atrial fibrillation is the most common sustained dysrhythmia, affecting about 2 million people in the United States. The disorder is caused by multiple atrial ectopic foci firing randomly; each focus stimulates a small area of atrial

muscle. This chaotic excitation produces a highly irregular atrial rhythm. Depending upon the extent of impulse transmission through the AV node, ventricular rate may be very rapid or nearly normal.

In addition to compromising cardiac performance, atrial fibrillation carries a high risk of stroke. Why? Because in patients with atrial fibrillation, some blood can become trapped in the atria (rather than flowing straight through to the ventricles), thereby permitting formation of a clot. When normal sinus rhythm is restored, the clot may become dislodged, and then may travel to the brain to cause stroke.

Treatment of atrial fibrillation has two goals: improvement of ventricular pumping and prevention of stroke. Pumping can be improved by either (1) restoring normal sinus rhythm or (2) slowing ventricular rate. The preferred method is to slow ventricular rate. How? By *long-term* therapy with a beta blocker (atenolol or metoprolol) or cardioselective calcium channel blocker (diltiazem or verapamil)—drugs that impede conduction through the AV node. If episodes of atrial fibrillation are infrequent (eg, less than 12 a year), they can be managed with PRN flecainide or propafenone. This so-called pill-in-the-pocket approach is analogous to treating infrequent attacks of angina with sublingual nitroglycerin. For patients who elect to restore normal rhythm, options are DC cardioversion, short-term treatment with drugs (eg, amiodarone, sotalol), or RF ablation of the dysrhythmia source.

To prevent stroke, most patients should be treated with warfarin. For those taking a drug long term to control ventricular rate, warfarin must be taken long term too. For those undergoing treatment to restore normal sinus rhythm, warfarin should be taken for 3 to 4 weeks prior to the procedure and for several weeks after.

Atrial Flutter.

Atrial flutter is caused by an ectopic atrial focus discharging at a rate of 250 to 350 times a minute. Ventricular rate is considerably slower, however, because the AV node is unable to transmit impulses at such a high rate. Typically, one atrial impulse out of two reaches the ventricles. The treatment of choice is DC cardioversion, which almost always converts atrial flutter to normal sinus rhythm. Cardioversion may also be achieved with IV ibutilide. To

prevent the dysrhythmia from recurring, patients may need long-term therapy with drugs—either a class IC agent (flecainide or propafenone) or a class III agent (amiodarone, sotalol, dofetilide).

There are two alternatives to cardioversion: (1) RF ablation of the dysrhythmia focus and (2) control of ventricular rate with drugs. As with atrial fibrillation, ventricular rate is controlled with drugs that suppress AV conduction: verapamil, diltiazem, or a beta blocker.

Like atrial fibrillation, atrial flutter poses a risk of stroke, which can be reduced by treatment with warfarin.

Sustained Supraventricular Tachycardia (SVT).

Sustained SVT is usually caused by an AV nodal reentrant circuit. Heart rate is increased to 150 to 250 beats/min. SVT often responds to interventions that increase vagal tone, such as carotid sinus massage or the Valsalva maneuver. If these are ineffective, an IV beta blocker or calcium channel blocker can be tried. With these drugs, ventricular rate will be slowed even if the dysrhythmia persists. Once the dysrhythmia has been controlled, beta blockers and/or calcium channel blockers can be taken orally to prevent recurrence. As a last resort, amiodarone can be used for prevention.

Ventricular Dysrhythmias

In contrast to atrial dysrhythmias, which are generally benign, ventricular dysrhythmias can cause significant disruption of cardiac pumping. Accordingly, the usual objective is to abolish the dysrhythmia. Cardioversion is often the treatment of choice. When antidysrhythmic drugs are indicated, agents in class I or class III are usually employed.

Sustained Ventricular Tachycardia.

Ventricular tachycardia arises from a single, rapidly firing ventricular ectopic focus, typically located at the border of an old infarction. The focus drives the ventricles at a rate of 150 to 250 beats/min. Since the ventricles cannot pump effectively at these rates, immediate treatment is required. Cardioversion is the treatment of choice. If cardioversion fails to normalize rhythm, IV amiodarone should be administered; lidocaine and procainamide are alternatives.

For long-term management, drugs (eg, sotalol, amiodarone) or an implantable cardioverter-defibrillator (ICD) may be employed.

Ventricular Fibrillation.

Ventricular fibrillation is a life-threatening emergency that requires immediate treatment. This dysrhythmia results from the asynchronous discharge of multiple ventricular ectopic foci. Because many different foci are firing, and because each focus initiates contraction in its immediate vicinity, localized twitching takes place all over the ventricles, making coordinated ventricular contraction impossible. As a result, the pumping action of the heart stops. In the absence of blood flow, the patient becomes unconscious and cyanotic. If heartbeat is not restored rapidly, death soon follows. Electrical countershock (defibrillation) is applied to eliminate fibrillation and restore cardiac function. If necessary, IV lidocaine can be used to enhance the effects of defibrillation. Procainamide and bretylium may also be helpful. Amiodarone can be used for long-term suppression. As an alternative, an ICD may be employed.

Ventricular Premature Beats (VPBs).

VPBs are beats that occur before they should in the cardiac cycle. These beats are caused by ectopic ventricular foci. VPBs may arise from a single ectopic focus or from several foci. In the absence of additional signs of heart disease, VPBs are benign and not usually treated. However, in the presence of acute myocardial infarction, VPBs may predispose the patient to ventricular fibrillation. In this case, therapy is required. A beta blocker is the agent of choice. Because VPBs are associated with a premature QRS complex on the ECG, this dysrhythmia is also known as *premature ventricular complexes*.

Digoxin-Induced Ventricular Dysrhythmias.

Digoxin toxicity can mimic practically all types of dysrhythmias. Varying degrees of AV block are among the most common. Ventricular flutter and ventricular fibrillation are the most dangerous. Digoxin causes dysrhythmias by increasing automaticity in the atria, ventricles, and His-Purkinje system, and by decreasing conduction through the AV node.

With proper treatment, digoxin-induced dysrhythmias can almost always be controlled. Treatment is discussed at length in Chapter 47. If antidysrhythmic

drugs are required, lidocaine and phenytoin are the agents of choice. In patients with digoxin toxicity, DC cardioversion may bring on ventricular fibrillation. Accordingly, this procedure should be used only when absolutely required.

Torsades de Pointes.

Torsades de pointes is an atypical, rapid, undulating ventricular tachydysrhythmia that can evolve into potentially fatal ventricular fibrillation. The main factor associated with development of torsades de pointes is prolongation of the QT interval, which can be caused by a variety of drugs (see Table 7-2 in Chapter 7), including class IA and class III antidysrhythmic agents. Acute management consists of IV magnesium plus cardioversion for sustained ventricular tachycardia.

PRINCIPLES OF ANTIDYSRHYTHMIC DRUG THERAPY

Balancing Risks and Benefits

Therapy with antidysrhythmic drugs is based on a simple but important concept: Treat only if there is a clear benefit—and then only if the benefit outweighs the risks. As a rule, this means that intervention is needed only when the dysrhythmia interferes with ventricular pumping.

Treatment offers two potential benefits: reduction of symptoms and reduction of mortality. Symptoms that can be reduced include palpitations, angina, dyspnea, and faintness. For most antidysrhythmic drugs, there is little or no evidence of reduced mortality. In fact, mortality may actually increase.

Antidysrhythmic therapy carries considerable risk. Because of their *prodysrhythmic actions,* antidysrhythmic drugs can exacerbate existing dysrhythmias and generate new ones. Examples abound: toxic doses of digoxin can generate a wide variety of dysrhythmias; drugs that prolong the QT interval can cause torsades de pointes; many drugs can cause ventricular ectopic beats; several drugs (quinidine, encainide, flecainide, propafenone) can cause atrial flutter; and two drugs—encainide and flecainide—can produce incessant ventricular tachycardia. Because of their prodysrhythmic actions, antidysrhythmic drugs can *increase mortality*. Other adverse effects include heart failure and third-degree AV block (caused by calcium channel blockers and beta blockers), as well

as many noncardiac effects, including severe diarrhea (quinidine), a lupus-like syndrome (procainamide), and pulmonary toxicity (amiodarone).

Properties of the Dysrhythmia to Be Considered

Sustained Versus Nonsustained Dysrhythmias.

As a rule, nonsustained dysrhythmias require intervention only when they are symptomatic; in the absence of symptoms, treatment is usually unnecessary. In contrast, sustained dysrhythmias can be dangerous; hence, the benefits of treatment generally outweigh the risks.

Asymptomatic Versus Symptomatic Dysrhythmias.

No study has demonstrated a benefit to treating dysrhythmias that are asymptomatic or minimally symptomatic. In contrast, therapy may be beneficial for dysrhythmias that produce symptoms (palpitations, angina, dyspnea, faintness).

Supraventricular Versus Ventricular Dysrhythmias.

Supraventricular dysrhythmias are generally benign. The primary harm comes from driving the ventricles too rapidly to allow adequate filling. The goal of treatment is to either (1) terminate the dysrhythmia or (2) prevent excessive atrial beats from reaching the ventricles (using a beta blocker, calcium channel blocker, or digoxin). In contrast to supraventricular dysrhythmias, ventricular dysrhythmias frequently interfere with pumping. Accordingly, the goal of treatment is to terminate the dysrhythmia and prevent its recurrence.

Phases of Treatment

Treatment has two phases: acute and long term. The goal of acute treatment is to terminate the dysrhythmia. For many dysrhythmias, termination is accomplished with DC cardioversion (electrical countershock) or vagotonic maneuvers (eg, carotid sinus massage), rather than drugs. The goal of long-term therapy is to prevent dysrhythmias from recurring. Quite often, the risks of long-term prophylactic therapy outweigh the benefits.

Long-Term Treatment: Drug Selection and Evaluation

Selecting a drug for long-term therapy is largely empiric. There are many drugs that might be employed, and we usually can't predict which one is going to work. Hence, finding an effective drug is done by trial and error.

Drug selection can be aided with electrophysiologic testing. In these tests, a dysrhythmia is generated artificially by programmed electrical stimulation of the heart. If a candidate drug is able to suppress the electrophysiologically induced dysrhythmia, it may also work against the real thing.

Holter monitoring can be used to evaluate treatment. A Holter monitor is a portable ECG device that is worn by the patient around-the-clock. If Holter monitoring indicates that dysrhythmias are still occurring with the present drug, a different drug should be tried.

Minimizing Risks

Several measures can help minimize risk. These include

- Starting with low doses and increasing them gradually.
- Using a Holter monitor during initial therapy to detect danger signs—especially QT prolongation, which can precede torsades de pointes.
- Monitoring plasma drug levels. Unfortunately, although drug levels can be good predictors of noncardiac toxicity (eg, quinidine-induced nausea), they are less helpful for predicting adverse cardiac effects.

PHARMACOLOGY OF THE ANTIDYSRHYTHMIC DRUGS

A discussed above, the antidysrhythmic drugs fall in to four main groups—classes I, II, III, and IV—plus a fifth group that includes adenosine and digoxin. The pharmacology of these drugs is presented below, and summarized in Table 48-2.

Drug	Usual Route	Effects on the ECG	Major Antidysrhythmic Applications
Class IA			
Quinidine	PO	Widens QRS, prolongs QT	Broad spectrum: used for long-term suppression of ventricular and supraventricular dysrhythmias
Procainamide	PO	Widens QRS, prolongs QT	Broad spectrum: similar to quinidine, but toxicity makes it less desirable for long-term use
Disopyramide	PO	Widens QRS, prolongs QT	Ventricular dysrhythmias
Class IB			
Lidocaine	IV	No significant change	Ventricular dysrhythmias
Mexiletine	PO	No significant change	Ventricular dysrhythmias
Phenytoin	PO	No significant change	Digoxin-induced ventricular dysrhythmias
Class IC			
Flecainide	PO	Widens QRS, prolongs PR	Maintenance therapy of supraventricular dysrhythmias
Propafenone	PO	Widens QRS, prolongs PR	Maintenance therapy of supraventricular dysrhythmias
Other Class I			
Moricizine	PO	Widens QRS, prolongs PR	Life-threatening ventricular dysrhythmias
Class II			
Propranolol	PO	Prolongs PR, bradycardia	Dysrhythmias caused by excessive sympathetic activity; control of ventricular rate in patients with supraventricular tachydysrhythmias

TABLE 48-2 Properties of Antidysrhythmic Drugs

CLASS I: SODIUM CHANNEL BLOCKERS

Class I antidysrhythmic drugs block cardiac sodium channels. By doing so, they decrease conduction velocity in the atria, ventricles, and His-Purkinje system.

There are three subgroups of class I agents. Drugs in all three groups block sodium channels. In addition, class IA agents delay repolarization, whereas class IB agents accelerate repolarization. Class IC agents have pronounced prodysrhythmic actions.

The class I drugs are similar in action and structure to the local anesthetics. In fact, one of these drugs—lidocaine—has both local anesthetic and antidysrhythmic applications. Because of their relationship to the local anesthetics, class I agents are sometimes referred to as *local anesthetic antidysrhythmic agents*.

Class IA Agents

Quinidine

Quinidine is the oldest and most thoroughly studied of the class IA drugs. Accordingly, quinidine will serve as our prototype for the group. Quinidine is the most frequently used oral antidysrhythmic agent. Like other antidysrhythmic drugs, quinidine has prodysrhythmic actions.

Chemistry and Source.

Quinidine is similar to quinine in structure and actions. The natural source of both drugs is the bark of the South American cinchona tree. Accordingly, these agents are referred to as *cinchona alkaloids*. Like quinine, quinidine has antimalarial and antipyretic properties.

Effects on the Heart.

By blocking sodium channels, quinidine *slows impulse conduction* in the atria, ventricles, and His-Purkinje system. In addition, the drug *delays repolarization* at these sites, apparently by blocking potassium channels. Both actions contribute to suppression of dysrhythmias.

Quinidine is strongly *anticholinergic* (atropine-like) and blocks vagal input to the heart. The resultant *increase* in SA nodal automaticity and AV conduction can drive the ventricles at an excessive rate. To prevent excessive ventricular stimulation, patients are usually pretreated with digoxin, verapamil, or a beta blocker, all of which suppress AV conduction.

Effects on the ECG.

Quinidine has two pronounced effects on the ECG. The drug *widens the QRS complex* (by slowing depolarization of the ventricles) and *prolongs the QT interval* (by delaying ventricular repolarization).

Therapeutic Uses.

Quinidine is a broad-spectrum agent active against *supraventricular* and *ventricular dysrhythmias*. The drug's principal indication is long-term suppression of dysrhythmias, including SVT, atrial flutter, atrial fibrillation, and sustained ventricular tachycardia. To prevent quinidine from increasing ventricular rate, patients are usually pretreated with an AV nodal blocking agent (digoxin, verapamil, beta blocker). An analysis of older studies indicates that quinidine may actually *increase* mortality in patients with *atrial flutter* and *atrial fibrillation*.

In addition to its antidysrhythmic applications, quinidine is a drug of choice for severe *malaria* (see Chapter 97).

Pharmacokinetics.

Quinidine is rapidly absorbed following oral administration. Peak responses to *quinidine sulfate* develop in 30 to 90 minutes; responses to *quinidine gluconate* develop more slowly, peaking after 3 to 4 hours. Elimination is by hepatic metabolism. Accordingly, patients with liver impairment may require a reduction in dosage. Therapeutic plasma levels are 2 to 5 mcg/mL.

Adverse Effects.

Diarrhea.

Diarrhea and other GI symptoms develop in about 33% of patients. These reactions can be immediate and intense, frequently forcing discontinuation of treatment. Gastric upset can be reduced by administering quinidine with food.

Cinchonism.

Cinchonism is characterized by tinnitus (ringing in the ears), headache, nausea, vertigo, and disturbed vision. These symptoms can develop with just one dose.

Cardiotoxicity.

At high concentrations, quinidine can cause severe cardiotoxicity (sinus arrest, AV block, ventricular tachydysrhythmias, asystole). These reactions occur secondary to increased automaticity of Purkinje fibers and reduced conduction throughout all regions of the heart.

As cardiotoxicity develops, the ECG changes. Important danger signals are *widening of the QRS complex* (by 50% or more) and *excessive prolongation of the QT interval*. The prescriber should be notified immediately if these changes occur.

Arterial Embolism.

Embolism is a potential complication of treating atrial *fibrillation*. During atrial fibrillation, thrombi may form in the atria. When sinus rhythm is restored, these thrombi may be dislodged and cause embolism. To reduce the risk of embolism, warfarin (an anticoagulant) is given for 3 to 4 weeks prior to quinidine, and is maintained for an additional 4 weeks. Signs of embolism (eg, sudden chest pain, dyspnea) should be reported immediately.

Other Adverse Effects.

Quinidine can cause alpha-adrenergic blockade, resulting in vasodilation and subsequent *hypotension*. This reaction is much more serious with IV therapy than with oral therapy. Rarely, quinidine has caused *hypersensitivity reactions,* including fever, anaphylactic reactions, and thrombocytopenia.

Drug Interactions.

Digoxin. Quinidine can double digoxin levels. The increase is caused by displacing digoxin from plasma albumin and by decreasing digoxin elimination. When these drugs are used concurrently, digoxin dosage must be reduced. Also, patients should be monitored closely for digoxin toxicity (dysrhythmias). Because of its interaction with digoxin, quinidine is a last-choice drug for treating digoxin-induced dysrhythmias.

Other Interactions.

Because of its anticholinergic actions, quinidine can intensify the effects of other atropine-like drugs; one possible result is excessive tachycardia. Phenobarbital, phenytoin, and other drugs that induce hepatic drug metabolism can shorten the half-life of quinidine by as much as 50%. Quinidine can intensify the effects of warfarin by a mechanism that is not known.

Preparations, Dosage, and Administration.

Preparations.

Quinidine is available as two salts: *quinidine sulfate* and *quinidine gluconate*. Because these salts have different molecular weights, equal doses (on a milligram basis) do not provide equal amounts of quinidine. A 200-mg dose of quinidine sulfate is equivalent to 275 mg of quinidine gluconate. Quinidine sulfate is available in immediate-release tablets (200 and 300 mg) and sustained-release tablets (300 mg). Quinidine gluconate is available in sustained-release tablets (324 mg) and in solution (80 mg/mL) for parenteral use.

Dosage.

The usual dosage of quinidine sulfate is 200 to 400 mg every 4 to 6 hours. The usual dosage of quinidine gluconate is 324 to 648 mg every 8 to 12 hours. Dosage is adjusted to produce plasma quinidine levels between 2 and 5 mcg/mL.

Administration.

Quinidine is almost always administered by mouth. If time permits, a small test dose (200 mg PO or IM) should be given prior to the full therapeutic dose to assess for hypersensitivity. Intramuscular administration is painful

and produces erratic absorption. Intravenous injection carries a high risk of adverse cardiovascular reactions, and hence continuous cardiovascular monitoring is required.

Procainamide

Procainamide [Procanbid] is similar to quinidine in actions and uses. Like quinidine, procainamide is active against a broad spectrum of dysrhythmias. Unfortunately, serious side effects frequently limit its use.

Effects on the Heart and ECG.

Like quinidine, procainamide blocks cardiac sodium channels, thereby decreasing conduction velocity in the atria, ventricles, and His-Purkinje system. Also, the drug delays repolarization. In contrast to quinidine, procainamide is only weakly anticholinergic, and hence is not likely to increase ventricular rate. Effects on the ECG are the same as with quinidine: widening of the QRS complex and prolongation of the QT interval.

Therapeutic Uses.

Procainamide is effective against a broad spectrum of atrial and ventricular dysrhythmias. Like quinidine, the drug can be used for long-term suppression. However, since prolonged therapy is often associated with serious adverse effects, procainamide is less desirable than quinidine for long-term use. In contrast to quinidine, procainamide can be used to terminate ventricular tachycardia and ventricular fibrillation.

Pharmacokinetics.

Routes are oral, IV, and IM. Peak plasma levels develop 1 hour after oral dosing. Procainamide has a short half-life and requires more frequent dosing than quinidine.

Elimination is by hepatic metabolism and renal excretion. The major metabolite—*N*-acetylprocainamide (NAPA)—has antidysrhythmic properties of its own. NAPA is excreted by the kidneys and can accumulate to toxic levels in patients with renal impairment.

Adverse Effects.

Systemic Lupus Erythematosus–like Syndrome. Prolonged treatment with procainamide is associated with severe immunologic reactions. Within a year, about 70% of patients develop antinuclear antibodies (ANAs)—antibodies directed against the patient's own nucleic acids. If procainamide is continued, between 20% and 30% of patients with ANAs go on to develop symptoms resembling those of systemic lupus erythematosus (SLE). These symptoms include pain and inflammation of the joints, pericarditis, fever, and hepatomegaly. When procainamide is withdrawn, symptoms usually slowly subside. If the patient has a life-threatening dysrhythmia for which no alternative drug is available, procainamide can be continued and the symptoms of SLE controlled with a nonsteroidal anti-inflammatory drug (eg, aspirin) or a glucocorticoid. All patients taking procainamide chronically should be tested for ANAs. If the ANA titer rises, discontinuing treatment should be considered.

Blood Dyscrasias.

About 0.5% of patients develop blood dyscrasias, including neutropenia, thrombocytopenia, and agranulocytosis. Fatalities have occurred. These reactions usually develop during the first 12 weeks of treatment. Complete blood counts should be obtained weekly during this time and periodically thereafter. Also, complete blood counts should be obtained promptly at the first sign of infection, bruising, or bleeding. If blood counts indicate bone marrow suppression, procainamide should be withdrawn. Hematologic status usually returns to baseline within 1 month.

Cardiotoxicity.

Procainamide has cardiotoxic actions like those of quinidine. Danger signs are QRS widening (more than 50%) and excessive QT prolongation. If these develop, the drug should be withheld and the prescriber informed.

Other Adverse Effects.

Like quinidine, procainamide can cause *GI symptoms* and *hypotension*. However, these are much less prominent than with quinidine. Procainamide is a derivative of procaine (a local anesthetic), and patients with a history of procaine allergy are at high risk of having an *allergic response* to procainamide. As with quinidine, *arterial embolism* may occur during treatment of atrial fibrillation.

Preparations, Dosage, and Administration.

Oral.

Procainamide is available in capsules (250, 375, and 500 mg) and sustained-release tablets (250, 500, 750, and 1000 mg). The usual maintenance dosage is 50 mg/kg/day in divided doses. The capsules are administered every 3 to 4 hours and the sustained-release tablets every 6 hours (or every 12 hours for *Procanbid* tablets). Dosage is adjusted to maintain plasma drug levels between 4 and 10 mcg/mL.

Parenteral.

Procainamide solution (500 mg/mL) is available for IM and IV administration. Intramuscular injection is made deep into the gluteal muscle; dosage is 0.5 to 1 gm repeated every 4 to 8 hours.

Intravenous infusion may be performed at an initial rate of 20 mg/min (maximal loading dose is 500 to 600 mg). After the loading period, an infusion rate of 2 to 6 mg/min should be employed. Once the dysrhythmia has been controlled, the patient should be switched to oral procainamide. Three hours should elapse between terminating the infusion and the first oral dose.

Disopyramide

Disopyramide [Norpace] is a class I drug with actions like those of quinidine. However, because of prominent side effects, indications for disopyramide are limited.

Effects on the Heart and ECG.

Cardiac effects are similar to those of quinidine. By blocking sodium channels, disopyramide decreases conduction velocity in the atria, ventricles, and His-Purkinje system. In addition, the drug delays repolarization. Anticholinergic actions are greater than those of quinidine. In contrast to quinidine, disopyramide causes a pronounced reduction in contractility. Like quinidine, disopyramide widens the QRS complex and prolongs the QT interval.

Adverse Effects.

Anticholinergic responses are most common. These include dry mouth, blurred vision, constipation, and urinary hesitancy or retention. Urinary retention frequently requires discontinuation of treatment.

Because of its negative inotropic effects, disopyramide can cause *severe hypotension* (secondary to reduced cardiac output) and can *exacerbate heart failure* (HF). The drug should not be administered to patients with HF or to patients taking a beta blocker. Whenever disopyramide is used, pressor drugs should be immediately available.

Therapeutic Uses.

Disopyramide is indicated only for ventricular dysrhythmias (VPBs, ventricular tachycardia, ventricular fibrillation). The drug is reserved for patients who cannot tolerate safer medications (eg, quinidine, procainamide).

Preparations, Dosage, and Administration.

Disopyramide [Norpace] is available in immediate- and extended-release capsules (100 and 150 mg). An initial loading dose (200 to 300 mg) is followed by maintenance doses (100 to 200 mg) every 6 hours.

Class IB Agents

As a group, class IB agents differ from quinidine and the other class IA agents in two respects: (1) whereas class IA agents *delay* repolarization, class IB agents *accelerate* repolarization; and (2) class IB agents have little or no effect on the ECG.

Lidocaine

Lidocaine [Xylocaine], an intravenous agent, is used only for ventricular dysrhythmias. In addition to its antidysrhythmic applications, lidocaine is employed as a local anesthetic (see Chapter 26).

Effects on the Heart and ECG.

Lidocaine has three significant effects on the heart: (1) like other class I drugs, lidocaine blocks cardiac sodium channels and thereby *slows conduction* in the atria, ventricles, and His-Purkinje system; (2) the drug *reduces automaticity* in

the ventricles and His-Purkinje system by a mechanism that is poorly understood; and (3) lidocaine *accelerates repolarization* (shortens the action potential duration and ERP). In contrast to quinidine and procainamide, lidocaine is devoid of anticholinergic properties. Also, lidocaine has no significant impact on the ECG: A small reduction in the QT interval may occur, but there is no QRS widening.

Pharmacokinetics.

Lidocaine undergoes rapid hepatic metabolism. If the drug were administered orally, most of each dose would be inactivated on its first pass through the liver. For this reason, administration is by IV infusion.

Because lidocaine is rapidly degraded, plasma drug levels can be easily controlled: If levels climb too high, the infusion can be slowed and the liver will quickly remove excess drug from the circulation. The therapeutic range for lidocaine is 1.5 to 5 mcg/mL.

Antidysrhythmic Use.

Antidysrhythmic use of lidocaine is limited to short-term therapy of *ventricular dysrhythmias*. Lidocaine is not active against supraventricular dysrhythmias.

Adverse Effects.

Lidocaine is generally well tolerated. However, adverse central nervous system (CNS) effects can occur. High therapeutic doses can cause *drowsiness, confusion,* and *paresthesias*. Toxic doses may produce *convulsions* and *respiratory arrest*. Consequently, whenever lidocaine is used, equipment for resuscitation must be available. Convulsions can be managed with diazepam or phenytoin.

Preparations, Dosage, and Administration.

Administration is parenteral only. The usual route is IV. Intramuscular injection can be used in emergencies. Blood pressure and the ECG should be monitored for signs of toxicity.

Intravenous.

Lidocaine [Xylocaine] preparations intended for IV administration are clearly labeled as such. They contain no preservatives or catecholamines. (Lidocaine used for local anesthesia frequently contains epinephrine.) *Preparations that contain epinephrine or another catecholamine must never be administered IV, since doing so can cause severe hypertension and life-threatening dysrhythmias*.

Intravenous therapy is initiated with a loading dose followed by continuous infusion for maintenance. The usual loading dose is 50 to 100 mg (1 mg/kg) administered at a rate of 25 to 50 mg/min. An infusion rate of 1 to 4 mg/min is used for maintenance; the rate is adjusted on the basis of cardiac response. Intravenous lidocaine should be discontinued as soon as possible, usually within 24 hours. Lidocaine for IV administration is supplied in concentrated and dilute formulations. The concentrated formulations must be diluted with 5% dextrose in water.

To avoid toxicity, dosage should be reduced in patients with impaired hepatic function or impaired hepatic blood flow (eg, elderly patients; patients with cirrhosis, shock, or HF).

Intramuscular.

Lidocaine is available in an automatic injection device [LidoPen Auto-Injector] for IM administration. A dose of 300 mg is injected into the deltoid muscle. This dose can be repeated in 60 to 90 minutes if necessary. The patient should be switched to IV lidocaine as soon as possible.

Phenytoin

Phenytoin [Dilantin] is an antiseizure drug that is also used to treat digoxin-induced dysrhythmias. The basic pharmacology of phenytoin is presented in Chapter 24 (Drugs for Epilepsy). Discussion here is limited to antidysrhythmic applications.

Effects on the Heart and ECG.

Like lidocaine, phenytoin reduces automaticity (especially in the ventricles), and has little or no effect on the ECG. In contrast to lidocaine (and practically all other antidysrhythmic agents), phenytoin increases AV nodal conduction.

Pharmacokinetics.

Phenytoin has two unfortunate kinetics properties. First, metabolism of the drug is subject to wide interpatient variation. Second, doses only slightly greater than therapeutic are likely to cause toxicity. Because of these characteristics, maintenance of therapeutic plasma levels (5 to 20 mcg/mL) is difficult.

Adverse Effects and Interactions.

The most common adverse reactions are sedation, ataxia, and nystagmus. With too-rapid IV administration, phenytoin can cause hypotension, dysrhythmias, and cardiac arrest. Gingival hyperplasia is a frequent complication of long-term treatment. Phenytoin is subject to multiple undesirable drug interactions (see Chapter 24).

Antidysrhythmic Applications.

Phenytoin has been used to treat digoxin-induced dysrhythmias and for acute and chronic suppression of ventricular dysrhythmias. The ability of phenytoin to increase AV nodal conduction can help counteract the reduction in AV conduction caused by digoxin intoxication. Phenytoin should not be used to treat atrial fibrillation or atrial flutter. Why? Because enhanced AV conduction could increase the number of atrial impulses reaching the ventricles, thereby driving the ventricles at an excessive rate.

Dosage and Administration.

Phenytoin [Dilantin] can be given PO or IV. For PO therapy, a loading dose (14 mg/kg) is followed by daily maintenance doses (200 to 400 mg).

Intravenous administration is reserved for severe, acute dysrhythmias. Blood pressure and the ECG must be monitored continuously. Phenytoin is not soluble in water and must be diluted in the medium supplied by the manufacturer. This medium is highly alkaline (pH 12) and will cause phlebitis if given by continuous infusion. Consequently, administration is by intermittent injections. Intravenous injections must be performed slowly (50 mg/min or less), since rapid injection can cause cardiovascular collapse. Treatment is begun with a series of loading doses (50 to 100 mg every 5 minutes until the dys-

rhythmia has been controlled or until toxicity appears). Maintenance dosages range from 200 to 400 mg/day.

Mexiletine

Mexiletine [Mexitil] is an oral analog of lidocaine used for symptomatic ventricular dysrhythmias. Principal indications are VPBs and sustained ventricular tachycardia. Like lidocaine, mexiletine does not alter the ECG. The drug is eliminated by hepatic metabolism, and hence effects may be prolonged in patients with liver disease or reduced hepatic blood flow. The most common adverse effects are GI (nausea, vomiting, diarrhea, constipation) and neurologic (tremor, dizziness, sleep disturbances, psychosis, convulsions). About 40% of patients find these intolerable. Like other class I agents, mexiletine has prodysrhythmic properties. The initial dosage is 100 to 200 mg every 8 hours. The maintenance dosage is 100 to 300 mg every 6 to 12 hours. All doses should be taken with food.

Mexiletine is also used to alleviate persistent pain of diabetic neuropathy. Benefits derive from lidocaine-like anesthetic actions. Because mexiletine can *cause* dysrhythmias, it should not be used by diabetic patients with heart disease.

Class IC Agents

Class IC antidysrhythmics block cardiac sodium channels and thereby reduce conduction velocity in the atria, ventricles, and His-Purkinje system. In addition, these drugs delay ventricular repolarization, causing a small increase in the effective refractory period. All class IC agents can exacerbate existing dysrhythmias and create new ones. Currently, only two class IC agents are available: flecainide and propafenone.

Flecainide

Flecainide [Tambocor] is active against a variety of ventricular and supraventricular dysrhythmias. However, use is restricted largely to maintenance therapy of supraventricular dysrhythmias. Like other class IC agents, flecainide decreases cardiac conduction and increases the effective refractory period. Prominent effects on the ECG are prolongation of the PR interval and widening of the QRS complex. Excessive QRS widening indicates a need for dosage

reduction. Flecainide has prodysrhythmic effects. As a result, the drug can intensify existing dysrhythmias and provoke new ones. In patients with asymptomatic ventricular tachycardia associated with acute myocardial infarction, flecainide has caused a twofold increase in mortality. Flecainide decreases myocardial contractility and can thereby exacerbate or precipitate heart failure. Accordingly, the drug should not be combined with other agents that can decrease contractile force (eg, beta blockers, verapamil, diltiazem). Elimination is by hepatic metabolism and renal excretion. Dosage is low initially (100 mg every 12 hours) and then gradually increased to a maximum of 400 mg/day. Because of its potential for serious side effects, flecainide should be reserved for severe ventricular dysrhythmias that have not responded to safer drugs. Patients should be monitored closely.

Propafenone

Propafenone [Rythmol] is similar to flecainide in actions and uses. By blocking cardiac sodium channels, the drug decreases conduction velocity in the atria, ventricles, and His-Purkinje system. In addition, it causes a small increase in the ventricular ERP. Prominent effects on the ECG are QRS widening and PR prolongation. Like flecainide, propafenone has prodysrhythmic actions that can exacerbate existing dysrhythmias and create new ones. It is not known if propafenone, like flecainide, increases mortality in patients with asymptomatic ventricular dysrhythmias after myocardial infarction. Propafenone has beta-adrenergic blocking properties and can thereby decrease myocardial contractility and promote bronchospasm. Accordingly, the drug should be used with caution in patients with heart failure, AV block, or asthma. Noncardiac adverse effects are generally mild and include dizziness, altered taste, blurred vision, and GI symptoms (abdominal discomfort, anorexia, nausea, vomiting). Because of its prodysrhythmic actions, propafenone should be reserved for patients who have not responded to safer drugs. Propafenone is available in immediate-release tablets (150, 225, and 300 mg) and extended-release capsules (225, 325, and 425 mg). For the immediate-release tablets, the dosage is 150 mg every 8 hours initially, and can be gradually increased to 300 mg every 8 hours.

Other Class I: Moricizine

Moricizine [Ethmozine] is a class I antidysrhythmic drug approved for oral therapy of life-threatening ventricular dysrhythmias. This agent shares properties with other class I drugs but doesn't quite fit any of the existing subclasses (IA, IB, and IC). Like other class I agents, moricizine blocks cardiac sodium channels and thereby decreases conduction velocity in the atria, ventricles, and His-Purkinje system. Prominent effects on the ECG are QRS widening and PR prolongation. The most common adverse effects are dizziness, nausea, and headache. Like other antidysrhythmic drugs, moricizine is prodysrhythmic. In addition, moricizine can cause bradycardia, AV heart block, and heart failure. Interactions with digoxin, diuretics, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and warfarin have not been reported. Because of its potential for adverse cardiac effects, moricizine should be reserved for life-threatening ventricular dysrhythmias that have not responded to safer drugs. Moricizine is available in 200-, 250-, and 300-mg tablets. The dosage is 200 mg every 8 hours initially, and may be gradually increased to a maximum of 300 mg every 8 hours.

CLASS II: BETA BLOCKERS

Class II consists of beta-adrenergic blocking agents. At this time only four beta blockers—propranolol, acebutolol, esmolol, and sotalol—are approved for treating dysrhythmias. One of these drugs—sotalol—also blocks potassium channels, and hence is discussed under class III. The basic pharmacology of the beta blockers is presented in Chapter 18. Discussion here is limited to their antidysrhythmic use.

Propranolol

Propranolol [Inderal] is considered a nonselective beta-adrenergic antagonist, in that it blocks both beta*1*- and beta*2*-adrenergic receptors. As discussed in Chapter 18, beta*1* blockade affects the heart and beta*2* blockade affects the bronchi.

Effects on the Heart and ECG.

Blockade of cardiac beta*1* receptors attenuates sympathetic stimulation of the heart. The result is (1) decreased automaticity of the SA node, (2) decreased velocity of conduction through the AV node, and (3) decreased myocardial

contractility. The reduction in AV conduction velocity translates to a prolonged PR interval on the ECG.

It is worth noting that cardiac beta*1* receptors are functionally coupled to calcium channels, and that beta*1* blockade causes these channels to close. Hence, the effects of beta blockers on heart rate, AV conduction, and contractility all result from decreased calcium influx. Because beta blockers and calcium channel blockers both decrease calcium entry, the cardiac effects of these drugs are very similar.

Therapeutic Use.

Propranolol is especially useful for treating dysrhythmias caused by excessive sympathetic stimulation of the heart. Among these are sinus tachycardia, severe recurrent ventricular tachycardia, exercise-induced tachydysrhythmias, and paroxysmal atrial tachycardia provoked by emotion or exercise. In patients with supraventricular tachydysrhythmias, propranolol has two beneficial effects: (1) suppression of excessive discharge of the SA node, and (2) slowing of ventricular rate by decreasing transmission of atrial impulses through the AV node.

Adverse Effects.

Beta blockers are generally well tolerated. Principal adverse effects concern the heart and bronchi. By blocking cardiac beta*1* receptors, propranolol can cause *heart failure, AV block*, and *sinus arrest*. Hypotension can occur secondary to reduced cardiac output. In patients with asthma, blocking beta*2* receptors in the lung can cause *bronchospasm*. Because of its cardiac and pulmonary effects, propranolol is contraindicated for patients with asthma, sinus bradycardia, high-degree heart block, and heart failure.

Dosage and Administration.

Propranolol can be administered orally and, in life-threatening emergencies, by IV injection. Dosages with either route show wide individual variation. Oral dosages range from 10 to 80 mg every 6 to 8 hours. The usual IV dose is 1 to 3 mg injected at a rate of 1 mg/min.

Acebutolol

Acebutolol [Sectral] is a cardioselective beta blocker approved for oral therapy of VPBs. Adverse effects are like those of propranolol: bradycardia, heart failure, AV block, and—despite cardioselectivity—bronchospasm. Accordingly, acebutolol is contraindicated for patients with heart failure, severe bradycardia, AV block, and asthma. Acebutolol can also cause adverse immunologic reactions; titers of antinuclear antibodies may rise, resulting in myalgia, arthralgia, and arthritis. For suppression of VPBs, the initial dosage is 200 mg twice daily. Usual maintenance dosages range from 600 to 1200 mg/day.

Esmolol

Esmolol [Brevibloc] is a cardioselective beta blocker with a very short half-life (9 minutes). Administration is by IV infusion. The drug is employed for immediate control of ventricular rate in patients with atrial flutter and atrial fibrillation. Use is short term only (eg, in patients with dysrhythmias associated with surgery). The most common adverse reaction is hypotension. However, like other beta blockers, esmolol can also cause bradycardia, heart block, heart failure, and bronchospasm (at higher doses). In addition, pain can occur at the infusion site. Esmolol is available in two concentrations: 10 mg/mL and 250 mg/mL. *The concentrated formulation must be diluted prior to use*. Treatment is begun with a loading dose of 500 mcg/kg infused over 1 minute. The usual maintenance infusion rate is 100 mcg/kg/min.

CLASS III: POTASSIUM CHANNEL BLOCKERS (DRUGS THAT DELAY REPOLARIZATION)

Five class III antidysrhythmics are available: bretylium, amiodarone, dofetilide, ibutilide, and sotalol (which is also a beta blocker). All five delay repolarization of fast potentials. Hence, all five prolong the action potential duration and ERP. By doing so, they prolong the QT interval. In addition, each drug can affect the heart in other ways, and hence they are not interchangeable.

Bretylium

Bretylium is used only for short-term therapy of severe ventricular dysrhythmias. The drug's principal adverse effect is profound hypotension.

Effects on the Heart and ECG.

Therapeutic effects result from blocking potassium channels in Purkinje fibers and ventricular muscle (see Fig. 48-2A). By doing so, bretylium delays repolarization and thereby prolongs both the action potential duration and ERP. Because ventricular repolarization is delayed, the QT interval is prolonged.

When first administered, bretylium is taken up by sympathetic neurons, where it causes a transient increase in catecholamine release, followed by blockade of further release. In the heart, the initial increase in release can briefly exacerbate dysrhythmias. In blood vessels, extended blockade of release produces hypotension.

Adverse Effects.

Profound and persistent hypotension is the most troubling side effect. This reaction is common, occurring in up to 66% of patients. Blood pressure may fall in patients who are supine as well as in those who are standing. Hypotension results from blockade of norepinephrine release in sympathetic neurons that promote contraction of vascular smooth muscle. Continuous monitoring of blood pressure is required. If hypotension develops, blood pressure may be raised with dopamine or norepinephrine.

Therapeutic Use.

Bretylium is indicated for short-term therapy of ventricular fibrillation and recurrent ventricular tachycardia in patients who have been refractory to more conventional therapy (cardioversion, amiodarone). For these patients, bretylium may be lifesaving.

Preparations, Dosage, and Administration.

Bretylium is supplied in solution (2, 4, and 50 mg/mL). The drug must be diluted for certain applications. In all cases, the ECG and blood pressure should be monitored continuously.

Intravenous.

For nonemergency treatment, bretylium is administered by slow IV infusion. Rapid injection is reserved for emergencies. To manage ventricular fibrilla-

tion, the following protocol may be employed: (1) rapid IV injection of a 5-mg/kg dose, (2) rapid IV injection of additional doses (10 mg/kg) until the dysrhythmia has been controlled, and (3) slow IV infusion of maintenance doses (5 to 10 mg/kg) every 6 hours. (Maintenance doses are infused slowly because rapid administration results in nausea and vomiting. Initial doses are injected rapidly, despite the risk of nausea and vomiting, because of the need for rapid control of rhythm.)

Intramuscular.

Bretylium is used undiluted for IM injection. The initial dose is 5 to 10 mg/kg. Dosing may be repeated every 6 to 8 hours. The injection site should be rotated.

Amiodarone

Amiodarone [Cordarone, Pacerone] is a class III antidysrhythmic agent that has complex effects on the heart. The drug is highly effective against both atrial and ventricular dysrhythmias. Unfortunately, serious toxicities (eg, lung damage, visual impairment) are common, and may persist for months after treatment has stopped. Because of toxicity, amiodarone is *approved* only for life-threatening ventricular dysrhythmias that have been refractory to safer agents. Nonetheless, because of its efficacy, amiodarone is one of our most frequently prescribed antidysrhythmic drugs, used for atrial and ventricular dysrhythmias alike.

Amiodarone is available for oral and IV use. Indications, electrophysiologic effects, time course of action, and adverse effects differ for each route. Accordingly, oral and IV therapy are discussed separately.

Oral Therapy

Therapeutic Use.

Although amiodarone is very effective, concerns about toxicity limit its indications. In the United States, oral amiodarone is approved only for long-term therapy of two life-threatening ventricular dysrhythmias: *recurrent ventricular fibrillation* and *recurrent hemodynamically unstable ventricular tachycardia*. Treatment should be reserved for patients who have not responded to safer drugs.

In addition to its approved uses, oral amiodarone has been used with success to convert *atrial fibrillation* to normal sinus rhythm, and to maintain normal sinus rhythm following conversion.

Effects on the Heart and ECG.

Amiodarone has complex effects on the heart. Like bretylium, amiodarone delays repolarization, and thereby prolongs the action potential duration and ERP. The underlying cause of these effects may be blockade of potassium channels. Additional cardiac effects include reduced automaticity in the SA node, reduced contractility, and reduced conduction velocity in the AV node, ventricles, and His-Purkinje system. These occur secondary to blockade of sodium channels, calcium channels, and beta receptors. Prominent effects on the ECG are QRS widening and prolongation of the PR and QT intervals. Amiodarone also acts on coronary and peripheral blood vessels to promote dilation.

Pharmacokinetics.

Amiodarone is highly lipid soluble and accumulates in many tissues, especially the liver and lungs. The drug is metabolized in the liver by CYP3A4 (the 3A4 isozyme of cytochrome P450) followed by excretion in the bile. Amiodarone has an extremely long half-life, ranging from 25 to 110 days. Because of its slow elimination, amiodarone continues to act long after dosing has ceased.

Adverse Effects.

Amiodarone produces many serious adverse effects. Furthermore, because the drug's half-life is protracted, toxicity can continue for weeks or months after drug withdrawal. To reduce adverse events, the Food and Drug Administration requires that all patients using amiodarone be given a Medication Guide describing potential toxicities.

Pulmonary Toxicity.

Lung damage—hypersensitivity pneumonitis, interstitial/alveolar pneumonitis, pulmonary fibrosis—is the greatest concern. Symptoms (dyspnea, cough, chest pain) resemble those of heart failure and pneumonia. Pulmonary toxicity develops in 2% to 17% of patients and carries a 10% risk of mortality. Patients at highest risk are those receiving long-term, high-dose therapy. A

baseline chest x-ray and pulmonary function test are required. Pulmonary function should be monitored throughout treatment.

Cardiotoxicity.

Amiodarone may cause a paradoxical increase in dysrhythmic activity. In addition, by suppressing the SA and AV nodes, the drug can cause sinus bradycardia and AV block. By reducing contractility, amiodarone can precipitate heart failure.

Toxicity in Pregnancy and Breast-feeding.

Amiodarone crosses the placental barrier and enters breast milk, and can thereby harm the developing fetus and breast-feeding infant. Accordingly, pregnancy and breast-feeding should be avoided while using the drug and for several months after stopping it.

Other Adverse Effects.

Virtually all patients develop *corneal microdeposits,* which may cause photophobia or blurred vision. *Optic neuropathy,* sometimes progressing to *blindness,* may also occur. Between 2% and 5% of patients experience *blue-gray discoloration of the skin. Gastrointestinal reactions* (anorexia, nausea, vomiting) are common. Possible *CNS reactions* include ataxia, dizziness, tremor, mood alteration, and hallucinations. *Hepatitis* and *thyroid dysfunction* (hypothyroidism, hyperthyroidism) have occurred, and hence all patients should undergo periodic tests of liver and thyroid function.

Drug Interactions.

Amiodarone is subject to significant interactions with many drug. The result can be toxicity or reduced therapeutic effects. Accordingly, combined use with these drugs should be avoided. When it cannot, the patient should be monitored closely. Interactions of concern include the following:

- Amiodarone can *increase* levels of several drugs, including quinidine, procainamide, phenytoin, digoxin, diltiazem, warfarin, cyclosporine, and three statins: lovastatin, simvastatin, and atorvastatin. Dosages of these agents often require reduction.

- Amiodarone levels can be *increased* by grapefruit juice and by inhibitors of CYP3A4. Toxicity can result.
- Amiodarone levels can be *reduced* by cholestyramine (which decreases amiodarone absorption) and by agents that induce CYP3A4 (eg, St. John's wort, rifampin).
- The risk of severe dysrhythmias is increased by diuretics (because they can reduce levels of potassium and magnesium) and by drugs that prolong the QT interval, of which there are many (see Chapter 7, Table 7-2).
- Combining amiodarone with a beta blocker, verapamil, or diltiazem can lead to excessive slowing of heart rate.

Dosage.

Oral amiodarone [Pacerone, Cordarone] is available in 100-, 200- and 400-mg tablets. Treatment should be initiated in a hospital. The following schedule is used for loading: 800 to 1600 mg daily for 1 to 3 weeks followed by 600 to 800 mg daily for 4 weeks. The daily maintenance dosage is 100 to 400 mg.

Intravenous Therapy

Therapeutic Use.

Intravenous amiodarone is approved only for initial treatment and prophylaxis of recurrent ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to safer drugs. For these indications, amiodarone may be more effective than IV bretylium.

In addition to its approved uses, IV amiodarone has been used with success against other dysrhythmias, including atrial fibrillation, AV nodal reentrant tachycardia, and shock-resistant ventricular fibrillation.

Effects on the Heart and ECG.

In contrast to oral amiodarone, which affects multiple aspects of cardiac function, IV amiodarone affects primarily the AV node. Specifically, the drug slows AV conduction and prolongs AV refractoriness. Both effects probably result from antiadrenergic actions. The mechanism underlying antidysrhythmic effects is unknown.

Adverse Effects.

The most common adverse effects are hypotension and bradydysrhythmias. Hypotension develops in 15% to 20% of patients, and may require discontinuation of treatment. Bradycardia or AV block occurs in 5% of patients; discontinuation of treatment or insertion of a pacemaker may be needed. Infused concentrations above 3 mg/mL (in 5% dextrose in water) produce a high incidence of phlebitis, and hence should be administered through a central venous catheter. Torsades de pointes in association with QT prolongation occurs rarely.

Dosage.

Dosing is complex. During the first 24 hours, a total dose of 1050 mg is infused. After that, a maintenance infusion (0.5 mg/min) is given around the clock. The usual duration of treatment is 2 to 4 days. However, maintenance infusions may be continued for up to 3 weeks before switching to oral amiodarone.

Sotalol

Actions and Uses.

Sotalol [Betapace] is a beta blocker that also delays repolarization. Hence, the drug has combined class II and class III properties. Prodysrhythmic properties are pronounced. Sotalol was initially approved only for ventricular dysrhythmias, such as sustained ventricular tachycardia, that are considered life threatening. In 1999, it was also approved for prophylaxis and treatment of atrial flutter and fibrillation, but only if symptoms are severe. The drug is not approved for hypertension or angina pectoris (the primary indications for other beta blockers).

Pharmacokinetics.

Sotalol is administered orally and undergoes nearly complete absorption. The drug is excreted unchanged in the urine. Its half-life is 12 hours.

Adverse Effects.

The major adverse effect is torsades de pointes, a serious dysrhythmia that develops in about 5% of patients. Risk is increased by hypokalemia and by other drugs that prolong the QT interval.

At therapeutic doses, sotalol produces substantial beta blockade. Hence, it can cause bradycardia, AV block, heart failure, and bronchospasm. Accordingly, the usual contraindications to beta blockers apply.

Preparations, Dosage, and Administration.

Sotalol is available in tablets (80, 120, 160, and 240 mg) for oral use. Treatment should start in a hospital. The initial dosage is 80 mg twice daily. The usual maintenance dosage is 160 to 320 mg/day in two or three divided doses. The dosing interval should be increased in patients with renal impairment.

Dofetilide

Therapeutic Use.

Dofetilide [Tikosyn] is an oral class III antidysrhythmic indicated for restoring and maintaining normal sinus rhythm in patients with atrial flutter or atrial fibrillation. The drug causes dose-related QT prolongation and thereby poses a serious risk of torsades de pointes. Accordingly, it should be reserved for patients with highly symptomatic atrial dysrhythmias. Initial treatment requires continuous ECG monitoring in a hospital. Dosage must be carefully titrated on the basis of renal function tests. Dofetilide is available only through authorized hospitals and prescribers.

Effects on the Heart and ECG.

Like other class III agents, dofetilide blocks cardiac potassium channels, and thereby delays repolarization, and hence prolongs the QT interval on the ECG. Dofetilide does not affect the PR interval or widen the QRS complex, and has no effect on cardiac beta receptors or sodium channels.

Pharmacokinetics.

Dofetilide is well absorbed (90%) both in the presence and absence of food. Very little is metabolized. About 80% of each dose is excreted in the urine, primarily unchanged. Renal excretion results largely from active tubular se-

cretion, mediated by *cationic pumps* (ie, pumps specific for molecules that are cations). In patients with normal renal function, the drug's half-life is about 10 hours. However, in patients with renal impairment, the half-life is increased. In patients with moderate impairment, dosage must be reduced; in patients with severe impairment, dofetilide must not be used.

Adverse Effects.

By increasing the QT interval, dofetilide predisposes to *torsades de pointes,* which can progress to fatal ventricular fibrillation. The risk is directly related to dofetilide blood levels, and is increased by hypokalemia and by other drugs that cause QT prolongation. To assess risk, an ECG should be obtained at baseline, and ECG monitoring should be continuous during the initial phase of treatment. Dofetilide is contraindicated for patients with a baseline QT interval greater than 440 milliseconds (or greater than 500 milliseconds in patients with ventricular conduction abnormalities). Other side effects include headache (11%), chest pain (10%), and dizziness (8%).

Drug Interactions.

Drugs that are excreted by renal cation pumps can interfere with the excretion of dofetilide, thereby causing its levels to rise. Accordingly, concurrent use of these drugs (eg, cimetidine, trimethoprim, ketoconazole, prochlorperazine, megestrol) is contraindicated.

Drugs that prolong the QT interval may increase the risk of dysrhythmias, and hence should be avoided. Among these are class I and class III antidysrhythmics, phenothiazines, tricyclic antidepressants, and some macrolide antibiotics.

Combining verapamil with dofetilide increases the risk of torsades de pointes, and should be avoided.

Preparations, Dosage, and Administration.

Dofetilide [Tikosyn] is available in capsules (125, 250, and 500 mg) for oral administration. Because of the risk of dysrhythmias, treatment must be initiated in a hospital with *continuous ECG monitoring for at least 3 days*. Because dysrhythmia risk is directly related to plasma drug levels, which in turn are dir-

ectly related to creatinine clearance (a measure of renal function), *creatinine clearance must be monitored*. Dosage should be reduced with decreasing creatinine clearance as follows: For patients with normal renal function (creatinine clearance greater than 60 mL/min), give 500 mg twice a day; for creatinine clearance 40 to 60 mL/min, give 250 mg twice a day; for creatinine clearance 20 to 39.9 mL/min, give 125 mg twice a day; and for creatinine clearance below 20 mL/min, withhold dofetilide. If the QT interval becomes excessively prolonged (greater than 500 milliseconds, or greater than 550 milliseconds in patients with ventricular conduction abnormalities), dosage should be reduced.

Ibutilide

Ibutilide [Corvert] is an IV agent used to terminate atrial flutter and atrial fibrillation of recent onset (ie, that has been present no longer than 90 days). Conversion to sinus rhythm occurs during the infusion or within 90 minutes of its termination. Ibutilide is more effective against atrial flutter (48% to 70% success) than atrial fibrillation (22% to 43% success). Like other class III agents, ibutilide blocks potassium channels and thereby prolongs the action potential duration and QT interval. Up to 8% of patients develop torsades de pointes, frequently in association with QT prolongation. Oral doses are teratogenic and embryocidal in rats. For patients who weigh over 60 kg, the dosage is 1 mg infused over 10 minutes. If the dysrhythmia does not convert within 10 minutes of terminating the infusion, a second 1-mg infusion may be tried.

CLASS IV: CALCIUM CHANNEL BLOCKERS

Only two calcium channel blockers—verapamil [Calan, Isoptin, Verelan] and diltiazem [Cardizem, others]—are able to block calcium channels in the heart. Accordingly, they are the only calcium channel blockers used to treat dysrhythmias. Their basic pharmacology is discussed in Chapter 44. Consideration here is limited to use against dysrhythmias.

Effects on the Heart and ECG.

Blockade of cardiac calcium channels has three effects:

- Slowing of SA nodal automaticity
- Delay of AV nodal conduction

• Reduction of myocardial contractility

Note that these are identical to the effects of beta blockers, which makes sense in that beta blockers promote calcium channel closure in the heart. The principal effect on the ECG is prolongation of the PR interval, reflecting delayed AV conduction.

Therapeutic Uses.

Verapamil and diltiazem have two antidysrhythmic uses. First, they can slow ventricular rate in patients with atrial fibrillation or atrial flutter. Second, they can terminate SVT caused by an AV nodal reentrant circuit. In both cases, benefits derive from suppressing AV nodal conduction. With IV administration, effects can be seen in 2 to 3 minutes. Verapamil and diltiazem are not active against ventricular dysrhythmias.

Adverse Effects.

Although generally safe, these drugs *can* cause undesired effects. Blockade of cardiac calcium channels can cause *bradycardia, AV block,* and *heart failure*. Blockade of calcium channels in vascular smooth muscle can cause vasodilation, resulting in *hypotension* and *peripheral edema*. Blockade of calcium channels in intestinal smooth muscle can produce *constipation*.

Drug Interactions.

Both verapamil and diltiazem can elevate levels of *digoxin,* thereby increasing the risk of digoxin toxicity. Also, since digoxin shares with verapamil and diltiazem the ability to decrease AV conduction, combining digoxin with either drug increases the risk of AV block.

Because verapamil, diltiazem, and *beta blockers* have nearly identical suppressant effects on the heart, combining verapamil or diltiazem with a beta blocker increases the risk of bradycardia, AV block, and heart failure.

Preparations, Dosage, and Administration.

Verapamil.

Dosing may be IV or oral. Intravenous therapy is preferred for initial treatment. Oral therapy is used for maintenance.

Verapamil for intravenous use is supplied in solution (5 mg/2 mL). The initial dose is 5 to 10 mg injected slowly (over 2 to 3 minutes). If the dysrhythmia persists, an additional 10 mg may be administered in 30 minutes. An IV infusion (0.375 mg/min) can be used for maintenance. Intravenous verapamil can cause serious cardiovascular effects. Accordingly, blood pressure and the ECG should be monitored, and equipment for resuscitation should be immediately available.

Verapamil for oral use is available in immediate- and sustained-release tablets. The maintenance dosage is 40 to 120 mg 3 or 4 times a day.

Diltiazem.

Like verapamil, diltiazem may be given IV or PO. Intravenous therapy is preferred for initial treatment, and oral therapy is used for maintenance.

Intravenous therapy is initiated with an IV bolus (0.25 mg/kg). If the response is inadequate, a second bolus (0.35 mg/kg) may be administered in 15 minutes. If appropriate, initial therapy may be followed with a continuous IV infusion (up to 24 hours' duration) at a rate of 5 to 15 mg/hr.

OTHER ANTIDYSRHYTHMIC DRUGS

Adenosine

Adenosine [Adenocard], a naturally occurring nucleotide, is a drug of choice for terminating paroxysmal SVT. The drug has an extremely short half-life, and hence must be administered IV. Adverse effects are minimal because adenosine is rapidly cleared from the blood.

Effects on the Heart and ECG.

Adenosine decreases automaticity in the SA node and greatly slows conduction through the AV node. The most prominent ECG change is prolongation of the PR interval, brought on by delayed AV conduction. Adenosine works in part by inhibiting cyclic AMP–induced calcium influx, thereby suppressing calcium-dependent action potentials in the SA and AV nodes.

Therapeutic Use.

Adenosine is approved only for termination of paroxysmal SVT, including Wolff-Parkinson-White syndrome. The drug is not active against atrial fibrillation, atrial flutter, or ventricular dysrhythmias.

Pharmacokinetics.

Adenosine has an extremely short plasma half-life (estimated at 1.5 to 10 seconds) owing primarily to rapid uptake by cells, and partly to deactivation by circulating adenosine deaminase. Because of its rapid clearance from the blood, adenosine must be administered by IV bolus, as close to the heart as possible.

Adverse Effects.

Adverse effects are short lived, lasting less than 1 minute. The most common are sinus bradycardia, dyspnea (from bronchoconstriction), hypotension and facial flushing (from vasodilation), and chest discomfort (perhaps from stimulation of pain receptors in the heart).

Drug Interactions.

Methylxanthines (aminophylline, theophylline, caffeine) block receptors for adenosine. Hence, asthma patients taking aminophylline or theophylline need larger doses of adenosine, and even then adenosine may not work.

Dipyridamole, an antiplatelet drug, blocks cellular uptake of adenosine, and can thereby intensify its effects.

Preparations, Dosage, and Administration.

Adenosine [Adenocard] is supplied in solution (3 mg/mL) for bolus IV administration. The injection should be made as close to the heart as possible, and should be followed by a saline flush. The initial dose is 6 mg. If there is no response in 1 or 2 minutes, 12 mg may be tried and repeated once. If a response is going to occur, it should happen as soon as the drug reaches the AV node.

Digoxin

Although its primary indication is heart failure, digoxin [Lanoxin] is also used to treat supraventricular dysrhythmias. The basic pharmacology of digoxin is discussed in Chapter 47. Consideration here is limited to treatment of dysrhythmias.

Effects on the Heart.

Digoxin suppresses dysrhythmias by decreasing conduction through the AV node and by decreasing automaticity in the SA node. The drug decreases AV conduction by (1) a direct depressant effect on the AV node and by (2) acting in the CNS to increase vagal (parasympathetic) impulses to the AV node. Digoxin decreases automaticity of the SA node by increasing vagal traffic to the node and by decreasing sympathetic traffic. It should be noted that, although digoxin decreases automaticity in the SA node, it can *increase* automaticity in *Purkinje fibers*. The latter effect contributes to dysrhythmias *caused* by digoxin.

Effects on the ECG.

By slowing AV conduction, digoxin prolongs the PR interval. The QT interval may be shortened, reflecting accelerated repolarization of the ventricles. Depression of the ST segment is common. The T wave may be depressed or even inverted. There is little or no change in the QRS complex.

Adverse Effects and Interactions.

The major adverse effect is *cardiotoxicity* (dysrhythmias). Risk is increased by hypokalemia, which can result from concurrent therapy with diuretics (thiazides and high-ceiling agents). Accordingly, it is essential that potassium levels be kept within the normal range (3.5 to 5 mEq/L). The most common adverse effects are GI disturbances (anorexia, nausea, vomiting, abdominal discomfort). CNS responses (fatigue, visual disturbances) are also relatively common.

Antidysrhythmic Uses.

Digoxin is used only for supraventricular dysrhythmias. The drug is inactive against ventricular dysrhythmias.

Atrial Fibrillation and Atrial Flutter.

Digoxin can be used to slow ventricular rate in patients with atrial fibrillation and atrial flutter. Ventricular rate is decreased by reducing the number of atrial impulses that pass through the AV node.

Supraventricular Tachycardia.

Digoxin may be employed acutely and chronically to treat SVT. Acute therapy is used to abolish the dysrhythmia. Chronic therapy is used to prevent its return. Digoxin suppresses SVT by increasing cardiac vagal tone and by decreasing sympathetic tone.

Dosage and Administration.

Oral therapy is generally preferred. The initial dosage is 1 to 1.5 mg administered in three or four doses over 24 hours. The maintenance dosage is 0.125 to 0.5 mg/day.

NONDRUG TREATMENT OF DYSRHYTHMIAS

Implantable Cardioverter-Defibrillators

ICDs are surgically implanted devices that monitor and analyze cardiac rhythm and, by delivering electrical shocks to the heart, terminate any dysrhythmias that develop. Termination is accomplished with either (1) a series of pacing stimuli, which are usually imperceptible; or (2) a defibrillating shock, which can be painful. It is important to note that ICDs do not prevent dysrhythmias. Rather, they neutralize the ones that occur. ICDs are indicated for patients with recurrent ventricular fibrillation or sustained ventricular tachycardia. For these patients, ICDs significantly reduce the risk of sudden death. The major complication associated with ICDs is mortality during surgical implantation. The mortality rate had been as high as 8%, but is declining due to use of newer techniques. ICDs cost about $20,000 to $25,000. The cost for implantation, including hospitalization, adds another $30,000 to $50,000.

Radiofrequency Catheter Ablation

Radiofrequency (RF) catheter ablation is a technique in which cardiac tissue responsible for causing a dysrhythmia is identified and destroyed. The result is often permanent cure. In preparation for RF ablation, the patient undergoes

electrophysiologic cardiac testing to identify the small region of the heart that is generating the dysrhythmia. Next, an RF catheter is placed at the site. Activation of the catheter generates RF energy, which heats (and thereby destroys) all tissue within 5 to 8 mm of the catheter tip. Destruction of the offending tissue eliminates the dysrhythmia. Success rates depend on the dysrhythmia being treated. In patients with atrial tachycardia, AV nodal reentrant tachycardia, or dysrhythmias associated with Wolff-Parkinson-White syndrome, the rate of permanent cure is between 90% and 100%. In patients with atrial flutter, initial responses are generally good, but recurrence is common. Complications develop in less than 5% of procedures. The most common complications are AV block and myocardial perforation. Complications that require intervention or that result in long-term injury occur in only 1% of patients. For treatment of atrial dysrhythmias, catheter ablation costs about $25,000 to $30,000.

KEY POINTS

- Dysrhythmias result from alteration of the electrical impulses that regulate cardiac rhythm. Antidysrhythmic drugs control rhythm by correcting or compensating for these alterations.
- In the healthy heart, the SA node is the pacemaker.
- Impulses originating in the SA node must travel through the AV node to reach the ventricles. Impulses arriving at the AV node are delayed before going on to excite the ventricles.
- The His-Purkinje system conducts impulses rapidly throughout the ventricles, thereby causing all parts of the ventricles to contract in near synchrony.
- The heart employs two kinds of action potentials: fast potentials and slow potentials.
- Fast potentials occur in the His-Purkinje system, atrial muscle, and ventricular muscle.
- Slow potentials occur in the SA node and AV node.

- Phase 0 of fast potentials (depolarization) is generated by rapid influx of sodium. Because depolarization is fast, these potentials conduct rapidly.
- During phase 2 of fast potentials, calcium enters myocardial cells, thereby promoting contraction.
- Phase 3 of fast potentials (repolarization) is generated by rapid extrusion of potassium.
- Phase 0 of slow potentials (depolarization) is caused by slow influx of calcium. Because depolarization is slow, these potentials conduct slowly.
- Spontaneous phase 4 depolarization—of fast or slow potentials—confers automaticity upon cells. Spontaneous phase 4 depolarization of cells in the SA node normally determines heart rate.
- The P wave of an ECG is caused by depolarization of the atria.
- The QRS complex is caused by depolarization of the ventricles. Widening of the QRS complex indicates slowed conduction through the ventricles.
- The T wave is caused by repolarization of the ventricles.
- The PR interval represents the time between onset of the P wave and onset of the QRS complex. PR prolongation indicates delayed AV conduction.
- The QT interval represents the time between onset of the QRS complex and completion of the T wave. QT prolongation indicates delayed ventricular repolarization.
- Dysrhythmias arise from disturbances of impulse formation (automaticity) or impulse conduction.
- Reentrant dysrhythmias result from a localized, self-sustaining circuit capable of repetitive cardiac stimulation.
- Tachydysrhythmias can be divided into two major groups: supraventricular dysrhythmias and ventricular dysrhythmias. In general, ventricular dysrhythmias disrupt cardiac pumping more than do supraventricular dysrhythmias.
- Treatment of supraventricular tachydysrhythmias is often directed at blocking impulse conduction through the AV node, rather than at eliminating the dysrhythmia.

- Treatment of ventricular dysrhythmias is usually directed at eliminating the dysrhythmia.
- All antidysrhythmic drugs are also prodysrhythmic (proarrhythmic). That is, they all can worsen existing dysrhythmias and generate new ones.
- Class I antidysrhythmic drugs block cardiac sodium channels, and thereby slow impulse conduction through the atria, ventricles, and His-Purkinje system.
- Slowing ventricular conduction widens the QRS complex.
- Quinidine (a class IA drug) blocks sodium channels and delays ventricular repolarization. Delaying ventricular repolarization prolongs the QT interval.
- Quinidine causes diarrhea and other GI symptoms in 33% of patients. These effects frequently force drug withdrawal.
- Quinidine can cause dysrhythmias. Widening of the QRS complex (by 50% or more) and excessive prolongation of the QT interval are warning signs.
- Quinidine elevates digoxin levels. If the drugs are used together, digoxin dosage must be reduced.
- Class IB agents differ from class IA agents in two ways: they accelerate repolarization and have little or no effect on the ECG.
- Lidocaine (a class IB agent) is used only for ventricular dysrhythmias. The drug is not active against supraventricular dysrhythmias.
- Lidocaine undergoes rapid inactivation by the liver. As a result, the drug must be administered by continuous IV infusion.
- Propranolol and other class II drugs block cardiac beta*1* receptors.
- By blocking cardiac beta*1* receptors, propranolol attenuates sympathetic stimulation of the heart, and thereby decreases SA nodal automaticity, AV conduction velocity, and myocardial contractility.
- By decreasing AV conduction velocity, propranolol prolongs the PR interval.
- The effects of propranolol on the heart result (ultimately) from suppressing calcium entry. Hence, the effects of propranolol and the effects of calcium channel blockers are nearly identical.

- Propranolol is especially useful for treating dysrhythmias caused by excessive sympathetic stimulation of the heart.
- In patients with supraventricular tachydysrhythmias, propranolol helps by (1) slowing discharge of the SA node and (2) decreasing conduction through the AV node, which prevents the atria from driving the ventricles at an excessive rate.
- Class III antidysrhythmics block potassium channels, and thereby delay repolarization of fast potentials. As a result, they prolong the action potential duration and the effective refractory period. By delaying ventricular repolarization, they prolong the QT interval.
- Bretylium (a class III agent) is used only for short-term therapy of severe ventricular dysrhythmias that have been refractory to safer treatments.
- Bretylium blocks release of norepinephrine from sympathetic nerves, and thereby causes profound and persistent hypotension in up to 66% of patients.
- Amiodarone (a class III agent) is highly effective against atrial and ventricular dysrhythmias, but can cause multiple serious adverse effects, including damage to the lungs, eyes, liver, and thyroid.
- Verapamil and diltiazem (class IV antidysrhythmics) block cardiac calcium channels, and thereby reduce automaticity of the SA node, slow conduction through the AV node, and decrease myocardial contractility. These effects are identical to those of the beta blockers.
- By suppressing AV conduction, verapamil and diltiazem prolong the PR interval.
- Verapamil and diltiazem are used to slow ventricular rate in patients with atrial fibrillation or atrial flutter and to terminate SVT caused by an AV nodal reentrant circuit. In both cases, benefits derive from suppressing AV nodal conduction.
- Adenosine is a drug of choice for terminating paroxysmal SVT.
- Adenosine has a very short half-life (less than 10 seconds), and hence must be given by IV bolus.

Summary of Major Nursing Implications*

Summaries are limited to the major antidysrhythmic drugs. Summaries for beta blockers (propranolol, acebutolol, and esmolol), phenytoin, calcium channel blockers (verapamil and diltiazem), and digoxin appear in Chapters 18, 24, 44, and 47, respectively.

QUINIDINE

Preadministration Assessment

Therapeutic Goal

The usual goal is long-term suppression of atrial and ventricular dysrhythmias.

Baseline Data

Obtain a baseline ECG and laboratory evaluation of liver function. Determine blood pressure.

Identifying High-Risk Patients

Quinidine is *contraindicated* for patients with a history of hypersensitivity to quinidine or other cinchona alkaloids and for patients with complete heart block, digoxin intoxication, or conduction disturbances associated with marked QRS widening and QT prolongation.

Exercise *caution* in patients with partial AV block, heart failure, hypotensive states, and hepatic dysfunction.

Implementation: Administration

Routes

Usual Route.

Oral.

Rare Routes.

IM and IV.

Administration

Before giving full therapeutic doses, assess for hypersensitivity by giving a small test dose (200 mg PO or IM).

Advise patients to take quinidine with meals. Warn them not to crush or chew sustained-release formulations.

Dosing must account for the particular quinidine salt being used: 200 mg of quinidine sulfate is equivalent to 275 mg of quinidine gluconate.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor for beneficial changes in the ECG. Plasma drug levels should be kept between 2 and 5 mcg/mL.

Minimizing Adverse Effects

Diarrhea.

Diarrhea and other GI disturbances occur in one third of patients and frequently force drug withdrawal. To reduce these effects, administer quinidine with meals.

Cinchonism.

Inform patients about symptoms of cinchonism (tinnitus, headache, nausea, vertigo, disturbed vision), and instruct them to notify the prescriber if these develop.

Cardiotoxicity.

Monitor the ECG for signs of cardiotoxicity, especially widening of the QRS complex (by 50% or more) and excessive prolongation of the QT interval. Monitor pulses for significant changes in rate or regularity. If signs of cardiotoxicity develop, withhold quinidine and notify the prescriber.

Arterial Embolism.

Embolism may occur during therapy of atrial fibrillation. The risk can be reduced with warfarin (an anticoagulant). Observe for signs of thromboembolism (eg, sudden chest pain, dyspnea) and report these immediately.

Minimizing Adverse Interactions

Digoxin.

Quinidine can double digoxin levels. When these drugs are combined, digoxin dosage should be reduced. Monitor patients for digoxin toxicity (dysrhythmias).

PROCAINAMIDE

Preadministration Assessment

Therapeutic Goal

Procainamide is indicated for acute and long-term management of ventricular and supraventricular dysrhythmias. Because procainamide can be toxic with long-term use, quinidine is preferred to procainamide for chronic suppression.

Baseline Data

Obtain a baseline ECG, complete blood count, and laboratory evaluations of liver and kidney function. Determine blood pressure.

Identifying High-Risk Patients

Procainamide is *contraindicated* for patients with systemic lupus erythematosus (SLE), complete AV block, and second-degree or third-degree AV block in the absence of an electronic pacemaker.

Exercise *caution* in patients with hepatic or renal dysfunction or a history of procaine allergy.

Implementation: Administration

Routes

Oral, IM, IV.

Administration

Instruct patients to administer procainamide at evenly spaced intervals around the clock. Warn patients not to crush or chew sustained-release formulations.

When switching from IV procainamide to oral procainamide, allow 3 hours to elapse between stopping the infusion and giving the first oral dose.

Give IM injections deep into the gluteal muscle.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor the ECG for beneficial changes. Plasma drug levels should be kept between 3 and 10 mcg/mL.

Minimizing Adverse Effects

SLE–like Syndrome.

Prolonged therapy can produce a syndrome resembling SLE. **Inform patients about manifestations of SLE (joint pain and inflammation; hepatomegaly; unexplained fever; soreness of the mouth, throat, or gums), and instruct them to notify the prescriber if these develop.** If SLE is diagnosed, procainamide should be discontinued. If discontinuation is impossible, signs and symptoms can be controlled with a nonsteroidal anti-inflammatory drug (eg, aspirin) or a glucocorticoid. The ANA titer should be measured periodically and, if it rises, procainamide withdrawal should be considered.

Blood Dyscrasias.

Procainamide can cause agranulocytosis, thrombocytopenia, and neutropenia. Deaths have occurred. Obtain complete blood counts weekly during the first 3 months of treatment and periodically thereafter. **Instruct patients to inform the prescriber at the first sign of infection (fever, chills, sore throat),**

bruising, or bleeding. If subsequent blood counts indicate hematologic disturbance, discontinue procainamide immediately.

Cardiotoxicity.

Procainamide can cause dysrhythmias. Monitor pulses for changes in rate or regularity. Monitor the ECG for excessive QRS widening (greater than 50%) and for PR prolongation. If these occur, withhold procainamide and notify the prescriber.

Arterial Embolism.

Embolism may occur during therapy of atrial fibrillation. The risk can be reduced with warfarin. Observe for signs of thromboembolism (eg, sudden chest pain, dyspnea) and report these immediately.

LIDOCAINE

Preadministration Assessment

Therapeutic Goal

Acute management of ventricular dysrhythmias.

Baseline Data

Obtain a baseline ECG and determine blood pressure.

Identifying High-Risk Patients

Lidocaine is *contraindicated* for patients with Stokes-Adams syndrome, Wolff-Parkinson-White syndrome, and severe degrees of SA, AV, or intraventricular block in the absence of electronic pacing.

Exercise *caution* in patients with hepatic dysfunction or impaired hepatic blood flow.

Implementation: Administration

Routes

Usual.

IV.

Emergencies.

IM.

Administration

Intravenous.

Make certain the lidocaine preparation is labeled for IV use (ie, is devoid of preservatives and catecholamines). Dilute concentrated preparations with 5% dextrose in water.

The initial dose is 50 to 100 mg (1 mg/kg) infused at a rate of 25 to 50 mg/min. For maintenance, monitor the ECG and adjust the infusion rate on the basis of cardiac response. The usual rate is 1 to 4 mg/min.

Intramuscular.

Reserve for emergencies. The usual dose is 300 mg injected into the deltoid muscle. Switch to IV lidocaine as soon as possible.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Continuous ECG monitoring is required. Plasma drug levels should be kept between 1.5 and 5 mcg/mL.

Minimizing Adverse Effects

Excessive doses can cause convulsions and respiratory arrest. Equipment for resuscitation should be available. Convulsions can be managed with diazepam or phenytoin.

49 Prophylaxis of Coronary Heart Disease: Drugs That Help Normalize Cholesterol and Triglyceride Levels

Marshal Shlafer

Our main topic for the chapter is drugs used to lower cholesterol. Drugs used to lower triglycerides are considered as well. Why focus on cholesterol? Because of its impact on *coronary artery atherosclerosis* (thickening of the coronary arteries), also known as coronary heart disease (CHD). Moderate CHD manifests as anginal pain. Severe CHD sets the stage for myocardial infarction (MI; heart attack). In the United States, CHD is the leading killer of men and women, causing over 450,000 deaths in 2004 alone. According to the American Heart Association, about 16 million Americans alive today have a history of coronary events (angina, MI, or both). More than half of these people are women. Additional sobering statistics are presented in Table 49-1.

Cardiovascular Disease of All Types

- Cardiovascular disease took nearly 870,000 lives in 2004 (the latest year for which good data are available)—accounting for 36% of all deaths that year, regardless of cause. In 2004, the number of deaths from cardiovascular disease was about
    - 1.6 times the number of deaths from all cancers
    - 8 times the number of deaths caused by accidents
    - 55 times the number of deaths from HIV/AIDS

Coronary Heart Disease

- Coronary heart disease (CHD), characterized by buildup of atherosclerotic plaque in coronary arteries, is the major cause of angina pectoris, heart attacks, and death.
- In 2004, CHD caused 451,326 deaths, and it is the single leading cause of death in the United States today.
- Each year, about 310,000 people die of heart attacks, either in an emergency department or without being hospitalized. Most of these are sudden deaths caused by cardiac arrest, usually resulting from ventricular fibrillation (a cardiac dysrhythmia that is fatal within seconds of onset).
- 16 million people alive today have a history of heart attack, angina pectoris, or both—roughly 8.7 million males and 7.3 million females.
- Each year, about 1.2 million Americans will have a new or recurrent heart attack.

Modified from data published by the American Heart Association (*www.americanheart.org/presenter.jhtml?identifier=4478*).

TABLE 49-1 Morbidity and Mortality from Cardiovascular Disease in General, and Coronary Heart Disease in Particular, United States

Until recently, atherosclerosis was largely a disease of older people. Not so any more. Why? Because lifestyles have changed. A generation ago, diets included generally healthy made-from-scratch "balanced" meals, and on nice days the children were shooed out of the house to play. Nowadays, we're so busy that fast-food restaurants and heat-and-eat meals are the new tradition, even though (or because?) they may be loaded with all sorts of heart-unhealthy fats, along with the heart's other big enemy: salt. And while many youngsters are shuttled off to school, then to soccer, then to baseball, track, or swimming, too many others seem to be in competition for Couch-Potato-of-the-Year. So now, rather than developing CHD in their fourth or fifth decade, people are getting the disease sooner, as can be attested to by attending clinicians and the pathologists doing the autopsies. Of course, this disturbing trend couldn't possibly apply to the young students reading this book.

How does atherosclerosis develop? It begins as a fatty streak in the arterial wall. This is followed by deposition of fibrous plaque. As atherosclerotic plaque grows, it impedes coronary blood flow, causing anginal pain. Worse yet, coronary atherosclerosis encourages formation of thrombi, which can block flow entirely, thereby causing MI.

It is important to appreciate that atherosclerosis is not limited to arteries of the heart: Atherosclerotic plaque can develop in any artery, and can thereby compromise circulation to any tissue. Furthermore, adverse effects can occur at sites distant from the original lesion: A ruptured lesion can produce a thrombus, which can travel downstream to block a new vessel. Blockage in the lungs and brain is of particular concern.

The risk of developing CHD is directly related to increased levels of blood cholesterol, in the form of low-density lipoproteins (LDLs). By reducing levels of LDL cholesterol, we can slow progression of atherosclerosis, reduce the risk of serious CHD, and prolong life. The preferred method for lowering LDL cholesterol is modification of diet combined with exercise. Drugs are employed only when diet modification and exercise are insufficient.

We approach our primary topic—cholesterol and its impact on CHD—in three stages. First, we discuss cholesterol itself, plasma lipoproteins (structures that transport cholesterol in blood), and the process of atherogenesis. Second, we discuss guidelines for cholesterol screening and management of high cholesterol. Third, we discuss the pharmacology of the cholesterol-lowering drugs, as well as drugs used to lower triglycerides.

CHOLESTEROL

Cholesterol has many physiologic roles. Of greatest importance, cholesterol is a component of all cell membranes and membranes of intracellular organelles. In addition, cholesterol is required for synthesis of certain hormones (estrogen, progesterone, testosterone, adrenal corticosteroids) and for synthesis of bile salts, which are needed to absorb and digest dietary fats. Also, cholesterol is deposited in the stratum corneum of the skin, where it reduces evaporation of water and blocks transdermal absorption of water-soluble compounds.

Some of our cholesterol comes from dietary sources (exogenous cholesterol) and some is manufactured by cells (endogenous cholesterol), primarily in the liver. More cholesterol comes from endogenous production than from the diet. A critical step in hepatic cholesterol synthesis is catalyzed by an enzyme named hydroxymethylglutaryl coenzyme A reductase, or simply HMG-CoA reductase. As discussed below, drugs that inhibit this enzyme—the statins—are our most widely used cholesterol-lowering agents.

An increase in dietary cholesterol produces only a small increase in cholesterol in the blood, primarily because increased ingestion of cholesterol inhibits endogenous cholesterol synthesis. Interestingly, an increase in dietary saturated fats produces a substantial (15% to 25%) increase in circulating cholesterol. Why? Because the liver uses saturated fats to make cholesterol. Accordingly, when we want to reduce cholesterol levels, it is more important to reduce intake of saturated fats than to reduce intake of cholesterol itself, although cholesterol intake should definitely be lowered.

PLASMA LIPOPROTEINS

Structure and Function of Lipoproteins

Function.

Lipoproteins serve as carriers for transporting lipids—cholesterol and triglycerides—in blood. Like all other nutrients and metabolites, lipids use the bloodstream to move throughout the body. However, since cholesterol and triglycerides are not water soluble, these substances cannot dissolve directly in plasma. Lipoproteins represent a means of solubilizing these lipids, thereby permitting transport.

Basic Structure.

The basic structure of lipoproteins is depicted in Figure 49-1. As indicated, lipoproteins are tiny, spherical structures that consist of a *hydrophobic core,* composed of cholesterol and triglycerides, surrounded by a *hydrophilic shell,* composed primarily of phospholipids. Because the hydrophilic (water-soluble) shell completely covers the lipid core, the entire structure is soluble in plasma.

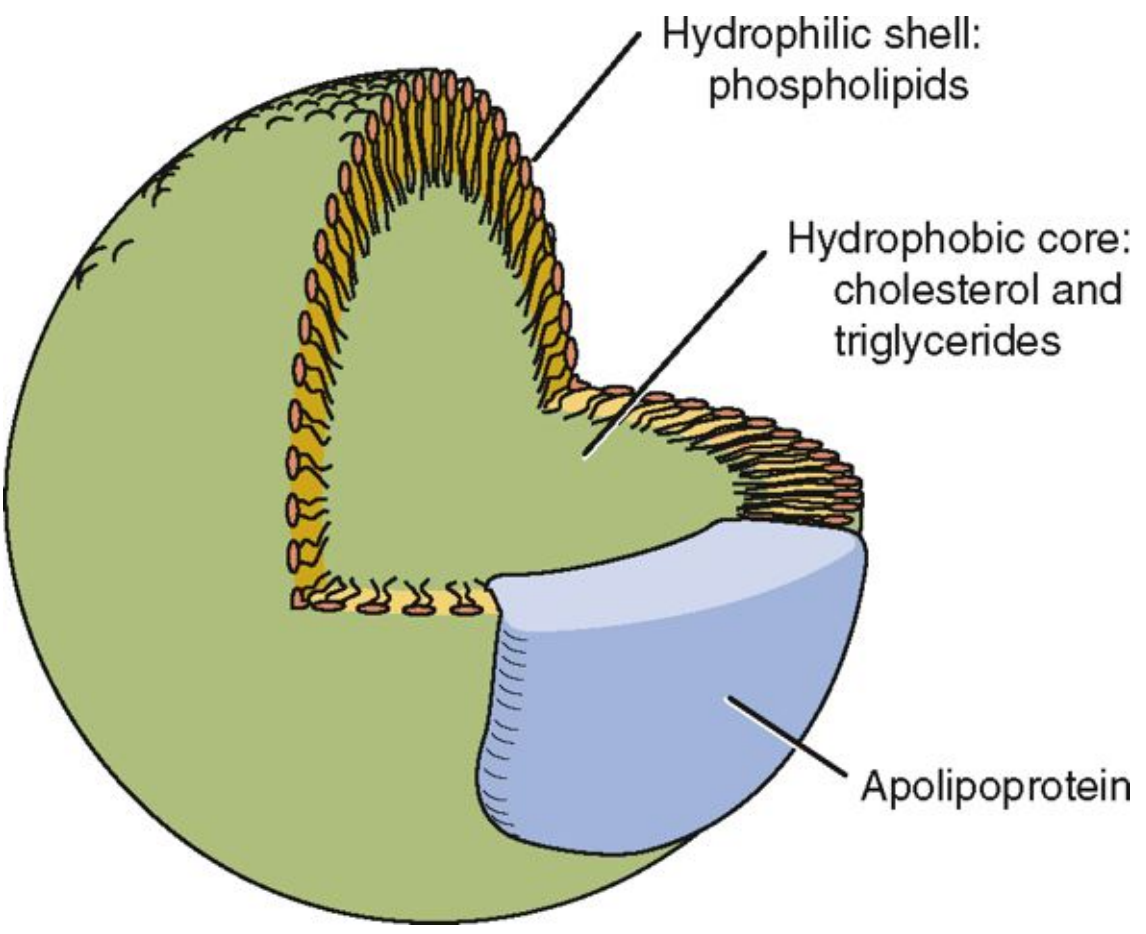

Figure 49-1 Basic structure of plasma lipoproteins.

Apolipoproteins.

All lipoproteins have one or more *apolipoprotein* molecules embedded in their shell (see Fig. 49-1). Apolipoproteins, which constitute the protein component of lipoproteins, have three functions:

- hey serve as recognition sites for cell-surface receptors, and thereby allow cells to bind with and ingest lipoproteins.
- hey activate enzymes that metabolize lipoproteins.
- hey increase the structural stability of lipoproteins.

The apolipoproteins of greatest clinical interest are labeled A-I, A-II, and B-100. All lipoproteins that deliver cholesterol and triglycerides to nonhepatic

tissues contain *apolipoprotein B-100*. Conversely, all lipoproteins that transport lipids from nonhepatic tissues back to the liver (ie, that remove lipids from tissues) contain *apolipoprotein A-I*.

Classes of Lipoproteins

There are six major classes of plasma lipoproteins. Distinctions among classes are based on size, density, apolipoprotein content, transport function, and primary core lipids (cholesterol or triglyceride). From a pharmacologic perspective, the features of greatest interest are *lipid content, apolipoprotein content,* and *transport function*.

The topic of lipoprotein density deserves comment for two reasons. First, naming of lipoprotein types is based on their density. Second, differences in density provide the basis for the physical isolation and subsequent measurement of plasma lipoproteins, as is done in research and clinical laboratories. The various classes of lipoproteins differ in density because they differ in their percent composition of lipid and protein. Because protein is more dense than lipid, lipoproteins that have a high percentage of protein (and a low percentage of lipid) have a relatively high density. Conversely, lipoproteins with a lower percentage of protein have a lower density.

Of the six major classes of lipoproteins, three are especially important in coronary atherosclerosis. These classes are named (1) very-low-density lipoproteins (VLDLs), (2) low-density lipoproteins (LDLs), and (3) high-density lipoproteins (HDLs). Properties of these classes are summarized in Table 49-2.

Lipoprotein Class*	Major Core Lipids	Apolipoproteins	Transport Function	Influence on Atherosclerosis
VLDL	Triglycerides	B-100, E, others	Delivery of triglycerides to nonhepatic tissues	*Probably contribute* to atherosclerosis
LDL	Cholesterol	B-100	Delivery of cholesterol to nonhepatic tissues	*Definitely contribute* to atherosclerosis
HDL	Cholesterol	A-I, A-II, A-IV	Transport of cholesterol from nonhepatic tissues back to the liver	*Protect* against atherosclerosis

TABLE 49-2 Properties of the Plasma Lipoproteins That Affect Atherosclerosis

* VLDL = very-low-density lipoproteins, LDL = low-density lipoproteins, HDL = high-density lipoproteins.

Very-Low-Density Lipoproteins

VLDLs contain *triglycerides* (and some cholesterol) as their core lipids, and account for nearly all of the triglycerides in blood. The main physiologic role of VLDLs is to *deliver triglycerides* from the liver to adipose tissue and muscle. Each VLDL particle contains one molecule of *apolipoprotein B-100,* which allows VLDLs to bind with cell-surface receptors and thereby transfer their lipid content to cells.

The role of VLDLs in atherosclerosis is unclear. Although several studies suggest a link between elevated levels of VLDLs and development of atherosclerosis, this link has not been firmly established. However, we do know that elevation of triglyceride levels (above 500 mg/dL) increases the risk of *pancreatitis*.

Low-Density Lipoproteins

LDLs contain *cholesterol* as their primary core lipid, and they account for the majority (60% to 70%) of all cholesterol in blood. The physiologic role of LDLs is *delivery of cholesterol to nonhepatic tissues*. Each LDL particle contains one molecule of *apolipoprotein B-100,* which is needed for binding of LDL particles to LDL receptors on cells. LDLs can be viewed as by-products of VLDL metabolism, in that the lipids and apolipoproteins that compose LDLs are remnants of VLDL degradation.

Cells that require cholesterol meet their needs through endocytosis (engulfment) of LDLs from the blood. The process begins with binding of LDL particles to LDL receptors on the surface of the cells. When cellular demand for cholesterol increases, cells synthesize more LDL receptors and thereby increase their capacity for LDL uptake. Cells that are unable to make more LDL receptors cannot increase cholesterol absorption. Increasing the number of LDL receptors on cells is an important mechanism by which certain drugs increase LDL uptake, and thereby reduce LDL levels in blood.

Of all lipoproteins, LDLs make the greatest contribution to coronary atherosclerosis. The probability of developing CHD is directly related to the level of LDLs in blood. Conversely, by reducing LDL levels, we decrease the risk of CHD. Accordingly, *when cholesterol-lowering drugs are used, the primary goal is to reduce elevated LDL levels*. Multiple studies have shown that, by reducing LDL levels, we can arrest or perhaps even reverse atherosclerosis, and can thereby reduce mortality from CHD. In fact, for each 1% reduction in the LDL level, there is a 1% reduction in the risk of a major cardiovascular (CV) event.

There is growing evidence that a genetic variant of LDL, known as *lipoprotein(a)* [Lp(a)], may be the form of LDL that is most responsible for increasing cardiovascular risk, especially in certain ethnic groups. However, since this evidence is limited, and since we lack drugs that specifically target Lp(a), we don't routinely measure Lp(a) levels in our patients.

High-Density Lipoproteins

Like LDLs, HDLs contain *cholesterol* as their primary core lipid, and account for 20% to 30% of all cholesterol in blood. In contrast to LDLs, whose function is delivery of cholesterol to peripheral tissues, HDLs carry cholesterol from peripheral tissues back to the liver. That is, *HDLs promote cholesterol removal*.

The influence of HDLs on CHD is dramatically different from that of LDLs. Whereas elevation of LDLs *increases* the risk of CHD, elevation of HDLs *reduces* the risk of CHD. That is, high HDL levels actively protect against CHD.

Not all HDL particles are the same. Some contain only apolipoprotein A-I, whereas others contain apolipoproteins A-I *and* A-II. Available data suggest that cardioprotection is conferred by the HDLs that contain only *apolipoprotein A-I*.

LDL Cholesterol Versus HDL Cholesterol

From the foregoing, it is clear that not all cholesterol in plasma has the same impact on CHD. As discussed, a rise in cholesterol associated with LDLs increases the risk of CHD. In contrast, a rise in cholesterol associated with HDLs lowers the risk of CHD. Consequently, when speaking of plasma cholesterol levels, we need to distinguish between cholesterol that is associated with HDLs and cholesterol that is associated with LDLs. To make this distinction, we use the terms *HDL cholesterol* and *LDL cholesterol*. Because it promotes atherosclerosis, LDL cholesterol has been dubbed *bad cholesterol*. Conversely, because it protects against atherosclerosis, HDL cholesterol is often called *good cholesterol* or *healthy cholesterol*.

ROLE OF LDL CHOLESTEROL IN ATHEROSCLEROSIS

LDLs initiate and fuel development of atherosclerosis. The process begins with transport of LDLs from the arterial lumen into endothelial cells, and from there into the space that underlies the arterial epithelium. Once in the subendothelial space, components of LDLs undergo *oxidation*. This step is critical in that oxidized LDLs

- Attract monocytes from the circulation into the subendothelial space, after which the monocytes are converted to macrophages
- Inhibit macrophage mobility, thereby keeping macrophages at the site of atherogenesis
- Undergo uptake by macrophages (macrophages do not take up LDLs that have not been oxidized)
- Are cytotoxic, and hence can damage the vascular endothelium directly

As macrophages engulf more and more cholesterol, they become large and vacuolated. When macrophages assume this form, they are referred to as *foam cells*. Accumulation of foam cells beneath the arterial epithelium produces a fatty streak, which makes the surface of the arterial wall lumpy. Continued accumulation of foam cells can eventually cause rupture of the endothelium, thereby exposing the underlying tissue to the blood. This results in platelet adhesion and formation of microthrombi. As the process continues, smooth muscle cells migrate to the site, synthesis of collagen increases, and there can be repeated rupturing and healing of the endothelium. The end result is a mature atherosclerotic lesion, characterized by a large lipid core and a tough fibrous cap. In less mature lesions, the fibrous cap is not strong, and hence the lesions are unstable. As a result, arterial pressure and shear forces from moving blood can cause the cap to rupture; accumulation of platelets at the site of rupture can rapidly cause thrombosis, and can thereby cause infarction. Infarction is less likely at sites of mature atherosclerotic lesions. The atherosclerotic process is depicted in Figure 49-2.

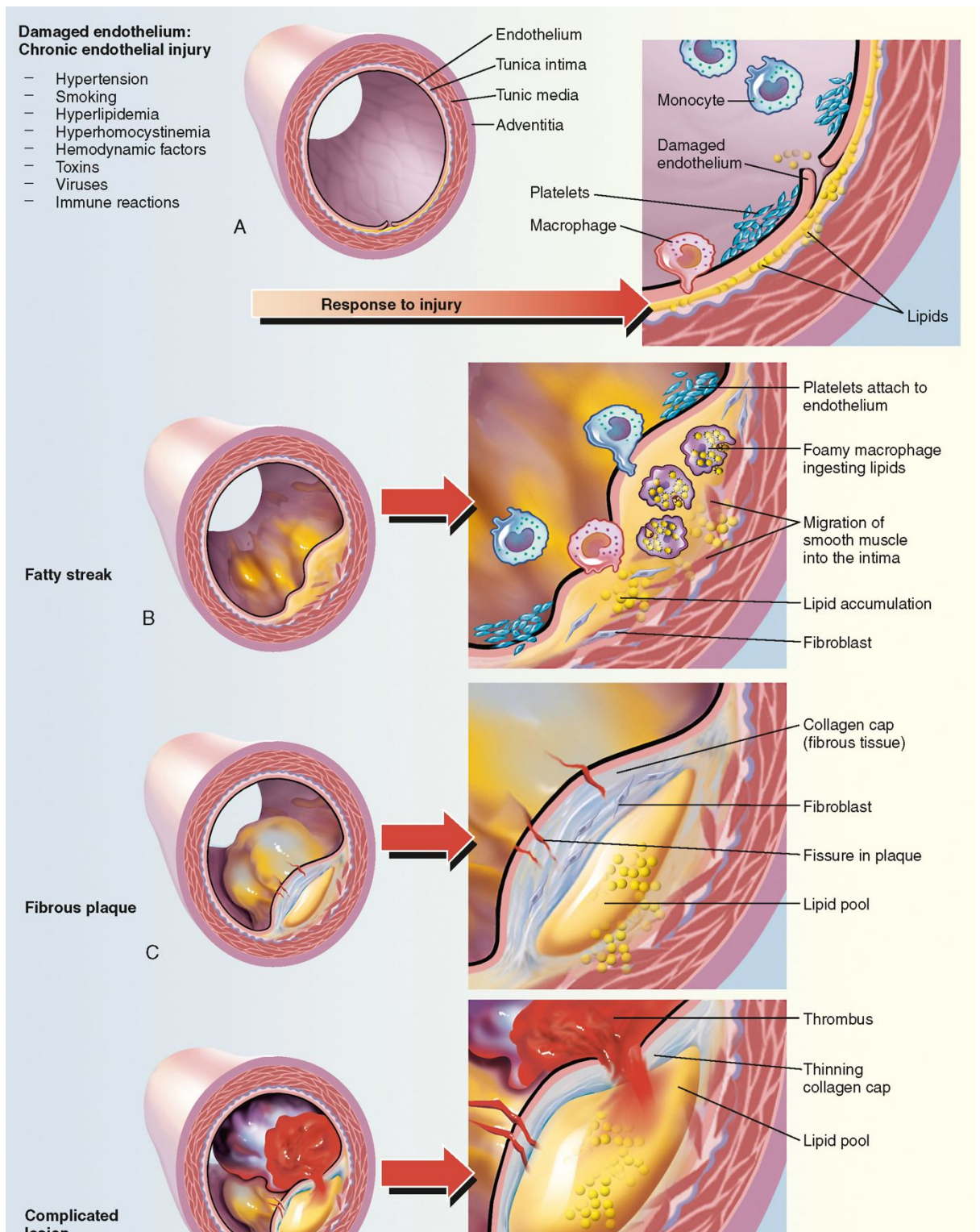
Damaged endothelium:
Chronic endothelial injury
– Hypertension
– Smoking
– Hyperlipidemia
– Hyperhomocystinemia
– Hemodynamic factors
– Toxins
– Viruses
– Immune reactions
Endothelium
Tunica intima
Tunic media
Adventitia
A
Monocyte
Damaged endothelium
Platelets
Macrophage
Lipids
Response to injury
Fatty streak
B
Platelets attach to endothelium
Foamy macrophage ingesting lipids
Migration of smooth muscle into the intima
Lipid accumulation
Fibroblast
Fibrous plaque
C
Collagen cap (fibrous tissue)
Fibroblast
Fissure in plaque
Lipid pool
Complicated
Thrombus
Thinning collagen cap
Lipid pool

Figure 49-2 Progression of atherosclerosis. A, Damaged endothelium. B, Diagram of fatty streak and lipid core formation. C, Diagram of fibrous plaque. Raised plaques are visible: some are yellow and some are white. D, Diagram of a complicated lesion, showing a thrombus (in red) and collagen (in blue).

It is important to appreciate that atherogenesis involves more than just deposition of lipids. In fact, atherogenesis is now considered primarily a chronic *inflammatory process*. When LDLs penetrate the arterial wall, they cause mild injury. The injury, in turn, triggers an inflammatory response, causing infiltration of macrophages, T lymphocytes, and other mediators of inflammation (eg, C-reactive protein [CRP]). In the late stage of the disease process, inflammation can weaken atherosclerotic plaque, leading to rupture of the plaque and subsequent thrombosis. The roles of inflammation and CRP in atherothrombosis are discussed further in Box 49-1 later in the chapter.

DETECTION, EVALUATION, AND TREATMENT OF HIGH CHOLESTEROL: RECOMMENDATIONS FROM ATP III

It is well established that high cholesterol levels cause substantial morbidity and mortality, and that aggressive treatment can save lives. Accordingly, periodic cholesterol screening and risk assessment are recommended. If the assessment indicates CHD risk, lifestyle changes—especially diet and exercise—should be implemented. If CHD risk is especially high, LDL-lowering drugs should be added to the regimen.

In 1988, the National Cholesterol Education Program (NCEP) began issuing guidelines on cholesterol detection and management. The most recent update was issued in 2001 and amended in 2004. A summary of the 2001 guidelines—*Executive Summary of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults* (also known as Adult Treatment Panel III or simply ATP III)—was published in *JAMA* (Vol. 285, No. 19, 2486–2497, 2001) and is available online at www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf. The 2004 changes to the 2001 guidelines were published in *Circulation* (Vol. 110, 227–239, 2004) and are available online at www.nhlbi.nih.gov/guidelines/cholesterol/atp3upd04.pdf. Previous NCEP guidelines were issued in 1988 (ATP I) and 1993 (ATP II). The discussion below reflects recommendations in ATP III, including the 2004

updates. The next update of these guidelines—ATP IV—is scheduled for release in 2010.

Like earlier NCEP guidelines, ATP III focuses on the role of high cholesterol in CHD and stresses the importance of treatment. However, owing to revised risk assessment criteria, ATP III recommends drug therapy for many more Americans: about 50 million, compared with only 13 million under ATP II. In addition, ATP III addresses two new concerns: *elevated triglycerides* and *metabolic syndrome* (formerly known as syndrome X or insulin resistance syndrome).

Cholesterol Screening

Adults

Management of high LDL cholesterol begins with screening, generally done every 5 years for adults over the age of 20. Under ATP II, only LDL and total cholesterol were usually measured. In contrast, ATP III recommends a more thorough screen, consisting of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (TGs). Blood for these tests should be drawn after fasting. Classification of total cholesterol and LDL cholesterol in ATP III (Table 49-3) is nearly identical to the classification in ATP II. The only change is that optimal LDL cholesterol is now defined as less than 100 mg/dL, compared with less than 130 mg/dL under ATP II. In addition, the cutoff for *low* HDL cholesterol is now less than 40 mg/dL, up from less than 35 mg/dL under ATP II. (Recall that low HDL cholesterol is detrimental, whereas high HDL cholesterol is protective.)

Cholesterol Type	Level (mg/dL)	Classification
LDL cholesterol	<100	Optimal
	100–129	Near optimal/above optimal
	130–159	Borderline high
	160–189	High
	≥190	Very high
Total cholesterol	<200	Desirable
	200–239	Borderline high
	≥240	High
HDL cholesterol	<40	Low
	≥60	High
Triglycerides	<150	Normal
	150–199	Borderline-high
	200–499	High
	≥500	Very high

TABLE 49-3 Health Classification of Blood Cholesterol and Triglyceride Levels*

* Cholesterol values are from the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497, 2001. Triglyceride values are from the National Heart, Lung, and Blood Institute of the National Institutes of Health (*nhlbisupport.com/chd1/tri.htm*).

Children and Adolescents

Elevated cholesterol in pediatric patients is a growing concern, and is not addressed in ATP III. Accordingly, in order to identify risk early in life and begin timely intervention, the American Academy of Pediatrics developed guidelines for lipid screening and treatment in at-risk children and adolescents. This document—*Lipid Screening and Cardiovascular Health in Child-*

hood—was published in the July 2008 issue of *Pediatrics* and is available online at *pediatrics.aappublications.org/cgi/reprint/122/1/198*. Cholesterol classification for children and adolescents is presented in Table 49-4.

Category	Total Cholesterol (mg/dL)	LDL Cholesterol (mg/dL)
Acceptable	<170	<110
Borderline	170–199	110–129
Elevated	≥200	≥130

Data from National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 89(3 Pt 2):525–584, 1992.

TABLE 49-4 NCEP Classification of Cholesterol Levels in Children 2 to 9 Years Old Who Have Premature Cardiovascular Disease or a Familial History of Hypercholesterolemia*

* HDL levels should be greater than or equal to 35 mg/dL and triglycerides should be less than or equal to 150 mg/dL.

Who should be tested? The guideline recommends screening for all children and adolescents with a family history of high cholesterol or heart disease. It also recommends screening children whose family history is unknown, as well as children who have other risk factors for heart disease, including obesity, high blood pressure, and diabetes.

When should screening begin? Long before it usually does. The Academy recommends screening for high-risk children when they reach age 2 years, and no later than age 10. If a child has values within the normal range, testing should be repeated in 3 to 5 years. The best method for testing is a fasting lipid profile.

If LDL cholesterol is high, what should be done? For children who are more than 8 years old, a cholesterol-reducing drug (ie, statin) should be considered. Younger patients should focus on weight reduction and increased activity. All patients should receive nutritional counseling. The statement also recom-

mends switching to reduced-fat dairy products, such as 2% milk, for children as young as 1 year of age for whom overweight or obesity is a concern.

CHD Risk Assessment

Under ATP III, CHD risk assessment is directed at determining the patient's *absolute risk of developing clinical coronary disease over the next 10 years*. The LDL goal and the mode of intervention are determined by the individual's degree of risk.

Factors in Risk Assessment

In order to assess the CHD risk for an individual, we need three kinds of information. Specifically, we need to (1) identify CHD risk factors, (2) calculate 10-year CHD risk, and (3) identify CHD risk equivalents.

Identifying CHD Risk Factors.

Major risk factors that modify LDL treatment goals are summarized in Table 49-5. The table lists five positive risk factors (advancing age, family history of premature CHD, hypertension, cigarette smoking, and low HDL cholesterol) and one negative risk factor (high HDL cholesterol). (LDL itself is not listed because the reason for counting these risk factors is to modify treatment of high LDL.) For the purpose of CHD risk assessment, each positive factor counts as 1 point; if the patient has high HDL cholesterol (a negative risk factor), 1 point is subtracted. For example, if the subject were a 62-year-old female hypertensive smoker with an HDL level of 62 mg/dL, her point total score would be 2 (3 points for the three positive risk factors minus 1 point for the one negative risk factor).

It should be noted that diabetes carries more weight in risk assessment in ATP III than in ATP II. Why? Because we now know that diabetes is a very strong predictor of developing CHD. Accordingly, we no longer consider diabetes to be a risk *factor* (as it was in ATP II). Instead, for the purpose of risk assessment, diabetes is now considered a CHD risk *equivalent*. That is, having diabetes is considered equivalent to having CHD as a predictor of a major coronary event.

Positive Risk Factors

- Age:
  - Men 45 yr or older
  - Women 55 yr or older
- Family history of premature CHD in a first-degree relative:
  - Male first-degree relative less than 55 yr old *or*
  - Female first-degree relative less than 65 yr old
- Hypertension:
  - Blood pressure 140/90 mm Hg or higher *or*
  - Taking antihypertensive medication
- Current cigarette smoking (smoked at least 1 in the last month)
- Low HDL cholesterol (below 40 mg/dL)

Negative Risk Factor

- High HDL cholesterol (60 mg/dL or higher)*

From the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497, 2001.

TABLE 49-5 Major Risk Factors (Other Than High LDL Cholesterol) That Modify LDL Treatment Goals

* High HDL cholesterol (60 mg/dL or higher) is protective, and hence counts as a "negative" risk factor; its presence removes one risk factor from the total count.

Box 49-1 discusses one additional factor—*C-reactive protein* (CRP)—that could aid with CHD risk prediction.

BOX 49-1 INFLAMMATION, C-REACTIVE PROTEIN, AND CARDIOVASCULAR RISK

Although we know about some risk factors for CHD—advancing age, obesity, hypertension, diabetes, smoking, high LDL cholesterol, and sedentary lifestyle—it is clear that other risk factors must exist. Why? Because many young, lean, active, normotensive, nondiabetic, nonsmokers with low cholesterol still manage to die from MI. Obviously, additional risk factors must be involved. The leading suspect is inflammation.

There is good evidence that inflammation plays a central role in atherosclerosis. Although inflammation normally protects tissues, it can also do harm. For example, inflammation in the lungs leads to bronchospasm in asthma, and inflammation of joints underlies tissue injury in arthritis. In arteries, inflammation appears to set the stage for atherogenesis. In addition, inflammation may weaken the surface of atherosclerotic plaques, thereby increasing the risk of plaque rupture. Factors that might evoke an inflammatory response include smoking, diabetes, and infection.

The strongest evidence implicating inflammation in CHD comes from measuring plasma levels of *C-reactive protein* (CRP), a compound that is produced when inflammation occurs. Large amounts are produced during major inflammatory disorders (eg, arthritis, infection), causing blood levels of CRP to climb very high. In contrast, relatively small amounts are produced by inflammation in arteries. Nonetheless, these amounts are still big enough to cause a measurable increase in blood levels, albeit much smaller than the increase seen in conditions like arthritis or infection. Please note that CRP itself is harmless: The compound is simply a *biomarker* for ongoing inflammatory processes; it does not cause injury by itself.

In clinical studies, elevation of CRP has been associated with increased CV risk. For example, in the *Physicians' Health Study,* high levels of CRP predicted danger 6 to 8 years *in advance:* Among people with no prior CV events, high levels of CRP were associated with a threefold increased risk of heart attacks and a twofold increased risk of stroke. In the *Women's Health Study,* similar results were obtained: Over an 8-year period, women with the highest levels of CRP experienced 4.5 times as many heart attacks or strokes as did women with the lowest levels. Furthermore, not only did elevated CRP predict CV risk, it

did so for women whose LDL cholesterol was *normal*—not just those whose LDL cholesterol was high. This is important. Why? Because it means that elevated CRP is an *independent* risk factor for CV events; it's not simply a surrogate for LDL cholesterol. Hence, measuring CRP *and* LDL cholesterol might identify different risk groups.

Cardiovascular protection conferred by aspirin and statins may result in part from anti-inflammatory actions. It is well known that aspirin suppresses platelet aggregation, and thereby helps protect against MI. However, there is evidence that aspirin is most beneficial in patients with high levels of CRP, suggesting that aspirin's anti-inflammatory actions may also contribute to CV benefits. Likewise, it is well known that statins reduce LDL cholesterol levels, and thereby protect against CHD. However, in patients with *normal* cholesterol levels and high levels of CRP, pravastatin still offers protection. Specifically, the drug can lower CRP levels by 17% and reduce the risk of recurrent MI—again suggesting that anti-inflammatory actions may partly explain clinical benefits.

Given that elevated CRP may predict CV events, should we screen people to see if their CRP is high? Yes, we should, according to a 2003 statement issued by an expert panel convened jointly by the American Heart Association (AHA) and the Centers for Disease Control and Prevention (CDC). However, the AHA/CDC panel does not recommend screening for everyone. Rather, screening should be limited to patients deemed at *intermediate* CV risk (ie, having a 10% to 20% risk of developing CHD in the next 10 years) as indicated by their age, LDL cholesterol level, and other traditional risk criteria. The panel does not recommend screening for patients considered at high or low risk. Why? Because the test results are unlikely to reveal information that would alter treatment decisions: With people at high risk, we already have sufficient information to guide treatment; with people at low risk, CRP tests are unlikely to reveal a previously unknown risk that would indicate a need for treatment.

How should CRP be tested? The AHA/CDC panel recommends using a *high-sensitivity CRP* (hsCRP) test, rather than a conventional CRP test, even though both tests measure the same molecule (CRP). Why use the high-sensitivity test? Because it can accurately measure *low levels* of CRP (1 to 10 mg/L)—levels in the range affected by arterial inflammation. The conventional test cannot accur-

ately measure levels this low. Because levels of hsCRP can vary over time, two tests should be done, about 2 weeks apart. The degree of CV risk associated with specific hsCRP levels is as follows:

- Less than 1 mg/L = low risk
- 1 to 3 mg/L = average risk
- More than 3 mg/L = high risk

People in the high-risk group have a twofold greater risk of an adverse CV event compared with people in the low-risk group.

If the hsCRP level indicates high risk, what should be done? Recall that hsCRP testing is recommended only for patients already classified as having intermediate risk, as determined by traditional risk criteria. For these people, a high level of hsCRP would signal a need for more intensive intervention.

It is important to note that hsCRP should not be tested in the presence of trauma, infection, or systemic inflammatory disorders. Why? Because these conditions can raise hsCRP levels substantially, up to 50 mg/L or even higher. Hence, if hsCRP test results were high, we couldn't tell if these conditions or vascular inflammation were the cause.

Does lowering CRP reduce CV risk? Yes! This was shown for the first time in two sister studies: the *Pravastatin or Atorvastatin Evaluation and Infection Therapy* (PROVE-IT) trial and the *Reversing Atherosclerosis with Aggressive Lipid Lowering* (REVERSAL) trial. In both studies, patients with existing CHD were randomized to receive either standard doses of pravastatin [Pravachol] or high doses of atorvastatin [Lipitor]. The results? In PROVE-IT, patients on the high-dose regimen experienced greater reductions in LDL and CRP levels than did patients on the standard regimen, and they also experienced fewer CV events. Furthermore, whether LDL levels were low or high, reducing CRP levels improved outcomes. The REVERSAL trial, which monitored progression of coronary atherosclerosis, produced parallel results. That is, reductions in LDL and CRP were independently associated with slowed progression of atheroma volume. In fact, among patients with the greatest reductions in LDL and CRP, atheroma volume actually declined.

The results of PROVE-IT and REVERSAL were reinforced and extended by a major new trial—*Justification for the Use of Statins in Prevention: an Intervention*

Trial Evaluating Rosuvastatin (JUPITER)—designed to see if statins can reduce CV events in people with elevated CRP, but with *healthy* levels of LDL cholesterol. The study enrolled nearly 18,000 healthy men and women with LDL cholesterol levels below 130 mg/dL, and with CRP levels of 2 mg/L or higher (ie, levels associated with increased cardiovascular risk). Half the participants received rosuvastatin (20 mg/day) and the other half received a daily placebo. JUPITER was supposed to last 4 years, but was stopped after just 1.9 years. Why? Because early results showed "unequivocal evidence" that rosuvastatin reduced cardiovascular morbidity and mortality: Compared with controls, the rosuvastatin group had a 55% relative reduction in nonfatal MI, a 48% reduction in nonfatal stroke, and a 47% reduction in "hard cardiac events," defined as the combination of MI (fatal or not), stroke (fatal or not), the need for coronary vessel revascularization (eg, by angioplasty and placement of a stent), and overall death from cardiovascular causes. What was the effect on LDL cholesterol and CRP? Rosuvastatin reduced LDL cholesterol by 50% and CRP by 37%. By comparison, LDL cholesterol and CRP were largely unchanged in the control group. Some experts reviewing these results were under-awed. Why? Because, although treatment produced a notable reduction in the *relative* risk, the reduction in *absolute* risk was less impressive. As one authority calculated, we would have to treat 120 patients for nearly 2 years to prevent just one death from cardiovascular causes. Nonetheless, when we consider that millions of patients are at risk, this treatment could easily save tens of thousands of lives.

Taken together, the PROVE-IT, REVERSAL, and JUPITER studies indicate that reducing CRP levels with statins provides protection against CV events independent of the protection ascribable to reducing LDL.

Since we know that reducing CRP is beneficial, how can we do it? Interestingly, the same measures that reduce LDL cholesterol—healthy diet, exercise, weight loss, smoking cessation, and statin therapy—also reduce levels of CRP. Drugs designed specifically to reduce CRP are in development.

Calculating 10-Year CHD Risk.

ATP III defines three 10-year risk categories: more than 20%, 10% to 20%, and less than 10%. Some people are automatically in the highest risk group—specifically, those with existing CHD (or other forms of atherosclerotic

disease) and those with diabetes. For all other people, 10-year risk must be calculated. The instrument employed is the Framingham Risk Prediction Score, which takes five factors into account: age, total cholesterol, HDL cholesterol, smoking status, and systolic blood pressure. Framingham scores can be determined using either (1) the tables for men and women shown in Figure 49-3 or (2) a web-based risk calculator, such as the one provided by the NCEP at *hp2010.nhlbihin.net/atpiii/calculator.asp*.

Estimate of 10-year risk for MEN

Age	Points
20–34	−9
35–39	−4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

	Points				
Total Cholesterol	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
<160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	−1
50–59	0
40–49	1
<40	2

Systolic BP (mm Hg)	If Untreated	If Treated
<120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	<1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20

10-Year Risk ____ %

Estimate of 10-year risk for WOMEN

Age	Points
20–34	−7
35–39	−3
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	12
70–74	14
75–79	16

	Points				
Total Cholesterol	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
<160	0	0	0	0	0
160–199	4	3	2	1	1
200–239	8	6	4	2	1
240–279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	−1
50–59	0
40–49	1
<40	2

Systolic BP (mm Hg)	If Untreated	If Treated
<120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
≥160	4	6

Point Total	10-Year Risk %
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27

10-Year Risk ____ %

Figure 49-3 Tables for calculating Framingham Risk Prediction Scores. To determine an individual's 10-year risk of developing clinical coronary disease, simply circle the appropriate points for each of the five risk factors considered (age, total cholesterol, smoking status, HDL cholesterol, and systolic blood pressure) and then add up the points. The point total indicates the 10-year risk. For example, a total of 13 points indicates a 10-year risk of 12% for men.

Identifying CHD Risk Equivalents.

A CHD risk equivalent is a condition that poses the same risk of a major coronary event as does established CHD (ie, more than 20% risk of a major event within 10 years). There are three basic CHD risk equivalents:

- Diabetes
- Atherosclerotic disease other than CHD (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease)
- The presence of multiple risk factors that confer a Framingham Risk Prediction Score greater than 20%

Identifying an Individual's CHD Risk Category

Under ATP III, there are four categories of CHD risk, labeled I, II, III, and IV (Table 49-6). People in category I are at highest risk: Their risk of a major coronary event within 10 years is over 20%. In comparison, the 10-year risk for people in category IV is low—less than 10%.

Category assignment is based on (1) the presence or absence of CHD (or a CHD risk equivalent, such as diabetes), (2) the number of risk factors the individual has (other than high LDL cholesterol), and (3) the individual's 10-year Framingham Risk Prediction Score. Although this assessment sounds complicated, it's not. Let's consider the hypothetical case of Ralph J.—and follow along by looking at Figure 49-3. Mr. J. is 62 years old, hypertensive, and smokes—but, remarkably, his HDL cholesterol is high (above 60 mg/dL). He has no family history of premature CHD, does not have CHD himself, and does not have diabetes. His 10-year Framingham Risk Prediction Score is 11%. What CHD risk category

does he belong in? Well, his age, blood pressure, and smoking status represent three major risk factors, but his high (healthy) HDL cholesterol allows subtraction of one risk factor, leaving a net of two major risk factors. The presence of two major risk factors plus the 11% Framingham score place Mr. J. in CHD risk category II (the next to highest risk group). Pretty easy, huh? And even easier if you use an online computational tool, such as the ones available at www.framinghamheartstudy.org/risk/index.html.

Risk category IV deserves comment. People assigned to this group have either no CHD risk factors or just one, and do not have CHD. As a rule, their 10-year CHD risk is not calculated. Why? Because there's no need: With so few risk factors, their 10-year risk is almost always below 10%.

CHD Risk Category	LDL Goal	LDL Level at Which to Initiate TLCs*	LDL Level at Which to Consider Drug Therapy
I *High Risk:* Has CHD or a CHD risk equivalent† (10-year risk is >20%)	<100 mg/dL (with an optional goal of <70 mg/dL)‡	Any level	≥100 mg/dL (at <100 mg/dL, LDL-lowering drugs are optional)§
II *Moderately High Risk:* Has 2 or more risk factors, but not CHD, and 10-year risk is 10–20%	<130 mg/dL (with an optional goal of <100 mg/dL)	Any level	≥130 mg/dL (between 100 and 129 mg/dL, LDL-lowering drugs are optional)§
III *Moderate Risk:* Has 2 or more risk factors, but not CHD, and 10-year risk is <10%	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
IV *Low to Moderate Risk:* Has 0–1 risk factor, but not CHD (10-year risk is probably <10%)¶	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (between 160 and 189 mg/dL, LDL-lowering drugs are optional)

Modified from the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497, 2001; as updated in Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 110:227–239, 2004.

TABLE 49-6 LDL Cholesterol Goals and Therapeutic Interventions for People in Specific CHD Risk Categories

* TLCs = therapeutic lifestyle changes.

† CHD risk equivalents include diabetes, forms of atherosclerosis other than CHD (eg, peripheral arterial disease, symptomatic coronary artery disease), and any combination of risk factors that creates a 10-year Framingham Risk Prediction Score of greater than 20%.

‡ For patients at very high risk (eg, those with a recent heart attack or those with CV disease combined with diabetes), the LDL goal may be set at less than 70 mg/dL, rather than 100 mg/Dl.

§ When LDL-lowering drugs are used in patients at high risk or moderately high risk, treatment should be sufficient to decrease the LDL level by 30% to 40%.

¶ Almost all people with 0 to 1 risk factor and no CHD have a 10-year risk below 10%, and hence formal evaluation of 10-year risk is not needed.

Final Note: Each Type of Dyslipidemia a Patient Has Contributes Independently to CHD Risk

Patients are likely to have more than one type of dyslipidemia—for example, high LDL cholesterol combined with low HDL cholesterol and high triglycerides—and each of these disorders contributes *independently* to cardiovascular risk. This means that fixing one just one of these problems will not eliminate the risk posed by the others. Accordingly, to get maximal risk reduction, we must correct all lipid abnormalities that are present.

Treatment of High LDL Cholesterol

Treatment of high LDL cholesterol is based on the individual's CHD risk category: The greater the 10-year risk, the more aggressive the treatment. As CHD risk increases, the target LDL goal gets lower, as does the LDL level at which treatment should commence. For example, among individuals in risk category I, the LDL goal is quite low (below 100 mg/dL—or below 70 in people at highest risk), compared with the higher goal (below 160 mg/dL) for people in category IV. Similarly, for individuals in category I, drugs are recommended if the LDL level is 100 mg/dL or above, compared with a much higher value (190 mg/dL or above) for those in category IV. Table 49-6 summarizes the LDL goal and the LDL levels at which to initiate treatment for people in all four CHD risk categories.

To reduce LDL levels, ATP III recommends two forms of intervention: (1) therapeutic lifestyle changes (TLCs) and (2) drug therapy. For some people, cholesterol can be reduced adequately with TLCs alone. Others require TLCs *plus* cholesterol-lowering drugs. Please note: Drugs should be used only as an *adjunct* to TLCs—not as a *substitute*.

Therapeutic Lifestyle Changes

Therapeutic lifestyle changes are nondrug measures used to lower LDL cholesterol. TLCs focus on three main issues: diet, weight control, and exercise. The measures are first-line treatment for LDL reduction, and should be implemented before trying drugs. Unfortunately, TLCs can be a challenge. Furthermore, arthritis and other physical conditions can limit attempts at exercise.

The TLC Diet.

This diet has two objectives: (1) reducing LDL cholesterol and (2) establishing and maintaining a healthy weight. The central feature of the diet is reduced intake of cholesterol and saturated fats: Individuals should limit intake of cholesterol to 200 mg/day or less and intake of saturated fat to 7% or less of total calories. Intake of *trans fats*— found primarily in crackers, commercial baked goods, and French fries—should be minimized. ATP III recommendations for cholesterol, fats, and other nutrients are summarized in Table 49-7. A list of specific foods to choose or avoid appears in Table 49-8.

If the basic TLC diet fails to lower LDL cholesterol adequately, ATP III recommends two additional measures: increased intake of soluble fiber (10 to 25 gm/day) and increased intake of plant stanols and sterols (2 gm/day). Oatmeal is a good source of soluble fiber. Plant stanols and sterols are available in the form of cholesterol-lowering margarines, commonly advertised as "buttery spreads" (see below under *Plant Stanol and Sterol Esters*).

Nutrient	Recommended Intake
Cholesterol	Less than 200 mg/day
Saturated fat*	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25–35% of total calories
Carbohydrates†	50–60% of total calories
Protein	About 15% of total calories
Fiber	20–30 gm/day
Total calories‡	Balance energy intake and expenditure to maintain a desirable body weight or prevent weight gain

From the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497, 2001.

TLC = therapeutic lifestyle changes.

TABLE 49-7 Nutrient Composition of the TLC Diet Described in ATP III

* *Trans*–fatty acids should be kept to a minimum.

† Carbohydrates should be derived mainly from foods rich in complex carbohydrates, such as fruits, vegetables, and grains (especially whole grains).

‡ Daily energy expenditure should include at least moderate physical activity (contributing about 200 kcal/day).

	Recommendation	
Food Type	**Choose**	**Decrease**
Fish, chicken, turkey, and lean meats	Fish; poultry without skin; lean cuts of beef, lamb, pork, or veal; shellfish	Fatty cuts of beef, lamb, or pork; spareribs; organ meats; regular cold cuts; sausage; hot dogs
Milk, cheese, yogurt, and dairy products	Skim and 1% fat milk (liquid, powdered, evaporated), buttermilk	4% fat milk (regular, evaporated, condensed), 2% fat milk, cream, half-and-half, imitation milk products, most nondairy creamers, whipped toppings
	Nonfat (%) or low-fat yogurt	Whole-milk yogurt
	Low-fat cottage cheese (1% or 2% fat)	Whole-milk cottage cheese (4%)
	Low-fat cheeses, farmer or pot cheeses (all of these cheeses should have no more than 2–6 gm of fat per ounce)	All-natural cheeses (eg, blue, Roquefort, Camembert, cheddar, Swiss)
		Cream cheese (including low-fat and "light" types), sour cream (including low-fat and "light" types)
	Sherbet, sorbet	Ice cream
Eggs	Egg whites (2 whites = 1 whole egg in recipes), cholesterol-free egg substitutes	Egg yolks*
Fruits and vegetables	Fresh, frozen, canned, and dried fruits and vegetables	Vegetables prepared in butter, cream, and other sauces
Breads and cereals	Homemade baked goods using unsaturated oils sparingly, angel food cake, low-fat crackers, low-fat cookies	Commercial baked goods: pies, cakes, muffins, doughnuts, croissants, biscuits, high-fat crackers, high-fat cookies
	Rice, pasta	Egg noodles
	Whole-grain breads and cereals (oatmeal, whole wheat, rye, bran, multigrain, etc.)	Breads in which eggs are a major ingredient
Fats and oils	Unsaturated vegetable oils: corn, olive, canola (rapeseed), safflower, sesame, soybean, sunflower oils	Butter, the so-called tropical oils (coconut oil, palm oil, palm kernel oil), lard, bacon fat
	Margarine (regular or diet),† shortening made from one of the unsaturated oils listed above	
	Mayonnaise, salad dressings made with one of the unsaturated oils listed above; low-fat or (preferred) fat-free dressings	Dressings made with egg yolk
	Seeds and nuts (especially walnuts)	Coconut
	Baking cocoa	Chocolate

From the National Cholesterol Education Program Adult Treatment Panel report. Arch Intern Med 148:36, 1988.

TABLE 49-8 Recommended Dietary Modifications to Lower Serum Cholesterol

* *Author's note:* Consuming up to 1 egg/day is not associated with an increased risk of fatal or nonfatal MI or ischemic or hemorrhagic stroke, except possibly in people with diabetes.

† *Author's note:* Since the publication of this table in 1988, new evidence indicates that *stick* margarine (but probably not newer low-fat spreads), which contains 17% trans-fat, raises LDL cholesterol and lowers HDL cholesterol, and hence should not be recommended.

Weight Control.

Being overweight or obese is a major risk factor for CHD. Conversely, weight loss can reduce both LDL cholesterol and CHD risk. Weight loss is especially important for people with metabolic syndrome (see below). In ATP III, achieving a healthy weight is encouraged for all people.

Exercise.

A sedentary lifestyle carries an increased risk of CHD. Conversely, performing regular exercise lowers CHD risk. Running and swimming, for example, can decrease LDL cholesterol and elevate HDL cholesterol, thereby reducing risk. In addition, exercise can reduce blood pressure, decrease insulin resistance, and improve overall CV performance. Accordingly, ATP III encourages regular physical activity (defined as 30 to 60 minutes of activity on most days). Improvements in the plasma lipid profile depend more on the total time spent exercising than on the intensity of exercise or improvements in fitness.

Smoking Cessation.

Smoking cigarettes raises LDL cholesterol and lowers HDL cholesterol, thereby increasing the risk of CHD. Smokers should be strongly encouraged to quit—and nonsmokers should be urged not to start.

Drug Therapy

Drugs are not the first-line therapy for lowering LDL cholesterol. Rather, drugs should be employed only if TLCs fail to reduce LDL cholesterol to an acceptable level—and then only if the combination of elevated LDL cholesterol and the patient's CHD risk category justify drug use (see Table 49-6). When drugs are employed, it is essential that

dietary modification continues. Why? Because the beneficial effects of diet and drugs are additive; drugs alone may be unable to achieve the LDL goal.

Table 49-9 summarizes properties of the drug families used to lower LDL cholesterol. The most effective agents are the *HMG-CoA reductase inhibitors* (eg, atorvastatin [Lipitor]), usually referred to simply as *statins*. Lesser used alternatives are *bile-acid sequestrants* (eg, cholestyramine) and *nicotinic acid* (niacin). Although fibrates are listed in Table 49-9, these drugs are used primarily to reduce levels of TGs—not LDLs. Treatment is initiated with a single drug, almost always a statin. If the statin is ineffective, a bile-acid sequestrant or nicotinic acid can be added to the regimen. Because LDL cholesterol levels will return to pretreatment values if drugs are withdrawn, *treatment must continue lifelong*. Patients should be made aware of this requirement. It is important to note that the principal benefit of drug therapy is *primary prevention:* Drugs are much better at preventing or retarding CHD than at promoting regression of established coronary atherosclerosis.

In addition to lowering LDL cholesterol, drugs may be used to raise HDL cholesterol. The most effective agents are nicotinic acid and the fibrates. However, as indicated in Table 49-9, virtually all of the drugs that we use to lower LDL cholesterol have the added benefit of increasing HDL cholesterol, at least to some degree.

Drug Class	Effect on LDL, HDL, and TGs	Common or Serious Adverse Effects	Contraindications	Clinical Trial Results
HMG-CoA reductase inhibitors (statins)	LDL ↓ 21–63% HDL ↑ 5–22% TG ↓ 6–43%	• Myopathy • Hepatotoxicity	*Absolute:* • Active or chronic liver disease • Pregnancy *Relative:* • Concurrent use of certain drugs*	Reduced major coronary events, stroke, CHD deaths, need for coronary procedures, and total mortality
Bile-acid sequestrants	LDL ↓ 15–30% HDL ↑ 3–5% TG ↓/no change	• GI distress • Constipation • Reduced drug absorption	*Absolute:* • Dysbetalipoproteinemia • TG above 400 mg/dL *Relative:* • TG above 200 mg/dL	Reduced major coronary events and CHD deaths
Nicotinic acid (niacin)	LDL ↓ 5–25% HDL ↑ 15–35% TG ↓ 20–50%	• Flushing • Hyperglycemia • Hyperuricemia • Upper GI distress • Hepatotoxicity	*Absolute* • Chronic liver disease • Gout *Relative:* • Diabetes • Hyperuricemia • Peptic ulcer disease	Reduced major coronary events and, possibly, reduced mortality
Fibrates	LDL ↓ 5–20%, but may increase if TGs are high HDL ↑ 10–20% TG ↓ 20–50%	• Dyspepsia • Gallstones • Myopathy	*Absolute:* • Severe renal disease • Severe liver disease	Reduced major coronary events
Ezetimibe	LDL ↓ 19% HDL ↑ 1–4% TG ↓ 5–10%	• Headache • Myalgia, arthralgia, possible myopathy • Abdominal pain, diarrhea	*Absolute:* • Moderate to severe liver injury, especially in patients taking a statin	Impact on coronary events and mortality has not been established

Modified from the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486–2497, 2001. Data on ezetimibe are from other sources.

TABLE 49-9 Drugs Used to Alter Plasma Levels of LDL, HDL, and Triglycerides

* Use caution in patients taking nicotinic acid, fibrates, and agents that inhibit cytochrome P450 isozyme 3A4, including cyclosporine, macrolide antibiotics (eg, erythromycin), azole antifungal drugs (eg, ketoconazole), and HIV protease inhibitors (eg, ritonavir).

Secondary Treatment Targets

Metabolic Syndrome

The term *metabolic syndrome* refers to a group of metabolic abnormalities associated with an increased risk of CHD and type 2 diabetes. The metabolic abnormalities involved are high blood glucose, high triglycerides, high apolipoprotein B, low HDL, small LDL particles, a prothrombotic state, and a proinflammatory state. Hypertension is both common and important. Metabolic syndrome is also known as *syndrome X*.

How is metabolic syndrome diagnosed? The ATP III panel proposed a simple set of diagnostic criteria, which was modified slightly in 2005 by a joint panel of the American Heart Association and the National Heart, Lung, and Blood Institute. According to the modified criteria, metabolic syndrome is diagnosed when three or more of the following are present:

- *Abdominal obesity*—waist circumference 40 inches or more for most men or 35 inches or more for most women (lower limits appear appropriate for Asian Americans)
- *High TG levels*—150 mg/dL or higher (or undergoing drug therapy for high TGs)
- *Low HDL cholesterol*—below 40 mg/dL for men or below 50 mg/dL for women (or undergoing drug therapy for reduced HDL)
- *Hyperglycemia*—fasting blood glucose 110 mg/dL or higher (or undergoing drug therapy for hyperglycemia)
- *High blood pressure*—130/85 mm Hg or higher (or undergoing drug therapy for hypertension)

Treatment has two primary goals: reducing the risk of atherosclerotic disease and reducing the risk of type 2 diabetes. According to ATP III, basic therapy consists of weight reduction and increased physical activity, which, together,

can reduce all symptoms of the metabolic syndrome. In addition, specific treatment should be directed at lowering blood pressure and TG levels. Patients should take low-dose aspirin to reduce the risk of thrombosis, unless they are at high risk of intracranial bleeds (hemorrhagic stroke).

Although the term *metabolic syndrome* is widely used, there is debate about its clinical relevance. In the cardiovascular community, most clinicians believe the term has great utility. By contrast, in the diabetes community, many clinicians feel the term is misleading, in that it implies the existence of a specific disease entity, even though it is defined only by a cluster of risk factors that may or may not have a common underlying cause. Furthermore, they point out that the risk associated with a diagnosis of metabolic syndrome is no greater than the sum of the risks of its components. Accordingly, until there is more proof that the metabolic syndrome actually exists, they believe the term serves no clinical purpose and hence should be avoided. This position was voiced in a joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. The American Heart Association and the National Heart, Lung, and Blood Institute countered with a joint statement of their own, reasserting their belief that the metabolic syndrome is an important clinical entity. Although the two camps disagree about whether the metabolic syndrome is an actual disease, both sides strongly agree that the risk factors that define the syndrome should be identified and treated.

High Triglycerides

High TG levels (above 200 mg/dL) are an independent risk factor for CHD. In clinical practice, high TGs are seen most often in patients with metabolic syndrome. However, high levels may also be associated with obesity, sedentary lifestyle, cigarette smoking, excessive alcohol intake, type 2 diabetes, certain genetic disorders, and high carbohydrate intake (when carbohydrates account for more than 60% of total caloric intake). In patients with high TG levels, the principal treatment goal is to achieve the original LDL goal. Dietary modification is always recommended. Statins being taken to lower cholesterol can help lower TGs as well, perhaps to a satisfactory level. However, if triglyceride levels remain unacceptably high, medications specific to TGs—nicotinic acid and fibrates—may be needed. Unfortunately, when these drugs are com-

bined with cholesterol-lowering drugs (as they often are), the adverse effects of cholesterol-lowering agents may be intensified.

DRUGS AND OTHER PRODUCTS USED TO ALTER PLASMA LIPID LEVELS

As discussed above, the lipid abnormality that contributes most to cardiovascular disease is high LDL cholesterol. Accordingly, we will focus primarily on drugs for this disorder. Nonetheless, we also need to consider other lipid abnormalities, especially (1) high total cholesterol,* (2) low HDL cholesterol, and (3) high TGs.

Some drugs for dyslipidemias are more selective than others. That is, whereas some drugs may improve just one dyslipidemia (eg, high TGs), others may improve two or more dyslipidemias. The highly selective agents can be useful as add-ons, to "target" a particular lipid abnormality when other medications prove inadequate.

Drugs that lower *LDL cholesterol* levels include HMG-CoA reductase inhibitors, bile-acid sequestrants, nicotinic acid, and ezetimibe. All are effective to varying degrees. The HMG-CoA reductase inhibitors are more effective than the others, cause fewer adverse effects, are better tolerated, and are more likely to improve clinical outcomes.

As we consider the drugs for lipid disorders, you should be aware of the following: Although all of these drugs can improve lipid profiles, not all of them improve clinical outcomes (reduced morbidity and mortality). This leads us to question whether some of the lipid abnormalities are a true cause of pathophysiology and ultimate death, or whether they are simply "associated markers" of some other pathophysiology that we don't yet understand.

HMG-CoA Reductase Inhibitors (Statins)

HMG-CoA reductase inhibitors, commonly called *statins* (because their generic names end in *statin*), are the most effective drugs for lowering LDL and total cholesterol. In addition, they can raise HDL cholesterol and lower TGs. Most importantly, these drugs have been shown to improve clinical outcomes, including lowering the risk of heart failure and sudden death. Because of these benefits, statins are among our most widely prescribed drugs, and have earned

tens of billions for their makers. For example, in 2007 atorvastatin [Lipitor] was the bestselling drug in the United States, generating $12.7 billion in sales.

Beneficial Actions

The statins have several actions that can benefit patients with (or at risk of) atherosclerosis. The most obvious is reduction of LDL cholesterol.

Reduction of LDL Cholesterol.

Statins have a profound effect on LDL cholesterol. Low doses decrease LDL cholesterol by about 25%, and larger doses decrease levels by as much as 63% (Table 49-10). Reductions are significant within 2 weeks and maximal within 4 to 6 weeks. Because cholesterol synthesis normally increases during the night, statins are most effective when given in the evening. If statin therapy is stopped, serum cholesterol will return to pretreatment levels within weeks to months. Hence, treatment should continue lifelong, unless serious adverse effects or specific contraindications (especially pregnancy or skeletal muscle damage) arise. The mechanism by which statins reduce cholesterol levels is discussed below.

* Note that total cholesterol is slightly different from the simple sum of LDL cholesterol (LDL-C) plus HDL cholesterol (HDL-C); triglycerides (TG) also contribute to the value, as in the following equation: total cholesterol = HDL-C + LDL-C + (TG/5) (provided TG levels are below 400 mg/dL).

Drug	% Change in Serum Lipids[*]			Liver Function Test (LFT) Monitoring[†]	Effect of CYP3A4 (Metabolism) Inhibitors on Statin Levels[‡]	Effect of Renal or Hepatic Impairment on Statin Levels
	LDL-C	HDL-C	TGs			
Atorvastatin [Lipitor]	↓ 27–60	↑ 6–14	↓ 17–53	At 12 wk and then every 6 mo	Moderate ↑	No change with renal disease; significant ↑ with hepatic impairment
Fluvastatin [Lescol]	↓ 22–38	↑ 2–11	↓ 12–25	At 12 wk and then every 6 mo	None	No change with renal disease; possible ↑ with hepatic impairment
Lovastatin [Mevacor]	↓ 21–42	↑ 5–10	↓ 6–27	At 6 and 12 wk and then every 6 mo	Significant ↑	↑ with significant renal dysfunction; no change with hepatic impairment
Pravastatin [Pravachol]	↓ 22–41	↑ 1–14	↓ 10–24	At 12 wk and then every 6 mo	None	Potential ↑ with either renal or hepatic dysfunction
Rosuvastatin [Crestor]	↓ 28–63	↑ 3–22	↓ 10–43	At 12 wk and then every 6 mo	None	↑ levels with severe renal impairment or hepatic

TABLE 49-10 HMG-CoA Reductase Inhibitors: Selected Aspects of Clinical Pharmacology

* LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TGs = triglycerides. Note that each of these drugs is available and administered in a range of doses; the changes in lipid levels reported above were obtained from a variety of studies and a variety of indications, and do not reflect the dose dependency of the drugs' effects.

† LFTs should always be performed before starting statin therapy (baseline) and at the indicated times after the first dose and after any change in dosage.

‡ CYP3A4 is an enzyme in the cytochrome P450 family. Inhibitors of CYP3A4 include itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, cyclosporine, nefazodone, and certain substances found in grapefruit juice.

Elevation of HDL Cholesterol.

Statins can increase levels of HDL cholesterol. Recall that low levels of HDL cholesterol (below 40 mg/dL) are an independent risk factor for CHD. Hence, by raising HDL cholesterol, statins can help reduce the risk of CV events. The objective is to raise levels to 50 mg/dL or more.

Reduction of Triglyceride Levels.

Although statins mainly affect cholesterol synthesis, and thereby lower cholesterol levels, these drugs may also raise HDL cholesterol and lower TGs. Just why these "anti-cholesterol" drugs lower TGs is unknown, but the response has been amply documented. Please note that, although statins may reduce TG levels, they are not actually prescribed for this action. Hence TG reduction is usually a side benefit in patients taking statins to lower their cholesterol. Of note, the fall of TG levels seems to be short lived, and hence a drug designed to lower TGs (eg, niacin) may eventually be needed.

Nonlipid Beneficial Cardiovascular Actions.

There is increasing evidence that statins do more than just alter lipid levels. Specifically, they can promote plaque stability (by decreasing plaque cholesterol content), reduce inflammation at the plaque site, slow progression of coronary artery calcification, improve abnormal endothelial function, enhance the ability of blood vessels to dilate, reduce the risk of atrial fibrillation, and reduce the risk of thrombosis by (1) inhibiting platelet deposition and aggregation and

(2) suppressing production of thrombin, a key enzyme in clot formation. All of these actions help reduce the risk of CV events.

Increased Bone Formation.

There is evidence that statins can promote bone formation, and may thereby reduce the risk of osteoporosis and related fractures. In animal studies, statins have increased bone formation, apparently by enhancing the activity of osteoblasts (the cells that lay down new bone). Several case-control studies in humans have shown an association between statin use and reduced risk of osteoporotic fractures. However, other case-control studies have failed to demonstrate a protective effect. The reason for this discrepancy could lie with the inherent weaknesses of case-control studies. Hence, the issue is likely to remain unresolved until data from randomized controlled trials are available. In the meantime, osteoporosis should be managed with bisphosphonates and/or other drugs with proven efficacy (see Chapter 74, Drugs Affecting Calcium Levels and Bone Mineralization).

Mechanism of Cholesterol Reduction

The mechanism by which statins decrease LDL cholesterol levels is complex, and depends ultimately on *increasing the number of LDL receptors on hepatocytes* (liver cells). The process begins with inhibition of hepatic HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. In response to decreased cholesterol production, hepatocytes synthesize more HMG-CoA reductase. As a result, cholesterol synthesis is largely restored to pretreatment levels. However—and for reasons that are not fully understood—inhibition of cholesterol synthesis causes hepatocytes to synthesize more LDL receptors. As a result, hepatocytes are able to remove more LDLs from the blood. In patients who are genetically unable to synthesize LDL receptors, statins fail to reduce LDL levels, indicating that (1) inhibition of cholesterol synthesis, by itself, is not sufficient to explain cholesterol-lowering effects; and (2) in order for statins to be effective, synthesis of LDL receptors must increase.

In addition to inhibiting HMG-CoA reductase, statins decrease production of apolipoprotein B-100. As a result, hepatocytes decrease production of VLDLs. This lowers VLDL levels along with LDL levels. Statins also raise HDL levels by 5% to 22%.

Clinical Trials

Statins slow progression of CHD and decrease the risk of stroke, hospitalization, cardiac events, peripheral vascular disease, and death. Benefits are seen in men and women, and in apparently healthy people as well as those with a history of CV events. Hence, the statins are useful for both primary and secondary prevention. Furthermore, these drugs can even help people with *normal* LDL levels, in addition to those whose LDL is high. Statins can also protect people with diabetes.

Secondary Prevention Studies.

In patients with evidence of existing CHD (angina pectoris or previous MI), statins reduce the risk of death from cardiac causes. This was first demonstrated conclusively in the landmark *Scandinavian Simvastatin Survival Study* (4S). After 4.9 to 6.3 years of follow-up, the death rate was 12% among patients taking placebo and 8% among those taking simvastatin—a 30% decrease in overall mortality. Benefits were due to a decrease in cardiac-related mortality; deaths from noncardiac causes were the same in both groups.

The *Cholesterol and Recurrent Events* (CARE) trial demonstrated the ability of statins to reduce the risk of stroke in addition to coronary events. In this study, 4159 people with a history of MI were given pravastatin (40 mg daily) or placebo. After 5 years, the incidence of MI (fatal or nonfatal) was 13.2% in those taking placebo and 10.2% in those taking the drug. Pravastatin also produced a 26% decrease in the risk of stroke.

The *Pravastatin or Atorvastatin Evaluation and Infection Therapy* (PROVE-IT) trial was the first to show that *intensive* reductions in LDL with statin therapy provide more CV protection than moderate reductions. In PROVE-IT, 4162 patients with acute coronary syndromes were randomized to either a moderate statin regimen (pravastatin, 40 mg daily) or an intensive statin regimen (atorvastatin, 80 mg daily). The result? LDL levels in the moderate group dropped to 95 mg/dL, compared with 62 mg/dL in the intensive group. Furthermore, not only did intensive therapy produce a greater decrease in LDL cholesterol, it produced a greater reduction in adverse outcomes: After 24 months, the incidence of CV events (death, MI, unstable angina, or revascularization) was only 22.4% in the intensive group compared with 26.3% in the moderate group.

These results led the ATP III panel to recommend lower target LDL levels in patients at very high CV risk.

Primary Prevention Studies.

Two studies have demonstrated the ability of statins to reduce mortality in people with no previous history of coronary events. In the first trial—the *West of Scotland Coronary Prevention Study* (WOSCOPS)—6595 men with high cholesterol were given either pravastatin (40 mg/day) or placebo. During an average follow-up of 4.9 years, 4.1% of those taking placebo died, compared with only 3.2% of those taking the drug. The second trial—the *Air Force/Texas Coronary Atherosclerosis Prevention Study* (AFCAPS/TexCAPS)—enrolled 6605 low-risk patients: men and women with average cholesterol levels (221 mg/dL) and no history of CV events. The subjects were randomly assigned to receive lovastatin (20 to 40 mg/day) or placebo. After an average follow-up of 5.5 years, the incidence of first major coronary events was 5.5% for those taking placebo and 3.5% for those taking the drug—representing a 36% decrease in risk.

Prevention in Patients with Normal Cholesterol Levels.

The landmark *Heart Protection Study,* published in 2002, was the first major trial to demonstrate that statins can reduce the risk of major coronary events in people who have normal levels of cholesterol. This double-blind, placebo-controlled trial enrolled 20,536 high-risk British patients: men and women with diabetes, prior MI, stroke, or angioplasty. Some had high levels of LDL and total cholesterol; others had normal levels. Subjects were randomly assigned to receive either simvastatin (40 mg/day) or placebo. After 5 years, the incidence of death was 12.9% in the treatment group, compared with 14.7% in the placebo group. Death from CHD was reduced by 18%. In addition, simvastatin reduced the risk of nonfatal MI by 38% and of stroke by 25%, and reduced the need for coronary revascularization (eg, angioplasty) by 30%. Most strikingly, benefits were seen in patients whose LDL cholesterol was *normal* or *low,* as well as in those whose levels were high. These data suggest a radical shift in practice. Specifically, they suggest *we should treat people at high CHD risk—not simply those with high cholesterol levels*. Obviously, doing so would greatly expand the number of patients receiving statin therapy.

Prevention in Patients with Diabetes.

Results of the *Collaborative Atorvastatin Diabetes Study* (CARDS) indicate that statin therapy can reduce the risk of CV events in diabetes patients, even if LDL levels are normal. This randomized trial, conducted in Britain and Ireland, enrolled 2838 patients with type 2 diabetes who had no history of CV disease. Half received 10 mg of atorvastatin [Lipitor] daily and half received a placebo. After a mean of 4 years, the combined incidence of acute coronary events, coronary revascularization, and stroke was only 5.8% in the atorvastatin group, compared with 9% in the placebo group, representing a 36% reduction in risk. These results suggest that statin therapy could benefit most patients with diabetes, regardless of their LDL level.

Therapeutic Uses

Indications for the statins keep expanding. When these drugs were introduced, they were approved only for hypercholesterolemia in adults. As understanding of their benefits has grown, so has the list of indications. Today the statins have nine FDA-approved indications, and can be prescribed for young patients as well as adults. Indications for individual statins are summarized in Table 49-11. Major indications are discussed below.

Indication	Atorvastatin [Lipitor]	Fluvastatin [Lescol]	Lovastatin [Altoprev, Mevacor]	Pravastatin [Pravachol]	Rosuvastatin [Crestor]	Simvastatin [Zocor]
Primary hypercholesterolemia	✓	✓	✓	✓	✓	✓
Homozygous familial hyperlipidemia	✓				✓	✓
Heterozygous familial hypercholesterolemia in adolescents	✓		✓	✓		✓
Mixed dyslipidemia	✓	✓	✓	✓	✓	✓
Primary dysbetalipoproteinemia	✓			✓		✓
Hypertriglyceridemia*	✓			✓	✓	✓
Primary prevention of coronary events	✓		✓	✓		✓
Secondary prevention of cardiovascular events		✓	✓	✓		✓
Increasing HDL cholesterol in primary hypercholesterolemia	✓	✓	✓	✓	✓	✓
Prevention of MI and stroke in type 2 diabetes	✓					

TABLE 49-11 HMG-CoA Reductase Inhibitors: FDA-Approved Indications

* Statins are not indicated in patients who have hypertriglyceridemia but also have low or normal LDL cholesterol, even if total cholesterol levels are elevated.

Hypercholesterolemia.

Statins are the most effective drugs we have for lowering cholesterol. In sufficient dosage, statins can decrease LDL cholesterol by more than 60%. For many patients, the treatment goal is to drop LDL cholesterol to below 100 mg/dL. For patients at very high CV risk, a target of 70 mg/dL may be appropriate.

Primary and Secondary Prevention of CV Events.

As discussed, statins can reduce the risk of CV events (eg, MI, angina, stroke) in patients who have never had one (primary prevention) and they can reduce the risk of a subsequent event after one has occurred (secondary prevention). Risk reduction is related to the reduction in LDL: the greater the LDL reduction, the greater the reduction in risk.

Post-MI Therapy.

Patients who have survived an MI, and who were not on statin therapy at the time of the event, are routinely started on a statin, the rationale being "better late than never." How soon should statin therapy start? Some clinicians would start "sometime" before hospital discharge. However, the current trend is to begin statins as soon as the patient is stabilized and able to take oral drugs. Other drugs for MI are discussed in Chapter 52.

Diabetes.

Cardiovascular disease is the primary cause of death in people with diabetes. Hence, to reduce mortality, controlling CV risk factors—especially hypertension and high cholesterol—is as important as controlling high blood glucose. The American Diabetes Association recommends a statin for all patients over the age of 40 whose *total* cholesterol is 135 mg/dL or higher—regardless of LDL cholesterol level. The American College of Physicians recommends a statin for (1) all patients with type 2 diabetes plus diagnosed CHD—*even if they don't have high cholesterol;* and (2) all adults with type 2 diabetes plus one additional risk factor (eg, hypertension, smoking, age over 55)—*even if they don't have high cholesterol*. Taken together, these guidelines suggest that most patients with diabetes should receive a statin.

Potential Uses.

Potential uses of statins extend well beyond diabetes and cardiovascular disorders. Judging from preliminary evidence, these drugs may eventually be used to prevent and/or treat a variety of conditions, including Parkinson's disease, Alzheimer's disease, kidney disease, multiple sclerosis, macular degeneration, glaucoma, rheumatoid arthritis, weak bones, and even cancer.

Pharmacokinetics

Statins are administered orally. The amount absorbed ranges between 30% and 90%, depending on the drug. Regardless of how much is absorbed, most of an absorbed dose is extracted from the blood on its first pass through the liver, the principal site at which statins act. Only a small fraction of each dose reaches the general circulation. Statins undergo rapid hepatic metabolism followed by excretion primarily in the bile. Only three agents—*lovastatin, pravastatin,* and *simvastatin*—undergo clinically significant (10% to 20%) excretion in the urine.

Three statins—*atorvastatin, lovastatin,* and *simvastatin*—are metabolized by the 3A4 isozyme of cytochrome P450 (CYP3A4). As a result, levels of these drugs can be lowered by agents that induce CYP3A4 synthesis. More importantly, their levels can be increased—sometimes dramatically—by agents that inhibit CYP3A4 (see below).

One agent—*rosuvastatin*—reaches abnormally high levels in people of Asian heritage. At usual therapeutic doses, rosuvastatin levels in these people are about twice those in whites. Accordingly, if rosuvastatin is used by Asians, dosage should be reduced.

Adverse Effects

Statins are generally well tolerated. Side effects are uncommon. Some patients develop headache, rash, or GI disturbances (dyspepsia, cramps, flatulence, constipation, abdominal pain). However, these effects are usually mild and transient. Serious adverse effects—hepatotoxicity and myopathy—are relatively rare. With one agent—rosuvastatin—serious effects may occur more often than with other statins.

Myopathy/Rhabdomyolysis.

Statins can injure muscle tissue. *Mild injury* occurs in 1% to 5% of patients. Characteristic symptoms are muscles aches, tenderness, and weakness that may be localized or diffuse. Rarely, mild injury progresses to *myositis,* defined as muscle inflammation associated with moderate elevation of creatine kinase (CK), an enzyme released from injured muscle. Release of potassium from muscle may cause blood potassium to rise. Rarely, myositis progresses to potentially fatal *rhabdomyolysis,* defined as muscle disintegration or dissolution,

associated with marked elevation of CK (greater than 10 times the upper limit of normal [ULN]) and possibly with renal failure. Fortunately, fatal rhabdomyolysis is extremely rare: the overall incidence is less than 0.15 case per 1 million prescriptions. Patients should be informed about the risk of myopathy and instructed to notify the prescriber if unexplained muscle pain or tenderness occurs. How statins cause myopathy is unknown.

Several factors increase the risk of myopathy. Among these are advanced age, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency, especially associated with diabetes), use of statins in high doses, concurrent use of fibrates (which can cause myopathy too), and use of drugs that can raise statin levels (see below). In addition, hypothyroidism increases risk. Accordingly, if muscle pain develops, thyroid function should be assessed.

Measurement of CK levels can facilitate diagnosis. The level should be determined at baseline, and again if symptoms of myopathy appear. If the CK level is more than 10 times the ULN, the statin should be discontinued. If the level is less than 10 times the ULN, the statin can be continued, provided myopathy symptoms and the CK level are followed weekly. Routine monitoring of CK in asymptomatic patients is unnecessary.

What is the risk with individual statins? Of the six statins in current use, *rosuvastatin* [Crestor] poses the highest risk of rhabdomyolysis. But even with this drug, the absolute number of cases is extremely low. With the other five statins, the risk is even lower. A seventh agent—*cerivastatin* [Baycol]—was withdrawn in 2001 because the risk was 16 to 80 times higher than with other statins.

Should concerns about myopathy discourage statin use? Definitely not! Remember that risk of serious myopathy is extremely low, whereas the risk of untreated high cholesterol is very high. Accordingly, when statins are used to lower cholesterol, the benefits of therapy (reduction of cardiovascular events) far outweigh the small risk of myopathy.

Hepatotoxicity.

Liver injury, as evidenced by elevations in serum transaminase levels, develops in 0.5% to 2% of patients treated 1 year or longer. However, jaundice and other clinical signs are rare. Progression to outright liver failure occurs very

rarely, if at all. Because of the risk of liver injury, product labeling recommends that liver function tests (LFTs) be done before treatment and every 6 to 12 months thereafter (see Table 49-10). However, there is evidence that routine monitoring may not really be needed. If serum transaminase levels rise to 3 times the ULN and remain there, statins should be discontinued. Transaminase levels decline to pretreatment levels following drug withdrawal.

Should statins be used by patients with active liver disease? The answer depends on the disease. In patients with viral or alcoholic hepatitis, statins should be avoided. However, in patients with the most common cause of hepatitis—nonalcoholic fatty liver disease—statins are acceptable therapy. In fact, in these patients, not only can statins reduce cholesterol levels, they may also decrease liver inflammation, improve LFTs, and reduce steatosis (fatty infiltration in the liver). Should LFTs be monitored? Yes—at baseline and every 3 months thereafter. If LFTs climb to 3 times the ULN, statin use should stop.

Peripheral Neuropathy.

Very rarely, peripheral neuropathy develops in statin users. Symptoms include weakness, difficulty walking, and tingling and pain in the hands and feet. The underlying mechanism could be disruption of neuronal integrity secondary to inhibition of cholesterol synthesis. Statin-related neuropathy is often reversible, but may take 3 to 12 months to resolve. At this time, solid proof that statins cause neuropathy is lacking—although the available data are strongly suggestive. Hence, if symptoms of neuropathy develop, the statin should be suspected.

Parkinson's Disease.

Recent evidence indicates a possible link between reduced LDL cholesterol levels and development of Parkinson's disease, and suggests that the statins employed to lower LDL levels might be the cause. There is no proof, however, that statins increase the risk for Parkinson's disease. Indeed, statins are being studied for their *protective* effects against this common neurologic condition. Here again, the well-established benefits of statin therapy would seem to clearly outweigh this potential risk.

Drug Interactions

With Other Lipid-Lowering Drugs.

Combining a statin with most other lipid-lowering drugs (except probably the bile-acid sequestrants) can increase the incidence and severity of the most serious statin-related adverse events: muscle injury, liver injury, and kidney damage. Increased risk occurs primarily with fibrates (gemfibrozil, fenofibrate), which are commonly combined with statins. The bottom line: When statins are combined with other lipid-lowering agents, use extra caution and monitor for adverse effects more frequently.

With Drugs That Inhibit CYP3A4.

Agents that inhibit CYP3A4 can raise levels of *lovastatin* and *simvastatin* substantially, and can raise levels of *atorvastatin* moderately. How? By slowing inactivation of these statins. Important inhibitors of CYP3A4 include macrolide antibiotics (eg, erythromycin), azole antifungal drugs (eg, ketoconazole, itraconazole), HIV protease inhibitors (eg, ritonavir), amiodarone (an antidysrhythmic drug), and cyclosporine (an immunosuppressant). If these drugs are combined with a statin, increased caution is advised. Some authorities recommend an automatic reduction in statin dosage if these inhibitors are used.

In addition to drugs, certain chemicals in grapefruit juice (and perhaps limes, tangelos, and Seville oranges) can inhibit CYP3A4—and the inhibition may persist for 3 days or more. How much grapefruit juice is needed for clinically significant inhibition? Older studies suggest that 1 quart (32 ounces) is required. In contrast, more recent studies suggest that as little as 8 ounces would do the job. Given this uncertainty, prudence dictates that, until more is known, statin users should avoid grapefruit juice entirely.

Use in Pregnancy

Statins are classified in Food and Drug Administration Pregnancy Risk Category X: the risks to the fetus outweigh any potential benefits of treatment. Some statins have been shown to produce fetal malformations in animal models—but only at doses far higher than are used in humans. Teratogenic effects in humans have not been reported. However, because statins inhibit synthesis of cholesterol, and since cholesterol is required for synthesis of cell membranes as

well as several fetal hormones, concern regarding human fetal injury remains. Moreover, there is no compelling reason to continue lipid-lowering drugs during pregnancy. Women of child-bearing age should be informed about the potential for fetal harm and warned against becoming pregnant. If pregnancy occurs, statins should be discontinued.

Preparations, Dosage, and Administration

Six statins are available for use alone: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Information on preparations, dosage, and administration is summarized in Table 49-12. Fixed-dose combination products are discussed separately below.

Drug	Dosage	Administration with Regard to Meals	Dosage Changes in Special Populations	Preparations
Atorvastatin [Lipitor]	*Initial:* 10 mg at bedtime *Maximum:* 80 mg at bedtime	Take without regard to meals	No changes needed	*Lipitor:* 10-, 20-, 40-, 80-mg tablets
Fluvastatin [Lescol, Lescol XL]	*Initial:* 20 mg at bedtime *Maximum:* 40 mg twice a day (Lescol); 80 mg at bedtime (Lescol XL)	Take without regard to meals	No changes needed	*Lescol:* 20-, 40-mg capsules *Lescol XL:* 80-mg extended-release tablets
Lovastatin [Altoprev, Mevacor, and generics]	*Initial:* 20 mg with the evening meal *Maximum:* 40 mg twice daily or 80 mg at bedtime	Take with evening meal to increase absorption	Reduce dosage for severe renal impairment	*Altoprev:* 10-, 20-, 40-, 60-mg extended-release tablets *Mevacor and generics:* 10-, 20-, 40-mg tablets
Pravastatin [Pravachol and generics]	*Initial:* 20 mg at bedtime *Maximum:* 40 mg at bedtime	Take without regard to meals	Reduce dosage for moderate to severe renal or hepatic impairment	*Pravachol and generics:* 10-, 20-, 40-, 80-mg tablets
Rosuvastatin [Crestor]	*Initial:* 20 mg at bedtime *Maximum:* 80 mg at bedtime	Take without regard to meals	Reduce dosage for severe renal impairment Reduce	*Crestor:* 5-, 10-, 20-, 40-mg tablets

TABLE 49-12 HMG-CoA Reductase Inhibitors: Preparations, Dosage, and Administration

Dosing is done once daily in the *evening,* either with the evening meal or at bedtime. Why take these drugs late in the day? Because endogenous cholesterol synthesis increases during the night. As a result, statins have the greatest impact when given in the evening.

Drug Selection

Several factors bear on statin selection, including the LDL goal, drug interactions, kidney function, safety in Asians, and price.

LDL Goal.

If a 30% to 40% reduction in LDL is deemed sufficient, any statin will do. However, if LDL must be lowered by more than 40%, then atorvastatin or simvastatin may be preferred. Although rosuvastatin is also highly effective, experience with this drug is relatively limited, and hence we can't be as comfortable regarding its safety or ability to reduce CV events.

Drug Interactions.

Drugs that inhibit CYP3A4 can raise levels of atorvastatin, lovastatin, and simvastatin, thereby increasing the risk of toxicity, especially myopathy and liver injury. Accordingly, in patients taking a CYP3A4 inhibitor, other statins are preferred.

Kidney Function.

For patients with normal renal function, any statin is acceptable. However, for patients with significant renal impairment, atorvastatin or fluvastatin is preferred (because no dosage adjustment is needed).

Safety in Asians.

The same dose of *rosuvastatin,* when given to Asian and Caucasian subjects, may produce twofold higher blood levels in the Asians. Accordingly, when rosuvastatin is used in Asians, start with the lowest available dosage and monitor diligently.

Price.

One agent—lovastatin—is available as a generic product, and hence is cheaper than all other statins. For patients who need a modest reduction in LDL and are not taking a CYP3A4 inhibitor, lovastatin would be the best choice.

Nicotinic Acid (Niacin)

Nicotinic acid [Niacor, Niaspan] reduces LDL and TG levels. In addition, it increases HDL levels better than any other drug. In patients with high LDL levels, nicotinic acid reduces the risk of major coronary events and may also reduce total mortality. Unfortunately, although nicotinic acid is effective, flushing and other side effects can be unpleasant, and may lead to nonadherence. Niacin is available in three formulations, which differ with respect to onset, duration, and the incidence and severity of side effects.

Mechanism of Action.

The primary effect of nicotinic acid is to decrease production of VLDLs. Since LDLs are by-products of VLDL degradation, the fall in VLDL levels causes LDL levels to fall as well. There appear to be several mechanisms by which nicotinic acid decreases VLDL production. Notable among these is inhibition of lipolysis in adipose tissue.

Effect on Plasma Lipoproteins.

Nicotinic acid reduces LDL cholesterol by 5% to 25% and TGs by 20% to 50%. In addition, it raises HDL cholesterol by 15% to 35%. Triglyceride levels begin to fall within the first 4 days of therapy. LDL levels decline more slowly, taking 3 to 5 weeks for maximum reductions. Combining nicotinic acid with lovastatin can reduce LDL cholesterol by 45% and can raise HDL cholesterol by 41%. Triple therapy (nicotinic acid plus a statin plus a bile-acid sequestrant) can decrease LDL cholesterol by 70% or more.

Therapeutic Use.

Nicotinic acid is a drug of choice for lowering TG levels in patients at risk of pancreatitis. Additional uses include mixed elevation of LDLs and TGs, and elevation of TGs in combination with low levels of HDLs. One formulation—sold as Niaspan—is approved for elevating HDL cholesterol.

Nicotinic acid (niacin) also has a role as a vitamin. The doses employed to correct niacin deficiency are much smaller than those employed to reduce lipoprotein levels. The role of nicotinic acid as a vitamin is discussed in Chapter 80.

Adverse Effects.

The most frequent adverse reactions involve the skin (flushing, itching) and GI tract (gastric upset, nausea, vomiting, diarrhea). *Intense flushing* of the face, neck, and ears occurs in practically all patients receiving nicotinic acid in pharmacologic doses. This reaction diminishes in several weeks, and can be attenuated by taking 325 mg of aspirin 30 minutes before each dose. (Aspirin reduces flushing by preventing synthesis of prostaglandins, which mediate the flushing response.) Flushing can also be reduced by using extended-release niacin (eg, Niaspan) rather than immediate-release niacin (eg, Niacor).

Nicotinic acid is *hepatotoxic*. Severe liver damage has occurred. Liver injury is most likely with Slo-Niacin (a *long-acting* formulation), especially in high doses (above 2 gm/day). Liver injury is less likely with Niaspan, the extended-release formulation noted above. Because of the risk of hepatotoxicity, liver function should be assessed before treatment and periodically thereafter.

Additional adverse effects are *hyperglycemia* and *gouty arthritis*.

Preparations, Dosage, and Administration.

Nicotinic acid (niacin) is marketed generically and under several trade names. The drug is available in tablets (immediate-release [IR], timed-release, controlled-release, sustained-release) or capsules (timed-release, extended-release, sustained-release).

With IR formulations (prescription Niacor and over-the-counter products), blood levels of niacin climb rapidly. As a result, these products are associated with the highest incidence and severity of facial and upper body flushing, at least for the first few weeks. Thereafter, the intensity of these responses tends to fade. To manage flushing, patients using IR niacin often take prophylactic aspirin. (The need for aspirin is much lower with the long-acting products.) With IR niacin, blood levels of niacin can fall relatively soon. Therefore, to

maintain steady blood levels, the total daily dose should be given as two or three divided doses (1 to 3 gm each), rather than as one large dose.

The most popular niacin formulation is Niaspan, a so-called slow-release formulation. Following oral dosing, the tablet slowly dissolves, causing blood levels to rise slowly and remain relatively steady. As a result, flushing is minimized, and once-daily dosing (usually 1 to 3 gm) is adequate. The major drawback to Niaspan is that it costs more than other niacin products.

Long-acting niacin [Slo-Niacin] has a longer half-life than other formulations. While this may seem like a therapeutic advantage (longer lasting high levels of drug), there is an increased risk of hepatotoxicity, and hence this product should be avoided.

(*Note:* When nicotinic acid is taken as a vitamin, the dosage is only about 25 mg/day—much lower than the dosages employed to lower plasma lipoproteins.)

Bile-Acid Sequestrants

Bile-acid sequestrants reduce LDL cholesterol levels. In the past, these drugs were a mainstay of lipid-lowering therapy. Today, they are used primarily as adjuncts to statins. Three agents are available: colesevelam, cholestyramine, and colestipol. Colesevelam is newer than the other two, and better tolerated.

Colesevelam

Colesevelam [Welchol], approved for hyperlipidemia in 2000, is the drug of choice when a bile-acid sequestrant is indicated. Like the older sequestrants, colesevelam is a nonabsorbable resin that binds (sequesters) bile acids and other substances in the GI tract, and thereby prevents their absorption and promotes their excretion. Colesevelam is preferred to the older sequestrants for three reasons: (1) the drug is better tolerated (less constipation, flatulence, bloating, and cramping); (2) it does not reduce absorption of fat-soluble vitamins (A, D, E, and K); and (3) it does not significantly reduce the absorption of statins, digoxin, warfarin, and most other drugs studied.

In addition to its beneficial effects on plasma lipids, colesevelam can help control hyperglycemia in patients with type 2 diabetes. The drug was approved

for adjunctive therapy of this disorder in 2008. Diabetes and its management are the subject of Chapter 56.

Effect on Plasma Lipoproteins.

The main response to bile-acid sequestrants is a reduction in LDL cholesterol. LDL decline begins during the first week of therapy, and becomes maximal (about a 20% drop) within about a month. When these drugs are discontinued, LDL cholesterol returns to pretreatment levels in 3 to 4 weeks.

Bile-acid sequestrants may increase VLDL levels in some patients. In most cases, the elevation is transient and mild. However, if VLDL levels are elevated prior to treatment, the increase induced by the bile-acid sequestrants may be sustained and substantial. Accordingly, bile-acid sequestrants are not drugs of choice for lowering LDL cholesterol in patients with high VLDL levels.

Pharmacokinetics.

Bile-acid sequestrants are biologically inert. Also, they are insoluble in water, cannot be absorbed from the GI tract, and are not attacked by digestive enzymes. Following oral administration, they simply pass through the intestine and become excreted in the feces.

Mechanism of Action.

The bile-acid sequestrants lower LDL cholesterol through a mechanism that ultimately depends on increasing LDL receptors on hepatocytes. As background, you need to know that bile acids secreted into the intestine are normally reabsorbed and reused. Bile-acid sequestrants prevent this reabsorption. Here's what happens. Following oral administration, these drugs form an insoluble complex with bile acids in the intestine; this complex prevents the reabsorption of bile acids, and thereby accelerates their excretion. Because bile acids are normally reabsorbed, the increase in excretion creates a demand for increased synthesis, which takes place in the liver. Since bile acids are made from cholesterol, liver cells must have an increased cholesterol supply in order to increase bile acid production. The required cholesterol is provided by LDL. To avail themselves of more LDL cholesterol, liver cells increase their number of LDL receptors, thereby increasing their capacity for LDL uptake. The result is an increase in LDL uptake from plasma, which decreases circu-

lating LDL levels. Individuals who are genetically incapable of increasing LDL receptor synthesis are unable to benefit from these drugs.

Therapeutic Use.

Colesevelam is indicated as adjunctive therapy to diet and exercise for reducing LDL cholesterol in patients with primary hypercholesterolemia. The drug may be used alone, but usually is combined with a statin. On average, colesevelam alone can lower LDL cholesterol by about 20% (the typical range is between 15% and 30%). In contrast, combined therapy with a statin can reduce LDL cholesterol by up to 50%. Similar results can be obtained by combining a sequestrant with nicotinic acid.

Adverse Effects.

The bile-acid sequestrants are not absorbed from the GI tract, and hence are devoid of systemic effects. Accordingly, they are safer than all other lipid-lowering drugs.

Adverse effects are limited to the GI tract. *Constipation* is the main complaint. This can be minimized by increasing dietary fiber and fluids. If necessary, a mild laxative may be used. Other GI effects include *bloating, indigestion,* and *nausea*. The older agents—cholestyramine and colestipol—can decrease fat absorption, and may thereby *decrease uptake of fat-soluble vitamins*. However, this does not seem to be a problem with colesevelam.

Drug Interactions.

The bile-acid sequestrants can form insoluble complexes with other drugs. Medications that undergo binding cannot be absorbed, and hence are not available for systemic effects. Drugs known to form complexes with the sequestrants include thiazide diuretics, digoxin, warfarin, and some antibiotics. To reduce formation of sequestrant-drug complexes, oral medications that are known to interact should be administered either 1 hour before the sequestrant or 4 hours after.

Preparations, Dosage, and Administration.

Colesevelam [Welchol] is supplied in 625-mg tablets for oral use. The initial dosage is 3 tablets (1.9 gm) twice daily or 6 tablets (3.8 gm) once daily. All doses

are taken with food and water. Of note, the dosage for colesevelam is much smaller than that of cholestyramine (8 to 24 gm/day) or colestipol (5 to 30 gm/day).

Older Agents: Cholestyramine and Colestipol

Cholestyramine and colestipol have been available for decades, but have been largely replaced by colesevelam. Why? Because colesevelam is better tolerated, does not impede absorption of fat-soluble vitamins, and has minimal effects on other drugs. Although cholestyramine and colestipol are very safe, they frequently cause constipation, abdominal discomfort, and bloating.

Cholestyramine [Questran, Questran Light, Prevalite, LoCHOLEST, LoCHOLEST Light] is supplied in powdered form. Patients should be instructed to mix the powder with fluid, because swallowing it dry can cause esophageal irritation and impaction. Appropriate liquids for mixing include water, fruit juices, and soups. Pulpy fruits with a high fluid content (eg, applesauce, crushed pineapple) may also be used. The dosage range is 4 to 16 gm/day.

Colestipol hydrochloride [Colestid] is supplied in granular form (5 gm) and in 1-gm tablets. The dosage for the *granules* is 5 to 30 gm/day administered in one or more doses. Patients should be instructed to mix the granules with fluids or pulpy fruits before ingestion. The dosage for the *tablets* is 2 to 16 gm/day administered in one or more doses. Tablets should be swallowed whole and taken with fluid.

Ezetimibe

Ezetimibe [Zetia] is a new and unique drug for reducing plasma cholesterol. Benefits derive from blocking cholesterol absorption.

Mechanism of Action and Effect on Plasma Lipoproteins.

Ezetimibe acts on cells of the brush border of the small intestine to inhibit cholesterol absorption. The drug blocks absorption of dietary cholesterol as well as cholesterol secreted in the bile. Treatment reduces plasma levels of total cholesterol, LDL cholesterol, triglycerides, and apolipoprotein B. In addition, ezetimibe can produce a small *increase* in HDL cholesterol.

Therapeutic Use.

Ezetimibe is indicated as an adjunct to diet modification for reducing total cholesterol, LDL cholesterol, and apolipoprotein B in patients with primary hypercholesteremia. The drug is approved for monotherapy and for combined use with a statin. In clinical trials, ezetimibe alone reduced LDL cholesterol by about 19%, increased HDL cholesterol by 1% to 4%, and decreased TGs by 5% to 10%. When ezetimibe was combined with a statin, the reduction in LDL cholesterol was about 25% greater than with the statin alone. Because ezetimibe is new, we do not yet know if it reduces CV morbidity or mortality.

Pharmacokinetics.

Ezetimibe is administered orally, and the amount absorbed is not affected by food. In the small intestine and liver, ezetimibe undergoes extensive conversion to ezetimibe glucuronide, an active metabolite. Both compounds—parent drug and metabolite—are eliminated primarily in the bile. The elimination half-life is about 22 hours.

Adverse Effects.

Ezetimibe is generally well tolerated. During clinical trials, the incidence of significant side effects was nearly identical to that seen with placebo. However, during postmarketing surveillance, there have been reports of myopathy, rhabdomyolysis, hepatitis, pancreatitis, and thrombocytopenia. In contrast to the bile-acid sequestrants, ezetimibe does not cause constipation and other adverse GI effects.

Drug Interactions.

Statins.

In patients taking a statin, adding ezetimibe slightly increases the risk of liver damage (as indicated by elevated transaminase levels). If the drugs are combined, transaminase levels should be carefully monitored. Combining ezetimibe with a statin may also increase the risk of myopathy.

Fibrates.

Both ezetimibe and fibrates (gemfibrozil and fenofibrate) can increase the cholesterol content of bile, and can thereby increase the risk of gallstones. Both also increase the risk of myopathy. Accordingly, combined use is not recommended.

Bile-Acid Sequestrants.

Cholestyramine (and probably colestipol) can significantly decrease the absorption of ezetimibe. To minimize effects on absorption, ezetimibe should be administered at least 2 hours before a sequestrant or 4 hours after.

Cyclosporine.

Cyclosporine may greatly increase levels of ezetimibe. If the drugs are combined, careful monitoring is needed.

Caution.

In patients with hepatic impairment, availability of ezetimibe is significantly increased. At this time, we do not know if increased availability is harmful. Until more is known, patients with moderate or severe hepatic insufficiency should not be given the drug.

Preparations, Dosage, and Administration.

Ezetimibe [Zetia] is available in 10-mg tablets for oral use. The recommended dosage is 10 mg once a day, taken with or without food. If ezetimibe is combined with a statin, both drugs can be taken at the same time. If ezetimibe is combined with a bile-acid sequestrant, ezetimibe should be taken 2 hours before the sequestrant or 4 hours after.

Fibric Acid Derivatives (Fibrates)

The fibric acid derivatives, also known as fibrates, are the most effective drugs available for lowering triglyceride levels. In addition, they can raise HDL cholesterol, but have little or no effect on LDL cholesterol. Fibrates can increase the risk of bleeding in patients taking warfarin (an anticoagulant) and the risk of rhabdomyolysis in patients taking statins. In the United States, three preparations are available: gemfibrozil [Lopid], fenofibrate [Tricor, others], and

fenofibric acid [TriLipix], a new delayed-release preparation noteworthy for being the first and only fibrate *approved* for use with a statin.

Gemfibrozil

Gemfibrozil [Lopid] decreases triglyceride (VLDL) levels and raises HDL cholesterol levels. The drug does not reduce LDL cholesterol to a significant degree. Its principal indication is hypertriglyceridemia.

Effect on Plasma Lipoproteins.

Gemfibrozil decreases plasma TG content by lowering VLDL levels. Maximum reductions in VLDLs range from 40% to 55%, and are achieved within 3 to 4 weeks of treatment. Gemfibrozil can raise HDL cholesterol by 6% to 10%. In patients with normal TG levels, the drug can produce a small reduction in LDL levels. However, if TG levels are high, gemfibrozil may actually increase LDL levels.

Mechanism of Action.

Gemfibrozil and other fibrates appear to work by interacting with a specific receptor subtype—known as peroxisome proliferator-activated receptor alpha (PPAR alpha)—present in the liver and brown adipose tissue. Activation of PPAR alpha leads to (1) increased synthesis of lipoprotein lipase (LPL) and (2) reduced production of apolipoprotein C-III (an inhibitor of LPL). Both actions accelerate the clearance of VLDLs, and thereby reduce levels of TGs. How do fibrates elevate HDL levels? By activating PPAR alpha, fibrates increase production of apolipoproteins A-I and A-II, which in turn facilitates HDL formation.

Therapeutic Use.

Gemfibrozil is used primarily to *reduce high levels of plasma triglycerides* (VLDLs). Treatment is limited to patients who have not responded adequately to weight loss and diet modification. Gemfibrozil can also reduce LDL cholesterol. However, other drugs (statins, cholestyramine, colestipol) are much more effective.

Gemfibrozil can be used to *raise HDL cholesterol,* although it is not approved for this application. When tested in patients with normal LDL cholesterol and low

HDL cholesterol, gemfibrozil reduced the risk of major CV events (eg, stroke, fatal and nonfatal MI) by 20%. Because LDL cholesterol was normal, it appears that benefits were due primarily to elevation of HDL cholesterol, along with reduction of plasma triglycerides.

Adverse Effects.

Gemfibrozil is generally well tolerated. The most common reactions are rashes and GI disturbances (nausea, abdominal pain, diarrhea).

Gallstones.

Gemfibrozil increases biliary cholesterol saturation, thereby increasing the risk of gallstones. Patients should be informed about manifestations of gallbladder disease (eg, upper abdominal discomfort, intolerance of fried foods, bloating) and instructed to notify the prescriber at once if these develop. Patients with pre-existing gallbladder disease should not take the drug.

Myopathy.

Like the statins, gemfibrozil and other fibrates can cause myopathy. Warn patients to report any signs of muscle injury, such as tenderness, weakness, or unusual muscle pain.

Liver Injury.

Gemfibrozil is hepatotoxic. The drug can disrupt liver function and may also pose a risk of liver cancer. Periodic tests of liver function are required.

Drug Interactions.

Gemfibrozil displaces warfarin from plasma albumin, thereby increasing anticoagulant effects. Prothrombin time (international normalized ratio) should be measured frequently to assess coagulation status. Warfarin dosage may need to be reduced.

Gemfibrozil increases the risk of *statin-induced myopathy*. Accordingly, the combination of a statin with gemfibrozil should be used with great caution, if at all.

Preparations, Dosage, and Administration.

Gemfibrozil [Lopid] is available in 600-mg tablets. The adult dosage is 600 mg twice a day. Dosing is done 30 minutes before the morning and evening meals.

Fenofibrate

Actions and Uses.

Fenofibrate [Tricor, Antara, Lofibra, Triglide] is indicated for hypertriglyceridemia in patients who have not responded to dietary measures. The drug lowers triglycerides by decreasing levels of VLDLs. Fenofibrate was approved for American use in 1998, but has been available in other countries for years.

Pharmacokinetics.

Fenofibrate is well absorbed from the GI tract, especially in the presence of food. Once absorbed, the drug is rapidly converted to fenofibric acid, its active form. In the blood, the drug is 98% protein bound. Elimination is the result of hepatic metabolism followed by renal excretion. The plasma half-life is about 20 hours.

Adverse Effects and Drug Interactions.

The most common adverse effects are rash and GI disturbances. Like gemfibrozil, fenofibrate can cause gallstones and liver injury. In animal models, doses 1 to 6 times the maximum human dose caused cancers of the pancreas and liver. Like gemfibrozil, fenofibrate can increase the risk of bleeding with warfarin and the risk of myopathy with statins.

Preparations, Dosage, and Administration.

Fenofibrate is available in several formulations that differ with respect to dosage and the impact of food on absorption. Four products are discussed below.

Tricor tablets (48 and 145 mg) are made using NanoCrystal technology to enhance absorption. As a result, dosing can be done with or without food. The dosage range is 48 to 148 mg/day.

Triglide tablets (50 and 160 mg), like TriCor tablets, may be administered with or without food. The dosage range is 50 to 160 mg/day.

Antara capsules, which contain micronized particles, must be administered with food to maximize absorption. The dosage range is 43 to 130 mg/day.

Lofibra capsules (67, 134, and 200 mg) contain micronized particles. Like Antara, Lofibra must be administered with food to maximize absorption. The dosage range is 67 to 200 mg/day.

Fenofibric Acid

Fenofibric acid [TriLipix], approved in December 2008, is the active metabolite of fenofibrate. Accordingly, the pharmacology of the drug is much like that of the parent compound. Fenofibric acid stands out from other fibrates for being the only group member *approved* for use with a statin. However, just like other fibrates and the statins, fenofibric acid can cause myopathy, and hence combined use with a statin still poses significant myopathy risk. Therefore, the combination must be employed with great care. Fenofibric acid is available in delayed-release capsules (45 and 135 mg). Daily dosages for hypertriglyceridemia range from 45 mg to 135 mg. In patients with renal impairment, a low dosage (45 mg/day) should be used. When combined with a statin for patients with mixed dyslipidemias, fenofibric acid should be dosed at 135 mg/day.

Drug Combinations

Lovastatin/Niacin

Actions and Uses.

Lovastatin (immediate-release) and niacin (extended-release) are available in fixed-dose combinations under the trade name *Advicor*. Lovastatin serves primarily to lower LDL cholesterol; niacin raises HDL cholesterol and lowers TGs. In one clinical trial, using the combination for 12 months lowered LDL cholesterol by 45%, raised HDL cholesterol by 41%, and lowered TGs by 42%. The product has two indications: primary hypercholesterolemia and mixed dyslipidemia. However, it should not be used for initial therapy of either con-

dition. Rather, it should be reserved for patients who have not responded adequately to lovastatin or niacin alone.

Adverse Effects.

The principal concerns are *flushing* (from the niacin) and *hepatotoxicity* (from both drugs). Flushing can be reduced by taking aspirin or ibuprofen 30 minutes before dosing. To monitor liver injury, LFTs should be obtained at baseline, every 6 to 12 weeks for the first 6 months of treatment, and every 6 months thereafter.

Lovastatin poses a very small risk of *myopathy*. Nonetheless, advise patients to report any muscle pain or weakness. Adding a fibrate to the regimen increases the risk of myopathy (because, like the statins, fibrates can promote muscle injury).

Preparations, Dosage, and Administration.

Advicor is available in three lovastatin/niacin strengths: 20/500 mg, 20/750 mg, and 20/1000 mg. The recommended initial dosage is 20/500 mg once a day at bedtime. At 4-week intervals, the niacin dosage can be increased by 500 mg/day. The maximum dosage is 40/2000 mg. All doses should be taken with a low-fat snack, which can enhance absorption and reduce GI distress.

Simvastatin/Niacin

Actions and Uses.

Simvastatin and extended-release niacin are marketed as a fixed-dose combination under the trade name *Simcor*. The product is indicated for hypercholesterolemia and hypertriglyceridemia. Benefits derive from the actions described above for these drugs individually. Most studies show that simvastatin/niacin is no better than simvastatin alone for lowering LDL cholesterol. However, and importantly, the combination *is* superior to simvastatin alone for raising HDL cholesterol and, especially, for lowering TGs.

Adverse Effects.

The most common side effects of Simcor, regardless of the dose, include flushing, pruritus, and headache. These are the classic and most common side effects of niacin.

Preparations, Dosage, and Administration.

Simcor tablets are available in three simvastatin/niacin strengths: 20/500 mg, 20/750 mg, and 20/1000 mg. Therapy usually starts with the 20/500-mg product, taken once daily at bedtime. Dosing with a low-fat snack is recommended to reduce the incidence and severity of niacin-related stomach upset. If needed and tolerated, the daily niacin dose can be gradually increased to 2000 mg (with 40 mg of simvastatin).

Simvastatin/Ezetimibe

Actions and Uses.

Simvastatin and ezetimibe are available in fixed-dose combination tablets under the trade name *Vytorin*. Following its approval in 2004, the product quickly became one of our "top 10" most-prescribed drugs. Vytorin has only one indication: hypercholesterolemia. Because ezetimibe has a different mechanism of action than simvastatin, the combination can lower cholesterol more effectively than simvastatin alone. Theoretically, this is an extraordinarily rational drug combination. Recall that cholesterol has two main sources: endogenous production by the liver, and dietary sources. Simvastatin reduces endogenous production, and ezetimibe reduces absorption of cholesterol from the diet.

With this combination, the dose of simvastatin required to effectively lower cholesterol may be lower than the dose required when simvastatin is used alone. As a result, the risk of statin-related adverse effects (which is low to start with) can be reduced. Additional benefits of the combination are convenience (take just one pill instead of two) and reduced cost (the combination costs less than both drugs purchased separately).

Despite the advantages of Vytorin, some authorities are concerned that the combination may be less beneficial than simvastatin alone. This concern is based on four facts:

- We have proof that simvastatin *alone* can decrease adverse outcomes (ie, MI and other CV events).
- We have no proof that the combination can decrease adverse outcomes of elevated cholesterol (even though it *can* reduce *levels* of cholesterol).
- In addition to lowering cholesterol, statins have other beneficial actions (eg, they often lower elevated TGs).
- When ezetimibe and simvastatin are combined, cholesterol goals can be met using simvastatin in reduced dosage.

Because the combination permits a reduction in simvastatin dosage, there is concern that, although the target cholesterol goal may be reached, the reduction in adverse outcomes may be smaller than when cholesterol is lowered using simvastatin alone. Until data on adverse outcomes with the combination are available, this concern will remain unresolved.

Adverse Effects and Drug Interactions.

Vytorin is generally well tolerated. However, myopathy is a concern (because both drugs can cause muscle injury). Concurrent use of a fibrate, which can also cause myopathy, increases the risk. The risk of myopathy and other adverse effects is also increased by inhibitors of CYP3A4, the enzyme that inactivates simvastatin. Because Vytorin contains a statin, the product is contraindicated for women who are pregnant and for patients with liver disease.

Preparations, Dosage, and Administration.

Vytorin tablets contain 10 mg of ezetimibe plus either 10, 20, 40, or 80 mg of simvastatin. The usual starting dosage is 10 mg ezetimibe/20 mg simvastatin each day. Dosing is done once daily, preferably in the evening. The simvastatin dosage can be increased as needed and tolerated.

Pravastatin/Aspirin

Pravastatin tablets and aspirin tablets are available co-packaged under the brand name *Pravigard PAC*. The product is approved for preventing MI, stroke, and death in patients with evidence of cardiovascular or cerebrovascular disease. Pravastatin improves lipid profiles, and aspirin suppresses aggregation of platelets.

Potential side effects include myopathy (from the statin), and bleeding and GI mucosal damage (from the aspirin). Pravigard PAC should not be used by patients under 18 years old, by women who are pregnant, by anyone with severe hepatic or renal impairment, or by any patient for whom aspirin alone is contraindicated.

Each Pravigard PAC package contains 30 pravastatin tablets and 30 buffered aspirin tablets. Six pravastatin/aspirin combinations are available: 20/81 mg, 20/325 mg, 40/81 mg, 40/325 mg, 80/81 mg, and 80/325 mg. The usual dosage is 40/81 mg or 40/325 mg. Administration is done once daily with a full glass of water, with or without food. Although this package may be convenient, please note that we can achieve the same benefits—at much lower cost—by purchasing generic simvastatin and the cheapest buffered aspirin available. The pharmacology of aspirin is discussed in Chapter 70.

Atorvastatin/Amlodipine

Atorvastatin and amlodipine (a calcium channel blocker) are available in fixed-dose combination tablets under the trade name *Caduet*. This is the first single product indicated for dyslipidemia combined with hypertension and/or angina. The combination has two advantages over taking each drug separately: fewer pills to swallow and slightly lower cost. Eleven amlodipine/atorvastatin combinations are available: 2.5 mg amlodipine with either 10, 20, or 40 mg atorvastatin; 5 mg amlodipine with either 10, 20, 40, or 80 mg atorvastatin; and 10 mg amlodipine with either 10, 20, 40, or 80 mg atorvastatin. Dosage is individualized on the basis of therapeutic response and tolerance of adverse effects. The pharmacology of amlodipine and other calcium channel blockers is discussed in Chapter 44.

Fish Oil

Consuming fatty fish or fish-oil supplements is associated with a decreased risk of CHD and CHD-related death. Fish oil may also decrease the risk of thrombotic stroke.

Why is fish oil beneficial? Because it contains two "heart healthy" compounds: *eicosapentaenoic acid* (EPA) and *docosahexaenoic acid* (DHA). Structures are shown in Figure 49-4. Both compounds are long-chain, omega-3 polyunsatur-

ated fatty acids, with a methyl group at one end and a carboxyl group at the other. They are called *omega-3 fatty acids* because they have a double bond located three carbons in from the methyl terminus.

Eicosapentaenoic acid (EPA)

Docosahexaenoic acid (DHA)

Figure 49-4 Structures of omega-3 fatty acids in fish oil.

How do omega-3 fatty acids help us? The answer is unclear. We know that *high* doses (1 to 4 gm) can lower TG levels. Benefits of *lower* doses (850 mg to 1 gm) may result from reducing platelet aggregation; reducing thrombosis (by effects on platelets and the vascular endothelium); reducing inflammation (which may help stabilize atherosclerotic plaques); and reducing blood pressure and cardiac dysrhythmias.

To reduce the risk of cardiovascular events, the American Heart Association recommends eating at least two servings of fish a week. Fish with high concentrations of EPA and DHA are preferred. Among these are mackerel, halibut, herring, salmon, albacore tuna, and trout. The goal is to take in, on average, about 1 gm of omega-3 fatty acids a day.

Because fish concentrate certain environmental contaminants—especially methylmercury, dioxins, and polychlorinated biphenyls (PCBs)—eating fish carries some risk. Methylmercury can cause heart disease as well as neurologic damage, manifesting as tremor, numbness, tingling, altered vision, and impaired concentration. Exposure *in utero* or during early childhood can lead to mental retardation, blindness, and seizures. With dioxin and PCBs, carcinogenesis is the major concern. Does this mean we should avoid eating fish? No. For postmenopausal women, and for men who are middle-aged or older,

the benefits of fish outweigh the risks. For women who are pregnant or breastfeeding, fish consumption should be limited to 12 ounces a week, and certain species—swordfish, king mackerel, shark, and golden snapper, all of which may have high levels of methylmercury—should be avoided entirely. Young children should limit fish consumption too. For people who like salmon, dioxin exposure can be reduced by eating wild salmon, which contains much less dioxin than farm-raised salmon. Exposure to all contaminants can be reduced by using fish-oil supplements, which have much less contamination than fish themselves.

Lovaza.

Lovaza, formerly sold as *Omacor,* is the trade name for the first preparation of omega-3-acid ethyl esters approved by the FDA. The product, available only by prescription, contains a combination of EPA and DHA. Lovaza is approved as an adjunct to dietary measures to reduce very high levels of TGs (500 mg/dL or greater). When used alone, Lovaza can reduce TG levels by 20% to 50%. Combining it with simvastatin produces a further decrease. Because large doses of omega-3 fatty acids can impair platelet function, leading to prolonged bleeding time, the product should be used with care in patients taking anticoagulants or antiplatelet drugs, including aspirin. Lovaza is supplied in 1-gm, liquid-filled, soft-gelatin capsules that contain approximately 465 mg of EPA

and approximately 375 mg of DHA. The recommended dosage is 4 gm/day, taken either all at once (4 capsules) or in two doses (2 capsules twice a day).

Plant Stanol and Sterol Esters

Stanol esters and sterol esters, which are analogs of cholesterol, can reduce intestinal absorption of cholesterol (by 10%), and can thereby reduce levels of LDL cholesterol (by 14%). These compounds do not affect HDL levels or TG levels. ATP III recommends adding plant stanols or sterols to the diet if the basic TLC diet fails to reduce LDL cholesterol to the target level. Where can you get plant stanols and sterols? Two good sources are the *Benecol* brand of margarine, and soft spreads sold under the trade name *Promise*.

Estrogen

In postmenopausal women, estrogen therapy (0.625 mg/day) reduces LDL cholesterol by 15% to 25% and increases HDL cholesterol by 10% to 15%. However, despite these beneficial effects on plasma lipids, estrogen therapy does not reduce CV morbidity or mortality. In fact, when estrogen is combined with a progestin for postmenopausal therapy, the risk of MI and other CV events actually goes up. Accordingly, estrogen therapy is no longer recommended for CV protection in postmenopausal women. The risks and benefits of estrogen therapy are discussed at length in Chapter 60 (Estrogens and Progestins).

Cholestin

Cholestin is the trade name for a dietary supplement that can lower cholesterol levels. The product is made from rice fermented with red yeast. Its principal active ingredient—*lovastatin*—is identical to the active ingredient in Mevacor, a brand-name cholesterol-lowering drug. In addition to lovastatin, Cholestin contains at least seven other HMG-CoA reductase inhibitors (statins).

Several clinical trials have demonstrated that Cholestin can lower cholesterol levels, although none has studied its effects on CV events. In a trial conducted at Tufts University School of Medicine, Cholestin reduced total cholesterol by 11.4% and LDL cholesterol by 21%, and increased HDL cholesterol by 14.6%. Similarly, in a study conducted at the University of California at Los Angeles Medical School, Cholestin reduced total cholesterol by 16% and LDL cholesterol by 22%. Whether Cholestin also reduces the incidence of CHD is unknown.

Information on Cholestin is lacking in four important areas: clinical benefits, adverse effects, drug interactions, and precise mechanism of action. As noted, there are no data on the ability of Cholestin to reduce the risk of MI, stroke, or any other CV event. In contrast, the clinical benefits of prescription statins (lovastatin and all the others) are fully documented. There is little or no information on the adverse effects or drug interactions of Cholestin. In contrast, the safety (and hazards) of prescription statins, as well as their drug interactions, have been studied extensively.

The mechanism by which Cholestin lowers cholesterol levels is only partly understood. The recommended daily dose of Cholestin contains only 5 mg of lovastatin and varying doses of other HMG-CoA reductase inhibitors, compared with 10 mg for the lowest recommended dose of Mevacor. Hence, it seems unlikely that the statins in Cholestin can fully account for the supplement's ability to reduce cholesterol levels. This implies that Cholestin has one or more active ingredients that have not yet been identified. What they are and how they may work is a mystery.

What's the bottom line? Until more is known about Cholestin, stick with statins—medications of proven safety and efficacy. Furthermore, for people with health insurance, using statins is cheaper: Most insurers will cover the cost of statins, but will not pay for Cholestin.

Legal note: The makers of Cholestin are under fire from the FDA. Why? Because the FDA has ruled that, owing to its lovastatin content, Cholestin is subject to the strict regulations that apply to *drugs*—not the lax regulations that apply to nutritional supplements. (The distinction is discussed at length in Chapter 107, Dietary Supplements). Hence, until the manufacturer conducts rigorous studies on safety, efficacy, and pharmacokinetics, sales of Cholestin must stop. The maker has received numerous warning letters from the FDA, and legal proceedings are ongoing.

KEY POINTS

- Lipoproteins are structures that transport lipids (cholesterol and triglycerides [TGs]) in blood.

- Lipoproteins consist of a hydrophobic core, a hydrophilic shell, plus at least one apolipoprotein, which serves as a recognition site for receptors on cells.
- Lipoproteins that contain apolipoprotein B-100 transport cholesterol and/or TGs from the liver to peripheral tissues.
- Lipoproteins that contain apolipoproteins A-I or A-II transport cholesterol from peripheral tissues back to the liver.
- There are three major types of lipoproteins: VLDLs (very-low-density lipoproteins), LDLs (low-density lipoproteins), and HDLs (high-density lipoproteins).
- VLDLs transport TGs to peripheral tissues.
- The contribution of VLDLs to CHD is unclear.
- LDLs transport cholesterol to peripheral tissues.
- Elevation of LDL cholesterol greatly increases the risk of CHD.
- By reducing LDL cholesterol levels, we can arrest or reverse atherosclerosis, and can thereby reduce morbidity and mortality from CHD.
- HDLs transport cholesterol back to the liver.
- HDLs protect against CHD.
- Atherogenesis is a chronic inflammatory process that begins with accumulation of LDLs beneath the arterial endothelium, followed by oxidation of LDLs.
- Under ATP III, all adults over the age of 20 should be screened every 5 years for total cholesterol, LDL cholesterol, HDL cholesterol, and TGs.
- Under ATP III, treatment of high LDL cholesterol is based on the individual's 10-year risk of having a major coronary event.
- Individuals with established CHD or a CHD risk equivalent (eg, diabetes) are in the highest 10-year risk group.
- The higher the 10-year risk, the lower the LDL goal and the LDL levels at which therapeutic lifestyle changes (TLCs) and drug therapy should be implemented.

- Diet modification along with exercise is the primary method for reducing LDL cholesterol. Drugs are employed only if diet modification and exercise fail to reduce LDL cholesterol to the target level.
- Therapy with cholesterol-lowering drugs must continue lifelong. If these drugs are withdrawn, cholesterol levels will return to pretreatment values.
- Statins (HMG-CoA reductase inhibitors) are the most effective drugs for lowering LDL cholesterol, and they cause few adverse effects.
- Statins can slow progression of CHD, decrease the number of adverse cardiac events, and reduce mortality.
- Statins reduce LDL cholesterol levels by increasing the number of LDL receptors on hepatocytes, thereby enabling hepatocytes to remove more LDLs from the blood. The process by which LDL receptor number is increased begins with inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis.
- Three statins—atorvastatin, lovastatin, and simvastatin—are metabolized by CYP3A4, and hence their levels can be increased by CYP3A4 inhibitors (eg, cyclosporine, erythromycin, ketoconazole, ritonavir).
- Rarely, statins cause liver damage. Tests of liver function should be done at baseline and every 6 to 12 months thereafter.
- Rarely, statins cause myopathy. Patients who experience unusual muscle pain or soreness should inform the prescriber. A marker for muscle injury—creatine kinase (CK)—should be measured at baseline and again if signs of myopathy develop.
- Statins should not be used during pregnancy.
- Bile-acid sequestrants (eg, colesevelam) reduce LDL cholesterol levels by increasing the number of LDL receptors on hepatocytes. The mechanism is complex and begins with preventing reabsorption of bile acids in the intestine.
- Bile-acid sequestrants are not absorbed from the GI tract, and hence do not cause systemic adverse effects. However, they can cause constipation and other GI effects. (GI effects with one agent—colesevelam—are minimal.)

- Bile-acid sequestrants form complexes with other drugs, and thereby prevent their absorption. Accordingly, oral medications should be administered 1 hour before the sequestrant or 4 hours after. (Interactions of colesevelam with other drugs are minimal.)
- Ezetimibe lowers LDL cholesterol by reducing cholesterol absorption in the small intestine.
- Like the statins, ezetimibe can cause muscle injury.
- Gemfibrozil and other fibrates are the most effective drugs for lowering TG levels.
- Like the statins, the fibrates can cause muscle injury.
- Nicotinic acid reduces LDL and TG levels and raises HDL levels. Unfortunately, the drug also causes adverse effects in nearly all patients.
- Immediate-release formulations of nicotinic acid cause intense flushing of the face, neck, and ears in most patients. Flushing can be reduced by taking aspirin or ibuprofen 30 minutes before dosing, by dividing the total daily dose into smaller doses taken more often, or by using an extended-release product (eg, Niaspan).
- Nicotinic acid can cause liver injury. The risk is greatest with older sustained-release formulations.

Summary of Major Nursing Implications*

IMPLICATIONS THAT APPLY TO ALL DRUGS THAT LOWER LDL CHOLESTEROL

Preadministration Assessment

Baseline Data

Obtain laboratory values for total cholesterol, LDL cholesterol, HDL cholesterol, and TGs (VLDLs).

Identifying CHD Risk Factors

The patient history and physical examination should identify CHD risk factors. These include smoking, obesity, advancing age (men over 45 years, women over 55 years), family history of premature CHD, a personal history of cerebrovascular or peripheral vascular disease, reduced levels of HDL cholesterol (below 40 mg/dL), and hypertension.

In the past, diabetes was considered a CHD risk factor. However, because the association between diabetes and CHD is so strong, diabetes is now considered a CHD risk *equivalent* (ie, it poses the same 10-year risk of a major coronary event as CHD itself).

Measures to Enhance Therapeutic Effects

Diet Modification

Diet modification should precede and accompany drug therapy for elevated LDL cholesterol. **Inform patients about the importance of diet in controlling cholesterol levels and arrange for dietary counseling. Advise patients to limit consumption of cholesterol (to below 200 mg/day) and saturated fat (to below 7% of caloric intake) and to follow the other dietary recommendations listed in** Tables 49-7 and 49-8. **If these measures fail to reduce LDL cholesterol to the target level, advise patients to add soluble fiber and plant stanols or sterols to the regimen.**

Exercise

Regular exercise can reduce LDL cholesterol and elevate HDL cholesterol, thereby reducing the risk of CHD. **Help the patient establish an appropriate exercise program.**

Reduction of CHD Risk Factors

Correctable CHD risk factors should be addressed. **Encourage cigarette smokers to quit. Encourage obese patients to lose weight.** Disease states that promote CHD—diabetes mellitus and hypertension—must be treated.

Promoting Compliance

Drug therapy for elevated LDL cholesterol must continue lifelong; if drugs are withdrawn, cholesterol levels will return to pretreatment values. **Inform patients about the need for continuous therapy, and encourage them to adhere to the prescribed regimen.**

HMG-COA REDUCTASE INHIBITORS (STATINS)

Atorvastatin

Fluvastatin

Lovastatin

Pravastatin

Rosuvastatin

Simvastatin

In addition to the implications discussed below, *see above* for implications that apply to all drugs that lower LDL cholesterol.

Preadministration Assessment

Therapeutic Goal

Statins, in combination with diet modification and exercise, are used primarily to lower levels of LDL cholesterol. Additional indications are shown in Table 49-11.

Baseline Data

Obtain a baseline lipid profile, consisting of total cholesterol, LDL cholesterol, HDL cholesterol, and TGs (VLDLs). Also, obtain baseline LFTs and a CK level.

Identifying High-Risk Patients

Statins are *contraindicated* for patients with viral or alcoholic hepatitis and for women who are pregnant.

Exercise *caution* in patients with nonalcoholic fatty liver disease, in those who consume alcohol to excess, and in those taking fibrates or ezetimibe, or agents that inhibit CYP3A4 (eg, cyclosporine, erythromycin, ketoconazole, ritonavir). Use *rosuvastatin* with *caution* in Asian patients.

Implementation: Administration

Route

Oral.

Administration

Instruct patients to take lovastatin with the evening meal; all other statins can be administered without regard to meals. Advise patients that dosing in the evening is preferred for all statins.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Cholesterol levels should be monitored monthly early in treatment and at longer intervals thereafter.

Minimizing Adverse Effects

Statins are very well tolerated. Side effects are uncommon, and serious adverse effects—hepatotoxicity and myopathy—are rare.

Hepatotoxicity.

Statins can injure the liver, but jaundice and other clinical signs are rare. Liver function should be assessed before treatment and every 6 to 12 months thereafter (see Table 49-10). If serum transaminase becomes persistently excessive (more than 3 times the ULN), statins should be discontinued. Statins should be avoided in patients with alcoholic or viral hepatitis, but may be used in patients with nonalcoholic fatty liver disease.

Myopathy.

Rarely, statins cause muscle injury. If statins are not withdrawn, injury may progress to severe myositis or potentially fatal rhabdomyolysis. **Inform patients about the risk of myopathy, and instruct them to notify the prescriber if unexplained muscle pain or tenderness develops.** If muscle pain does develop, the CK level should be measured, and, if it is more than 10 times the ULN, the statin should be withdrawn.

Minimizing Adverse Interactions

The risk of myopathy is increased by (1) gemfibrozil, fenofibrate, and ezetimibe, which promote myopathy themselves; and by (2) inhibitors of CYP3A4—such as cyclosporine, macrolide antibiotics (eg, erythromycin), azole antifungal drugs (eg, ketoconazole), and HIV protease inhibitors (eg, ritonavir)—which can cause statin levels to rise. The combination of a statin with any of these drugs should be used with caution.

Use in Pregnancy

Statins are contraindicated during pregnancy. **Inform women of child-bearing age about the potential for fetal harm and warn them against becoming pregnant.** If pregnancy occurs, statins should be withdrawn.

NICOTINIC ACID (NIACIN)

In addition to the implications discussed below, *see above* for implications that apply to all drugs that lower LDL cholesterol.

Preadministration Assessment

Therapeutic Goal

Nicotinic acid, in conjunction with diet modification and exercise, is used to reduce levels of LDL cholesterol, VLDLs, and TGs. It is also used to raise HDL cholesterol.

Baseline Data

Obtain laboratory values for total cholesterol, LDL cholesterol, HDL cholesterol, and TGs (VLDLs). Obtain a baseline test of liver function.

Identifying High-Risk Patients

Nicotinic acid is *contraindicated* for patients with active liver disease or severe or recurrent gout.

Exercise *caution* in patients with diabetes mellitus, asymptomatic hyperuricemia, mild gout, and peptic ulcer disease.

Implementation: Administration

Formulations

Advise patients to use an immediate-release formulation (eg, Niacor) or an extended-release formulation (eg, Niaspan), but not a long-acting formulation (eg, Slo-Niacin).

Route

Oral.

Administration

Instruct patients to take nicotinic acid with meals to reduce GI upset.

Measures to Enhance Therapeutic Effects

Dietary Therapy

Diet modification should precede and accompany drug therapy for elevated TGs and VLDLs. **Inform patients about the importance of diet in controlling lipid levels and arrange for dietary counseling.** In addition to following the guidelines presented above for all drugs that reduce LDL cholesterol, patients with hypertriglyceridemia should restrict consumption of alcohol and other sources of triglycerides.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Blood lipid levels should be monitored monthly early in treatment and at longer (3- to 6-month) intervals thereafter.

Minimizing Adverse Effects

Flushing.

Nicotinic acid causes flushing of the face, neck, and ears in most patients. **Advise patients that flushing can be reduced by taking 325 mg of aspirin 30**

minutes before each dose, or by using an extended-release product (eg, Niaspan).

Hepatotoxicity.

Nicotinic acid may injure the liver, causing jaundice or other symptoms. Liver function should be assessed before treatment and periodically thereafter. Hepatotoxicity is most likely with long-acting niacin (eg, Slo-Niacin), and much less likely with immediate-release niacin (eg, Niacor) or extended-release niacin (eg, Niaspan). Use with any statin also increases the risks.

Hyperglycemia.

Nicotinic acid may cause hyperglycemia and reduced glucose tolerance. Blood glucose should be monitored frequently. Exercise caution in patients with diabetes.

Hyperuricemia.

Nicotinic acid can elevate blood levels of uric acid. Exercise caution in patients with gout, and even in patients who have hyperuricemia but no symptoms of gout.

BILE-ACID SEQUESTRANTS

Cholestyramine

Colesevelam

Colestipol

In addition to the implications discussed below, *see above* for implications that apply to all drugs that lower LDL cholesterol.

Preadministration Assessment

Therapeutic Goal

Bile-acid sequestrants, in conjunction with diet modification and exercise (and a statin if necessary), are used to reduce elevated levels of LDL cholesterol.

Baseline Data

Obtain laboratory values for total cholesterol, LDL cholesterol, HDL cholesterol, and TGs (VLDLs).

Implementation: Administration

Route

Oral.

Administration

Instruct patients to mix cholestyramine powder and colestipol granules with water, fruit juice, soup, or pulpy fruit (eg, applesauce, crushed pineapple) to reduce the risk of esophageal irritation and impaction. Inform patients that the sequestrants are not water soluble, and hence the mixtures will be cloudy suspensions, not clear solutions.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Cholesterol levels should be monitored monthly early in treatment and at longer intervals thereafter.

Minimizing Adverse Effects

Constipation.

Cholestyramine and *colestipol*—but not colesevelam—can cause constipation. **Inform patients that constipation can be minimized by increasing dietary fiber and fluids. A mild laxative may be used if needed. Instruct patients taking cholestyramine or colestipol to notify the prescriber if constipation becomes bothersome, in which case a switch to colesevelam should be considered.**

Vitamin Deficiency.

Cholestyramine and *colestipol*—but not colesevelam—can impair absorption of fat-soluble vitamins (A, D, E, and K). Vitamin supplements may be required. Colesevelam does not reduce vitamin absorption.

Minimizing Adverse Interactions

Cholestyramine and *colestipol*—but not colesevelam—can bind with other drugs and prevent their absorption. **Advise patients to administer other medications 1 hour before these sequestrants or 4 hours after.**

GEMFIBROZIL

Preadministration Assessment

Therapeutic Goal

Gemfibrozil, in conjunction with diet modification, is used to reduce elevated levels of TGs (VLDLs). The drug is not very effective at lowering LDL cholesterol. It may also be used to raise low levels of HDL cholesterol.

Baseline Data

Obtain laboratory values for total cholesterol, LDL cholesterol, HDL cholesterol, and TGs (VLDLs).

Identifying High-Risk Patients

Gemfibrozil is *contraindicated* for patients with liver disease, severe renal dysfunction, and gallbladder disease.

Use with *caution* in patients taking statins or warfarin.

Implementation: Administration

Route

Oral.

Administration

Instruct patients to administer gemfibrozil 30 minutes before the morning and evening meals.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Obtain periodic tests of blood lipids.

Minimizing Adverse Effects

Gallstones.

Gemfibrozil increases gallstone development. **Inform patients about symptoms of gallbladder disease (eg, upper abdominal discomfort, intolerance of fried foods, bloating), and instruct them to notify the prescriber if these develop.**

Myopathy.

Gemfibrozil can cause muscle damage. **Warn patients to report any signs of muscle injury, such as tenderness, weakness, or unusual muscle pain.**

Liver Disease.

Gemfibrozil may disrupt liver function. Cancer of the liver may also be a risk. Obtain periodic tests of liver function.

Minimizing Adverse Interactions

Warfarin.

Gemfibrozil enhances the effects of warfarin, thereby increasing the risk of bleeding. Obtain more frequent measurements of prothrombin time and assess the patient for signs of bleeding. Reduction of warfarin dosage may be required, and reassessment and readjustment of the warfarin dosage may be needed if the fibrate is stopped.

Statins.

Gemfibrozil and statins both cause muscle injury. Risks rise when both are used. Use the combination with caution.

50 Drugs for Angina Pectoris

Angina pectoris is defined as sudden pain beneath the sternum, often radiating to the left shoulder and arm. Anginal pain is precipitated when the oxygen supply to the heart is insufficient to meet oxygen demand. Most often, angina occurs secondary to atherosclerosis of the coronary arteries. Hence, angina should be seen as a symptom of a disease and not as a disease in its own right. In the United States, over 7 million people have chronic stable angina; about 350,000 new cases develop annually.

Drug therapy of angina has two goals: (1) prevention of myocardial infarction (MI) and death and (2) prevention of myocardial ischemia and anginal pain. Two types of drugs are employed to decrease the risk of MI and death: cholesterol-lowering drugs and antiplatelet drugs. These agents are discussed in Chapters 49 and 51, respectively.

In this chapter, we focus on antianginal drugs (ie, drugs that prevent myocardial ischemia and anginal pain). There are three main families of antianginal agents: *organic nitrates* (eg, nitroglycerin), *beta blockers* (eg, propranolol), and *calcium channel blockers* (eg, verapamil). In addition, a fourth agent—*ranolazine*—can be combined with these drugs to supplement their effects. Most of the chapter focuses on the organic nitrates. Beta blockers and calcium channel blockers are discussed at length in previous chapters, and hence consideration here is limited to their use in angina. Ranolazine, a new drug with limited indications, is introduced here.

DETERMINANTS OF CARDIAC OXYGEN DEMAND AND OXYGEN SUPPLY

Before discussing angina pectoris, we need to review the major factors that determine cardiac oxygen demand and supply.

Oxygen Demand.

The principal determinants of cardiac oxygen demand are heart rate, myocardial contractility, and, most importantly, intramyocardial wall tension. Wall tension is determined by two factors: cardiac preload and cardiac afterload.

(Preload and afterload are defined in Chapter 42.) In summary, cardiac oxygen demand is determined by (1) heart rate, (2) contractility, (3) preload, and (4) afterload. Drugs that reduce these factors reduce oxygen demand.

Oxygen Supply.

Cardiac oxygen supply is determined by myocardial blood flow. Under resting conditions, the heart extracts nearly all of the oxygen delivered to it by the coronary vessels. Hence, the only way to accommodate an increase in oxygen demand is to increase blood flow. When oxygen demand increases, coronary arterioles dilate; the resultant decrease in vascular resistance allows blood flow to increase. During exertion, coronary blood flow increases four- to fivefold over the flow rate at rest. It is important to note that myocardial perfusion takes place only during diastole (ie, when the heart relaxes). Perfusion does not take place during systole. Why? Because the vessels that supply the myocardium are squeezed shut when the heart contracts.

ANGINA PECTORIS: PATHOPHYSIOLOGY AND TREATMENT STRATEGY

Angina pectoris has three forms: (1) *chronic stable angina* (exertional angina), (2) *variant angina* (Prinzmetal's or vasospastic angina), and (3) *unstable angina*. Our focus is on stable angina and variant angina. Consideration of unstable angina is brief.

Chronic Stable Angina (Exertional Angina)

Pathophysiology.

Stable angina is triggered most often by an increase in physical activity. Emotional excitement, large meals, and cold exposure may also precipitate an attack. Because stable angina usually occurs in response to strain, this condition is also known as *exertional angina* or *angina of effort*.

The underlying cause of exertional angina is coronary artery disease (CAD), a condition characterized by deposition of fatty plaque in the arterial wall. If an artery is only partially occluded by plaque, blood flow will be reduced and angina pectoris will result. However, if complete vessel blockage occurs, blood flow will stop and MI (heart attack) will result.

The impact of CAD on the balance between myocardial oxygen demand and oxygen supply is illustrated in Figure 50-1. As depicted, in both the healthy heart and the heart with CAD, oxygen supply and oxygen demand are in balance during rest. (In the presence of CAD, resting oxygen demand is met through dilation of arterioles distal to the partial occlusion. This dilation reduces resistance to blood flow and thereby compensates for the increase in resistance created by plaque.)

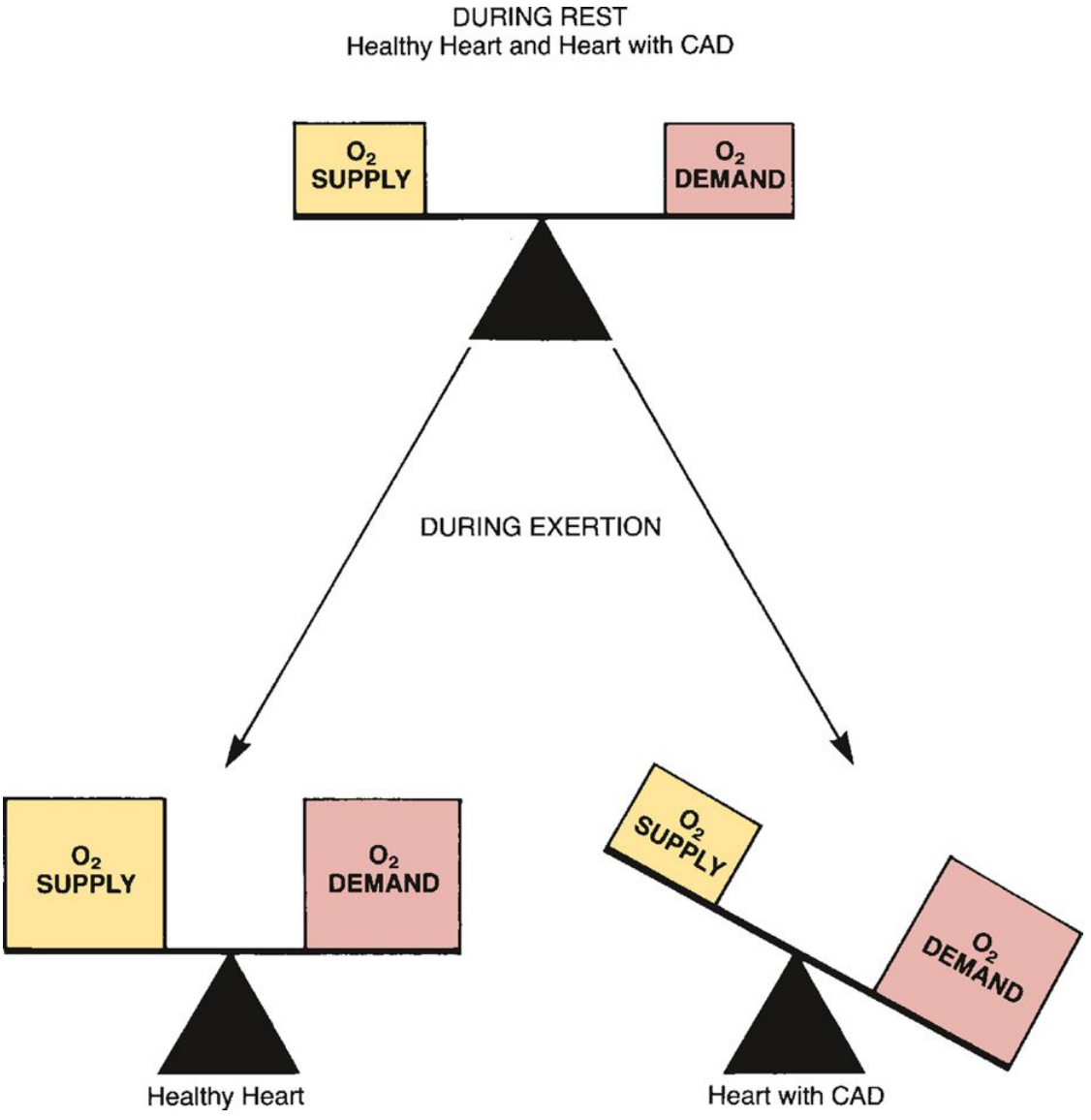

Figure 50-1 Effect of exertion on the balance between oxygen supply and oxygen demand in the healthy heart and the heart with CAD. In the healthy heart, O2 supply and O2 demand are always in balance; during exertion, coronary arteries dilate, producing an increase in blood flow to meet the increase in O2 demand. In the heart with CAD, O2 supply and O2 demand are in balance only during rest. During exertion, dilation of coronary arteries cannot compensate for the increase in O2 demand, and an imbalance results.

The picture is very different during exertion. In the healthy heart, as cardiac oxygen demand rises, coronary arterioles dilate, causing blood flow to increase. The increase keeps oxygen supply in balance with oxygen demand. By contrast, in people with CAD, arterioles in the affected region are already fully dilated during rest. Hence, when exertion occurs, there is no way to increase blood flow to compensate for the increase in oxygen demand. The resultant imbalance between oxygen supply and oxygen demand causes anginal pain.

Treatment Strategy.

The goal of antianginal therapy is to reduce the intensity and frequency of anginal attacks. Because anginal pain results from an imbalance between oxygen supply and oxygen demand, logic dictates two possible remedies: (1) increase cardiac oxygen supply or (2) decrease oxygen demand. Since the underlying cause of stable angina is occlusion of the coronary arteries, there is little we can do to increase cardiac oxygen supply. Hence, the first remedy is not a real option. Consequently, all we really can do is *decrease cardiac oxygen demand*. As discussed above, oxygen demand can be reduced with drugs that decrease heart rate, contractility, afterload, and preload.

Overview of Therapeutic Agents.

Stable angina can be treated with three main types of drugs: *organic nitrates, beta blockers,* and *calcium channel blockers*. As noted above, *ranolazine* can be combined with these drugs for additional benefit. All four groups relieve the pain of stable angina primarily by decreasing cardiac oxygen demand (Table 50-1). Please note that drugs only provide symptomatic relief; they do not affect the underlying pathology. To reduce the risk of MI, all patients should

receive an antiplatelet drug (eg, aspirin) unless it is contraindicated. Other measures to reduce the risk of infarction are discussed later under *Drugs Used to Prevent Myocardial Infarction and Death*.

	Mechanism of Pain Relief	
Drug Class	**Stable Angina**	**Variant Angina**
Nitrates	*Decrease oxygen demand* by dilating veins, which decreases preload	*Increase oxygen supply* by relaxing coronary vasospasm
Beta Blockers	*Decrease oxygen demand* by decreasing heart rate and contractility	Not used
Calcium Channel Blockers	*Decrease oxygen demand* by dilating arterioles, which decreases afterload (all calcium blockers), and by decreasing heart rate and contractility (verapamil and diltiazem)	*Increase oxygen supply* by relaxing coronary vasospasm
Ranolazine	*Appears to decrease oxygen demand,* possibly by helping the myocardium generate energy more efficiently	Not used

TABLE 50-1 Mechanisms of Antianginal Action

Nondrug Therapy.

Patients should attempt to avoid factors that can precipitate angina. These include overexertion, heavy meals, emotional stress, and exposure to cold.

Risk factors for stable angina should be corrected. Important among these are smoking, obesity, hypertension, hyperlipidemia, and a sedentary lifestyle. Patients should be strongly encouraged to quit smoking. Overweight patients should be given a restricted-calorie diet; the diet should be low in saturated fats (less than 7% of total caloric intake), and total fat content should not ex-

ceed 30% of caloric intake. The target weight is 110% of ideal or less. Patients with a sedentary lifestyle should be encouraged to establish a regular program of aerobic exercise (eg, walking, jogging, swimming, biking). Hypertension and hyperlipidemia are major risk factors and should be treated. These disorders are discussed in Chapters 46 and 49, respectively.

Variant Angina (Prinzmetal's Angina, Vasospastic Angina)

Pathophysiology.

Variant angina is caused by *coronary artery spasm,* which restricts blood flow to the myocardium. Hence, as in stable angina, pain is secondary to insufficient oxygenation of the heart. In contrast to stable angina, whose symptoms occur primarily at times of exertion, variant angina can produce pain at any time, even during rest and sleep. Frequently, variant angina occurs in conjunction with stable angina. Alternative names for variant angina are *vasospastic angina* and *Prinzmetal's angina*.

Treatment Strategy.

The goal is to reduce the incidence and severity of attacks. In contrast to stable angina, which is treated primarily by reducing oxygen demand, variant angina is treated by *increasing cardiac oxygen supply*. This makes sense in that the pain is caused by a reduction in oxygen supply, rather than by an increase in demand. Oxygen supply is increased with vasodilators, which prevent or relieve coronary artery spasm.

Overview of Therapeutic Agents.

Vasospastic angina is treated with two groups of drugs: *calcium channel blockers* and *organic nitrates*. Both relax coronary artery spasm. Beta blockers and ranolazine, which are effective in stable angina, are not effective in variant angina. As with stable angina, therapy is symptomatic only; drugs do not alter the underlying pathology.

Unstable Angina

Pathophysiology.

Unstable angina is a medical emergency. Symptoms result from severe CAD complicated by vasospasm, platelet aggregation, and transient coronary thrombi or emboli. The patient may present with either (1) symptoms of angina at rest, (2) new-onset exertional angina, or (3) intensification of existing angina. Unstable angina poses a much greater risk of death than stable angina, but a smaller risk of death than MI. The risk of dying is greatest initially and then declines to baseline in about 2 months.

Treatment.

In March of 2002, the American College of Cardiology (ACC) and the American Heart Association (AHA) issued updated guidelines for the diagnosis and management of unstable angina. The document—*ACC/AHA 2002 Guideline Update for the Management of Patients with Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction*—is available free online at www.acc.org and www.americanheart.org. According to the guideline, the treatment strategy is to *maintain oxygen supply* and *decrease oxygen demand*. The goal is to reduce pain and prevent progression to MI or death. All patients should be hospitalized. Acute management consists of anti-ischemic therapy combined with antiplatelet and anticoagulation therapy.

Anti-ischemic therapy consists of

- Nitroglycerin—give the first dose sublingually (tablet or spray) and follow with IV therapy.
- A beta blocker—give the first dose IV if chest pain is ongoing. If beta blockers are contraindicated, substitute a nondihydropyridine calcium channel blocker (verapamil or diltiazem).
- Supplemental oxygen—for patients with cyanosis or respiratory distress.
- IV morphine sulfate—if pain is not relieved immediately by nitroglycerin, or if pulmonary congestion or severe agitation is present.
- An angiotensin-converting enzyme inhibitor—but only for patients with persistent hypertension, and only if they have left ventricular dysfunction or congestive heart failure.

Antiplatelet therapy, which should be started promptly, consists of

- Aspirin—continue indefinitely.

- Clopidogrel [Plavix]—continue for at least 1 month.
- Abciximab [ReoPro], a glycoprotein IIb/IIIa inhibitor—but only if angioplasty is planned.
- Eptifibatide [Integrilin] or tirofiban [Aggrastat] (both are glycoprotein IIb/IIIa inhibitors)—but only in high-risk patients with continuing ischemia, and only if angioplasty is *not* planned.

Anticoagulant therapy consists of subcutaneous low-molecular-weight heparin (eg, dalteparin [Fragmin]) or intravenous unfractionated heparin.

ORGANIC NITRATES

The organic nitrates are the oldest and most frequently used antianginal drugs. These agents relieve angina by causing vasodilation. Nitroglycerin, the most familiar organic nitrate, will serve as our prototype.

Nitroglycerin

Nitroglycerin has been used to treat angina since 1879. The drug is effective, fast acting, and inexpensive. Despite availability of newer antianginal agents, nitroglycerin remains the drug of choice for relieving acute anginal attacks.

Vasodilator Actions

Nitroglycerin acts directly on vascular smooth muscle (VSM) to promote vasodilation. At usual therapeutic doses, the drug acts primarily on *veins;* dilation of arterioles is only modest.

The biochemical events that lead to vasodilation are outlined in Figure 50-2. The process begins with uptake of nitrate by VSM, followed by conversion of nitrate to its active form: *nitric oxide*. As indicated, conversion requires the presence of *sulfhydryl groups*. Nitric oxide then activates guanylyl cyclase, an enzyme that catalyzes the formation of cyclic GMP (cGMP). Through a series of reactions, elevation of cGMP leads to dephosphorylation of light-chain myosin in VSM. (Recall that, in all muscles, phosphorylated myosin interacts with actin to produce contraction.) As a result of dephosphorylation, myosin is unable to interact with actin, and hence VSM relaxes, causing vasodilation. For our purposes, the most important aspect of this sequence is the conversion of nitrate to its active form—nitric oxide—in the presence of a sulfhydryl source.

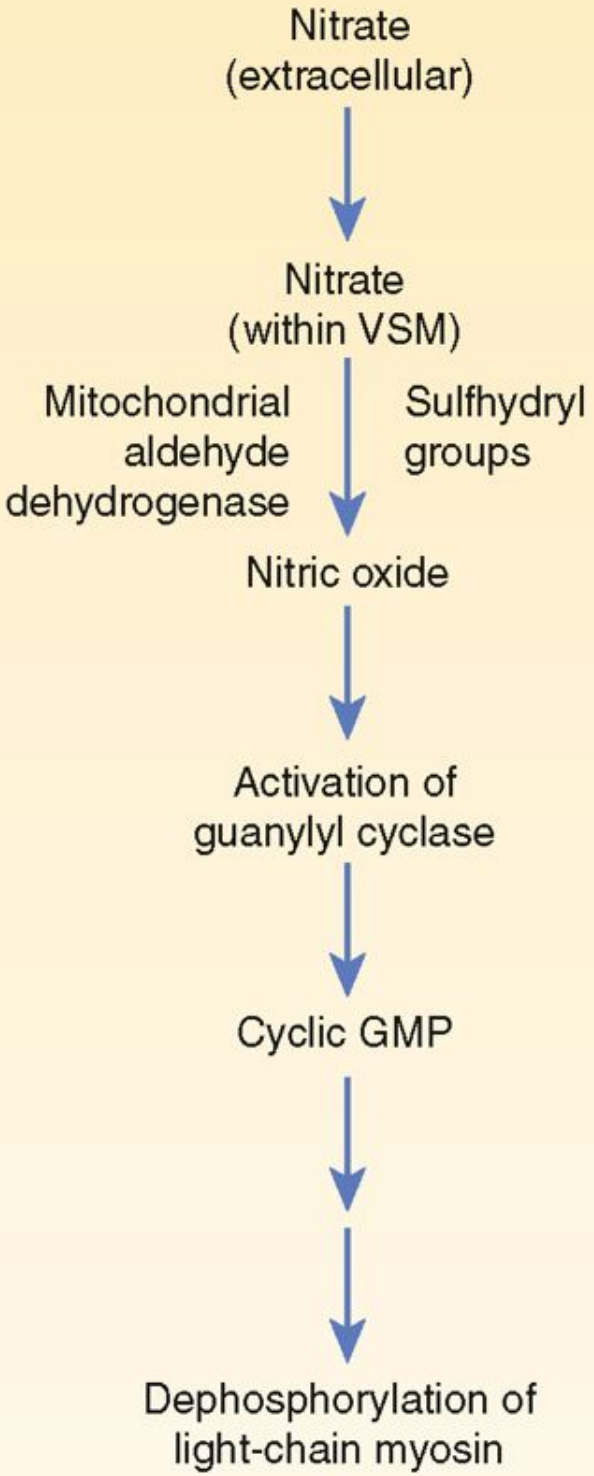
Nitrate
(extracellular)
Nitrate
(within VSM)
Mitochondrial
aldehyde
dehydrogenase
Sulfhydryl
groups
Nitric oxide
Activation of
guanylyl cyclase
Cyclic GMP
Dephosphorylation of
light-chain myosin

Figure 50-2 Biochemistry of nitrate-induced vasodilation. Note that sulfhydryl groups are needed to catalyze the conversion of nitrate to its active form, nitric oxide. If sulfhydryl groups are depleted from VSM, tolerance to nitrates will occur.

Mechanism of Antianginal Effects

Stable Angina.

Nitroglycerin decreases the pain of exertional angina primarily by *decreasing cardiac oxygen demand*. Oxygen demand is decreased as follows: By dilating veins, nitroglycerin decreases venous return to the heart, and thereby decreases ventricular filling; the resultant decrease in wall tension (preload) decreases oxygen demand.

In patients with stable angina, nitroglycerin does not appear to increase blood flow to ischemic areas of the heart. This statement is based on two observations. First, nitroglycerin does not dilate atherosclerotic coronary arteries. Second, when nitroglycerin is injected directly into coronary arteries during an anginal attack, it does not relieve pain. Both observations suggest that pain relief results from effects of nitroglycerin on peripheral blood vessels—not from effects on coronary blood flow.

Variant Angina.

In patients with variant angina, nitroglycerin acts by relaxing or preventing spasm in coronary arteries. Hence, the drug *increases oxygen supply*. It does not reduce oxygen demand.

Pharmacokinetics

Absorption.

Nitroglycerin is *highly lipid soluble* and crosses membranes with ease. Because of this property, nitroglycerin can be administered by uncommon routes (sublingual, buccal, transdermal) as well as by more conventional routes (oral, intravenous).

Metabolism.

Nitroglycerin undergoes *rapid inactivation* by hepatic enzymes (organic nitrate reductases). As a result, the drug has a plasma half-life of only 5 to 7 minutes. When nitroglycerin is administered orally, most of each dose is destroyed on its first pass through the liver.

Adverse Effects

Nitroglycerin is generally well tolerated. Principal adverse effects—headache, hypotension, and tachycardia—occur secondary to vasodilation.

Headache.

Initial therapy can produce severe headache. This response diminishes over the first few weeks of treatment. In the meantime, headache can be reduced with aspirin, acetaminophen, or some other mild analgesic.

Orthostatic Hypotension.

Relaxation of VSM causes blood to pool in veins when the patient assumes an erect posture. Pooling decreases venous return to the heart, which reduces cardiac output, causing blood pressure to fall. Symptoms of orthostatic hypotension include lightheadedness and dizziness. Patients should be instructed to sit or lie down if these occur. Lying with the feet elevated promotes venous return, and can thereby help restore blood pressure.

Reflex Tachycardia.

Nitroglycerin lowers blood pressure—primarily by decreasing venous return, and partly by dilating arterioles. By lowering blood pressure, the drug can activate the baroreceptor reflex, thereby causing sympathetic stimulation of the heart. The resultant increase in both heart rate and contractile force increases cardiac oxygen demand, which negates the benefits of therapy. Pretreatment with a beta blocker or verapamil (a calcium channel blocker that directly suppresses the heart) can prevent sympathetic cardiac stimulation.

Drug Interactions

Hypotensive Drugs.

Nitroglycerin can intensify the effects of other hypotensive agents. Consequently, care should be exercised when nitroglycerin is used concurrently with beta blockers, calcium channel blockers, diuretics, and all other drugs that can lower blood pressure, including inhibitors of phosphodiesterase type 5 (PDE5). Also, patients should be advised to avoid alcohol.

Phosphodiesterase Type 5 Inhibitors.

As discussed in Chapter 65, PDE5 inhibitors—sildenafil [Viagra], tadalafil [Cialis], and vardenafil [Levitra]—are used for erectile dysfunction. All three drugs can greatly intensify nitroglycerin-induced vasodilation. Life-threatening hypotension can result. Accordingly, concurrent use of PDE5 inhibitors with nitroglycerin is *absolutely contraindicated*.

What's the mechanism of the interaction? Nitroglycerin and the PDE5 inhibitors both increase cGMP (nitrates increase cGMP formation and PDE5 inhibitors decrease cGMP breakdown). Hence, if these drugs are combined, levels of cGMP can rise dangerously high, thereby causing excessive vasodilation and a precipitous drop in blood pressure.

Beta Blockers, Verapamil, and Diltiazem.

These drugs can suppress nitroglycerin-induced tachycardia. Beta blockers do so by preventing sympathetic activation of beta***1***-adrenergic receptors on the heart. Verapamil and diltiazem prevent tachycardia through direct suppression of pacemaker activity in the sinoatrial node.

Tolerance

Tolerance to nitroglycerin-induced vasodilation can develop rapidly (over the course of a single day). One possible mechanism is depletion of sulfhydryl groups in VSM: In the absence of sulfhydryl groups, nitroglycerin cannot be converted to nitric oxide, its active form. Another possible mechanism is reversible oxidative injury to mitochondrial aldehyde dehydrogenase, an enzyme needed to convert nitroglycerin into nitric oxide. Patients who develop tolerance to nitroglycerin display cross-tolerance to all other nitrates and vice versa. Development of tolerance is most likely with high-dose therapy and uninterrupted therapy. To prevent tolerance, nitroglycerin and other nitrates should be used in the lowest effective dosages; long-acting formulations

(eg, patches, sustained-release preparations) should be used on an intermittent schedule that allows at least 8 drug-free hours every day, usually during the night. If pain occurs during the nitrate-free interval, it can be managed with sparing use of a short-acting nitrate (eg, sublingual nitroglycerin) or by adding a beta blocker or calcium channel blocker to the regimen. Tolerance can be reversed by withholding nitrates for a short time.

Preparations and Routes of Administration

Nitroglycerin is available in an assortment of formulations for administration by a variety of routes. This proliferation of dosage forms reflects efforts to delay hepatic metabolism, and thereby prolong therapeutic effects.

All nitroglycerin preparations produce qualitatively similar responses; differences relate only to onset and duration of action (Table 50-2). With two preparations, effects begin rapidly (in 1 to 5 minutes) and then fade in less than 1 hour. With three others, effects begin slowly but last several hours. Only one preparation has both a rapid onset and long duration.

Drug and Dosage Form	Onset*	Duration†
Nitroglycerin		
Sublingual tablets	Rapid (1–3 min)	Brief (30–60 min)
Translingual spray	Rapid (2–3 min)	Brief (30–60 min)
Transmucosal tablets	Rapid (1–2 min)	Long (3–5 hr)
Oral capsules, SR	Slow (20–45 min)	Long (3–8 hr)
Transdermal patches	Slow (30–60 min)	Long (24 hr)‡
Topical ointment	Slow (30–60 min)	Long (2–12 hr)
Isosorbide Mononitrate		
Oral tablets, IR	Slow (30–60 min)	Long (6–10 hr)
Oral tablets, SR	Slow (30–60 min)	Long (7–12 hr)
Isosorbide Dinitrate		
Sublingual tablets	Rapid (2–5 min)	Long (1–3 hr)
Oral tablets, IR	Slow (20–40 min)	Long (4–6 hr)
Oral tablets, SR	Slow (30 min)	Long (6–8 hr)
Oral capsules, SR	Slow (30 min)	Long (6–8 hr)

IR = immediate release, SR = sustained release.

TABLE 50-2 Organic Nitrates: Time Course of Action

* Nitrates with a *rapid* onset have two uses: (1) termination of an ongoing anginal attack and (2) short-term prophylaxis prior to anticipated exertion. Of the rapid-acting nitrates, nitroglycerin (sublingual or spray) is preferred to the others for terminating an ongoing attack.

† *Long-acting* nitrates are used for sustained prophylaxis (prevention) of anginal attacks. All cause tolerance if used without interruption.

‡ Although patches can release nitroglycerin for up to 24 hours, they should be removed after 12 to 14 hours to avoid tolerance.

Applications of specific preparations are based on their time course. Preparations with a *rapid onset* are employed to *terminate an ongoing anginal attack.*

When used for this purpose, rapid-acting preparations are administered as soon as pain begins. Rapid-acting preparations can also be used for *acute prophylaxis of angina*. For this purpose, they are taken just prior to anticipated exertion. *Long-acting preparations* are used to provide *sustained protection* against anginal attacks. To provide protection, they are administered on a fixed schedule (but one that permits at least 8 drug-free hours each day).

Trade names and dosages for nitroglycerin preparations are summarized in Table 50-3.

Drug and Formulation	Trade Name	Usual Dosage
Nitroglycerin		
Sublingual tablets	Nitrostat, NitroQuick, Nitrotab	0.3–0.6 mg as needed
Translingual spray	Nitrolingual	0.4 mg as needed
Transmucosal tablets	Nitrogard	1–3 mg 3 times daily
Oral capsules, SR	generic only	2.5–6.5 mg 3 or 4 times daily; to avoid tolerance, administer only once or twice daily; do not crush or chew
Transdermal patches	Minitran, Nitrodisc, Nitro-Dur, Nitrek, Transderm-Nitro	1 patch a day; to avoid tolerance, remove after 12–14 hr, allowing 10–12 patch-free hours each day. Patches come in sizes that release 0.1–0.8 mg/hr
Topical ointment	Nitro-Bid	1–2 inches (7.5–40 mg) every 4–8 hr
Intravenous	Nitro-Bid IV, Tridil	5 mcg/min initially, then increased gradually as needed (max 200 mcg/min); tolerance develops with prolonged continuous infusion
Isosorbide Mononitrate		
Oral tablets, IR	ISMO, Monoket	20 mg twice daily; to avoid tolerance, take the first dose upon awakening and the second dose 7 hr later
Oral tablets, SR	Isotrate ER, Imdur	60–240 mg once a day; do not crush or chew
Isosorbide Dinitrate		
Sublingual tablets	Isordil	2.5–15 mg every 4–6 hr; do not crush or chew

TABLE 50-3 Organic Nitrates: Trade Names and Dosages

Sublingual Tablets.

When administered sublingually (beneath the tongue), nitroglycerin is absorbed directly through the oral mucosa and into the bloodstream. Hence, unlike orally administered drugs, which must pass through the liver on their way to the systemic circulation, sublingual nitroglycerin bypasses the liver, and thereby temporarily avoids inactivation. Because the liver is bypassed, sublingual doses can be low (between 0.3 and 0.6 mg). These doses are about 10 times lower than those required when nitroglycerin is taken orally.

Effects of sublingual nitroglycerin begin rapidly—in 1 to 3 minutes—and persist up to 1 hour. Because sublingual administration works fast, this route is ideal for (1) terminating an ongoing attack and (2) short-term prophylaxis when exertion is anticipated.

To terminate an acute anginal attack, sublingual nitroglycerin should be administered as soon as pain begins. Administration should not be delayed until the pain has become severe. According to current guidelines, if pain is not relieved in 5 minutes, the patient should call 911 or report to an emergency department, since anginal pain that does not respond to nitroglycerin may indicate MI. While awaiting emergency care, the patient can take 1 more tablet, and then a third tablet 5 minutes later.

Sublingual administration is unfamiliar to most patients. Accordingly, education is needed. The patient should be instructed to place the tablet under the tongue and leave it there while it dissolves. Nitroglycerin tablets formulated for sublingual use are ineffective if swallowed.

Nitroglycerin tablets are chemically unstable and can lose effectiveness over time. Shelf life can be prolonged by storing tablets in a tightly closed, dark container. Under these conditions, most tablets made today remain effective for at least 24 months after the container is first opened.* As a rule, nitroglycerin tablets should be discarded after this time. Patients should be instructed to write the date of opening on the container and to discard unused tablets 24 months later.

* Nitroglycerin tablets sold as NitroQuick are only stable for 8 to 10 months, rather than 24 months.

Sustained-Release Oral Capsules.

Sustained-release oral capsules are intended for long-term prophylaxis only; these formulations cannot act fast enough to terminate an ongoing anginal attack. Sustained-release capsules contain a large dose of nitroglycerin that is slowly absorbed across the GI wall. In theory, doses are large enough so that amounts of nitroglycerin sufficient to produce a therapeutic response will survive passage through the liver. Because they produce sustained blood levels of nitroglycerin, these formulations can cause tolerance. To reduce the risk of tolerance, these products should be taken only once or twice daily. Patients should be instructed to swallow sustained-release capsules intact.

Transdermal Delivery Systems.

Nitroglycerin patches look like Band-Aids and contain a reservoir from which nitroglycerin is slowly released. Following release, the drug is absorbed through the skin and then into the blood. The rate of release is constant for any particular transdermal patch and, depending upon the patch used, can range from 0.1 to 0.8 mg/hr. Effects begin within 30 to 60 minutes and persist as long as the patch remains in place (up to 14 hours). Patches are applied once daily to a hairless area of skin. The site should be rotated to avoid local irritation.

Tolerance develops if patches are used continuously (24 hours a day every day). Accordingly, a daily "patch-free" interval of 10 to 12 hours is recommended. This can be accomplished by applying a new patch each morning, leaving it in place for 12 to 14 hours, and then removing it in the evening.

Because of their long duration, patches are well suited for sustained prophylaxis. Since patches have a delayed onset, they cannot be used to abort an ongoing attack.

Translingual Spray.

Nitroglycerin can be delivered to the oral mucosa using a metered-dose spray device. Each activation delivers a 0.4-mg dose. Indications for nitroglycerin spray are the same as for sublingual tablets: suppression of an acute anginal attack and prophylaxis of angina when exertion is anticipated. As with sub-

lingual tablets, no more than three doses should be administered within a 15-minute interval. *Patients should be instructed not to inhale the spray*.

Transmucosal (Buccal) Tablets.

Administration of transmucosal nitroglycerin tablets consists of placing the tablet between the upper lip and the gum, or in the buccal area between the cheek and the gum. The tablet adheres to the oral mucosa and slowly dissolves over 3 to 5 hours. As the tablet dissolves, nitroglycerin is absorbed directly through the oral mucosa and then into the blood, thereby bypassing the liver. Like sublingual nitroglycerin, transmucosal nitroglycerin has a rapid onset. Hence, transmucosal administration can be used to terminate an ongoing anginal attack and to provide short-term prophylaxis prior to exertion. In addition, since the effects of transmucosal nitroglycerin are prolonged, this formulation can be used for sustained prophylaxis. Patients should be instructed not to chew or swallow these tablets.

Topical Ointment.

Topical nitroglycerin ointment is used for sustained protection against anginal attacks. The ointment is applied to the skin of the chest, back, abdomen, or anterior thigh. (Since nitroglycerin acts primarily by dilating peripheral veins, there is no mechanistic advantage to applying topical nitroglycerin directly over the heart.) Following topical application, nitroglycerin is absorbed through the skin and then into the blood. Effects begin within 20 to 60 minutes and may persist up to 12 hours.

Nitroglycerin ointment (2%) is dispensed from a tube, and the length of the ribbon squeezed from the tube determines dosage. (One inch contains about 15 mg of nitroglycerin.) The usual adult dosage is 1 to 2 inches applied every 4 to 8 hours. The ointment should be spread over an area at least 2.5 inches by 3.5 inches and then covered with plastic wrap. Sites of application should be rotated to minimize skin irritation. As with other long-acting formulations, uninterrupted use can cause tolerance.

Intravenous Infusion.

Intravenous nitroglycerin is employed only rarely to treat angina pectoris. When used for angina, IV nitroglycerin is limited to patients who have failed

to respond to other medications. Additional uses of IV nitroglycerin include treatment of heart failure associated with acute MI, treatment of perioperative hypertension, and production of controlled hypotension for surgery.

Intravenous nitroglycerin has a very short duration of action, and hence continuous infusion is required. The infusion rate is 5 mcg/min initially and then is increased gradually until an adequate response has been achieved. Heart rate and blood pressure must be monitored continuously.

Stock solutions of nitroglycerin must be diluted for IV use. Since ampules of nitroglycerin prepared by different manufacturers can differ in both volume and nitroglycerin concentration, the label must be read carefully when dilutions are made.

Administer using a glass IV bottle and the administration set provided by the manufacturer. Nitroglycerin absorbs into standard polyvinyl chloride tubing, and hence this tubing should be avoided.

Discontinuing Nitroglycerin

Long-acting preparations (transdermal patches, topical ointment, sustained-release oral tablets or capsules) should be discontinued slowly. If they are withdrawn abruptly, vasospasm may result.

Summary of Therapeutic Uses

Acute Therapy of Angina.

For acute treatment of angina pectoris, nitroglycerin is administered in sublingual tablets, transmucosal tablets, and a translingual spray. All three formulations can be used to abort an ongoing anginal attack and to provide prophylaxis in anticipation of exertion.

Sustained Therapy of Angina.

For sustained prophylaxis against angina, nitroglycerin is administered in the following formulations: transdermal patches, topical ointment, transmucosal tablets, and sustained-release oral capsules.

Intravenous Therapy.

Intravenous nitroglycerin is indicated for perioperative control of blood pressure, production of controlled hypotension during surgery, and treatment of heart failure associated with acute MI. In addition, IV nitroglycerin is used to treat unstable angina and chronic angina when symptoms cannot be controlled with preferred medications.

Isosorbide Mononitrate and Isosorbide Dinitrate

Both of these drugs have pharmacologic actions identical to those of nitroglycerin. Both drugs are used for angina, both are taken orally, and both produce headache, hypotension, and reflex tachycardia. Differences between them relate only to route of administration and time course of action. Time course determines whether a particular drug or dosage form will be used for acute therapy, sustained prophylaxis, or both. As with nitroglycerin, tolerance can develop to long-acting preparations. To avoid tolerance, long-acting preparations should be used on an intermittent schedule that allows at least 8 drug-free hours a day. Time courses are summarized in Table 50-2, and trade names and dosages are summarized in Table 50-3.

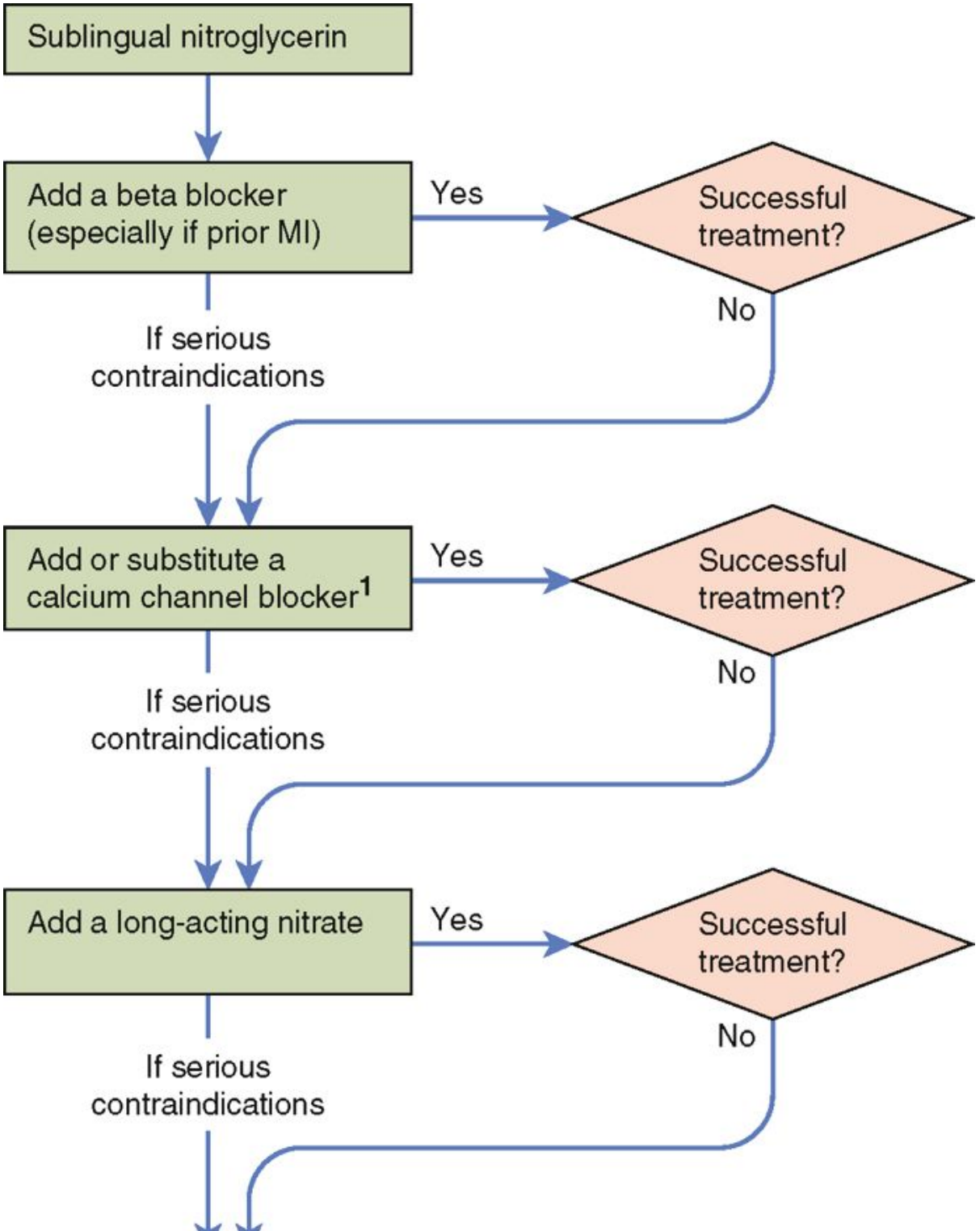
Sublingual nitroglycerin
Add a beta blocker (especially if prior MI)
Yes
Successful treatment?
No
If serious contraindications
Add or substitute a calcium channel blocker[1]
Yes
Successful treatment?
No
If serious contraindications
Add a long-acting nitrate
Yes
Successful treatment?
No
If serious contraindications

Figure 50-3 Flow plan for antianginal drug selection in patients with chronic stable angina.1 Avoid short-acting dihydropyridines.2At any point in this process, based on coronary anatomy, severity of angina symptoms, and patient preference, it is reasonable to consider evaluation for coronary revascularization (PCI or CABG). Unless a patient is documented to have left main, three-vessel, or two-vessel CAD with significant stenosis of the proximal left anterior descending coronary artery, there is no demonstrated survival advantage associated with CABG or PCI in low-risk patients with chronic stable angina. Accordingly, medical therapy should be attempted in most patients before considering PCI or CABG.

Amyl Nitrite

Amyl nitrite is an ultrashort-acting agent used to treat acute episodes of angina pectoris. The drug has the same mechanism as nitroglycerin. Amyl nitrite is a volatile liquid dispensed in glass ampules. For administration, 1 ampule (0.18 or 0.3 mL) is crushed, allowing the volatile compound to be inhaled. Effects begin within 30 seconds and terminate in 3 to 5 minutes. Amyl nitrite is highly flammable and hence should not be used near flame. The drug is reputed to intensify sexual orgasm and has been abused for that purpose (see Chapter 39).

BETA BLOCKERS

Beta blockers (eg, propranolol, metoprolol) are first-line drugs for *angina of effort,* but are *not* effective against vasospastic angina. When administered on a fixed schedule, beta blockers can provide sustained protection against effort-induced anginal pain. Exercise tolerance is increased and the frequency and intensity of anginal attacks are lowered. All of the beta blockers appear equally effective. In addition to reducing anginal pain, beta blockers decrease the risk of death, especially in patients with a prior MI.

Beta blockers reduce anginal pain primarily by *decreasing cardiac oxygen demand.* This is accomplished mainly through blockade of beta*1* receptors in the heart, which decreases heart rate and contractility. Beta blockers reduce oxygen demand further by causing a modest reduction in arterial pressure (afterload).

In addition to decreasing oxygen demand, beta blockers help increase oxygen supply. How? By slowing heart rate, they increase time in diastole, and thereby increase the time during which blood flows through myocardial vessels. (Recall that blood does not flow in these vessels during systole.) In patients taking vasodilators (eg, nitroglycerin), beta blockers provide the additional benefit of blunting reflex tachycardia.

For treatment of stable angina, dosage should be low initially and then gradually increased. The dosing goal is to reduce resting heart rate to 50 to 60 beats/min, and limit exertional heart rate to about 100 beats/min. Beta blockers should not be withdrawn abruptly, since doing so can increase the incidence and intensity of anginal attacks, and may even precipitate MI.

Beta blockers can produce a variety of adverse effects. Blockade of cardiac beta***1*** receptors can produce *bradycardia, decreased atrioventricular (AV) conduction,* and *reduction of contractility*. Consequently, beta blockers should not be used by patients with sick sinus syndrome, heart failure, or second-degree or third-degree AV block. Blockade of beta***2*** receptors in the lung can promote bronchoconstriction. Accordingly, beta blockers should be avoided by patients with asthma. If an asthmatic individual absolutely must use a beta blocker, a beta***1***-selective agent (eg, metoprolol) should be chosen. Beta blockers can mask signs of hypoglycemia, and therefore must be used with caution in patients with diabetes. Through effects on the central nervous system, these drugs can cause *insomnia, depression, bizarre dreams,* and *sexual dysfunction*.

The basic pharmacology of the beta blockers is discussed in Chapter 18.

CALCIUM CHANNEL BLOCKERS

The calcium channel blockers (CCBs) used most frequently are *verapamil, diltiazem,* and *nifedipine* (a dihydropyridine-type calcium channel blocker). Accordingly, our discussion focuses on these three drugs. *All three* can block calcium channels in VSM, primarily in arterioles. The result is arteriolar dilation and reduction of peripheral resistance (afterload). In addition, all three can relax coronary vasospasm. *Verapamil* and *diltiazem* also block calcium channels in the heart, and can thereby decrease heart rate, AV conduction, and contractility.

Calcium channel blockers are used to treat both stable angina and variant angina. In *variant angina,* these drugs promote relaxation of coronary artery spasm, thereby *increasing cardiac oxygen supply*. In *stable angina,* they promote relaxation of peripheral arterioles; the resultant decrease in afterload *reduces cardiac oxygen demand*. Verapamil and diltiazem can produce modest additional reductions in oxygen demand by suppressing heart rate and contractility.

The major adverse effects of the CCBs are cardiovascular. Dilation of peripheral arterioles lowers blood pressure, and can thereby induce *reflex tachycardia*. This reaction is greatest with nifedipine and minimal with verapamil and diltiazem. Because of their suppressant effects on the heart, verapamil and diltiazem must be used cautiously in patients taking beta blockers and in patients with bradycardia, heart failure, or AV block. These precautions do not apply to nifedipine or other dihydropyridines.

The basic pharmacology of the CCBs is discussed in Chapter 44.

RANOLAZINE

Actions and Therapeutic Use

Ranolazine [Ranexa] represents the first new class of antianginal agents to be approved in more than 25 years. In clinical trials, the drug reduced the number of angina episodes per week and increased exercise tolerance. However, these benefits were modest, and were smaller in women than in men. Unlike most other antianginal drugs, ranolazine does not reduce heart rate, blood pressure, or vascular resistance. However, it *can* prolong the QT interval, and is subject to multiple drug interactions. How does ranolazine work? We know it can reduce accumulation of sodium and calcium in myocardial cells, and might thereby help the myocardium use energy more efficiently. However, the exact mechanism of action is unknown. Because of its limited efficacy and a risk of dysrhythmias (see below), ranolazine is not indicated for first-line therapy. Rather, it should be reserved for patients who have not responded adequately to nitrates, beta blockers, or CCBs, and should always be combined with at least one of these agents.

Pharmacokinetics

Absorption from the GI tract is highly variable, but not affected by food. Plasma levels peak 2 to 5 hours after dosing. In the liver, ranolazine undergoes rapid and extensive metabolism, mainly by CYP3A4 (the 3A4 isozyme of cytochrome P450). The drug has a plasma half-life of 7 hours, and is excreted in the urine (75%) and feces (25%), almost entirely as metabolites.

Adverse Effects

QT Prolongation.

Ranolazine can cause a dose-related increase in the QT interval, and may thereby increase the risk of torsades de pointes, a serious ventricular dysrhythmia. Accordingly, the drug is contraindicated for patients with pre-existing QT prolongation and for those taking other drugs that can increase the QT interval. In addition, ranolazine is contraindicated for patients at risk of developing high levels of the drug—namely, patients with hepatic impairment or those taking drugs that inhibit CYP3A4. The issue of drug-induced QT prolongation is discussed further in Chapter 7 (Adverse Drug Reactions and Medication Errors).

Elevation of Blood Pressure.

In patients with severe renal impairment, ranolazine can raise blood pressure by about to 15 mm Hg. Accordingly, blood pressure should be monitored often in these people.

Other Adverse Effects.

The most common adverse effects are constipation (8%), dizziness (5%), nausea (4%), and headache (3%).

Drug Interactions

CYP3A4 Inhibitors.

Agents that inhibit CYP3A4 can increase levels of ranolazine, and can thereby increase the risk of torsades de pointes. Accordingly, moderate or strong CYP3A4 inhibitors should be avoided. Among these agents are grapefruit juice, HIV protease inhibitors (eg, ritonavir), macrolide antibiotics (eg, erythro-

mycin), azole antifungal drugs (eg, itraconazole), and some calcium channel blockers (but not amlodipine).

QT Drugs.

Drugs that prolong the QT interval (eg, quinidine, sotalol) can increase the risk of torsades de pointes in patients taking ranolazine, and hence should be avoided. Table 7-2 (see Chapter 7) presents a comprehensive list of QT drugs.

Calcium Channel Blockers.

Most CCBs—but not amlodipine—can inhibit CYP3A4, and can thereby increase levels of ranolazine. Accordingly, when combined use of ranolazine and a CCB is indicated, amlodipine is the only CCB that should be used.

Preparations, Dosage, and Administration

Ranolazine [Ranexa] is formulated in extended-release tablets (500 and 1000 mg) that should be swallowed intact, with or without food. Dosing begins at 500 mg twice daily, and may be increased to a maximum of 1000 mg twice daily. Ranolazine should be used in combination with a nitrate, beta blocker, or the CCB amlodipine.

REVASCULARIZATION THERAPY: CABG AND PCI

If drug therapy of angina fails to control symptoms, surgical revascularization should be considered. The two principal forms of revascularization are coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI).

Coronary Artery Bypass Graft Surgery

CABG surgery is used to increase blood flow to ischemic areas of the heart. In this procedure, one end of a segment of healthy blood vessel (internal mammary artery or saphenous vein) is grafted onto the aorta, and the other end is connected to the diseased coronary artery at a point distal to the region of atherosclerotic plaque. Hence, the graft constitutes a shunt whereby blood flow can circumvent the occluded section of a diseased coronary vessel. Following surgery, most patients remain in the hospital for a week, and then recuperate for another 6 weeks at home. Once considered exotic, CABG surgery

is now commonplace; more than 300,000 Americans undergo the procedure each year.

Vessel blockage can recur over time, thereby requiring repeat surgery. When an artery is used for the graft, the incidence of reblockage is only 4% after 10 years. In contrast, when a vein is used, the incidence of reblockage is nearly 50% after 10 years.

A relatively new procedure, called *minimally invasive direct coronary artery bypass* (MIDCAB) surgery, is an alternative to CABG surgery for some patients. MIDCAB surgery is much less invasive than CABG surgery, and therefore faster and cheaper. Furthermore, MIDCAB surgery is performed on the beating heart, and hence, heart-lung bypass machinery is not needed. At this time, MIDCAB surgery is used only to bypass blockage in the left ascending coronary artery.

Percutaneous Coronary Intervention

PCI is an alternative to CABG surgery for patients with stable angina. As performed today, PCI typically consists of two steps: balloon angioplasty followed by stenting. In balloon angioplasty, a miniature catheter containing a deflated balloon is inserted into the femoral artery, threaded up into the aorta, and then manipulated into the occluded coronary artery. The balloon is then inflated, thereby flattening the obstruction and allowing blood to flow. After the vessel has been opened with the balloon, the cardiologist implants a stent (a tiny tube made of stainless steel mesh) to help prevent restenosis. (Restenosis is caused by hyperplasia of neointimal cells and constrictive remodeling of the injured artery.) To further reduce the risk of restenosis, most stents employed today are coated with sirolimus or paclitaxel—drugs that suppress the proliferation and migration of neointimal cells. The incidence of restenosis with either drug-eluting stent is much lower than with bare-metal stents—and restenosis with the sirolimus-eluting stent is lower than with the paclitaxel-eluting stent.

Comparison of CABG Surgery with PCI

CABG surgery and PCI are equally safe and almost equally effective. The 5-year survival rate after either procedure is about 90%. However, in other respects,

the procedures differ substantially. Compared with PCI, CABG surgery is more traumatic and more expensive, it requires a longer hospital stay, and recovery is slower. On the other hand, CABG surgery is more effective: coronary blood flow is better, relief of angina is superior, exercise tolerance is higher, and patients require less antianginal medication. Moreover, the incidence of reblockage after CABG surgery is lower. At this time, CABG surgery is considered the treatment of choice for patients with multivessel disease. For patients with single-vessel disease, either procedure is generally appropriate; the choice is based on patient preference.

SUMMARY OF TREATMENT MEASURES

Guidelines for Management of Chronic Stable Angina

In 1999, three organizations—the American Heart Association, the American College of Cardiology, and the American College of Physicians–American Society of Internal Medicine—joined forces to produce the first national guidelines on the management of chronic stable angina. The 1999 guidelines were updated in 2002 and again in 2007. Both updates—*ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina,* and *2007 Chronic Angina Focused Update of the ACC/AHA 2002 Guidelines for the Management of Patients with Chronic Stable Angina*—are available free online at *circ.ahajournals.org*. The discussion below reflects recommendations in these guidelines.

Treatment of stable angina has two objectives: (1) prevention of MI and death, and (2) reduction of cardiac ischemia and associated anginal pain. Although both goals are desirable, prevention of MI and death is clearly more important. Hence, if two treatments are equally effective at decreasing anginal pain, but one also decreases the risk of death, then the latter is preferred.

Drugs Used to Prevent Myocardial Infarction and Death

We now have medical treatments that can decrease the risk of MI and death in patients with chronic stable angina. Therapy directed at prevention of MI and death is a new paradigm in the management of stable angina, and all practitioners should become familiar with it.

Antiplatelet Drugs.

These agents decrease platelet aggregation and thereby decrease the risk of thrombus formation in coronary arteries. The most effective agents are *aspirin* and *clopidogrel*. In patients with stable angina, low-dose aspirin produces a 33% decrease in the risk of adverse cardiovascular events. Benefits of clopidogrel seem equal to those of aspirin, although they are not as well documented. The guidelines recommend that all patients with stable angina take 75 to 162 mg of aspirin daily, unless there is a specific reason not to. Aspirin, clopidogrel, and other antiplatelet drugs are discussed in Chapter 51.

Cholesterol-Lowering Drugs.

Elevated cholesterol is a major risk factor for coronary atherosclerosis. Drugs that lower cholesterol can slow the progression of CAD, stabilize atherosclerotic plaques, and even cause plaque regression. Therapies that reduce cholesterol are associated with decreased mortality from coronary heart disease. For example, in patients with established CAD, taking simvastatin can decrease the risk of mortality by 35%. Because of the well-established benefits of cholesterol-lowering therapy, the guidelines recommend that all patients with stable angina receive a cholesterol-lowering drug. The pharmacology of the cholesterol-lowering drugs is discussed in Chapter 49.

Angiotensin-Converting Enzyme (ACE) Inhibitors.

There is strong evidence that, in patients with CAD, ACE inhibitors greatly reduce the incidence of adverse outcomes. In the Heart Outcomes Prevention Evaluation (HOPE) trial, for example, ramipril reduced the incidence of stroke, MI, and cardiovascular death. Among one subset of patients—those with diabetes—benefits were particularly striking. Ramipril decreased the risk of stroke by 33%, MI by 22%, and cardiovascular death by 37%; also, the drug reduced the risk of nephropathy, retinopathy, and other microvascular complications of diabetes. Because of these well-documented benefits, the guidelines now recommend ACE inhibitors for most patients with established CAD, and especially for those with diabetes. The pharmacology of the ACE inhibitors is discussed in Chapter 43.

Antianginal Agents: Drugs Used to Reduce Anginal Pain

The goal of antianginal therapy is to achieve complete (or nearly complete) elimination of anginal pain—along with a return to normal activities. This should be accomplished with a minimum of adverse drug effects.

The basic strategy of antianginal therapy is to provide baseline protection using one or more long-acting drugs (beta blocker, calcium channel blocker [CCB], long-acting nitrate) supplemented with sublingual nitroglycerin when breakthrough pain occurs. A flow plan for drug selection is shown in Figure 50-3. As indicated, treatment is approached sequentially. Progression from one step to the next is based on patient response. Some patients can be treated with a single long-acting drug, some require two or three, and some require revascularization.

Initial treatment consists of sublingual nitroglycerin plus a long-acting antianginal drug. As indicated in Figure 50-3, beta blockers are the preferred agents for baseline therapy. Why? Because they can decrease mortality, especially in patients with a prior MI. In addition to providing prophylaxis, beta blockers suppress nitrate-induced reflex tachycardia.

If a beta blocker is inadequate, or if there are contraindications to beta blockade, a long-acting CCB should be added or substituted. Because CCBs do not promote bronchoconstriction, they are preferred to beta blockers for patients with asthma. Dihydropyridine-type CCBs (eg, nifedipine) lack cardiosuppressant actions, and hence are safer than beta blockers for patients with bradycardia, AV block, or heart failure. When a CCB is to be *combined* with a beta blocker, a dihydropyridine is preferred to verapamil or diltiazem. Why? Because verapamil and diltiazem will intensify the cardiosuppressant actions of the beta blocker, whereas a dihydropyridine will not.

If a CCB is inadequate, or if there are contraindications to calcium channel blockade, a long-acting nitrate (eg, transdermal nitroglycerin) should be added or substituted. However, because tolerance can develop quickly, these nitrate preparations are less well suited than beta blockers or CCBs for continuous protection.

Note that, as we proceed along the drug-selection flow plan, drugs are *added* to the regimen, resulting in treatment with two or more agents. Combination therapy increases our chances of success because oxygen demand is decreased by multiple mechanisms: beta blockers reduce heart rate and con-

tractility; CCBs reduce afterload (by dilating arterioles); and nitrates reduce preload (by dilating veins).

If combined treatment with a beta blocker, CCB, and long-acting nitrate fails to provide relief, CABG surgery or PCI may be indicated. Note that these invasive procedures should be considered only after more conservative treatment has been tried.

How should we treat angina in patients who have a coexisting condition? The antianginal drugs employed—nitrates, beta blockers, and CCBs—are the same ones used in patients who have angina alone. However, when selecting among these drugs, we must consider the coexisting disorder as well as the angina. For example, as noted above, in patients with asthma, CCBs are preferred to beta blockers (because beta blockers promote bronchoconstriction, whereas CCBs do not). Table 50-4 lists over 20 coexisting conditions, and indicates which antianginal agents to use as well as which ones to avoid.

Coexisting Condition	Recommended Treatment (Alternative Treatment)	Drugs to Avoid
Medical Conditions		
Systemic hypertension	Beta blockers (long-acting, slow-release CCBs)	
Migraine or vascular headache	Beta blockers (verapamil or diltiazem)	
Asthma or COPD with bronchospasm	Verapamil or diltiazem	Beta blockers
Hyperthyroidism	Beta blockers	
Raynaud's disease	Long-acting, slow-release CCBs	Beta blockers
Type 1 diabetes	Beta blockers, particularly if prior MI, or long-acting, slow-release CCBs	
Type 2 diabetes	Beta blockers or long-acting, slow-release CCBs	
Depression	Long-acting, slow-release CCBs	Beta blockers
Mild peripheral vascular disease	Beta blockers or long-acting, slow-release CCBs	
Severe peripheral vascular disease with ischemia at rest	Long-acting, slow-release CCBs	Beta blockers
Cardiac Dysrhythmias and Conduction Abnormalities		
Sinus bradycardia	Long-acting, slow-release CCBs that do not decrease heart rate	Beta blockers, diltiazem, verapamil
Sinus tachycardia (not due to heart failure)	Beta blockers	
Supraventricular tachycardia	Verapamil, diltiazem, or beta blockers	
AV block	Long-acting, slow-release CCBs that do not slow AV conduction	Beta blockers, diltiazem, verapamil
Rapid atrial fibrillation (with digoxin)	Verapamil, diltiazem, or beta blockers	
Ventricular dysrhythmias	Beta blockers	
Left Ventricular Dysfunction		
Heart failure		
Mild (LVEF ≥40%)	Beta blockers	
Moderate to severe (LVEF <40%)	Amlodipine or felodipine (nitrates)	Diltiazem, verapamil
Left-sided valvular heart disease		
Mild aortic stenosis	Beta blockers	
Aortic insufficiency	Long-acting, slow-release dihydropyridine CCBs	
Mitral regurgitation	Long-acting, slow-release dihydropyridine CCBs	
Mitral stenosis	Beta blockers	
Hypertropic cardiomyopathy	Beta blockers, verapamil, diltiazem	Dihydropyridine CCBs, nitrates

Adapted from Gibbons RJ, Chatterjee K, Daley J, et al: ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina). 2002. Available online at *circ.ahajournals.org/*.

AV = atrioventricular, CCB = calcium channel blocker, COPD = chronic obstructive pulmonary disease, LVEF = left ventricular ejection fraction, MI = myocardial infarction.

TABLE 50-4 Choosing Between Beta Blockers and Calcium Channel Blockers for Treating Angina in Patients Who Have a Coexisting Condition

Reduction of Risk Factors

The treatment program should reduce anginal risk factors: smokers should quit; obese patients should lose weight; sedentary patients should get aerobic exercise; and patients with diabetes, hypertension, or high cholesterol should receive appropriate therapy.

Smoking.

Smoking increases the risk of cardiovascular mortality by 50%. Fortunately, smoking cessation greatly decreases cardiovascular risk. Accordingly, all patients who smoke should be strongly encouraged to quit. Drugs employed as an aid to smoking cessation are discussed in Chapter 39.

High Cholesterol.

As noted, high cholesterol levels increase the risk of adverse cardiovascular events, and therapies that reduce cholesterol reduce that risk. Accordingly, all patients with high cholesterol levels should receive cholesterol-lowering therapy.

Hypertension.

High blood pressure increases the risk of cardiovascular mortality, and lowering blood pressure reduces the risk. Accordingly, all patients with hypertension should receive treatment. Blood pressure should be reduced to 140/90 mm Hg or less. In patients with additional risk factors (eg, diabetes, heart failure, retinopathy), the target blood pressure is 130/80 mm Hg or less. Management of hypertension is discussed in Chapter 46.

Diabetes.

Both type 1 (insulin-dependent) and type 2 (non–insulin-dependent) diabetes increase the risk of cardiovascular mortality. Type 1 increases the risk 3- to 10-fold; type 2 increases the risk 2- to 4-fold. Although there is good evidence that tight glycemic control decreases the risk of microvascular complications

of diabetes, there is little evidence to show that tight glycemic control decreases the risk of cardiovascular complications. Nonetheless, it is prudent to strive for optimal glycemic control.

Obesity.

Obesity is associated with an increased risk of coronary disease and mortality; weight reduction is likely to reduce that risk. Accordingly, a program of diet and exercise is recommended for all patients whose body weight exceeds 120% of ideal. Weight reduction is especially important for patients with diabetes, hypertension, and hypertriglyceridemia. Obesity and its management are discussed in Chapter 81.

Physical Inactivity.

Increased physical activity has multiple benefits. In patients with chronic stable angina, exercise increases exercise tolerance and the sense of well-being, and decreases anginal symptoms, cholesterol levels, and objective measures of ischemia. Accordingly, the guidelines recommend that patients perform 30 to 60 minutes of a moderate-intensity activity 3 to 4 times a week. Such activities include walking, jogging, cycling, and other aerobic exercises. Exercise by moderate- to high-risk patients should be medically supervised.

Management of Variant Angina

Treatment of vasospastic angina can proceed in three steps. For initial therapy, either a calcium channel blocker or a long-acting nitrate is selected. If either drug alone is inadequate, then combined therapy with a calcium channel blocker *plus* a nitrate should be tried. If the combination fails to control symptoms, CABG surgery may be indicated. Beta blockers are not effective in vasospastic angina.

KEY POINTS

- Anginal pain occurs when cardiac oxygen supply is insufficient to meet oxygen demand.

- Cardiac oxygen demand is determined by heart rate, contractility, preload, and afterload. Drugs that reduce these factors can help relieve anginal pain.
- Cardiac oxygen supply is determined by myocardial blood flow. Drugs that increase oxygen supply will reduce anginal pain.
- Angina pectoris has three forms: chronic stable angina, variant (vasospastic) angina, and unstable angina.
- The underlying cause of stable angina is coronary artery atherosclerosis.
- The underlying cause of variant angina is coronary artery spasm.
- Drugs relieve pain of stable angina by decreasing cardiac oxygen demand. They do not increase oxygen supply.
- Drugs relieve pain of variant angina by increasing cardiac oxygen supply. They do not decrease oxygen demand.
- Nitroglycerin and other organic nitrates are vasodilators.
- To cause vasodilation, nitroglycerin must first be converted to nitric oxide, its active form. This reaction requires a sulfhydryl source.
- Nitroglycerin relieves pain of stable angina by dilating veins, which decreases venous return, which decreases preload, which decreases oxygen demand.
- Nitroglycerin relieves pain of variant angina by relaxing coronary vasospasm, which increases oxygen supply.
- Nitroglycerin is highly lipid soluble, and therefore is readily absorbed through the skin and oral mucosa.
- Nitroglycerin undergoes very rapid inactivation in the liver. Hence, when the drug is administered orally, most of each dose is destroyed before reaching the systemic circulation.
- When nitroglycerin is administered sublingually, it is absorbed directly into the systemic circulation, and therefore temporarily bypasses the liver. Hence, to produce equivalent effects, sublingual doses can be much smaller than oral doses.

- Nitroglycerin causes three characteristic side effects: headache, orthostatic hypotension, and reflex tachycardia. All three occur secondary to vasodilation.
- Reflex tachycardia from nitroglycerin can be prevented with a beta blocker, verapamil, or diltiazem.
- Continuous use of nitroglycerin can produce tolerance within 24 hours. The mechanism may be depletion of sulfhydryl groups.
- To prevent tolerance, nitroglycerin should be used in the lowest effective dosage, and long-acting formulations should be used on an intermittent schedule that allows at least 8 drug-free hours every day, usually during the night.
- Nitroglycerin preparations that have a rapid onset (eg, sublingual nitroglycerin) are used to abort an ongoing anginal attack and to provide acute prophylaxis when exertion is expected. Administration is PRN.
- Nitroglycerin preparations that have a long duration (eg, patches, sustained-release oral capsules) are used for extended protection against anginal attacks. Administration is on a fixed schedule (but one that allows at least 8 drug-free hours a day).
- Nitroglycerin should be used cautiously with most vasodilators, and must not be used at all with sildenafil [Viagra] and other PDE5 inhibitors.
- Beta blockers prevent pain of stable angina primarily by decreasing heart rate and contractility, which reduces cardiac oxygen demand.
- Beta blockers are administered on a fixed schedule, not PRN.
- Beta blockers are not used for variant angina.
- Calcium channel blockers relieve pain of stable angina by reducing cardiac oxygen demand. Two mechanisms are involved. First, all CCBs relax peripheral arterioles, and thereby decrease afterload. Second, verapamil and diltiazem reduce heart rate and contractility (in addition to decreasing afterload).
- Calcium channel blockers relieve pain of variant angina by increasing cardiac oxygen supply. The mechanism is relaxation of coronary artery spasm.

- When a CCB is combined with a beta blocker, a dihydropyridine (eg, nifedipine) is preferred to verapamil or diltiazem. Why? Because verapamil and diltiazem will intensify cardiosuppression caused by the beta blocker, whereas a dihydropyridine will not.
- Ranolazine appears to reduce anginal pain by helping the heart generate energy more efficiently.
- Ranolazine should not be used alone. Rather, it should be combined with a nitrate, a beta blocker, or the CCB amlodipine.
- Ranolazine increases the QT interval, and may thereby pose a risk of torsades de pointes, a serious ventricular dysrhythmia.
- In patients with chronic stable angina, treatment has two objectives: (1) prevention of MI and death and (2) prevention of anginal pain.
- The risk of MI and death can be decreased with two types of drugs: (1) antiplatelet agents (eg, aspirin) and (2) cholesterol-lowering drugs.
- Anginal pain is prevented with one or more long-acting antianginal drugs (beta blocker, calcium channel blocker, long-acting nitrate) supplemented with sublingual nitroglycerin when breakthrough pain occurs.
- As a rule, revascularization with CABG surgery or PCI is indicated only after treatment with two or three antianginal drugs has failed.

Summary of Major Nursing Implications*

NITROGLYCERIN

Preadministration Assessment

Therapeutic Goal

Reduction of the frequency and intensity of anginal attacks.

Baseline Data

Obtain baseline data on the frequency and intensity of anginal attacks, the location of anginal pain, and the factors that precipitate attacks.

The patient interview and physical examination should identify risk factors for angina pectoris, including treatable contributing pathophysiologic conditions (eg, hypertension, hyperlipidemia).

Identifying High-Risk Patients

Use with *caution* in hypotensive patients and patients taking drugs that can lower blood pressure, including alcohol and antihypertensive medications. Use with sildenafil [Viagra] and other PDE5 inhibitors is *contraindicated*.

Implementation: Administration

Routes and Administration

Sublingual Tablets.

Use.

Prophylaxis or termination of an acute anginal attack.

Technique of Administration.

Instruct patients to place the tablet under the tongue and leave it there until fully dissolved; the tablet should not be swallowed.

Instruct patients to call 911 or go to an emergency department if pain is not relieved in 5 minutes. While awaiting emergency care, they can take 1 more tablet, and then a third tablet 5 minutes later.

Instruct patients to store tablets in a dark, tightly closed bottle that contains no other medications. Instruct patients to write the date of opening on the bottle and to discard unused medication after 24 months. (Products sold as Nitro-Quick should be discarded after 8 to 10 months).

Sustained-Release Oral Capsules.

Use.

Sustained protection against anginal attacks.

To avoid tolerance, administer only once or twice daily.

Technique of Administration.

Instruct patients to swallow these preparations intact, without chewing or crushing.

Transdermal Delivery Systems.

Use.

Sustained protection against anginal attacks.

Technique of Administration.

Instruct patients to apply transdermal patches to a hairless area of skin, using a new patch and a different site each day.

Instruct patients to remove the patch after 12 to 14 hours, allowing 10 to 12 "patch-free" hours each day. This will prevent tolerance.

Translingual Spray.

Use.

Prophylaxis or termination of an acute anginal attack.

Technique of Administration.

Instruct patients to direct the spray against the oral mucosa. Warn patients not to inhale the spray.

Transmucosal (Buccal) Tablets.

Uses.

(1) Prophylaxis or termination of an acute anginal attack and (2) sustained prophylaxis.

Technique of Administration.

Instruct patients to place the transmucosal tablet between the upper lip and the gum or in the buccal area between the cheek and the gum. Inform patients that the tablet will adhere to the oral mucosa and slowly dissolve over 3 to 5 hours. To achieve sustained prophylaxis, a tablet should be administered every 3 to 8 hours.

Topical Ointment.

Use.

Sustained protection against anginal attacks.

Before applying a new dose, remove ointment remaining from the previous dose.

Technique of Administration.

(1) Squeeze a ribbon of ointment of prescribed length onto the applicator paper provided; (2) using the applicator paper, spread the ointment over an area at least 2.5 inches by 3.5 inches (application may be made to the chest, back, abdomen, upper arm, or anterior thigh); and (3) cover the ointment with plastic wrap. Avoid touching the ointment.

Rotate the application site to minimize local irritation.

Intravenous.

Uses.

(1) Angina pectoris refractory to more conventional therapy, (2) perioperative control of blood pressure, (3) production of controlled hypotension during surgery, and (4) heart failure associated with acute MI.

Technique of Administration.

Perform IV administration using a glass IV bottle and the administration set provided by the manufacturer; avoid standard IV tubing. Dilute stock solutions before use.

Administer by continuous infusion. The rate is slow initially (5 mg/min) and then gradually increased until an adequate response is achieved.

Monitor cardiovascular status constantly.

Terminating Therapy

Warn patients against abrupt withdrawal of long-acting preparations (transdermal systems, topical ointment, sustained-release tablets and capsules).

Implementation: Measures to Enhance Therapeutic Effects

Reducing Risk Factors

Precipitating Factors.

Advise patients to avoid activities that are likely to elicit an anginal attack (eg, overexertion, heavy meals, emotional stress, cold exposure).

Weight Reduction.

Help overweight patients develop a restricted-calorie diet. The diet should be low in saturated fats, and total fat should not exceed 30% of caloric intake. Target weight is 110% of ideal or less.

Exercise.

Encourage patients who have a sedentary lifestyle to establish a regular program of aerobic exercise (eg, walking, jogging, swimming, biking).

Smoking Cessation.

Strongly encourage patients to quit smoking.

Contributing Disease States.

Ensure that patients with contributing pathology (especially hypertension or hypercholesterolemia) are receiving appropriate treatment.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Have the patient keep a record of the frequency and intensity of anginal attacks, the location of anginal pain, and the factors that precipitate attacks.

Minimizing Adverse Effects

Headache.

Inform patients that headache will diminish with continued drug use. Advise patients that headache can be relieved with aspirin, acetaminophen, or some other mild analgesic.

Orthostatic Hypotension.

Inform patients about symptoms of hypotension (eg, dizziness, lightheadedness), and advise them to sit or lie down if these occur. Inform patients that hypotension can be minimized by moving slowly when changing from a sitting or supine position to an upright posture.

Reflex Tachycardia.

This reaction can be suppressed by concurrent treatment with a beta blocker, verapamil, or diltiazem.

Minimizing Adverse Interactions

Hypotensive Agents, Including PDE5 Inhibitors.

Nitroglycerin can interact with other hypotensive drugs to produce excessive lowering of blood pressure. **Advise patients to avoid alcohol.** Exercise caution when nitroglycerin is used in combination with beta blockers, calcium channel blockers, diuretics, and all other drugs that can lower blood pressure.

Combining nitroglycerin with a PDE5 inhibitor (eg, sildenafil [Viagra]) can cause life-threatening hypotension. Accordingly, these combinations are absolutely contraindicated.

ISOSORBIDE MONONITRATE AND ISOSORBIDE DINITRATE

Both drugs have pharmacologic actions identical to those of nitroglycerin. Differences relate only to dosage forms, routes of administration, and time

course of action. Hence, the implications presented for nitroglycerin apply to these drugs as well.

51 Anticoagulant, Antiplatelet, and Thrombolytic Drugs

The drugs discussed in this chapter are used to prevent formation of thrombi (intravascular blood clots) and dissolve thrombi that have already formed. These drugs act in several ways: some suppress coagulation, some inhibit platelet aggregation, and some promote clot degradation. They all interfere with normal hemostasis. As a result, they all carry a significant risk of bleeding.

COAGULATION: PHYSIOLOGY AND PATHOPHYSIOLOGY

Hemostasis

Hemostasis is the physiologic process by which bleeding is stopped. Hemostasis occurs in two stages: (1) formation of a platelet plug, followed by (2) reinforcement of the platelet plug with fibrin. Both processes are set in motion by blood vessel injury.

Stage One: Formation of a Platelet Plug.

Platelet aggregation is initiated when platelets come in contact with collagen on the exposed surface of a damaged blood vessel. In response to contact with collagen, platelets adhere to the site of vessel injury. Adhesion initiates platelet *activation,* which in turn leads to massive platelet *aggregation*.

Platelet aggregation is a complex process that ends with formation of *fibrinogen bridges* between *glycoprotein IIb/IIIa (GP IIb/IIIa) receptors* on adjacent platelets (Fig. 51-1). In order for these bridges to form, GP IIb/IIIa receptors must first undergo activation—that is, they must undergo a configurational change that allows them to bind with fibrinogen. As indicated in Figure 51-1*A*, activation of GP IIb/IIIa can be stimulated by multiple factors, including thromboxane A***2*** (TXA***2***), thrombin, collagen, platelet activation factor, and ADP. Under the influence of these factors, GP IIb/IIIa changes its shape, binds with fibrinogen, and thereby causes aggregation (Fig. 51-1*B*). The aggregated platelets constitute a plug that stops bleeding. This plug is unstable, however, and must be reinforced with *fibrin* if protection is to last.

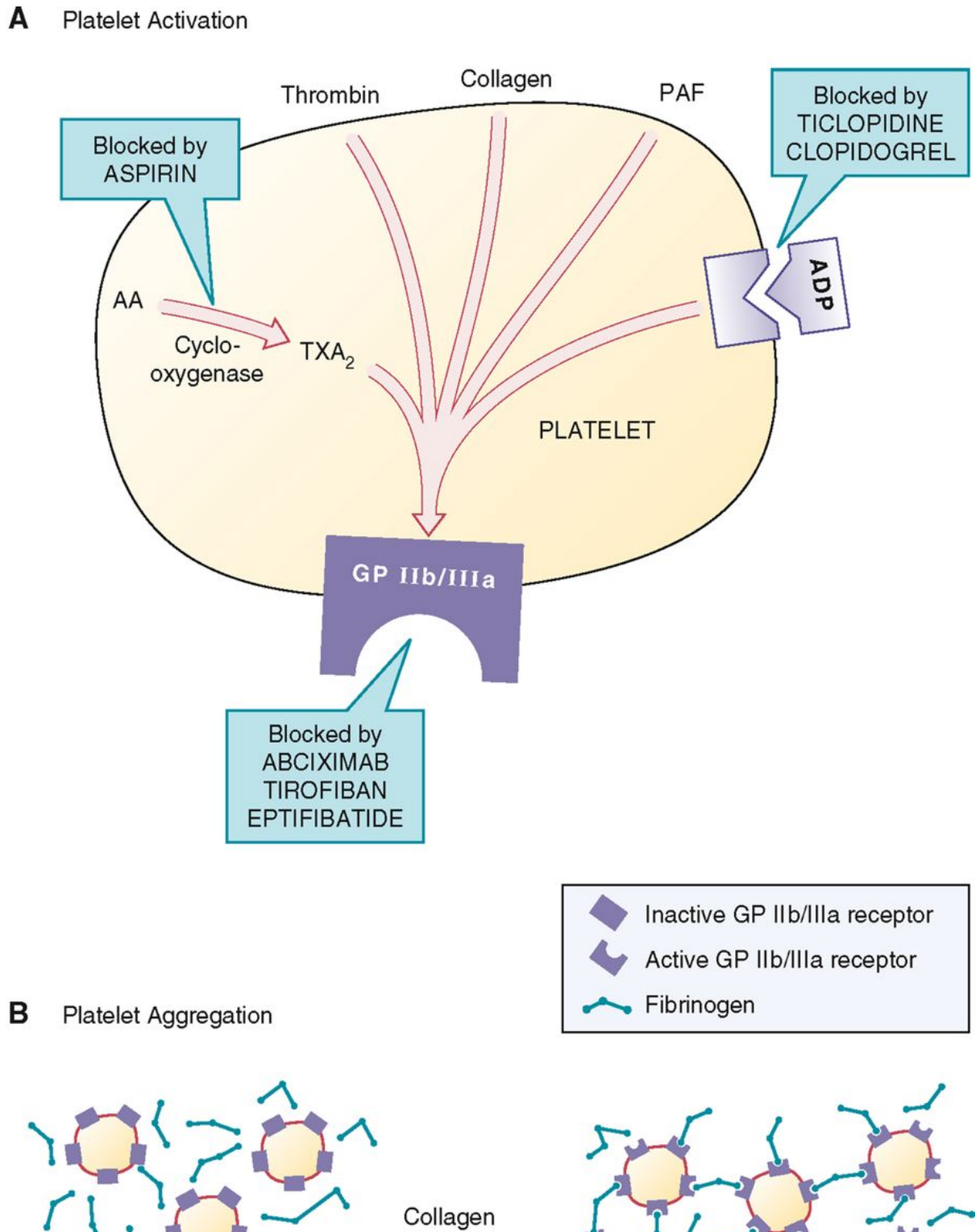
A
Platelet Activation
Thrombin
Collagen
PAF
Blocked by
ASPIRIN
Blocked by
TICLOPIDINE
CLOPIDOGREL
AA
Cyclo-
oxygenase
TXA2
ADP
PLATELET
GP IIb/IIIa
Blocked by
ABCIXIMAB
TIROFIBAN
EPTIFIBATIDE
Inactive GP IIb/IIIa receptor
Active GP IIb/IIIa receptor
Fibrinogen
B
Platelet Aggregation
Collagen

Figure 51-1 Mechanism of platelet aggregation and actions of antiplatelet drugs. A, Multiple factors—TXA2, thrombin, collagen, PAF, and ADP—promote activation of the GP IIb/IIIa receptor. Each platelet has 50,000 to 80,000 GP IIb/IIIa receptors, although only one is shown. B, Activation of the GP IIb/IIIa receptor permits binding of fibrinogen, which then causes aggregation by forming cross-links between platelets. After aggregation occurs, the platelet plug is reinforced with fibrin (not shown). (AA = arachidonic acid, ADP = adenosine diphosphate, GP IIb/IIIa = glycoprotein IIb/IIIa receptor, PAF = platelet activation factor, TXA2 = thromboxane A2.)

Stage Two: Coagulation.

Coagulation is defined as production of *fibrin,* a thread-like protein that reinforces the platelet plug. Fibrin is produced by two convergent pathways (Fig. 51-2), referred to as the *contact activation pathway* (also known as the *intrinsic pathway*) and the *tissue factor pathway* (also known as the *extrinsic pathway*). As shown in Figure 51-2, the two pathways converge at factor Xa, after which they employ the same final series of reactions. In both pathways, each reaction in the sequence amplifies the reaction that follows. Hence, once this sequence is initiated, it becomes self-sustaining and self-reinforcing.

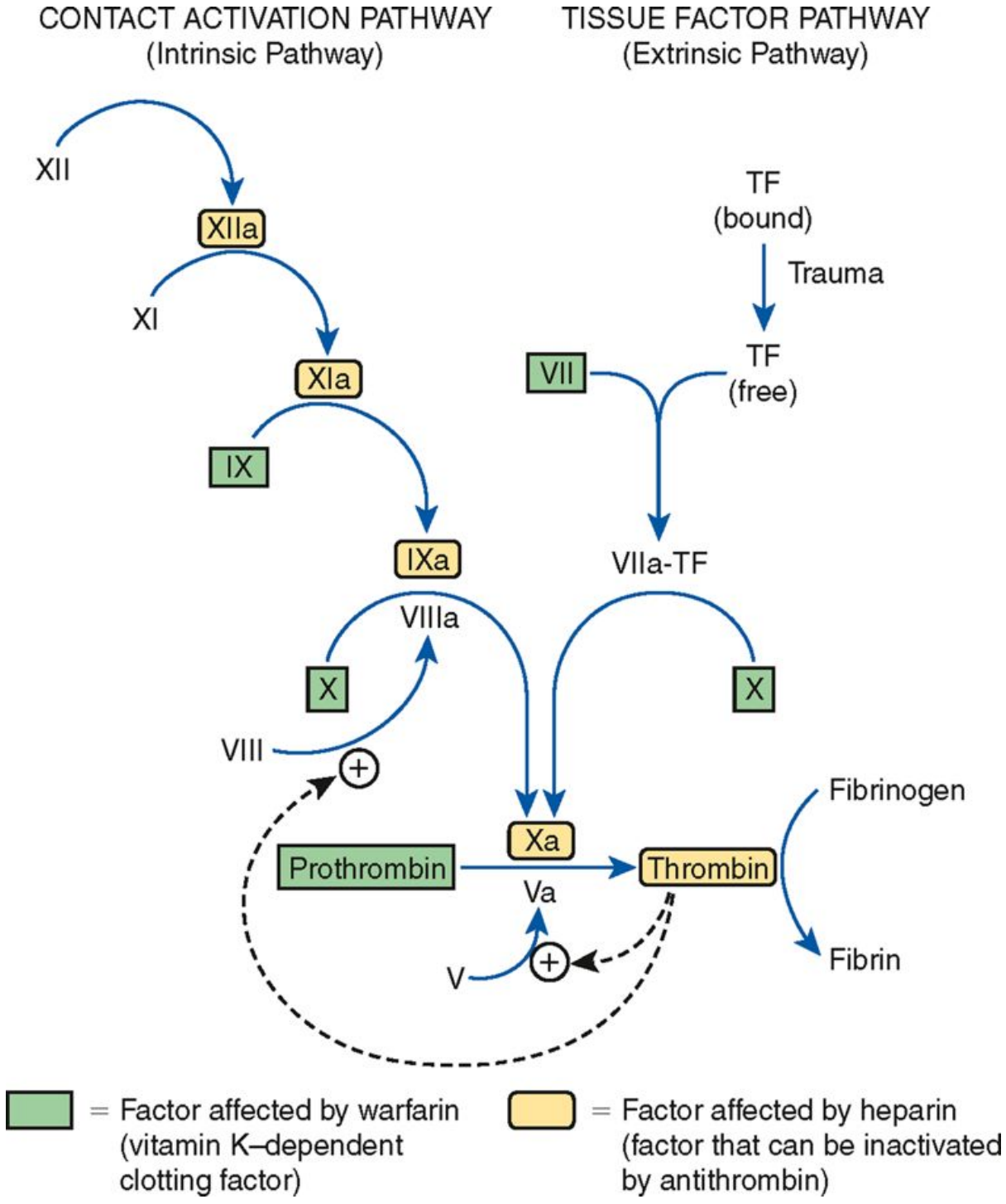
CONTACT ACTIVATION PATHWAY
(Intrinsic Pathway)
TISSUE FACTOR PATHWAY
(Extrinsic Pathway)
XII
XIIa
XI
XIa
IX
IXa
TF
(bound)
Trauma
TF
(free)
VII
VIIa-TF
VIIIa
VIII
X
X
Xa
Prothrombin
Thrombin
Fibrinogen
Fibrin
Va
V
= Factor affected by warfarin (vitamin K–dependent clotting factor)
= Factor affected by heparin (factor that can be inactivated by antithrombin)

Figure 51-2 Outline of coagulation pathways showing factors affected by warfarin and heparin. TF = tissue factor. Common names for factors shown in roman numerals: V = proaccelerin, VII = proconvertin, VIII = antihemophilic factor, IX = Christmas factor, X = Stuart factor, XI = plasma thromboplastin antecedent, and XII = Hageman factor. The letter "a" after a factor's name (eg, factor VIIIa) indicates the active form of the factor.

The *tissue factor pathway* is turned on by trauma to the vascular wall, which triggers release of tissue factor,* also known as *tissue thromboplastin*. Tissue factor then combines with and thereby activates factor VII, which in turn activates factor X, which then catalyzes the conversion of *prothrombin* (factor II) into *thrombin* (factor IIa). As shown in Figure 51-2, factor IIa (thrombin) then does three things. First, it catalyzes the conversion of fibrinogen into fibrin. Second, it catalyzes the conversion of factor V into *its* active form (Va), a compound that greatly increases the activity of factor Xa, even though it has no direct catalytic activity of its own. Third, factor IIa catalyzes the conversion of factor VIII into *its* active form (VIIIa), a compound that greatly increases the activity of factor IXa in the contact activation pathway.

The *contact activation pathway* is turned on when blood makes contact with collagen that has been exposed as a result of trauma to a blood vessel wall. Collagen contact stimulates conversion of factor XII into its active form, XIIa (see Figure 51-2). Factor XIIa then activates factor XI, which activates factor IX, which activates factor X. After this, the contact activation pathway is the same as the tissue factor pathway. As noted, factor VIIIa, which is produced under the influence of prothrombin, greatly increases the activity of factor IXa, even though it has no direct catalytic activity of its own.

Important to our understanding of anticoagulant drugs is the fact that *four coagulation factors—factors VII, IX, X, and II (prothrombin)—require vitamin K for their synthesis*. These factors appear in green boxes in Figure 51-2. The significance of the vitamin K–dependent factors will become apparent when we discuss warfarin, an oral anticoagulant.

* FYI: the term *tissue factor* refers not to a single compound but rather to a complex of several compounds, including a proteolytic enzyme and phospholipids released from tissue membranes.

Keeping Hemostasis Under Control.

To protect against widespread coagulation, the body must inactivate any clotting factors that stray from the site of vessel injury. This inactivation is accomplished with *antithrombin* (formerly known as *antithrombin III*), a protein that forms a complex with clotting factors, and thereby inhibits their activity. The clotting factors that can be neutralized by antithrombin appear in yellow in Figure 51-2. As we shall see, antithrombin is intimately involved in the action of *heparin,* an injectable anticoagulant drug.

Physiologic Removal of Clots.

As healing of an injured vessel proceeds, removal of the clot is eventually necessary. The body accomplishes this with *plasmin,* an enzyme that degrades the fibrin meshwork of the clot. Plasmin is produced through the activation of its precursor, *plasminogen*. The *thrombolytic drugs* (eg, streptokinase, alteplase) act by promoting conversion of plasminogen into plasmin.

Thrombosis

A thrombus is a blood clot formed within a blood vessel or within the heart. Thrombosis (thrombus formation) reflects pathologic functioning of hemostatic mechanisms.

Arterial Thrombosis.

Formation of an arterial thrombus begins with adhesion of platelets to the arterial wall. (Adhesion is stimulated by damage to the wall or rupture of an atherosclerotic plaque.) Following adhesion, platelets release ADP and TXA2, and thereby attract additional platelets to the evolving thrombus. With continued platelet aggregation, occlusion of the artery takes place. As blood flow comes to a stop, the coagulation cascade is initiated, causing the original plug to undergo reinforcement with fibrin. The consequence of an arterial thrombus is localized tissue injury owing to lack of perfusion.

Venous Thrombosis.

Venous thrombi develop at sites where blood flow is slow. Stagnation of blood initiates the coagulation cascade, resulting in the production of fibrin, which enmeshes red blood cells and platelets to form the thrombus. The typical ven-

ous thrombus has a long tail that can break off to produce an *embolus*. Such emboli travel within the vascular system and become lodged at faraway sites, frequently the pulmonary arteries. Hence, unlike an arterial thrombus, whose harmful effects are localized, injury from a venous thrombus occurs secondary to embolization at a site distant from the original thrombus.

OVERVIEW OF DRUGS FOR THROMBOEMBOLIC DISORDERS

The drugs considered in this chapter fall into three major groups: (1) anticoagulants, (2) antiplatelet drugs, and (3) thrombolytic drugs. *Anticoagulants* (eg, heparin, warfarin) disrupt the coagulation cascade, and thereby suppress production of fibrin. *Antiplatelet drugs* (eg, aspirin, clopidogrel) inhibit platelet aggregation. *Thrombolytic drugs* (eg, alteplase, streptokinase) promote lysis of fibrin, and thereby cause dissolution of thrombi. Drugs that belong to these groups are listed in Table 51-1.

Although the anticoagulants and the antiplatelet drugs both suppress thrombosis, they do so by different mechanisms. As a result, they differ in their effects and applications. The *antiplatelet drugs* are most effective at preventing *arterial* thrombosis, whereas *anticoagulants* are most effective against *venous* thrombosis.

Generic Name	Trade Name	Route	Action	Therapeutic Use
ANTICOAGULANTS			Anticoagulants decrease formation of fibrin	Used primarily to prevent *venous* thrombosis
Vitamin K Antagonist				
Warfarin	Coumadin	PO		
Factor Xa and Thrombin Inhibitors				
Heparin		subQ, IV		
LMW Heparins*				
Dalteparin	Fragmin	subQ		
Enoxaparin	Lovenox	subQ		
Tinzaparin	Innohep	subQ		
Selective Factor Xa Inhibitors				
Fondaparinux	Arixtra	subQ		
Rivaroxaban‡	Xarelto	PO		
Direct Thrombin Inhibitors				
Argatroban	Acova	IV		
Bivalirudin	Angiomax	IV		
Lepirudin	Refludan	IV		
Desirudin	Ipravask	subQ		
Dabigatran‡	Pradaxa	PO		
ANTIPLATELET DRUGS			Antiplatelet drugs suppress platelet aggregation	Used primarily to prevent *arterial* thrombosis
Cyclooxygenase Inhibitor				
Aspirin		PO		
Adenosine Diphosphate Receptor Antagonists				
Clopidogrel	Plavix	PO		
Prasugrel‡	Effient	PO		
Ticlopidine	Ticlid	PO		
Glycoprotein IIb/IIIa Receptor Antagonists				
Abciximab	ReoPro	IV		
Eptifibatide	Integrilin	IV		
Tirofiban	Aggrastat	IV		
Other Antiplatelet Drugs				
Dipyridamole	Persantine	PO		
Cilostazol	Pletal	PO		
THROMBOLYTIC DRUGS				
Alteplase	Activase	IV	Thrombolytic drugs promote breakdown of fibrin	Used to dissolve newly formed thrombi
Streptokinase	Streptase	IV, IA		
Reteplase	Retavase	IV		
Tenecteplase	TNKase	IV		

IA = intra-arterial (into an occluded artery); LMW = low molecular weight.

TABLE 51-1 Overview of Drugs for Thromboembolic Disorders

* LMW heparins inactivate factor Xa more effectively than they inactivate thrombin.

† Not approved in the United States.

ANTICOAGULANTS

By definition, anticoagulants are drugs that *reduce formation of fibrin*. Two basic mechanisms are involved. One anticoagulant—warfarin—inhibits the *synthesis* of clotting factors, including factor X and thrombin. All other anticoagulants inhibit the *activity* of clotting factors (either factor Xa, thrombin, or both).

Traditionally, anticoagulants have been grouped into two major classes: *oral anticoagulants* and *parenteral anticoagulants*. This scheme was reasonable because, until recently, all oral anticoagulants belonged to just one pharmacologic class: the vitamin K antagonists, of which warfarin is the principal member. Today, however, anticoagulants in two other pharmacologic classes—factor Xa inhibitors and direct thrombin inhibitors—can also be administered by mouth (see Table 51-1). Hence, grouping the anticoagulants by route of administration makes less sense than in the past. Accordingly, in this chapter, these drugs are grouped only by pharmacologic class, and not by whether they are given orally or by injection.

HEPARIN AND HEPARIN DERIVATIVES

All of the drugs in this section share the same mechanism of action. Specifically, they greatly enhance the activity of antithrombin, a protein that inactivates two major clotting factors: thrombin and factor Xa. In the absence of thrombin and factor Xa, production of fibrin is reduced, and hence clotting is suppressed.

Heparin (Unfractionated)

Heparin is a rapid-acting anticoagulant administered only by injection. Heparin differs from warfarin (an oral anticoagulant) in several respects, including mechanism, time course, indications, and management of overdose.

Source

Heparin is present in various mammalian tissues. The heparin employed clinically is prepared from two sources: lungs of cattle and intestines of pigs. The an-

ticoagulant activity of heparin from either source is equivalent. Although heparin occurs naturally, its physiologic role is unknown.

Chemistry

Heparin is not a single molecule, but rather a mixture of long polysaccharide chains, with molecular weights that range from 3000 to 30,000. The active region is a unique pentasaccharide (five-sugar) sequence found randomly along the chain. An important feature of heparin's structure is the presence of many negatively charged groups. Because of these negative charges, heparin is highly polar, and hence cannot readily cross membranes.

Mechanism of Anticoagulant Action

Heparin suppresses coagulation by helping antithrombin inactivate clotting factors, primarily thrombin and factor Xa. As shown in Figure 51-3, binding of heparin to antithrombin produces a conformational change in antithrombin that greatly enhances its ability to inactivate both thrombin and factor Xa. However, the process of inactivating these two clotting factors is not identical. In order to inactivate thrombin, heparin must simultaneously bind with both thrombin and antithrombin, thereby forming a ternary complex (see Fig. 51-3). In contrast, in order to inactivate factor Xa, heparin binds only with antithrombin; heparin itself does not bind with factor Xa.

By promoting the inactivation of thrombin and factor Xa, heparin ultimately suppresses formation of fibrin. Since fibrin forms the framework of thrombi in *veins,* heparin is especially useful for prophylaxis of *venous thrombosis*. Because thrombin and factor Xa are inhibited as soon as they bind with the heparin-antithrombin complex, the anticoagulant effects of heparin develop *quickly* (within minutes of IV administration). This contrasts with warfarin, whose full effects are not seen for *days*.

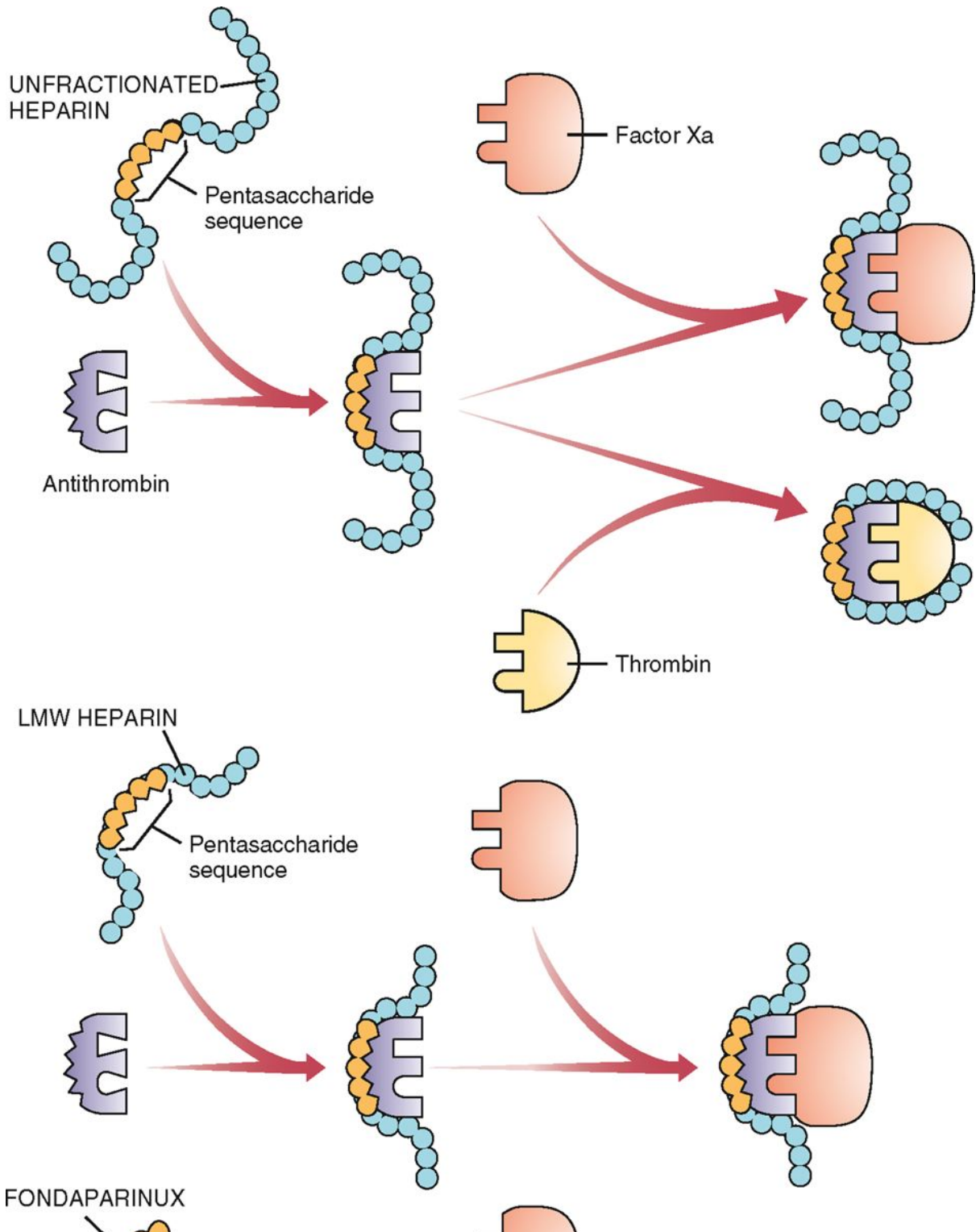
UNFRACTIONATED HEPARIN
Pentasaccharide sequence
Factor Xa
Antithrombin
Thrombin
LMW HEPARIN
Pentasaccharide sequence
FONDAPARINUX

Figure 51-3 Mechanism of action of heparin, LMW heparins, and fondaparinux. All three drugs share a pentasaccharide sequence that allows them to bind with—and thereby activate—antithrombin, a protein that inactivates two major clotting factors: thrombin and factor Xa. All three drugs enable antithrombin to inactivate factor Xa, but only heparin also facilitates inactivation of thrombin. Upper Panel: Unfractionated heparin binds with antithrombin, thereby causing a conformational change in antithrombin that greatly increases its ability to interact with factor Xa and thrombin. As shown, when the heparin-antithrombin complex binds with thrombin, heparin changes its conformation such that both heparin and antithrombin come in contact with thrombin. Formation of this ternary complex is necessary for thrombin inactivation. Inactivation of factor Xa is different: it only requires contact between activated antithrombin and factor Xa; contact between heparin and factor Xa is unnecessary. Middle Panel: Low-molecular-weight (LMW) heparins have the same pentasaccharide sequence as unfractionated heparin, and hence can bind with and thereby activate antithrombin. However, in contrast to unfractionated heparin, which promotes inactivation of both thrombin and factor Xa, most molecules of LMW heparin can only inactivate factor Xa; they are unable to inactivate thrombin. Why? Because most molecules of LMW heparin are too small to form a ternary complex with thrombin and antithrombin. Lower Panel: Fondaparinux is a synthetic pentasaccharide identical in structure to the antithrombin binding sequence found in unfractionated heparin and LMW heparins. Being even smaller than LMW heparins, fondaparinux is too small to form a ternary complex with thrombin, and hence can only inactivate factor Xa.

Pharmacokinetics

Absorption and Distribution.

Because of its polarity and large size, heparin is unable to cross membranes, including those of the GI tract. Consequently, heparin cannot be absorbed if given orally, and therefore must be given by injection (IV or subQ). Since it cannot cross membranes, heparin does not traverse the placenta and does not enter breast milk.

Protein and Tissue Binding.

Heparin binds nonspecifically to plasma proteins, mononuclear cells, and endothelial cells. As a result, plasma levels of free heparin can be highly variable following IV or subQ administration. Because of this variability, intensive monitoring is required (see below).

Metabolism and Excretion.

Heparin undergoes hepatic metabolism followed by renal excretion. Under normal conditions, the half-life is short (about 1.5 hours). However, in patients with hepatic or renal disease, the half-life is increased.

Time Course.

Therapy is initiated with a bolus IV injection, and effects begin immediately. Duration of action is brief (hours) and varies with dosage. Effects are prolonged in patients with hepatic or renal impairment.

Therapeutic Uses

Heparin is a preferred anticoagulant for use during *pregnancy* and in situations that require rapid onset of anticoagulant effects, including *pulmonary embolism* (PE), *evolving stroke,* and *massive deep vein thrombosis* (DVT). In addition, heparin is used for patients undergoing *open heart surgery* and *renal dialysis;* during these procedures, heparin serves to prevent coagulation in devices of extracorporeal circulation (heart-lung machines, dialyzers). Low-dose therapy is used to *prevent postoperative venous thrombosis*. Heparin may also be useful for treating *disseminated intravascular coagulation,* a complex disorder in which fibrin clots form throughout the vascular system and in which bleeding tendencies may be present; bleeding can occur because massive fibrin production consumes available supplies of clotting factors. Heparin is also used as an adjunct to thrombolytic therapy of *acute myocardial infarction* (MI).

Adverse Effects

Hemorrhage.

Bleeding develops in about 10% of patients and is the principal complication of treatment. Hemorrhage can occur at any site and may be fatal. Patients should be monitored closely for signs of blood loss. These include reduced blood pressure, increased heart rate, bruises, petechiae, hematomas, red or black stools, cloudy or discolored urine, pelvic pain (suggesting ovarian hemorrhage), headache or faintness (suggesting cerebral hemorrhage), and lumbar pain (suggesting adrenal hemorrhage). If bleeding develops, heparin should be withdrawn. Severe overdose can be treated with *protamine sulfate* (see below).

The risk of hemorrhage can be decreased in several ways. First, dosage should be carefully controlled so that the activated partial thromboplastin time (see below) does not exceed 2 times the control value. In addition, candidates for heparin therapy should be screened for risk factors (see *Warnings and Contraindications*). Finally, antiplatelet drugs (eg, aspirin) should be avoided.

Heparin-Induced Thrombocytopenia.

Heparin-induced thrombocytopenia (HIT) is a potentially fatal immune-mediated disorder characterized by reduced platelet counts (thrombocytopenia) and a seemingly paradoxical *increase* in thrombotic events. The underlying cause is development of antibodies against heparin–platelet protein complexes. These antibodies activate platelets and damage the vascular endothelium, thereby promoting both thrombosis and a rapid loss of circulating platelets. Thrombus formation poses a risk of DVT, PE, cerebral thrombosis, and MI. Ischemic injury secondary to thrombosis in the limbs may require amputation of an arm or leg. Coronary thrombosis can be fatal. The primary treatment for HIT is discontinuation of heparin and, if anticoagulation is still needed, substitution of a nonheparin anticoagulant, typically lepirudin or argatroban. The incidence of HIT is between 1% and 3% among patients who receive heparin for more than 4 days.

HIT should be suspected whenever platelet counts fall significantly or when thrombosis develops despite adequate anticoagulation. Accordingly, to reduce the risk of HIT, patients should be monitored for signs of thrombosis and for reductions in platelets. Platelet counts should be determined frequently (2 to

3 times a week) during the first 3 weeks of heparin use, and monthly thereafter. If severe thrombocytopenia develops (platelet count below 100,000/mm3), heparin should be discontinued.

Hypersensitivity Reactions.

Because commercial heparin is extracted from animal tissues, these preparations may be contaminated with antigens that can promote allergy. Possible allergic responses include chills, fever, and urticaria. Anaphylactic reactions are rare. To minimize the risk of severe reactions, patients should receive a small test dose of heparin prior to the full therapeutic dose.

Other Adverse Effects.

Subcutaneous administration may produce *local irritation* and *hematoma. Vasospastic reactions* that persist for several hours may develop after 1 or more weeks of treatment. Long-term, high-dose therapy may cause *osteoporosis*.

Warnings and Contraindications

Warnings.

Heparin must be used with extreme caution in all patients who have a high likelihood of bleeding. Among these are individuals with hemophilia, increased capillary permeability, dissecting aneurysm, peptic ulcer disease, severe hypertension, or threatened abortion. Heparin must also be used cautiously in patients with severe disease of the liver or kidneys.

Contraindications.

Heparin is contraindicated for patients with thrombocytopenia and uncontrollable bleeding. In addition, heparin should be avoided both during and immediately after surgery of the eye, brain, or spinal cord. Lumbar puncture and regional anesthesia are additional contraindications.

Drug Interactions

In heparin-treated patients, platelet aggregation is the major remaining defense against hemorrhage. Aspirin and other drugs that depress platelet function will weaken this defense, and hence must be employed with caution.

Protamine Sulfate for Heparin Overdose

Protamine sulfate is an antidote to severe heparin overdose. Protamine is a small protein that has multiple positively charged groups. These groups bond ionically with the negative groups on heparin, thereby forming a heparin-protamine complex that is devoid of anticoagulant activity. Neutralization of heparin occurs immediately and lasts for 2 hours, after which additional protamine may be needed. Protamine is administered by slow IV injection (no faster than 20 mg/min or 50 mg in 10 minutes). Dosage is based on the fact that 1 mg of protamine will inactivate 100 units of heparin. Hence, for each 100 units of heparin in the body, 1 mg of protamine should be injected.

Laboratory Monitoring

The objective of anticoagulant therapy is to reduce blood coagulability to a level that is low enough to prevent thrombosis but not so low as to promote spontaneous bleeding. Because heparin levels can be highly variable, achieving this goal is difficult, and requires careful control of dosage based on frequent tests of coagulation. The laboratory test employed most commonly is the *activated partial thromboplastin time* (aPTT). The normal value for the aPTT is 40 seconds. At therapeutic levels, heparin *increases* the aPTT by a factor of 1.5 to 2, making the aPTT 60 to 80 seconds. Since heparin has a rapid onset and brief duration, if an aPTT value should fall outside the therapeutic range, coagulability can be quickly corrected through an adjustment in dosage: if the aPTT is too long (more than 80 seconds), the dosage should be lowered; conversely, if the aPTT is too short (less than 60 seconds), the dosage should be increased. Measurements of aPTTs should be made frequently (every 4 to 6 hours) during the initial phase of therapy. Once an effective dosage has been established, one aPTT measurement a day will suffice.

Unitage and Preparations

Unitage.

Heparin is prescribed in units, not in milligrams. The heparin unit is an index of anticoagulant activity, and is defined as the amount of heparin that will prevent 1 mL of sheep plasma from coagulating for 1 hour. Heparin is prescribed

in units because heparin preparations tend to differ from one another in anticoagulant activity when compared on a milligram basis.

Preparations.

Heparin sodium is supplied in single-dose vials; multidose vials; and unit-dose, preloaded syringes that have their own needles. Concentrations range from 1000 to 40,000 units/mL. Heparin sodium for use in heparin locks [Hep-Lock] is supplied in *dilute* solutions (10 and 100 units/mL) that are too weak to produce systemic anticoagulant effects.

Dosage and Administration

General Considerations.

Heparin is administered by injection only. Two routes are employed: *intravenous* (either intermittent or continuous) and *subcutaneous*. Intramuscular injection causes hematoma and must not be used. Heparin is not administered orally because heparin is too large and too polar to permit intestinal absorption.

Dosage varies with the application. Postoperative prophylaxis of thrombosis, for example, requires relatively small doses. In other situations, such as open heart surgery, much larger doses are used. The dosages given below are for "general anticoagulant therapy." As a rule, the aPTT should be employed as a guideline for dosage titration; increases in the aPTT of 1.5- to 2-fold are therapeutic. Since heparin is formulated in widely varying concentrations, you must read the label with care to ensure that dosing is correct.

Intermittent IV Therapy.

Intermittent IV heparin is administered via an indwelling needle with a rubber-capped port (heparin lock). Therapy is initiated with a dose of 10,000 units. Subsequent doses of 5000 to 10,000 units are given every 4 to 6 hours. The aPTT should be taken 1 hour before each injection until dosage is stabilized. To avoid venous injury, the site of the heparin lock should be moved every 2 or 3 days. When heparin is administered intermittently, plasma levels of the drug will fluctuate, possibly causing alternating periods of excessive and insufficient anticoagulation.

Continuous IV Infusion.

Intravenous infusion provides steady levels of heparin, and therefore is preferred to intermittent injections. Dosing consists of a bolus (5000 to 10,000 units), followed by infusion at a rate of 1000 units/hr. During the initial phase of treatment, the aPTT should be measured once every 4 hours and the infusion rate adjusted accordingly. To decrease the risk of overdose, when heparin solutions are prepared, the amount made up should be sufficient for no more than a 6-hour infusion. Heparin should be infused using an electric pump, and the rate should be checked every 30 to 60 minutes.

Deep SubQ Injection.

Subcutaneous injections are made deep into the fatty layer of the abdomen (but not within 2 inches of the umbilicus). The heparin solution should be drawn up using a 20- to 22-gauge needle. This needle is then discarded and replaced with a small needle (½ to ⅝ inch, 25 or 26 gauge) to make the injection. Following administration, firm but gentle pressure should be applied to the injection site for 1 to 2 minutes. The initial subQ dose is 10,000 to 20,000 units (preceded immediately by an IV loading dose of 5000 units). The initial subQ dose is followed by either (1) 8000 to 10,000 units every 8 hours or (2) 15,000 to 20,000 units every 12 hours. Dosage is adjusted on the basis of aPTTs taken 4 to 6 hours after each injection. The injection site should be rotated.

Low-Dose Therapy.

Heparin in low doses is given for prophylaxis against postoperative thromboembolism. The initial dose (5000 units subQ) is given 2 hours prior to surgery. Additional doses of 5000 units are given every 8 to 12 hours for 7 days (or until the patient is ambulatory). Low-dose heparin is also employed as adjunctive therapy for patients with MI. During low-dose therapy, monitoring of the aPTT is not usually required.

Low-Molecular-Weight Heparins

Group Properties

Low-molecular-weight (LMW) heparins are simply heparin preparations composed of molecules that are shorter than those found in unfractionated hep-

arin. LMW heparins are as effective as unfractionated heparin and are easier to use. Why? Because LMW heparins can be given on a fixed-dose schedule and don't require aPTT monitoring. As a result, LMW heparins can be used at home, whereas unfractionated heparin must be given in a hospital. Because of these advantages, LMW heparins are now considered first-line therapy for prevention and treatment of DVT. In the United States, three LMW heparins are available: enoxaparin [Lovenox], dalteparin [Fragmin], and tinzaparin [Innohep]. Differences between LMW heparins and unfractionated heparin are summarized in Table 51-2.

Property	Unfractionated Heparin	Low-Molecular-Weight Heparin
Molecular weight range	3000–30,000	1000–9000
Mean molecular weight	12,000–15,000	4000–5000
Mechanism of action	Inactivation of factor Xa and thrombin	Preferential inactivation of factor Xa
Routes	IV, subQ	subQ only
Nonspecific binding	Widespread	Minimal
Laboratory monitoring	aPTT monitoring is essential	No aPTT monitoring required
Dosage	Dosage must be adjusted on basis of aPTT	Dosage is fixed
Setting for use	Hospital	Hospital or home
Cost	$3/day for heparin itself, but hospitalization and aPTT monitoring greatly increase the real cost	$14/day for LMW heparin, but home use and absence of aPTT monitoring greatly reduce the real cost

TABLE 51-2 Comparison of Unfractionated Heparin with Low-Molecular-Weight Heparin

Production.

LMW heparins are made by depolymerizing unfractionated heparin (ie, breaking unfractionated heparin into smaller pieces). Molecular weights in LMW preparations range between 1000 and 9000, with a mean of 4000 to 5000. In comparison, molecular weights in unfractionated heparin range between 3000 and 30,000, with a mean of 12,000 to 15,000.

Mechanism of Action.

Anticoagulant activity of LMW heparin is mediated by the same active pentasaccharide sequence that mediates anticoagulant action of standard heparin. However, because LMW heparin molecules are short, they do not have quite the same effect as standard heparin. Specifically, whereas standard heparin is equally good at inactivating factor Xa *and* thrombin, *LMW heparins preferentially inactivate factor Xa,* being much less able to inactivate thrombin. Why the difference? In order to inactivate thrombin, a heparin chain must not only contain the pentasaccharide sequence that activates antithrombin, it must also be long enough to provide a binding site for thrombin. This binding site is necessary because inactivation of thrombin requires simultaneous binding of thrombin with heparin and antithrombin (see Fig. 51-3). In contrast to standard heparin chains, most (but not all) LMW heparin chains are too short to allow thrombin binding, and hence LMW heparins are less able to inactivate thrombin.

Condition Being Treated	Recommended Ranges	
	Observed PT Ratio*	INR†
Acute myocardial infarction‡	1.3–1.5	2–3
Atrial fibrillation‡	1.3–1.5	2–3
Valvular heart disease‡	1.3–1.5	2–3
Pulmonary embolism	1.3–1.5	2–3
Venous thrombosis§	1.3–1.5	2–3
Tissue heart valves‡	1.3–1.5	2–3
Mechanical heart valves	1.5–2	3–4.5
Systemic embolism		
Prevention	1.3–1.5	2–3
Recurrent	1.5–2	3–4.5

TABLE 51-3 Monitoring Warfarin Therapy: Recommended Ranges of Prothrombin Time–Derived Values

* Observed PT ratio = ratio of patient's PT to a control PT value. In this particular case, the reagent used to determine the control PT value is one of the preparations of rabbit brain thromboplastin employed in the United States. Had a different preparation of thromboplastin been used, the observed PT ratio could be very different.

† INR = international normalized ratio. This value is calculated from the observed PT ratio. The INR is equivalent to the PT ratio that would have been obtained if the patient's PT has been compared to a PT value obtained using the International Reference Preparation, a standardized human brain thromboplastin prepared by the World Health Organization. In contrast to PT ratios, INR values are comparable from one laboratory to the next throughout the United States and the rest of the world.

‡ For prevention of systemic embolism.

§ Prophylaxis in high-risk surgery; treatment.

Therapeutic Use.

LMW heparins are *approved* for (1) prevention of DVT following abdominal surgery, hip replacement surgery, or knee replacement surgery; (2) treatment of established DVT, with or without PE; and (3) prevention of ischemic complications in patients with unstable angina, non–Q-wave MI, and ST-elevation MI (STEMI). In addition, these drugs have been used extensively *off label* to prevent DVT after general surgery and in patients with multiple trauma and acute spinal injury. When used for prophylaxis or treatment of DVT, LMW heparins are at least as effective as unfractionated heparin, and possibly more effective.

Pharmacokinetics.

Compared with unfractionated heparin, LMW heparins have higher bioavailability and longer half-lives. Bioavailability is higher because LMW heparins do not undergo nonspecific binding to proteins and tissues, and hence are more available for anticoagulant effects. Half-lives are prolonged (up to 6 times longer than that of unfractionated heparin) because LMW heparins undergo less binding to macrophages, and hence undergo slower clearance by the liver. Because of increased bioavailability, plasma levels of LMW heparin are highly predictable. As a result, these drugs can be given on a fixed schedule with no need for routine monitoring of coagulation. Because of their long half-lives, LMW heparins can be given just once or twice a day.

Administration, Dosing, and Monitoring.

LMW heparins are administered subQ. Dosage is based on body weight. Because plasma levels of LMW heparins are predictable for any given dose, these drugs can be administered on a fixed schedule without laboratory monitoring. This contrasts with unfractionated heparin, which requires dosage adjustments on the basis of aPTT measurements. Because LMW heparins have an extended half-life, dosing can be done once or twice daily. For prophylaxis of DVT, dosing is begun in the perioperative period and continued 5 to 10 days.

Adverse Effects and Interactions.

Bleeding is the major adverse effect. However, the incidence of bleeding complications is less than with unfractionated heparin. Despite the potential for bleeding, LMW heparins are considered safe for outpatient use. Like unfractionated heparin, LMW heparins can cause immune-mediated *thrombocyt-*

openia. As with unfractionated heparin, overdose with LMW heparins can be treated with protamine sulfate.

Like unfractionated heparin, LMW heparins can cause *severe neurologic injury,* including permanent paralysis, when given to patients undergoing spinal puncture or spinal or epidural anesthesia. Neurologic injury results from pressure on the spinal cord generated by an epidural or spinal bleed. The risk of serious harm is increased by concurrent use of antiplatelet drugs (eg, aspirin, ticlopidine) or warfarin. Patients should be monitored closely for signs of neurologic impairment.

Cost.

LMW heparins cost more than unfractionated heparin (eg, about $63/day for dalteparin vs. $8/day for unfractionated heparin). However, since LMW heparins can be used at home and don't require monitoring of the aPTT, the overall cost of treatment is far less than with unfractionated heparin.

Individual Preparations

In the United States, three LMW heparins are available: enoxaparin, dalteparin, and tinzaparin. Additional LMW heparins are available in other countries. Each preparation is unique. Hence clinical experience with one may not apply fully to the others.

Enoxaparin.

Enoxaparin [Lovenox] was the first LMW heparin available in the United States. The drug is prepared by depolymerization of unfractionated porcine heparin. Molecular weights range between 2000 and 8000.

Enoxaparin is approved for prevention of DVT following hip and knee replacement surgery or abdominal surgery in patients considered at high risk of thromboembolic complications (eg, obese patients, those over age 40, and those with malignancy or a history of DVT or pulmonary embolism). The drug is also approved for preventing ischemic complications in patients with unstable angina, non–Q-wave MI, or STEMI. Administration is by deep subQ injection. For patients with normal renal function (or moderate renal impairment), dosages are as follows:

- *Prevention of DVT after hip or knee replacement surgery*—30 mg every 12 hours starting 12 to 24 hours after surgery and continuing 7 to 10 days
- *Prevention of DVT after abdominal surgery*—40 mg once daily, beginning 2 hours before surgery and continuing 7 to 10 days
- Treatment *of established DVT*—1 mg/kg every 12 hours for 7 days
- *Patients with unstable angina or non-Q-wave MI*—1 mg/kg every 12 hours (in conjunction with oral aspirin, 100 to 325 mg once daily) for 2 to 8 days
- *Patients with acute STEMI*—30 mg by IV bolus plus 1 mg/kg subQ, followed by 1 mg/kg subQ every 12 hours for up to 8 days

For patients with severe renal impairment, dosage should be reduced.

In the event of overdose, hemorrhage can be controlled with protamine sulfate. The dosage is 1 mg of protamine sulfate for each milligram of enoxaparin administered.

Dalteparin.

Dalteparin [Fragmin] was the second LMW heparin to be marketed in the United States. The drug is prepared by depolymerization of porcine heparin. Molecular weights range between 2000 and 9000, the mean being 5000. Approved indications are prevention of DVT following hip replacement surgery or abdominal surgery in patients considered at high risk of thromboembolic complications, prevention of ischemic complications in patients with unstable angina or non–Q-wave MI, and management of symptomatic venous thromboembolism (VTE). Administration is by deep subQ injection. Dosages are as follows:

- *Prevention of DVT after hip replacement surgery*—2500 anti–factor Xa international units (IU) 1 or 2 hours before surgery, 2500 IU that evening (at least 6 hours after the first dose), and then 5000 IU once daily for 5 to 10 days.
- *Prevention of DVT after abdominal surgery*—2500 IU once daily for 5 to 10 days, starting 1 to 2 hours before surgery.
- *Patients with unstable angina or non-Q-wave MI*—120 IU/kg (but not more than 10,000 IU total) every 12 hours for 5 to 8 days. Concurrent therapy with aspirin (75 to 165 mg/day) is required.

- *Patients with symptomatic VTE*—200 IU/kg (but not more than 18,000 IU total) once daily for 1 month, then 150 IU/kg (but not more than 18,000 IU total) once daily for months 2 through 6.

Overdose is treated with 1 mg of protamine sulfate for every 100 anti–factor Xa IU of dalteparin administered.

Tinzaparin.

Tinzaparin [Innohep] is indicated for acute symptomatic DVT (with or without PE) and should be used in conjunction with warfarin. Tinzaparin has a mean molecular weight of 6500 and a half-life of 3 to 4 hours. Excretion is via the urine. In clinical trials, bleeding developed in 0.8% of patients and thrombocytopenia in 1%. Eight men experienced priapism (persistent erection). Recent data indicate that, in elderly patients with renal impairment, tinzaparin *increases* the risk of death, and hence should be avoided in this population. Tinzaparin is supplied in 2-mL vials containing 20,000 anti–factor Xa IU/mL. Administration is by subQ injection in the abdominal region. The recommended dosage is 175 anti-Xa IU/kg once daily for 6 or more days. Warfarin should be initiated when appropriate, usually 1 to 3 days after starting tinzaparin. When warfarin has taken effect, as indicated by an international normalized ratio (INR; see below) of 2 or more for 2 consecutive days, tinzaparin can be discontinued. Overdose is treated with 1 mg of protamine sulfate for every 100 anti–factor Xa IU of dalteparin administered.

SELECTIVE FACTOR Xa INHIBITORS

Unlike heparin, which inactivates thrombin *and* factor Xa, the drugs discussed below—fondaparinux and rivaroxaban—produce *selective inhibition of factor Xa*. Like heparin, fondaparinux acts by an *indirect* mechanism (activation of antithrombin). In contrast, rivaroxaban binds *directly* with factor Xa to cause inactivation. Of greater importance, rivaroxaban is dosed orally, whereas fondaparinux is dosed by injection. In contrast to heparin, the selective factor Xa inhibitors do not require anticoagulant monitoring. Fondaparinux was approved in 2001. Rivaroxaban is under investigation.

Fondaparinux

Actions.

Fondaparinux [Arixtra] is a synthetic, subQ anticoagulant that enhances the activity of antithrombin, and thereby causes *selective inhibition of activated factor X* (factor Xa). As a result, production of thrombin is inhibited, and hence coagulation is suppressed.

Fondaparinux is closely related in structure and function to heparin and the LMW heparins. Structurally, fondaparinux is a pentasaccharide identical to the antithrombin-binding region of the heparins. Hence, like the heparins, fondaparinux is able to induce a conformational change in antithrombin, thereby increasing antithrombin's activity—but only against factor Xa, not against thrombin. Why is fondaparinux selective for factor Xa? Because the drug is quite small—even smaller than the LMW heparins. As a result, it is too small to form a complex with both antithrombin and thrombin, and hence cannot reduce thrombin activity (see Fig. 51-3).

Fondaparinux has no effect on prothrombin time, aPTT, bleeding time, or platelet aggregation.

Therapeutic Use.

Fondaparinux is approved for (1) preventing DVT following hip fracture surgery, hip replacement surgery, or knee replacement surgery; (2) treating acute PE (in conjunction with warfarin); and (3) treating acute DVT (in conjunction with warfarin). The drug is somewhat more effective than enoxaparin (an LMW heparin) at preventing DVT, but may cause slightly more bleeding. Fondaparinux is administered just once a day. Routine laboratory monitoring is unnecessary. Anticoagulation may persist for 2 to 4 days after the last dose.

Pharmacokinetics.

Fondaparinux is administered subQ, and bioavailability is 100%. Plasma levels peak 2 hours after injection. The drug is eliminated by the kidneys with a half-life of 17 to 21 hours. The half-life is increased by renal dysfunction.

Adverse Effects.

As with other anticoagulants, *bleeding* is the biggest concern. The risk is increased by advancing age and renal impairment. Fondaparinux should be

used with caution in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min/1.73 m2) and avoided in patients with severe renal impairment (creatinine clearance below 30 mL/min/1.73 m2). The drug should also be avoided in patients weighing less than 50 kg. Why? Because low body weight increases bleeding risk. Aspirin and other drugs that interfere with hemostasis should be used with caution. In contrast to overdose with heparin or LMW heparins, overdose with fondaparinux cannot be treated with protamine sulfate.

Fondaparinux does not promote immune-mediated HIT, although it still can lower platelet counts. During clinical trials, *thrombocytopenia* developed in 3% of patients. Platelet counts should be monitored and, if they fall below 100,000/mm3, fondaparinux should be discontinued.

In patients undergoing anesthesia using an epidural or spinal catheter, fondaparinux (as well as other anticoagulants) can cause *spinal or epidural hematoma,* which can result in permanent paralysis. However, in clinical trials, when fondaparinux was administered no sooner than 2 hours after catheter removal, no hematomas were reported.

Preparations, Dosage, and Administration.

Fondaparinux [Arixtra] is available in single-dose, pre-filled syringes (2.5, 5, 7.5, and 10 mg). Dosing is done once daily by subQ injection. For *prevention of DVT,* the recommended dosage is 2.5 mg/day, starting 6 to 8 hours after surgery. The usual duration is 5 to 9 days. For *treatment of acute DVT or acute PE,* dosage is based on body weight: daily dosage is 5 mg for patients under 50 kg, 7.5 mg for patients 50 to 100 kg, and 10 mg for patients over 100 kg. The usual duration is 5 to 9 days.

Rivaroxaban

Rivaroxaban [Xarelto] is an investigational *oral* anticoagulant that causes *selective inhibition of factor Xa.* Unlike fondaparinux, which acts indirectly (by activating antithrombin), rivaroxaban binds directly with the active center of factor Xa, and thereby inhibits production of thrombin. In contrast to warfarin (the only oral anticoagulant used in the United States), rivaroxaban has few significant drug interactions, and does not require monitoring of antico-

agulant activity. In a series of trials known as RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism), rivaroxaban was compared with enoxaparin (an LMW heparin) in patients who had undergone hip or knee replacement surgery. The result? Patients who received rivaroxaban (10 mg once daily) were much less likely to experience DVT, VTE, PE, or death, compared with patients who received enoxaparin (40 mg once daily or 30 mg twice daily). With both drugs, the incidence of major bleeding episodes was low (0.2%). Other trials are evaluating rivaroxaban in patients with acute coronary syndrome and patients with atrial fibrillation at high risk of stroke.

DIRECT THROMBIN INHIBITORS

The anticoagulants discussed in this section work by direct inhibition of thrombin. Hence, they differ from the heparin-like anticoagulants, which inhibit thrombin indirectly (by enhancing the activity of antithrombin). Three direct thrombin inhibitors—bivalirudin, lepirudin, and argatroban—are administered by continuous IV infusion; one—desirudin—is administered subQ; and one—dabigatran—is administered PO. Only the subQ and PO drugs are suitable for outpatient use.

Bivalirudin

Therapeutic Use.

Bivalirudin [Angiomax], formerly known as *Hirulog,* is an IV anticoagulant given in combination with aspirin to prevent clot formation in patients with unstable angina who are undergoing coronary angioplasty. At this time, the standard therapy for these patients is aspirin combined with a platelet GP IIb/IIIa inhibitor combined with low-dose, unfractionated heparin. Bivalirudin, an alternative to heparin in this regimen, has been studied only in combination with aspirin; it has not been studied in combination with GP IIb/IIIa inhibitors. In one trial—the Hirulog Angioplasty Study—bivalirudin plus aspirin was compared with heparin plus aspirin. Bivalirudin was at least as effective as heparin at preventing ischemic complications (MI, abrupt vessel closure, death), and caused fewer bleeding complications. In a subgroup of patients—those with

postinfarction angina—bivalirudin was significantly *more* effective than heparin.

Mechanism of Action.

Bivalirudin is a *direct,* reversible inhibitor of thrombin—in contrast to heparin, which acts *indirectly* by facilitating the actions of antithrombin. Bivalirudin binds with and inhibits thrombin that is free in the blood as well as thrombin that is bound to clots. In contrast, heparin inhibits only free thrombin. By inhibiting thrombin, bivalirudin prevents (1) the conversion of fibrinogen into fibrin and (2) the activation of factor XIII, thereby preventing the conversion of soluble fibrin into insoluble fibrin. Bivalirudin is a synthetic, 20–amino acid peptide chemically related to *hirudin,* an anticoagulant isolated from the saliva of leeches.

Adverse Effects.

The most common side effects are back pain (42%), nausea (15%), hypotension (12%), and headache (12%). Other relatively common effects (incidence greater than 5%) include vomiting, abdominal pain, pelvic pain, anxiety, nervousness, insomnia, bradycardia, and fever.

Bleeding is the effect of greatest concern. However, compared with heparin, bivalirudin causes fewer incidents of major bleeding (3.7% vs. 9.3%) and fewer patients require transfusions (2% vs. 5.7%). Coadministration of bivalirudin with heparin, warfarin, or thrombolytic drugs increases the risk of bleeding.

Pharmacokinetics.

With IV dosing, anticoagulation begins immediately. Drug levels are maintained by continuous infusion. Bivalirudin is eliminated primarily by renal excretion, and partly by proteolytic cleavage. The half-life is short (25 minutes) in patients with normal renal function, but may be longer in patients with renal impairment. Coagulation returns to baseline about 1 hour after stopping the infusion. Anticoagulation can be monitored by measuring activated clotting time.

Comparison with Heparin.

Bivalirudin is just as effective as heparin and has several advantages: it works independently of antithrombin, inhibits clot-bound thrombin as well as free thrombin, and causes less bleeding and fewer ischemic events. However, the drug also has two disadvantages. First, there is little information on using bivalirudin with GP IIb/IIIa inhibitors, the antiplatelet drugs employed most commonly during angioplasty. In the absence of such data, cardiologists may be reluctant to switch from heparin. Second, bivalirudin is more expensive than heparin: One single-use vial, good for a full course of treatment, costs about $420, compared with $10 for an equivalent course of heparin. However, the manufacturer estimates that reductions in bleeding and ischemic complications would save, on average, $500 to $1000 per patient, which would more than offset the greater cost of bivalirudin. The bottom line? Bivalirudin works as well as heparin, is safer, and may be equally cost-effective, but more clinical experience is needed before the drug is likely to replace heparin as the preferred anticoagulant in patients undergoing angioplasty.

Preparations, Dosage, and Administration.

Bivalirudin [Angiomax] is supplied as a lyophilized powder (250 mg) for reconstitution in sterile water. Dosing consists of an initial IV bolus (1 mg/kg) followed by a 4-hour infusion (2.5 mg/kg/hr). If necessary, the drug may be infused for up to 20 additional hours at a rate of 0.2 mg/kg/hr. Treatment should begin just prior to angioplasty. Dosage should be reduced in patients with severe renal impairment. All patients should take aspirin (300 to 325 mg).

Lepirudin

Like bivalirudin, lepirudin [Refludan] is an intravenous anticoagulant that works by direct inhibition of thrombin. The drug is indicated for prophylaxis and treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT). As discussed above, when HIT develops, the primary treatment is to withdraw heparin and substitute a nonheparin anticoagulant—usually lepirudin or argatroban. In clinical trials, lepirudin produced effective anticoagulation in about 80% of patients, and thereby significantly reduced the risk of death and new thrombotic complications. Like other anticoagulants, lepirudin poses a risk of bleeding. The risk is increased by liver dysfunction, renal insufficiency, recent stroke or surgery, and recent therapy with throm-

bolytic drugs. Dosing consists of an initial IV bolus (0.4 mg/kg infused over 15 to 20 seconds) followed by a continuous infusion (0.15 mg/kg/hr) for 2 to 10 days. Dosage should be titrated to achieve an aPTT ratio (ie, the ratio between the patient's aPTT and a reference aPTT) of 1.5 to 2.5. Treatment is expensive: One week of therapy costs about $4700.

Argatroban

Like bivalirudin and lepirudin, argatroban (formerly available as Acova) is an intravenous anticoagulant that works by direct inhibition of thrombin. Like lepirudin, the drug is indicated for prophylaxis and treatment of thrombosis in patients with HIT. In clinical trials, argatroban reduced development of new thrombosis and permitted restoration of platelet counts. Like other anticoagulants, argatroban poses a risk of hemorrhage. About 12% of patients experience hematuria. Allergic reactions (dyspnea, cough, rash), which develop in 10% of patients, occur almost exclusively in those receiving either thrombolytic drugs (eg, streptokinase) or contrast media for coronary angioplasty. Argatroban has a short half-life (about 45 minutes) owing to rapid metabolism by the liver. Treatment is monitored by measuring the aPTT. When infusion of argatroban is discontinued, the aPTT returns to baseline in 2 to 4 hours.

Argatroban is supplied in 2.5-mL single-dose vials (100 mg/mL) intended for dilution followed by continuous IV infusion. In patients with normal liver function, the initial infusion rate is 2 mcg/kg/min. In patients with liver dysfunction, the initial rate is only 0.5 mcg/kg/min. Dosage is adjusted to maintain the aPTT at 1.5 to 3 times the baseline value. As with lepirudin, treatment is expensive: The cost for the first day alone is over $550.

Desirudin

Desirudin [Iprivask] is a direct thrombin inhibitor similar to bivalirudin, lepirudin, and argatroban. However, unlike the other three drugs, which are given by IV infusion, desirudin is given by subQ injection. Desirudin is indicated for prevention of DVT in patients undergoing elective hip replacement surgery. In clinical trials, patients experienced fewer thromboembolic events than those given unfractionated heparin or enoxaparin.

Desirudin is completely absorbed following subQ injection, achieving peak plasma levels in 1 to 3 hours. Elimination is primarily by renal secretion, and partly by proteolytic cleavage. In patients with normal renal function, the elimination half-life is 2 to 3 hours. By contrast, in those with severe renal impairment, the half-life is greatly prolonged (up to 12 hours).

As with other anticoagulants, hemorrhage is the adverse effect of greatest concern. In clinical trials, the incidence of hemorrhage was 30% in the desirudin group, compared with 33% in the enoxaparin group and 20% in the heparin group. Less serious effects include wound secretion (4%), injection site mass (4%), anemia (3%), nausea (2%), and deep thrombophlebitis (2%).

In patients undergoing spinal or epidural anesthesia, desirudin may cause spinal or epidural hematoma, which can result in long-term or even permanent paralysis. Hematoma risk is increased by use of other drugs that impair hemostasis (eg, nonsteroidal anti-inflammatory drugs, antiplatelet drugs, warfarin, heparin). Patients should be monitored for signs of neurologic impairment, and given immediate treatment if they develop.

Desirudin [Iprivask] is supplied as a lyophilized powder (15 mg) in single-use vials. Immediately after reconstitution (with 0.5 mL of 3% mannitol in sterile water), the drug is administered by deep subQ injection into the thigh or abdominal wall. For patients with normal renal function, the dosage is 15 mg every 12 hours, beginning 5 to 15 minutes before hip surgery (but after induction of regional block anesthesia, if used). For patients with *moderate* renal impairment (creatinine clearance 31 to 60 mL/min/1.73 m2), dosage is reduced to 5 mg every 12 hours. For those with *severe* renal impairment (creatinine clearance less than 31 mL/min/1.73 m2), dosage is reduced to 1.7 mg every 12 hours. For all patients, the usual duration of treatment is 9 to 12 days.

Dabigatran

Dabigatran etexilate [Pradaxa] is an *oral* prodrug that undergoes rapid conversion to dabigatran, a reversible, direct inhibitor of thrombin. In contrast to warfarin—the only oral anticoagulant currently used in the United States—dabigatran has three major advantages: it does not require monitoring of anticoagulation; there is little risk of adverse interactions; and, since responses are predictable, the same dose can be used for all patients, regardless

of weight or age. In clinical trials, dabigatran has been compared with enoxaparin (a LMW heparin) in patients who had undergone knee and hip replacements. The result? Both drugs were comparable with respect to preventing VTE and VTE-related mortality—and both carried the same risk of major bleeding (about 1%). Trials of dabigatran are underway in patients with acute coronary syndromes and atrial fibrillation. Dabigatran is approved in Canada and Europe, but is not yet approved here.

WARFARIN

Warfarin [Coumadin, Jantoven], a vitamin K antagonist, is the only oral anticoagulant currently available in the United States. Two others—dabigatran [Pradaxa], a direct thrombin inhibitor, and rivaroxaban [Xarelto], a factor Xa inhibitor—are nearing approval (see above).

Warfarin is similar to heparin in some respects and quite different in others. Like heparin, warfarin is used to prevent thrombosis. In contrast to heparin, warfarin has a delayed onset, which makes it inappropriate for emergencies. However, because it doesn't require injection, warfarin is well suited for long-term prophylaxis. Like heparin, warfarin carries a significant risk of hemorrhage, which is amplified by the many drug interactions to which warfarin is subject.

History

The history of warfarin underscores the potential hazards of oral anticoagulants. The warfarin story began with the observation that ingesting spoiled clover silage could induce bleeding in cattle. The causative agent was identified as bishydroxycoumarin (dicumarol). Research into derivatives of dicumarol led to the synthesis of warfarin. When warfarin was first developed, clinical use was ruled out owing to concerns about hemorrhage. So, instead of becoming a medicine, warfarin was used to kill rats. The drug proved especially effective in this application and remains one of our most widely used rodenticides. Clinical interest in warfarin was renewed following the report of a failed suicide attempt using huge doses of a warfarin-based rat poison. The clinical trials triggered by that event soon demonstrated that warfarin could be employed safely to treat humans.

Mechanism of Action

Warfarin suppresses coagulation by decreasing production of four clotting factors, namely, factors VII, IX, X, and prothrombin. These factors are known as *vitamin K–dependent clotting factors*, because an active form of vitamin K is needed to make them. Warfarin works by inhibiting *vitamin K–epoxide reductase complex 1* (VKORC1), the enzyme needed to convert vitamin K to the required active form. Because of its mechanism, warfarin is referred to as a *vitamin K antagonist,* a term that is somewhat misleading. Why? Because the term implies antagonism of vitamin K *actions,* not antagonism of vitamin K *activation*. In therapeutic doses, warfarin reduces production of vitamin K–dependent clotting factors by 30% to 50%.

Pharmacokinetics

Absorption, Distribution, and Elimination.

Warfarin is readily absorbed following oral dosing. Once in the blood, about 99% of warfarin binds to albumin. Warfarin molecules that remain free (unbound) can readily cross membranes, including those of the placenta and milk-producing glands. Warfarin is inactivated in the liver, mainly by CYP2C9, the 2C9 isozyme of cytochrome P450. Metabolites are excreted in the urine and feces.

Time Course.

Although warfarin acts quickly to inhibit clotting factor *synthesis,* noticeable *anticoagulant effects* are delayed. Why? Because warfarin has no effect on clotting factors already in circulation. Hence, until these clotting factors decay, coagulation remains unaffected. Since decay of clotting factors occurs with a half-life of 6 hours to 2.5 days (depending on the clotting factor under consideration), initial responses may not be evident until 8 to 12 hours after the first dose. Peak effects take several days to develop.

After warfarin is discontinued, coagulation remains inhibited for 2 to 5 days. Why? Because warfarin has a long half-life (1.5 to 2 days), and hence synthesis of new clotting factors remains suppressed, despite stopping dosing.

Therapeutic Uses

Warfarin is employed most frequently for long-term prophylaxis of thrombosis. Specific indications are (1) prevention of venous thrombosis and associated pulmonary embolism, (2) prevention of thromboembolism in patients with prosthetic heart valves, and (3) prevention of thrombosis during atrial fibrillation. For all of these indications, warfarin is the oral anticoagulant of choice. The drug has also been used to reduce the risk of recurrent transient ischemic attacks (TIAs) and recurrent MI. Because onset of effects is delayed, warfarin is not useful in emergencies. When rapid action is needed, anticoagulant therapy can be initiated with heparin.

Monitoring Treatment

The anticoagulant effects of warfarin are evaluated by monitoring *prothrombin time* (PT)—a coagulation test that is especially sensitive to alterations in vitamin K–dependent factors. The average pretreatment value for PT is 12 seconds. Treatment with warfarin prolongs PT.

Traditionally, PT test results have been reported as a *PT ratio,* which is simply the ratio of the patient's PT to a control PT. However, there is a serious problem with this form of reporting: test results can vary widely among laboratories. The underlying cause of variability is thromboplastin, a critical reagent employed in the PT test. To ensure that test results from different laboratories are comparable, results are now reported in terms of an INR. The INR is determined by multiplying the observed PT ratio by a correction factor specific to the particular thromboplastin preparation employed for the test.

The objective of treatment is to raise the INR to an appropriate value. Recommended INR ranges are summarized in Table 51-3. As indicated, an INR of 2 to 3 is appropriate for most patients—although for some the target INR is 3 to 4.5. If the INR is below the recommended range, warfarin dosage should be increased. Conversely, if the INR is above the recommended range, dosage should be reduced. Unfortunately, since warfarin has a delayed onset and prolonged duration of action, the INR cannot be altered quickly: Once the dosage has been changed, it may take a week or more to reach the desired INR.

PT must be determined frequently during warfarin therapy. PT should be measured daily during the first 5 days of treatment, twice a week for the next 1 to 2 weeks, once a week for the next 1 to 2 months, and every 2 to 4 weeks

thereafter. In addition, PT should be determined whenever a drug that interacts with warfarin is added to or deleted from the regimen.

Concurrent therapy with heparin can influence PT values. To minimize this influence, blood for PT determinations should be drawn no sooner than 5 hours after an IV injection of heparin, and no sooner than 24 hours after a subQ injection.

PT can now be monitored at home. Two monitoring devices are available: *CoaguChek* and the *ProTime Microcoagulation System*. These small, hand-held machines are easy to use and provide reliable results. Both devices determine PT and INR values. In addition, the ProTime meter can be programmed by the prescriber with upper and lower INR values appropriate for the individual patient. When this is done, the meter will display either *In Range, INR High,* or *INR Low,* depending on the degree of anticoagulation. Home monitoring is more convenient than laboratory monitoring and gives patients a sense of empowerment. In addition, it improves anticoagulation control. In theory, home monitoring should help reduce bleeding (from excessive anticoagulation) and thrombosis (from insufficient anticoagulation). The CoaguChek meter costs about $1300 and the ProTime meter costs about $2000. Each test costs about $10.

Adverse Effects

Hemorrhage.

Bleeding is the major complication of warfarin therapy. Hemorrhage can occur at any site. Patients should be monitored closely for signs of bleeding. (For specific signs, refer to the discussion of heparin-induced hemorrhage above.) If bleeding develops, warfarin should be discontinued. Severe overdose can be treated with *vitamin K* (see below). Patients should be encouraged to carry identification (eg, Medic Alert bracelet) to inform emergency personnel of warfarin use.

Several measures can reduce the risk of bleeding. Candidates for treatment must be carefully screened for risk factors (see *Warnings and Contraindications* below). Prothrombin time must be measured frequently. A variety of drugs can potentiate warfarin's effects (see below), and hence must be used with

care. Patients should be given detailed verbal and written instructions regarding signs of bleeding, dosage size and timing, and scheduling of PT tests. When a patient is incapable of accurate self-medication, a responsible individual must supervise treatment. Patients should be advised to make a record of each dose, rather than relying on memory. A soft toothbrush can reduce gingival bleeding. An electric razor can reduce cuts from shaving.

Warfarin intensifies bleeding during surgery. Accordingly, surgeons must be informed of warfarin use. Patients anticipating elective procedures should discontinue warfarin several days prior to the appointment. If an emergency procedure must be performed, injection of vitamin K can help suppress bleeding.

Does warfarin increase bleeding during dental surgery? Yes, but not that much. Accordingly, most patients needn't interrupt warfarin for dental procedures, including dental surgery. However, it is important that the INR be in the target range.

Fetal Hemorrhage and Teratogenesis from Use During Pregnancy.

Warfarin can cross the placenta and affect the developing fetus. Fetal hemorrhage and death have occurred. In addition, warfarin can cause gross malformation, central nervous system (CNS) defects, and optic atrophy. Accordingly, *warfarin is classified in Food and Drug Administration Pregnancy Risk Category X: The risks to the developing fetus outweigh any possible benefits of treatment*. Women of child-bearing age should be informed about the potential for teratogenesis and advised to postpone pregnancy. If pregnancy occurs, the possibility of termination should be discussed. If an anticoagulant is needed during pregnancy, heparin, which does not cross the placenta, should be employed.

Use During Lactation.

Warfarin enters breast milk. Women should be advised against breast-feeding.

Other Adverse Effects.

Adverse effects other than hemorrhage are uncommon. Possible undesired responses include skin necrosis, alopecia, urticaria, dermatitis, fever, GI disturbances, and red-orange discoloration of urine, which must not be confused

with hematuria. Long-term warfarin use (more than 12 months) may weaken bones, and thereby increase the risk of fractures.

Drug Interactions

General Considerations.

Warfarin is subject to a large number of clinically significant adverse interactions—perhaps more than any other drug. As a result of interactions, anticoagulant effects may be reduced to the point of permitting thrombosis, or they may be increased to the point of causing hemorrhage. Patients must be informed about the potential for hazardous interactions and instructed to avoid *all* drugs not specifically approved by the prescriber. This prohibition includes prescription drugs and over-the-counter preparations.

Interactions between warfarin and other drugs are summarized in Table 51-4. As indicated, the interactants fall into three major categories: (1) *drugs that increase anticoagulant effects,* (2) *drugs that promote bleeding,* and (3) *drugs that decrease anticoagulant effects*. The major mechanisms by which anticoagulant effects can be *increased* are (1) displacement of warfarin from plasma albumin and (2) inhibition of the hepatic enzymes that degrade warfarin. The major mechanisms for *decreasing* anticoagulant effects are (1) acceleration of warfarin degradation through induction of hepatic drug-metabolizing enzymes, (2) increased synthesis of clotting factors, and (3) inhibition of warfarin absorption. Mechanisms by which drugs can *promote bleeding,* and thereby complicate anticoagulant therapy, include (1) inhibition of platelet aggregation, (2) inhibition of the coagulation cascade, and (3) generation of GI ulcers.

Drug Category	Mechanism of Interaction	Representative Interacting Drugs
Drugs that *increase* the effects of warfarin	Displacement of warfarin from albumin	Aspirin and other salicylates
		Sulfonamides
	Inhibition of warfarin degradation	Acetaminophen
		Amiodarone
		Azole antifungal agents
		Cimetidine
		Disulfiram
		Sulfonamides
	Decreased synthesis of clotting factors	Certain parenteral cephalosporins, including cefoperazone and cefamandole
Drugs that *promote bleeding*	Inhibition of platelet aggregation	Abciximab
		Aspirin and other salicylates
		Cilostazol
		Clopidogrel
		Dipyridamole
		Eptifibatide
		Prasugrel*
		Ticlopidine
		Tirofiban
	Inhibition of clotting factors	Antimetabolites
		Heparin
	Promotion of ulcer	Aspirin

TABLE 51-4 Interactions Between Warfarin and Other Drugs

* Investigational in the United States.

The existence of an interaction between warfarin and another drug does not absolutely preclude using the combination. Such an interaction does mean, however, that the combination must be used with due caution. The potential for harm is greatest when an interacting drug is being added to or deleted from the regimen. At these times, prothrombin time must be monitored, and the dosage of warfarin adjusted to compensate for the impact of removing or adding an interacting drug.

Specific Interacting Drugs.

Of the many drugs listed in Table 51-4, a few are especially likely to produce interactions of clinical significance. Three are discussed below.

Heparin.

The interaction of heparin with warfarin is obvious: Being an anticoagulant itself, heparin directly increases the bleeding tendencies brought on by warfarin. Combined therapy with heparin plus warfarin must be performed with care.

Aspirin.

Aspirin inhibits platelet aggregation. By blocking aggregation, aspirin can suppress formation of the platelet plug that initiates hemostasis. To make matters worse, aspirin can act directly on the GI tract to cause ulcers, thereby initiating bleeding. Hence, when the antifibrin effects of warfarin are coupled with the antiplatelet and ulcerogenic effects of aspirin, the potential for hemorrhagic disaster is substantial. Accordingly, patients should be warned specifically against using any product that contains aspirin, unless the provider has prescribed aspirin therapy. Drugs similar to aspirin (eg, indomethacin, ibuprofen) should be avoided as well.

Nonaspirin Antiplatelet Drugs.

Like aspirin, other antiplatelet drugs can increase the risk of bleeding with warfarin. Accordingly, these drugs (eg, clopidogrel, dipyridamole, ticlopidine, abciximab) should be used with caution.

Acetaminophen.

In the past, acetaminophen was considered safe for patients on warfarin. In fact, acetaminophen was routinely recommended as an aspirin substitute for patients who needed a mild analgesic. Now, however, it appears that acetaminophen can increase the risk of bleeding: Compared with nonusers of acetaminophen, those who take just 4 regular-strength tablets a day for a week are 10 times more likely to have a dangerously high INR. Unlike aspirin, which promotes bleeding by inhibiting platelet aggregation, acetaminophen is believed to act by inhibiting warfarin degradation, thereby raising warfarin levels. At this time, the interaction between acetaminophen and warfarin has not been proved. Nonetheless, when the drugs are combined, the INR should be monitored closely.

Other Notable Interactions.

Several drugs, including *phenobarbital, carbamazepine,* and *rifampin,* are powerful inducers of hepatic drug-metabolizing enzymes. As a result, these drugs can accelerate warfarin degradation, thereby decreasing anticoagulant effects. Accordingly, if one of these drugs is added to the regimen, warfarin dosage must be increased. Of equal importance, when an inducer is withdrawn, causing rates of drug metabolism to decline, a compensatory decrease in warfarin dosage must be made.

Intravaginal miconazole can intensify the anticoagulant effects of warfarin. (Miconazole is the antifungal agent found in Monistat brand vaginal suppositories and cream, used for vaginal candidiasis [yeast infection].) One woman using the combination reported bruising, bleeding gums, and a nosebleed. We have long known that *systemic* miconazole (as well as other azole antifungal agents) can inhibit the metabolism of warfarin, and can thereby cause warfarin levels to rise. Apparently, intravaginal miconazole can be absorbed in amounts sufficient to do the same. Because of this interaction, women taking warfarin should not use intravaginal miconazole. If the drugs must be used concurrently, anticoagulation should be monitored closely and warfarin dosage reduced as indicated.

Like the azole antifungal agents, *cimetidine* (a drug for ulcers) and *disulfiram* (a drug for alcoholism) can inhibit warfarin metabolism, and can thereby increase anticoagulant effects.

Vitamin K increases clotting factor synthesis, and can thereby decrease anticoagulant effects.

Sulfonamide antibacterial drugs can displace warfarin from albumin, and thereby increase anticoagulant effects.

Leflunomide [Arava], a drug for arthritis, can significantly increase the INR in just a few days, probably by inhibiting warfarin degradation. Case reports suggest that two other antiarthritic agents—*glucosamine* and *chondroitin*—may also potentiate warfarin action.

Warnings and Contraindications

Like heparin, warfarin is contraindicated for patients with severe thrombocytopenia or uncontrollable bleeding and for patients undergoing lumbar puncture, regional anesthesia, or surgery of the eye, brain, or spinal cord. Also like heparin, warfarin must be used with extreme caution in patients at high risk of bleeding, including those with hemophilia, increased capillary permeability, dissecting aneurysm, GI ulcers, and severe hypertension, and in women anticipating abortion. In addition, warfarin is contraindicated in the presence of vitamin K deficiency, liver disease, and alcoholism—conditions that can disrupt hepatic synthesis of clotting factors. Warfarin is also contraindicated during pregnancy and lactation.

Vitamin K*1* for Warfarin Overdose

The effects of warfarin overdose can be overcome with vitamin K*1* (phytonadione). Vitamin K*1* antagonizes warfarin's actions and can thereby reverse warfarin-induced inhibition of clotting factor synthesis. (Vitamin K*3*—menadione—has no effect on warfarin action.)

Vitamin K may be given orally or IV; subQ administration is less effective and should be avoided. Intravenous vitamin K acts faster than oral vitamin K, but can cause severe anaphylactoid reactions, characterized by flushing, hypotension, and cardiovascular collapse. To reduce this risk, vitamin K should be diluted and infused slowly.

As a rule, small doses—2.5 mg PO or 0.5 to 1 mg IV—are preferred. Why? Because large doses (eg, 10 mg PO) can cause prolonged resistance to warfarin, thereby hampering restoration of anticoagulation once bleeding is controlled.

If vitamin K fails to control bleeding, levels of clotting factors can be raised quickly by infusing fresh whole blood, fresh-frozen plasma, or plasma concentrates of vitamin K–dependent clotting factors.

What About Dietary Vitamin K?

Like medicinal vitamin K, dietary vitamin K can reduce the anticoagulant effects of warfarin. Rich dietary sources include mayonnaise, canola oil, soybean oil, and green leafy vegetables. Must patients avoid these foods? No. But they should keep intake of vitamin K constant. If vitamin K intake does increase, then warfarin dosage should be increased as well. Conversely, if vitamin K intake decreases, the warfarin dosage should decrease too.

Contrasts Between Warfarin and Heparin

Although heparin and warfarin are both anticoagulants, they differ in important ways. Whereas warfarin is given orally, heparin is given by injection. Although both drugs decrease fibrin formation, they do so by different mechanisms: heparin inactivates thrombin and factor Xa, whereas warfarin inhibits synthesis of clotting factors. Heparin and warfarin differ markedly with respect to time course of action: effects of heparin begin and fade rapidly, whereas effects of warfarin begin slowly but then persist several days. Different tests are used to monitor therapy: changes in aPTT are used to monitor heparin treatment; changes in PT are used to monitor warfarin. Finally, these drugs differ with respect to management of overdose: protamine is given to counteract heparin; vitamin K***1*** is given to counteract warfarin. These differences are summarized in Table 51-5.

	Heparin	Warfarin
Mechanism of action	Activates antithrombin, which then inactivates thrombin and factor Xa	Inhibits synthesis of vitamin K–dependent clotting factors, including prothrombin and factor X
Route	IV or subQ	PO
Onset	Rapid (minutes)	Slow (hours)
Duration	Brief (hours)	Prolonged (days)
Monitoring	aPTT*	PT†
Antidote for overdose	Protamine	Vitamin K_1

TABLE 51-5 Summary of Contrasts Between Heparin and Warfarin

* aPTT = Activated partial thromboplastin time.

† PT = Prothrombin time. Test results are reported as a PT ratio or an INR (international normalized ratio).

Dosage

Basic Considerations.

Dosage requirements for warfarin vary widely among individuals, and hence dosage must be tailored to each patient. Traditionally, dosage adjustments have been done empirically (ie, by trial and error). Dosing is usually begun at 2 to 5 mg/day. Maintenance dosages, which typically range from 2 to 10 mg/day, are determined by the target INR value. For most patients, dosage should be adjusted to produce an INR between 2 and 3.

Genetics and Dosage Adjustment.

Patients with variant genes that code for VKORC1 and CYP2CP are at increased risk of warfarin-induced bleeding, and hence require reduced doses. As noted above, VKORC1 is the target enzyme that warfarin inhibits, and CYP2C9 is the enzyme that metabolizes warfarin. Variations in VKORC1 increase the en-

zyme's sensitivity to inhibition by warfarin, and variations in CYP2C9 delay warfarin breakdown. With either variation, effects of warfarin are increased. To reduce the risk of bleeding, the FDA now recommends—but does not require—that patients undergo genetic testing for these variants. Dosage reductions based on this information can be determined using the online calculator at www.warfarindosing.org.

Preparations

Warfarin sodium [Coumadin, Jantoven] is available in tablets (1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg) for oral use. In addition, warfarin is available in a formulation for parenteral dosing, which is not commonly done.

ANTIPLATELET DRUGS

Antiplatelet drugs suppress platelet aggregation. Since a platelet core constitutes the bulk of an *arterial thrombus,* the principal indication for the antiplatelet drugs is prevention of thrombosis in *arteries*. In contrast, the principal indication for anticoagulants (eg, heparin, warfarin) is prevention of thrombosis in veins.

There are three major groups of antiplatelet drugs: aspirin (a “group” with one member), ADP receptor antagonists, and GP IIb/IIIa receptor antagonists. As indicated in Figure 51-1, aspirin and the ADP antagonists affect only one pathway in platelet activation, and hence their antiplatelet effects are limited. In contrast, the GP IIb/IIIa antagonists block the final common step in platelet activation, and hence have powerful antiplatelet effects. Properties of the major classes of antiplatelet drugs are summarized in Table 51-6.

	Aspirin, a Cyclooxygenase Inhibitor	Adenosine Diphosphate Receptor Blockers	Glycoprotein IIb/IIIa Receptor Blockers
Representative drug	Aspirin	Clopidogrel [Plavix]	Tirofiban [Aggrastat]
Mechanism of antiplatelet action	Irreversibly inhibits cyclooxygenase, and thereby blocks synthesis of TXA_2	Irreversibly blocks receptors for ADP	Reversibly blocks receptors for GP IIb/IIIa
Route	PO	PO	IV infusion
Duration of effects	Effects persist 7–10 days after the last dose	Effects persist 7–10 days after the last dose	Effects stop within 4 hr of stopping the infusion
Cost	$3/month	$87/month	$1000/course

TABLE 51-6 Properties of the Major Classes of Antiplatelet Drugs

Aspirin

The basic pharmacology of aspirin is discussed in Chapter 70. Consideration here is limited to aspirin's role in preventing arterial thrombosis.

Mechanism of Antiplatelet Action.

Aspirin suppresses platelet aggregation by causing *irreversible inhibition of cyclooxygenase,* an enzyme required by platelets to synthesize thromboxane A2 (TXA2). As noted, TXA2 is one of the factors that can promote platelet activation. In addition to activating platelets, TXA2 acts on vascular smooth muscle to promote vasoconstriction. Both actions promote hemostasis. By inhibiting cyclooxygenase, aspirin suppresses both TXA2-mediated vasoconstriction and platelet aggregation, thereby reducing the risk of arterial thrombosis. Since inhibition of cyclooxygenase by aspirin is irreversible, and since platelets lack the machinery to synthesize new cyclooxygenase, the effects of a single dose of aspirin persist for the life of the platelet (7 to 10 days).

In addition to inhibiting the synthesis of TXA2, aspirin can inhibit synthesis of *prostacyclin* by the blood vessel wall. Since prostacyclin has effects that are exactly opposite to those of TXA2—namely, suppression of platelet aggregation and promotion of vasodilation—suppression of prostacyclin synthesis can partially offset the beneficial effects of aspirin therapy. Fortunately, aspirin is able to inhibit synthesis of TXA2 at doses that are lower than those needed to inhibit synthesis of prostacyclin. Accordingly, if we keep the dosage of aspirin *low* (325 mg/day or less), we can minimize inhibition of prostacyclin production while maintaining inhibition of TXA2 production.

Indications for Antiplatelet Therapy.

Antiplatelet therapy with aspirin has multiple indications of proven efficacy, namely

- *Ischemic stroke* (to reduce the risk of death and nonfatal stroke)
- *Transient ischemic attacks* (to reduce the risk of death and nonfatal stroke)
- *Chronic stable angina* (to reduce the risk of MI and sudden death)
- *Unstable angina* (to reduce the combined risk of death and nonfatal MI)
- *Coronary stenting* (to prevent reocclusion)
- *Acute MI* (to reduce the risk of vascular mortality)
- *Previous MI* (to reduce the combined risk of death and nonfatal MI)
- *Primary prevention of MI* (to prevent a first MI in men and in women age 65 and older)

In all of these situations, prophylactic therapy with aspirin can reduce morbidity, and possibly mortality. Primary prevention of MI is discussed further immediately below.

Primary Prevention of MI.

In January of 2002, the U.S. Preventive Services Task Force (USPSTF) issued updated guidelines on the use of aspirin for primary prevention of MI. The USPSTF noted that the benefit/risk ratio is most favorable for people at high risk of MI, defined as a 3% (or higher) risk of a cardiovascular event within the next 5 years.* For these people, daily aspirin lowers the risk of MI by 28%.

Unfortunately, although aspirin lowers the risk of MI, it does *not* reduce the risk of death. Cardiovascular risk is based on five factors—age, gender, cholesterol levels, blood pressure, and smoking status—and can be calculated using an online risk assessment tool, such as those at www.med-decisions.com and www.intmed.mcw.edu/clincalc/heartrisk.html. Although the optimal aspirin dosage for primary prevention is unknown, low doses (eg, 81 mg/day) appear as effective as higher ones.

* Data from the Women's Health Study, released in 2005, show that aspirin does *not* prevent a first MI in middle-aged women, but does protect women 65 and older.

Adverse Effects.

Even in low doses, aspirin increases the risk of GI bleeding and hemorrhagic stroke. Among middle-aged people taking aspirin for 5 years, the estimated rate of major GI bleeding episodes is 2 to 4 per 1000 patients, and the rate of hemorrhagic stroke is 0 to 2 episodes per 1000 patients. Use of enteric-coated or buffered aspirin may *not* reduce the risk of GI bleeding. Benefits of treatment must be weighed against bleeding risks. If GI bleeding occurs, adding a proton pump inhibitor (eg, omeprazole [Prilosec]) to reduce gastric acidity can help.

Dosing.

Dosage for preventing cardiovascular events should be low. Maximal inhibition of platelet cyclooxygenase, and hence maximal effects on platelet function, can be produced in a few days by taking 81 mg/day. Dosages above 81 mg/day offer no increase in benefits, but do increase the risk of GI bleeding and stroke. Accordingly, for *chronic therapy,* a dosage of 81 mg/day is probably adequate. A higher dosage (eg, 325 mg/day) is indicated for *initial* treatment of an acute event, such as MI, in order to establish full antiplatelet effects rapidly—after which 81 mg/day can be taken for maintenance.

Adenosine Diphosphate Receptor Antagonists

Two ADP receptor antagonists—clopidogrel and ticlopidine—are currently approved, and a third agent—prasugrel—may be approved soon. All three drugs cause irreversible blockade of ADP receptors on the platelet surface, and thereby prevent ADP-stimulated aggregation (see Fig. 51-1). Indications for

clopidogrel include recent stroke and acute coronary syndromes. Ticlopidine is approved only to prevent stroke. Both drugs are taken orally, and both can cause potentially fatal hematologic effects, although the risks are much higher with ticlopidine.

Clopidogrel

Clopidogrel [Plavix] is an oral antiplatelet drug with effects similar to those of aspirin. The drug is taken to prevent stenosis of coronary stents, and for secondary prevention of MI, ischemic stroke, and other vascular events. Use is widespread: In 2007, total sales were around $8 billion.

Antiplatelet Actions.

Clopidogrel blocks ADP receptors on platelets, and thereby prevents ADP-stimulated aggregation. As with aspirin, antiplatelet effects are irreversible, and hence persist for the life of the platelet. Effects begin 2 hours after the first dose, and plateau after 3 to 7 days of treatment. At the recommended dosage, platelet aggregation is inhibited by 40% to 60%. Platelet function and bleeding time return to baseline about 7 to 10 days after the last dose.

Pharmacokinetics.

Clopidogrel is rapidly absorbed from the GI tract, both in the presence and absence of food. Bioavailability is about 50%. Clopidogrel is inactive as administered and must be converted to its active form in the liver, in part through the actions of CYP2C19 (the 2C19 isozyme of cytochrome P450). The primary metabolite found in blood is a carboxylic acid derivative. However, neither the parent drug nor this derivative affects platelet aggregation. The metabolite responsible for inhibiting aggregation has not been identified.

Therapeutic Use.

Clopidogrel is used widely to prevent blockage of coronary artery stents, and to reduce thrombotic events—MI, ischemic stroke, and vascular death—in patients with acute coronary syndromes and in those with atherosclerosis documented by recent MI, recent stroke, or established peripheral arterial disease. In the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, which enrolled 19,185 high-risk patients, clopidogrel (75 mg

once daily) was slightly better than aspirin (325 mg once daily) at reducing the combined risk of MI, ischemic stroke, or vascular death. The trial indicated that, for every 1000 patients treated for 1 year, clopidogrel would prevent 24 vascular events, compared with 19 for aspirin. However, even though clopidogrel is slightly more effective than aspirin, it is much more expensive: A 1-month supply costs about $87, compared with $3 for aspirin. Accordingly, it would seem best to reserve clopidogrel for patients who cannot tolerate aspirin or haven't responded to it adequately.

Adverse Effects and Interactions.

Clopidogrel is generally well tolerated. Adverse effects are about the same as with aspirin. The most common effects are abdominal pain (6%), dyspepsia (5%), diarrhea (5%), and rash (4%). Compared with aspirin, clopidogrel causes less intracranial hemorrhage (0.4% vs. 0.5%) and less GI bleeding (2% vs. 2.7%). In contrast to ticlopidine (see below), clopidogrel does not cause neutropenia or granulocytopenia. However, it *can* cause thrombotic thrombocytopenic purpura (TTP), usually during the first 2 weeks of treatment. At least 11 cases have been reported, including one that was fatal. Fortunately, the risk of TTP is low—even lower than with ticlopidine. Clopidogrel should be used with caution in patients taking other drugs that promote bleeding (eg, heparin, warfarin, aspirin, and other nonsteroidal anti-inflammatory drugs).

Omeprazole [Prilosec] and other *proton pump inhibitors* (PPIs) may reduce the antiplatelet effects of clopidogrel. (Some clopidogrel patients take PPIs to reduce gastric acidity, and thereby reduce the risk of GI bleeding.) PPIs may lower clopidogrel effects by inhibiting CYP2C19, the liver enzyme that helps convert clopidogrel to its active form.

Preparations, Dosage, and Administration.

Clopidogrel [Plavix] is available in 75-mg tablets. The maintenance dosage is 75 mg once a day, taken with or without food. A 300-mg loading dose may be used for some patients. Dosage needn't be changed for elderly patients or those with renal impairment. To prevent a possible rebound effect when clopidogrel is withdrawn, some experts recommend that the dosage be tapered, by giving 75 mg every other day for a few weeks. However, there is no proof that doing so is needed.

Ticlopidine

Actions.

Ticlopidine [Ticlid] is a chemical relative of clopidogrel, but causes more adverse hematologic effects. Like clopidogrel, ticlopidine causes irreversible inhibition of platelet aggregation.

Uses.

Ticlopidine has only one approved indication: prevention of thrombotic stroke. The drug is at least as beneficial as aspirin, but is much more expensive. More importantly, ticlopidine can cause life-threatening adverse effects. Accordingly, the drug should be reserved for patients who have not responded to aspirin or cannot use aspirin because of intolerance.

Pharmacokinetics.

Ticlopidine is well absorbed following oral administration. Antiplatelet effects begin within 48 hours and become maximal in about a week. The drug undergoes extensive hepatic metabolism followed by renal excretion. Ticlopidine has a long half-life (4 to 5 days). Effects persist for 7 to 10 days after drug withdrawal (ie, until new platelets have been synthesized).

Adverse Effects.

Hematologic Effects.

Ticlopidine can cause life-threatening hematologic reactions, including neutropenia/agranulocytosis and TTP.

Neutropenia develops in 2.4% of patients, and is sometimes severe. Rarely, agranulocytosis develops. Both effects reverse within 1 to 3 weeks after drug withdrawal.

TTP occurs in 0.02% of patients with coronary stents who are taking ticlopidine. The mortality rate is 20% to 30%. TTP is characterized by thrombocytopenia, fever, anemia, renal dysfunction, and neurologic disturbances. The risk is highest during the first few weeks of treatment. After 12 weeks, the risk

is very low. Patients should be instructed to report potential signs of TTP (eg, unusual bleeding, bruising, rash).

To reduce the risk from hematologic reactions, complete blood counts and a white cell differential should be obtained every 2 weeks during the first 12 weeks of treatment, and at any sign of infection. Ticlopidine should be withdrawn if neutropenia, agranulocytosis, or TTP develops.

Other Adverse Effects.

The most common side effects are *GI disturbances* (diarrhea, abdominal pain, flatulence, nausea, dyspepsia) and *dermatologic reactions* (rash, purpura, pruritus).

Preparations and Dosage.

Ticlopidine [Ticlid] is available in 250-mg tablets. The recommended dosage is 250 mg twice a day, taken with food.

Prasugrel

Prasugrel [Effient] is an investigational agent similar to clopidogrel. Like clopidogrel, prasugrel blocks ADP receptors on platelets, and thereby causes irreversible inhibition of aggregation. Also like clopidogrel, prasugrel is a prodrug that undergoes conversion to its active form in the liver. In one trial, known as Triton-TIMI, prasugrel was compared directly with clopidogrel. The goal with both drugs was to prevent thrombotic complications in patients with acute coronary syndrome who were scheduled for percutaneous coronary intervention (PCI). The result? Compared with patients taking clopidogrel, patients taking prasugrel experienced significantly fewer thrombotic events, including stent thrombosis. Unfortunately, those taking prasugrel also experienced an increased risk of major bleeding, including fatal bleeding. Prasugrel is under FDA review for approval in the United States.

Glycoprotein IIb/IIIa Receptor Antagonists

Group Properties

The GP IIb/IIIa receptor antagonists, sometimes called “super aspirins,” are the most effective antiplatelet drugs on the market. Three agents are avail-

able: abciximab, tirofiban, and eptifibatide. All three are administered IV, usually in combination with aspirin and low-dose heparin. Treatment is expensive, costing $1000 or more for a brief course. Dosages are summarized in Table 51-7.

Application	Tirofiban [Aggrastat]	Eptifibatide [Integrilin]	Abciximab [ReoPro]
Acute coronary syndromes (ACSs)	0.4 mcg/kg/min for 30 min, then 0.1 mcg/kg/min for 48–108 hr	180-mcg/kg bolus, then 2 mcg/kg/min for up to 72 hr	0.25-mg/kg bolus, then 10 mcg/kg/min for 18–24 hr
Percutaneous coronary intervention* (PCI) following treatment for ACSs	Continue 0.1 mcg/kg/min for the procedure and 12–24 hr after	Consider decreasing the infusion rate to 0.5 mcg/kg/min for the procedure and 20–24 hr after	Continue 10 mcg/kg/min for the procedure and 1 hr after
PCI without prior treatment for ACSs	Not FDA approved for this application	135-mcg/kg bolus prior to procedure, then 0.5 mcg/kg/min for 20–24 hr	0.25-mg/kg bolus 10–60 min before the procedure, then 0.125 mcg/kg/min (max 10 mcg/min) for 12 hr

FDA = Food and Drug Administration.

TABLE 51-7 Dosages for Glycoprotein IIb/IIIa Receptor Antagonists

* Balloon or laser angioplasty, or atherectomy.

Actions.

The GP IIb/IIIa antagonists cause *reversible* blockade of platelet GP IIb/IIIa receptors, and thereby inhibit the final step in aggregation (see Fig. 51-1). As a result, these drugs can prevent aggregation stimulated by all factors, including collagen, TXA2, ADP, thrombin, and platelet activation factor.

Therapeutic Use.

The GP IIb/IIIa antagonists are used short term to prevent ischemic events in patients with acute coronary syndromes (ACSs) and those undergoing percutaneous coronary intervention (PCI).

Acute Coronary Syndromes.

ACSs have two major manifestations: unstable angina and non–Q-wave MI. In both cases, symptoms result from thrombosis triggered by disruption of atherosclerotic plaque. When added to traditional drugs for ACSs (heparin and aspirin), GP IIb/IIIa antagonists reduce the risk of ischemic complications.

Percutaneous Coronary Intervention.

GP IIb/IIIa antagonists reduce the risk of rapid reocclusion following coronary artery revascularization with PCI (balloon or laser angioplasty, or atherectomy using an intra-arterial rotating blade). Reocclusion is common because PCI damages the arterial wall, and thereby encourages platelet aggregation.

Properties of Individual GP IIb/IIIa Antagonists

Abciximab.

Description and Use.

Abciximab [ReoPro] is a purified Fab fragment of a monoclonal antibody. The drug binds to platelets in the vicinity of GP IIb/IIIa receptors, and thereby prevents the receptors from binding fibrinogen. Abciximab, in conjunction with aspirin and heparin, is approved for IV therapy of ACSs and for patients undergoing PCI. In addition, clinical studies indicate it can accelerate revascularization in patients undergoing thrombolytic therapy for acute MI. Antiplatelet effects persist for 24 to 48 hours after stopping the infusion. The cost of a single course of treatment is about $1200. Dosages for ACSs and PCI are summarized in Table 51-7.

Adverse Effects and Interactions.

Abciximab doubles the risk of major bleeding, especially at the PCI access site in the femoral artery. The drug may also cause GI, urogenital, and retroperitoneal bleeds. However, it does not increase the risk of fatal hemorrhage or

hemorrhagic stroke. In the event of severe bleeding, infusion of abciximab and heparin should be discontinued. Other drugs that impede hemostasis will increase the risk of bleeding.

Eptifibatide.

Eptifibatide [Integrilin] is a small peptide that causes reversible and highly selective inhibition of GP IIb/IIIa receptors. The drug is approved for patients with ACSs and those undergoing PCI. Antiplatelet effects reverse by 4 hours after stopping the infusion. The most important adverse effect is bleeding, which occurs most often at the site of PCI catheter insertion, and in the GI and urinary tracts. As with other GP IIb/IIIa inhibitors, the risk of bleeding is increased by concurrent use of other drugs that impede hemostasis. Dosages are summarized in Table 51-7.

Tirofiban.

Tirofiban [Aggrastat] causes selective and reversible inhibition of GP IIb/IIIa receptors. The drug—neither an antibody nor a peptide—was modeled after a platelet inhibitor isolated from the venom of the saw-scaled viper, a snake indigenous to Africa. Like other GP IIb/IIIa inhibitors, tirofiban is used to reduce ischemic events associated with ACSs and PCI. Platelet function returns to baseline within 4 hours of stopping the infusion. Bleeding is the primary adverse effect. The risk of bleeding can be increased by other drugs that suppress hemostasis. Dosages for ACSs and PCI are summarized in Table 51-7.

Other Antiplatelet Drugs

Dipyridamole

Dipyridamole [Persantine] suppresses platelet aggregation, perhaps by increasing plasma levels of adenosine. The drug is approved only for prevention of thromboembolism following heart valve replacement. For this application, dipyridamole is always combined with warfarin. The recommended dosage is 75 to 100 mg 4 times a day. A fixed-dose combination of dipyridamole and aspirin is indicated for recurrent stroke (see below).

Dipyridamole plus Aspirin

Actions and Use.

Dipyridamole combined with aspirin is available in a fixed-dose formulation sold as *Aggrenox*. The product is used to prevent recurrent ischemic stroke in patients who have had a previous stroke or TIA. Both drugs—aspirin and dipyridamole—suppress platelet aggregation. However, since they do so by different mechanisms, the combination is more effective than either drug alone.

Clinical Trial.

The benefit of combining aspirin and dipyridamole was demonstrated in the second *European Stroke Prevention Study* (ESPS-2), a randomized controlled trial that enrolled over 6000 patients who had suffered a prior ischemic stroke or TIA. Some patients took aspirin alone (25 mg twice daily), some took dipyridamole alone (200 mg twice daily), some took both drugs, and some took placebo. The result? After 24 months, the incidence of fatal or nonfatal ischemic stroke was reduced by 16% with dipyridamole alone, 18% with aspirin alone, and 37% with the combination. Unfortunately, ESPS-2 was tainted by scientific scandal (one investigator, who later resigned, was charged with creating and falsifying data). Although all fraudulent data were discarded prior to publication, some authorities remain skeptical of the results.

Adverse Effects.

The most common adverse effects of the combination are headache, dizziness, and GI disturbances (nausea, vomiting, diarrhea, abdominal pain, dyspepsia). Of course, bleeding is a concern: The product can cause hemorrhage (3.2% vs. 1.5% with placebo), nosebleed (2.4% vs. 1.5%), and purpura (1.4% vs. 0.4%). The aspirin in Aggrenox poses a risk of GI bleeding from peptic ulcers.

Preparations, Dosage, and Administration.

Aggrenox capsules contain 25 mg of aspirin and 200 mg of extended-release dipyridamole. The recommended dosage is 2 capsules a day—one in the morning and one at night. The cost is about $90 a month, compared with $3 a month for aspirin alone. It is important to note that the daily dose of aspirin (50 mg) is lower than the dose recommended to prevent MI (at least 80 mg/day). Accordingly, supplemental aspirin may be needed.

Cilostazol

Actions and Therapeutic Use.

Cilostazol [Pletal], a platelet inhibitor and vasodilator, is indicated for *intermittent claudication*. (Intermittent claudication is a syndrome characterized by pain, cramping, and weakness of the calf muscles brought on by walking and relieved by resting a few minutes. The underlying cause is atherosclerosis in the legs.) Cilostazol suppresses platelet aggregation by inhibiting type 3 phosphodiesterase (PDE3) in platelets, and promotes vasodilation by inhibiting PDE3 in blood vessels (primarily in the legs). Inhibition of platelet aggregation is greater than with aspirin, ticlopidine, or dipyridamole. Full effects take up to 12 weeks to develop, but reverse quickly (within 48 hours) following drug withdrawal.

Adverse Effects.

Cilostazol causes a variety of untoward effects. The most common is headache (34%). Others include diarrhea (19%), abnormal stools (15%), palpitations (10%), dizziness (10%), and peripheral edema (7%).

Other drugs that inhibit PDE3 have increased mortality in patients with heart failure. Whether cilostazol represents a risk is unknown. Nonetheless, heart failure is a contraindication to cilostazol use.

Drug and Food Interactions.

Cilostazol is metabolized by the 3A4 isozyme of cytochrome P450 (CYP3A4), and hence cilostazol levels can be increased by CYP3A4 inhibitors (eg, ketoconazole, itraconazole, erythromycin, fluoxetine, fluvoxamine, nefazodone, sertraline, and grapefruit juice). Metabolism of cilostazol can also be inhibited by omeprazole.

Preparations, Dosage, and Administration.

Cilostazol [Pletal] is available in 50- and 100-mg tablets. The usual dosage is 100 mg twice daily, taken 30 minutes before or 2 hours after breakfast and the evening meal. Dosage should be reduced to 50 mg twice daily in patients taking omeprazole and drugs or foods that inhibit CYP3A4.

THROMBOLYTIC DRUGS

As their name implies, thrombolytic drugs are given to remove thrombi that have already formed. This contrasts with the anticoagulants, which are given to prevent thrombus formation. In the United States, four thrombolytic drugs are currently available: streptokinase, alteplase, reteplase, and tenecteplase. All carry a risk of serious bleeding, and hence should be administered only by clinicians skilled in their use. Thrombolytics are employed acutely and only for severe thrombotic disease. Because of their mechanism of action, these agents are also known as *fibrinolytics* (and informally as *clot busters*). Properties of individual agents are summarized in Table 51-8.

	Streptokinase	Alteplase (tPA)	Tenecteplase	Reteplase
Trade name	Streptase	Activase	TNKase	Retavase
Description	A compound that forms an active complex with plasminogen	A compound identical to human tPA	Modified form of tPA with a prolonged half-life	A compound that contains the active sequence of amino acids present in tPA
Source	Streptococcal culture	Recombinant DNA technology	Recombinant DNA technology	Recombinant DNA technology
Mechanism	These drugs promote conversion of plasminogen to plasmin, an enzyme that degrades the fibrin matrix of thrombi			
Adverse effects				
Bleeding	Yes	Yes	Yes	Yes
Allergic reactions	Yes	No	No	No
Half-life (min)	40–80	5	20–24	13–16
Dosage and administration for acute MI	*Intravenous:* 1.5 million IU infused over 30–60 min *Intracoronary:* 20,000 IU bolus, then 2000 IU/min for 60 min	*Intravenous:* 15-mg bolus, then 50 mg infused over 30 min, then 35 mg infused over 60 min	*Intravenous:* Bolus based on body weight (see text)	*Intravenous:* 10-IU bolus 2 times, separated by 30 min
Cost	$540	$2750	$3750	$2750

IU = international unit.

TABLE 51-8 Properties of Thrombolytic Drugs

Streptokinase

Streptokinase [Streptase] was the first thrombolytic drug available and will serve as our prototype for the group.

Mechanism of Action.

Streptokinase acts by an indirect mechanism. The drug first binds to *plasminogen* to form an active complex. The streptokinase-plasminogen complex then catalyzes the conversion of other plasminogen molecules into plasmin, an enzyme that digests the fibrin meshwork of clots. In addition to digesting fibrin in clots, plasmin degrades fibrinogen and other clotting factors. These actions do not contribute to lysis of thrombi, but they do increase the risk of hemorrhage.

Therapeutic Uses.

Streptokinase has three major indications: (1) acute coronary thrombosis (acute MI), (2) DVT, and (3) massive pulmonary emboli. In all three settings, timely intervention is essential. For example, in patients with acute MI, results are best when thrombolytic therapy is started within 4 to 6 hours of symptom onset, and preferably sooner. Thrombolytic therapy of acute MI is discussed further in Chapter 52.

Pharmacokinetics.

Streptokinase may be administered by IV infusion or by infusion directly into an occluded coronary artery. Owing to rapid inactivation, the drug's half-life is only 40 to 80 minutes.

Adverse Effects.

Bleeding.

Bleeding is the major complication of treatment. Intracranial hemorrhage (ICH), which occurs in 1% of patients, is by far the most serious concern. Bleeding occurs for two reasons: (1) plasmin can destroy pre-existing clots, and can thereby promote recurrence of bleeding at sites of recently healed injury; and (2) by degrading clotting factors, plasmin can disrupt coagulation, and can

thereby interfere with new clot formation in response to vascular injury. Likely sites of bleeding include recent wounds, sites of needle puncture, and sites at which invasive procedures have been performed. Anticoagulants (eg, heparin, warfarin) and antiplatelet drugs (eg, aspirin) further increase the risk of hemorrhage. Accordingly, high-dose therapy with these drugs must be avoided until thrombolytic effects of streptokinase have abated.

Management of bleeding depends on severity. Oozing at sites of cutaneous puncture can be controlled with a pressure dressing. If severe bleeding occurs, streptokinase should be discontinued. Patients who require blood replacement can be given whole blood or blood products (packed red blood cells, fresh-frozen plasma). As a rule, blood replacement restores hemostasis. However, if this approach fails, excessive fibrinolysis can be reversed with IV *aminocaproic acid* [Amicar], a compound that prevents activation of plasminogen and directly inhibits plasmin.

The risk of bleeding can be lowered by

- Minimizing physical manipulation of the patient
- Avoiding subQ and IM injections
- Minimizing invasive procedures
- Minimizing concurrent use of anticoagulants (eg, heparin, warfarin)
- Minimizing concurrent use of antiplatelet drugs (eg, aspirin)

Because of the risk of hemorrhage, streptokinase and other thrombolytic drugs must be avoided by patients at high risk for bleeding complications, and must be used with great caution in patients at lower risk of bleeding. A list of absolute and relative contraindications to thrombolytic therapy is presented in Table 51-9.

Absolute Contraindications

- Any prior intracranial hemorrhage
- Known structural cerebral vascular lesion
- Ischemic stroke within last 3 months *except* ischemic stroke within 3 hours
- Known intracranial neoplasm
- Active internal bleeding (other than menses)
- Suspected aortic dissection

Relative Contraindications/Cautions

- Severe, uncontrolled hypertension on presentation (blood pressure above 180/110 mm Hg)
- History of chronic, severe, poorly controlled hypertension
- History of prior ischemic stroke, dementia, or known intracerebral pathology not covered in absolute contraindications
- Current use of anticoagulants in therapeutic doses (INR 2–3 or greater); known bleeding diathesis
- Traumatic or prolonged (more than 10 min) CPR or major surgery (less than 3 weeks ago)
- Recent internal bleeding (within 2–4 weeks)
- Noncompressible vascular punctures
- For streptokinase: prior exposure (more than 5 days ago) or prior allergic reaction
- Pregnancy
- Active peptic ulcer

Adapted from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. A report of the

TABLE 51-9 Contraindications and Cautions Regarding Thrombolytic Use for Myocardial Infarction

Antibody Production.

Streptokinase is a foreign protein extracted from cultures of streptococci. As a result, antibodies may form. Two consequences are possible: *allergic reactions* and *neutralization of streptokinase*. The most common allergic reactions are urticaria, itching, flushing, and headache. These can be treated with antihistamines. Severe anaphylaxis is rare. Because neutralizing antibodies may develop within a few days of streptokinase administration, repeat courses of streptokinase may be ineffective. Hence, if a repeat course is needed, a different thrombolytic agent (eg, alteplase) should be used.

Hypotension.

Streptokinase may cause significant hypotension soon after dosing. The incidence is between 1% and 10%. Hypotension is not related to bleeding or allergic reactions. Blood pressure should be monitored. If hypotension develops, it may be necessary to slow the streptokinase infusion.

Fever.

Temperature elevation of 1.5°F or more occurs in one-third of patients. Only 3.5% of patients develop temperatures above 104°F. Acetaminophen—not aspirin—should be used to lower temperature.

Preparations, Dosage, and Administration.

Streptokinase [Streptase] is supplied as a powder (250,000, 750,000, and 1,500,000 international units [IU]) for reconstitution with 0.9% saline or 5% dextrose.

For *pulmonary embolism, DVT,* and *arterial thrombosis or embolism,* streptokinase is administered by IV infusion. Therapy is usually initiated with an IV loading dose of 250,000 IU infused over 30 minutes. After the loading dose, the infusion is continued for 1 to 3 days at a rate of 100,000 IU/hr.

For an *evolving MI,* streptokinase may be infused through a catheter placed in the occluded coronary artery. This technique offers two benefits: (1) high levels

of streptokinase are achieved at the site where the drug is actually needed, and (2) high levels are avoided elsewhere, thereby minimizing generalized bleeding. Timing of therapy is critical: Streptokinase is most effective when therapy is begun within 6 hours of symptom onset, and preferably sooner.

Alteplase (tPA)

Alteplase [Activase, Cathflo Activase], also known as *tissue plasminogen activator* (tPA), is produced commercially by recombinant DNA technology. The commercial preparation is identical to naturally occurring human tPA, an enzyme that promotes conversion of plasminogen to plasmin, an enzyme that digests the fibrin matrix of clots. Low therapeutic doses produce selective activation of plasminogen that is bound to fibrin in thrombi. As a result, activation of plasminogen in the general circulation is minimized. However, despite selective activation of fibrin-bound plasminogen, bleeding tendencies with alteplase are equivalent to those seen with the other thrombolytic drugs. Furthermore, the risk of intracranial bleeding is higher with alteplase than with streptokinase. Since alteplase is devoid of foreign proteins, it does not cause allergic reactions. In contrast to streptokinase, alteplase does not induce hypotension. Alteplase has a short half-life (about 5 minutes) owing to rapid hepatic inactivation.

Like streptokinase, alteplase is indicated for acute MI and pulmonary embolism. In addition, alteplase is approved for ischemic stroke. As discussed below, the GUSTO-I trial has shown that alteplase is slightly better than streptokinase for treating acute MI. Unfortunately, alteplase is also much more expensive: A single course of alteplase costs about $2750, compared with $540 for streptokinase.

Alteplase is now given by an "accelerated" or "front-loaded" schedule. In this schedule, the infusion time is only 90 minutes, compared with the 3-hour infusion employed in the past. For patients who weigh over 67 kg, the total dose for treating acute MI is 100 mg. Administration is divided into three phases: a 15-mg IV bolus, followed by 50 mg infused over 30 minutes, followed in turn by 35 mg infused over 60 minutes. Total doses in excess of 100 mg are associated with an increased risk of intracranial bleeding and should be avoided.

Tenecteplase

Tenecteplase [TNKase], a variant of human tissue plasminogen activator (tPA, alteplase), is approved for patients undergoing acute MI. Except for the substitution of three amino acids, the drug is structurally identical to tPA. However, because of this small structural change, the pharmacokinetics of tenecteplase are much different from those of tPA. Specifically, tenecteplase is 80 times more resistant than tPA to circulating inhibitors and has a much longer half-life (20 to 24 minutes vs. 5 minutes for tPA). Like tPA, tenecteplase acts by converting plasminogen into plasmin, an enzyme that digests fibrin clots. *Tenecteplase is just as safe and effective as tPA, but much easier to use: Whereas tPA must be infused over 90 minutes, tenecteplase is given by bolus injection.* As a result, thrombolysis develops faster, and emergency personnel are spared the trouble of monitoring a prolonged infusion. Because tenecteplase is so easy to administer, it has the potential to allow dosing before the patient reaches a hospital.

Tenecteplase was compared with tPA in the second Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) study, which enrolled 16,949 patients. Tenecteplase was given as a 5-second IV bolus; tPA was infused over 90 minutes. The median time between symptom onset and starting treatment was 2.7 hours for tenecteplase and 2.8 hours for tPA. Thirty days after treatment, outcomes were equivalent with respect to mortality (6.2% with each drug), intracranial hemorrhage (0.93% with tenecteplase vs. 0.94% with tPA), and total stroke (1.78% vs. 1.66% with tPA). Of significance, the incidence of major hemorrhage (other than intracranial) was *lower* with tenecteplase (4.7% vs. 5.9%).

Dosage of tenecteplase is based on body weight (BW) as follows:

- BW below 60 kg: dose 30 mg
- BW 60 to 69.9 kg: dose 35 mg
- BW 70 to 79.9 kg: dose 40 mg
- BW 80 to 89.9 kg: dose 45 mg
- BW above 90 kg: dose 50 mg

Note that no one is given more than 50 mg. Interestingly, the price of tenecteplase ($2750/dose) is identical to that of tPA [Activase] and reteplase [Retavase].

Reteplase and Urokinase

Reteplase and urokinase are similar to streptokinase with regard to mechanism, indications, and ability to promote bleeding. Principal differences between these drugs relate to half-life, source, antigenicity, cost, and indications.

Reteplase.

Reteplase [Retavase] is a derivative of tPA produced by recombinant DNA technology. In contrast to tPA itself, which contains 527 amino acids, reteplase is composed of only 355 amino acids. Like tPA, reteplase converts plasminogen to plasmin, which in turn digests the fibrin matrix of the thrombus. Reteplase has a short half-life (13 to 16 minutes) owing to rapid clearance by the liver and kidneys. As with other thrombolytic drugs, bleeding is the major adverse effect. The risk of bleeding is increased by concurrent use of heparin and aspirin. Allergic reactions have not been reported.

Reteplase is approved only for acute MI. Treatment consists of two 10-unit doses separated by 30 minutes. Each dose is given by IV bolus injected over a 2-minute interval. Reteplase should not be administered through a line that contains heparin. If a heparin-containing line must be used, it should be flushed prior to giving reteplase.

Urokinase.

Urokinase [Abbokinase] is an enzyme that occurs naturally in human urine. Commercial urokinase is prepared by extraction from cultures of human fetal kidney cells. Like streptokinase, urokinase promotes the conversion of plasminogen into plasmin, its active form. As with other thrombolytics, bleeding is the principal adverse effect. Since urokinase is human derived, it is not antigenic, and hence allergic reactions do not occur. Urokinase has a short half-life (15 to 20 minutes) owing to rapid inactivation by the liver. The drug is approved for acute MI, DVT, and clearance of IV catheters. For treatment of acute MI, urokinase is infused for 2 hours or less at a rate of 6000 IU/hr. Because of its high cost (see Table 51-8), urokinase is used much less frequently than streptokinase. Urokinase in no longer available in the United States.

Streptokinase Versus Alteplase: The GUSTO-I Trial

The GUSTO-I (Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries) trial is the largest study ever conducted on the treatment of acute MI. Over 41,000 subjects from 15 countries participated. The results indicate that *mortality* from MI in patients receiving alteplase (tPA) is somewhat lower than in patients receiving streptokinase (SK)—although the risk of *hemorrhagic stroke* with tPA is higher. However, as discussed below, the apparent superiority of tPA as seen in GUSTO may not be relevant to everyday clinical practice.

In GUSTO-I, each participant received one of the following treatments (30-day mortality rates are in parentheses):

- PA + IV heparin (6.3%)
- SK + IV heparin (7.4%)
- SK + subQ heparin (7.2%)
- SK + tPA + IV heparin (7%)

As the mortality figures indicate, 7.4 of each 100 patients who received streptokinase (plus IV heparin) died within 30 days. In contrast, only 6.3 of each 100 patients who received tPA (plus IV heparin) died within 30 days. Hence, by using tPA instead of streptokinase, we might expect to save one additional life for each 100 patients.

What the above figures don't indicate is the timing of tPA administration with respect to onset of MI symptoms. In GUSTO-I, nearly 90% of patients received treatment within 2 to 4 hours of symptom onset. Among patients who received tPA within 2 hours of symptom onset, the death rate was only 5.4%; among those treated 2 to 4 hours after symptom onset, the rate increased to 6.6%; and among those treated 4 to 6 hours after symptom onset, the rate jumped to 9.4%. Not only do these figures underscore the importance of early treatment, they bring into question the relevance of GUSTO-I to ordinary clinical practice. Why? Because, in usual practice, very few patients are treated as early as those in GUSTO. Furthermore, among patients who are treated *after* 4 hours, GUSTO-I showed no significant difference in mortality between treatment with tPA and treatment with streptokinase. Hence, although tPA may be superior to streptokinase when these drugs are employed under *ideal* conditions, tPA may not be superior in everyday practice. When this observation is

coupled with two others—the much higher cost of tPA and the greater incidence of hemorrhagic stroke with tPA—the desirability of tPA over streptokinase is less obvious. Regardless of whether tPA is significantly better than streptokinase, there is no question that treatment with either drug is much better than no treatment at all. Put another way, selecting some thrombolytic drug is much more important than which one is selected.

KEY POINTS

- Hemostasis occurs in two stages: formation of a platelet plug, followed by coagulation (ie, production of fibrin, a protein that reinforces the platelet plug).
- Platelet aggregation depends on activation of GP IIb/IIIa receptors, which bind fibrinogen to form cross-links between platelets.
- Fibrin is produced by two pathways—the contact activation pathway (aka intrinsic pathway) and the tissue factor pathway (aka extrinsic pathway)—which converge at clotting factor Xa, which catalyzes formation of thrombin, which in turn catalyzes formation of fibrin.
- Four factors in the coagulation pathways require an activated form of vitamin K for their synthesis.
- Plasmin, the active form of plasminogen, serves to degrade the fibrin meshwork of clots.
- A thrombus is a blood clot formed within a blood vessel or within the heart.
- Arterial thrombi begin with formation of a platelet plug, which is then reinforced with fibrin.
- Venous thrombi begin with formation of fibrin, which then enmeshes red blood cells and platelets.
- Arterial thrombi are best prevented with antiplatelet drugs (eg, aspirin), whereas venous thrombi are best prevented with anticoagulants (warfarin, heparin).

- Heparin is a large polymer (molecular weight range = 3000 to 30,000) that carries many negative charges.
- Heparin suppresses coagulation by helping antithrombin inactivate thrombin and factor Xa.
- Heparin is administered IV or subQ. Because of its large size and negative charges, heparin is unable to cross membranes, and hence cannot be administered PO.
- Anticoagulant effects of heparin develop within minutes of IV administration.
- The major adverse effect of heparin is bleeding.
- Severe heparin-induced bleeding can be treated with protamine sulfate, a drug that binds heparin and thereby stops it from working.
- Heparin-induced thrombocytopenia is a potentially fatal condition caused by development of antibodies against heparin–platelet protein complexes.
- Heparin is contraindicated for patients with thrombocytopenia or uncontrollable bleeding, and must be used with extreme caution in all patients for whom there is a high likelihood of bleeding.
- Heparin therapy is monitored by measuring the aPTT (activated partial thromboplastin time). The target aPTT is 60 to 80 seconds (ie, 1.5 to 2 times the normal value of 40 seconds).
- Low-molecular-weight (LMW) heparins are produced by breaking molecules of unfractionated heparin into smaller pieces.
- In contrast to unfractionated heparin, which inactivates factor Xa and thrombin equally, LMW heparins preferentially inactivate factor Xa.
- In contrast to unfractionated heparin, LMW heparins do not bind nonspecifically to plasma proteins and tissues. As a result, their bioavailability is high, making their plasma levels predictable.
- Because plasma levels of LMW heparins are predictable, these drugs can be administered on a fixed schedule with no need for routine laboratory monitoring. As a result, LMW heparins can be used at home.

- Warfarin is the only oral anticoagulant currently available in the United States (although two others are nearing approval).
- Warfarin prevents the activation of vitamin K, and thereby blocks the biosynthesis of vitamin K–dependent clotting factors.
- Anticoagulant responses to warfarin develop slowly and persist for several days after warfarin is discontinued.
- Warfarin therapy is monitored by measuring prothrombin time (PT). Results are expressed as an international normalized ratio (INR). An INR of 2 to 3 is the target for most patients.
- Bleeding is the major complication of warfarin therapy.
- Genetic testing for variant genes that code for VKORC1 and CYP2C9 can identify people with increased sensitivity to warfarin, and who therefore may need a dosage reduction.
- Moderate warfarin overdose is treated with vitamin K.
- Warfarin must not be used during pregnancy. The drug can cause fetal malformation, CNS defects, and optic atrophy.
- Warfarin is subject to a large number of clinically significant drug interactions. Drugs can increase anticoagulant effects by displacing warfarin from plasma albumin and by inhibiting hepatic enzymes that degrade warfarin. Drugs can decrease anticoagulant effects by inducing hepatic drug-metabolizing enzymes, increasing synthesis of clotting factors, and inhibiting warfarin absorption. Drugs that promote bleeding, such as heparin and aspirin, will obviously increase the risk of bleeding in patients taking warfarin. Instruct patients to avoid all drugs—prescription and nonprescription—that have not been specifically approved by the prescriber.
- Aspirin and other antiplatelet drugs suppress thrombus formation in arteries.
- Aspirin inhibits platelet aggregation by causing irreversible inhibition of cyclooxygenase. Since platelets are unable to synthesize new cyclooxygenase, inhibition persists for the life of the platelet (7 to 10 days).

- In its role as an antiplatelet drug, aspirin is given for primary prophylaxis of MI, prevention of MI recurrence, and prevention of stroke in patients with a history of TIAs.
- When used to suppress platelet aggregation, aspirin is administered in low doses—typically 80 to 325 mg/day.
- The GP IIb/IIIa receptor blockers (eg, abciximab) inhibit the final common step in platelet aggregation, and hence are the most effective antiplatelet drugs available.
- Thrombolytic drugs (eg, streptokinase, alteplase [tPA]) are used to dissolve existing thrombi (rather than prevent thrombi from forming).
- Thrombolytic drugs work by converting plasminogen to plasmin, an enzyme that degrades the fibrin matrix of thrombi.
- Thrombolytic therapy is most effective when started early (ie, within 4 to 6 hours of symptom onset, and preferably sooner).
- Thrombolytic drugs carry a significant risk of bleeding. Intracranial hemorrhage is the greatest concern.
- For patients with acute MI, tPA is slightly more effective than streptokinase, but costs much more and causes more intracranial bleeding.

Summary of Major Nursing Implications*

HEPARIN

Preadministration Assessment

Therapeutic Goal

The objective is to prevent thrombosis without inducing spontaneous bleeding.

Heparin is the preferred anticoagulant for use during pregnancy and in situations that require rapid onset of effects, including pulmonary embolism, evolving stroke, and massive DVT. Other indications include open heart sur-

gery, renal dialysis, and disseminated intravascular coagulation. Low doses are used to prevent postoperative venous thrombosis and to enhance thrombolytic therapy of MI.

Baseline Data

Obtain baseline values for blood pressure, heart rate, complete blood cell counts, platelet counts, hematocrit, and aPTT.

Identifying High-Risk Patients

Heparin is *contraindicated* for patients with severe thrombocytopenia or uncontrollable bleeding and for patients undergoing lumbar puncture, regional anesthesia, or surgery of the eye, brain, or spinal cord.

Use with *extreme caution* in patients at high risk of bleeding, including those with hemophilia, increased capillary permeability, dissecting aneurysm, GI ulcers, or severe hypertension. Caution is also needed in patients with severe hepatic or renal dysfunction.

Implementation: Administration

Routes

Intravenous (continuous infusion or intermittent) and subQ. Avoid IM injections!

Administration

General Considerations.

Dosage is prescribed in units, not milligrams. Heparin preparations vary widely in concentration; read the label carefully to ensure correct dosing.

Intermittent IV Administration.

Administer through a heparin lock every 4 to 6 hours. Determine the aPTT before each dose during the early phase of treatment, and daily thereafter. Rotate the injection site every 2 to 3 days.

Continuous IV Infusion.

Administer with a constant infusion pump or some other approved volume-control unit. Policy may require that dosage be double-checked by a second person. Check the infusion rate every 30 to 60 minutes. During the early phase of treatment, the aPTT should be determined every 4 hours. Check the site of needle insertion periodically for extravasation.

Deep SubQ Injection.

Perform subQ injections into the fatty layer of the abdomen (but not within 2 inches of the umbilicus). Draw up the heparin solution using a 20- to 22-gauge needle, and then discard that needle and replace it with a small needle (½ to ⅝ inch, 25 or 26 gauge) to make the injection. Apply firm but gentle pressure to the injection site for 1 to 2 minutes following administration. Rotate and record injection sites.

Ongoing Evaluation and Interventions

Evaluating Treatment

Periodic determinations of the aPTT are used to evaluate treatment. Heparin should increase the aPTT by 1.5- to 2-fold above baseline.

Minimizing Adverse Effects

Hemorrhage.

Heparin overdose may cause hemorrhage. Monitor closely for signs of bleeding. These include reduced blood pressure, elevated heart rate, discolored urine or stool, bruises, petechiae, hematomas, persistent headache or faintness (suggestive of cerebral hemorrhage), pelvic pain (suggestive of ovarian hemorrhage), and lumbar pain (suggestive of adrenal hemorrhage). Laboratory data suggesting hemorrhage include reductions in the hematocrit and blood cell counts. If bleeding occurs, heparin should be discontinued. Severe overdose can be treated with *protamine sulfate* administered by slow IV injection. The risk of bleeding can be reduced by ensuring that the aPTT does not exceed 2 times the baseline value.

Heparin-Induced Thrombocytopenia.

HIT, characterized by reduced platelet counts and increased thrombotic events, poses a risk of DVT, pulmonary embolism, cerebral thrombosis, MI, and ischemic injury to the arms and legs. To reduce risk, monitor platelet counts 2 to 3 times a week during the first 3 weeks of heparin use, and monthly thereafter. If severe thrombocytopenia develops (platelet count below 100,000/mm3), discontinue heparin and, if anticoagulation is still needed, substitute lepirudin or argatroban.

Hypersensitivity Reactions.

Allergy may develop to antigens in heparin preparations. To minimize the risk of severe reactions, administer a small test dose prior to the full therapeutic dose.

Minimizing Adverse Interactions

Antiplatelet Drugs.

Concurrent use of aspirin and other antiplatelet drugs increases the risk of bleeding. Use these agents with caution.

WARFARIN

Preadministration Assessment

Therapeutic Goal

The goal is to prevent thrombosis without inducing spontaneous bleeding. Specific indications include prevention of venous thrombosis and associated pulmonary embolism, prevention of thromboembolism in patients with prosthetic heart valves, and prevention of thrombosis during atrial fibrillation.

Baseline Data

Obtain a thorough medical history. Be sure to identify use of any medications that might interact adversely with warfarin. Obtain baseline values of vital signs and PT. Genetic testing for variants of CYP2C9 and VKORC1 may be done to identify patients in whom anticoagulation may be especially intense.

Identifying High-Risk Patients

Warfarin is *contraindicated* in the presence of vitamin K deficiency, liver disease, alcoholism, thrombocytopenia, uncontrollable bleeding, pregnancy, and lactation, and for patients undergoing lumbar puncture, regional anesthesia, or surgery of the eye, brain, or spinal cord.

Use with *extreme caution* in patients at high risk of bleeding, including those with hemophilia, increased capillary permeability, dissecting aneurysm, GI ulcers, and severe hypertension.

Use with *caution* in patients with variant forms of CYP2C9 or VKORC1.

Implementation: Administration

Route

Oral.

Administration

For most patients, dosage is adjusted to maintain an INR value of 2 to 3. Maintain a flow chart for hospitalized patients indicating INR values and dosage size and timing.

Implementation: Measures to Enhance Therapeutic Effects

Promoting Adherence

Safe and effective therapy requires rigid adherence to the dosing schedule. Achieving adherence requires active and informed participation by the patient. **Provide the patient with detailed written and verbal instructions regarding the purpose of treatment, dosage size and timing, and the importance of strict adherence to the dosing schedule. Also, provide the patient with a chart on which to keep an ongoing record of warfarin use.** If the patient is incompetent (eg, mentally ill, alcoholic, senile), ensure that a responsible individual supervises treatment.

Nondrug Measures

Advise the patient to (1) avoid prolonged immobility, (2) elevate the legs when sitting, (3) avoid garments that can restrict blood flow in the legs, (4) participate in exercise activities, and (5) wear support hose. These measures will reduce venous stasis, and will thereby reduce the risk of thrombosis.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitoring Prothrombin Time.

Evaluate therapy by monitoring PT. Test results are reported as an INR. For most patients, the target INR is 2 to 3. If the INR is below this range, dosage should be increased. Conversely, if the INR is above this range, dosage should be reduced.

PT should be measured frequently: daily during the first 5 days, twice a week for the next 1 to 2 weeks, once a week for the next 1 to 2 months, and every 2 to 4 weeks thereafter. In addition, PT should be determined whenever a drug that interacts with warfarin is added to or deleted from the regimen.

If heparin is being employed concurrently, blood for PT determinations should be drawn no sooner than 5 hours after giving heparin IV, and no sooner than 24 hours giving heparin subQ.

If appropriate, teach patients how to monitor their PT and INR at home.

Minimizing Adverse Effects

Hemorrhage.

Hemorrhage is the major complication of warfarin therapy. **Warn patients about the danger of hemorrhage, and inform them about signs of bleeding. These include reduced blood pressure, elevated heart rate, discolored urine or stools, bruises, petechiae, hematomas, persistent headache or faintness (suggestive of cerebral hemorrhage), pelvic pain (suggestive of ovarian hemorrhage), and lumbar pain (suggestive of adrenal**

hemorrhage). Laboratory data suggesting hemorrhage include reductions in the hematocrit and blood cell counts.

Instruct the patient to withhold warfarin and notify the prescriber if signs of bleeding are noted. Advise the patient to wear some form of identification (eg, Medic Alert bracelet) indicating warfarin use.

To reduce the incidence of bleeding, **advise the patient to avoid excessive consumption of alcohol. Suggest use of a soft toothbrush to prevent bleeding from the gums. Advise patients to shave with an electric razor.**

Warfarin intensifies bleeding during surgical procedures. **Instruct the patient to make certain the surgeon is aware of warfarin use.** Warfarin should be discontinued several days prior to elective procedures. If emergency surgery must be performed, vitamin K***1*** can help reduce bleeding.

Warfarin-induced bleeding can be controlled with vitamin K***1***. For most patients, oral vitamin K will suffice. For patients with severe bleeding or a very high INR, vitamin K is given by injection (usually IV). The prescriber may advise the patient to keep a supply of vitamin K on hand for use in emergencies, but only after consultation with an informed clinician.

Use in Pregnancy and Lactation.

Warfarin can cross the placenta, causing fetal hemorrhage and malformation. **Inform women of child-bearing age about potential risks to the fetus, and warn them against becoming pregnant.** If pregnancy develops, termination should be considered.

Warfarin enters breast milk and may harm the nursing infant. **Warn women against breast-feeding.**

Minimizing Adverse Interactions

Inform patients that warfarin is subject to a large number of potentially dangerous drug interactions. Instruct them to avoid all drugs—prescription and nonprescription—that have not been specifically approved by the prescriber. Prior to treatment, take a complete medication history to identify any drugs that might interact adversely with warfarin.

THROMBOLYTIC DRUGS

Alteplase (tPA)

Reteplase

Streptokinase

Tenecteplase

Preadministration Assessment

Therapeutic Goal

Thrombolytic drugs are used to treat acute MI, massive pulmonary emboli, ischemic stroke, and DVT.

Baseline Data

Obtain baseline values for blood pressure, heart rate, platelet counts, hematocrit, aPTT, PT, and fibrinogen level.

Identifying High-Risk Patients

Thrombolytic drugs are *contraindicated* for patients with active bleeding, aortic dissection, acute pericarditis, cerebral neoplasm, cerebral vascular disease, or a history of intracranial bleeding.

Use with *great caution* in patients with relative contraindications, including pregnancy, severe hypertension, ischemic stroke within the prior 6 months, and major surgery within the prior 2 to 4 weeks. See Table 51-9 for a complete list of absolute and relative contraindications.

Implementation: Administration

Routes

Intracoronary, intravenous (see Table 51-8).

Administration

Depending on the drug employed and the specific application, administration may be by IV infusion, slow IV injection, IV bolus, intracoronary infusion, or intracoronary bolus. (See Table 51-8 for administration during acute MI.)

Do not administer heparin and streptokinase through the same IV line.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Hemorrhage.

Thrombolytics may cause bleeding; ICH is the greatest concern. To reduce the risk of major bleeding, minimize manipulation of the patient, avoid subQ and IM injections, minimize invasive procedures, and minimize concurrent use of anticoagulants (eg, heparin, warfarin) and antiplatelet drugs (eg, aspirin). Manage oozing at cutaneous puncture sites with a pressure dressing.

For severe bleeding, discontinue streptokinase and give whole blood or blood products (packed red blood cells, fresh-frozen plasma). If bleeding continues, give IV aminocaproic acid.

Minimizing Adverse Interactions

Anticoagulants and Antiplatelet Drugs.

Anticoagulants (eg, heparin, warfarin) and antiplatelet drugs (eg, aspirin) increase the risk of bleeding from antithrombotics. Avoid high-dose therapy with these drugs until thrombolytic effects have subsided.

52 Management of ST-Elevation Myocardial Infarction

Myocardial infarction (MI), also known as heart attack, is defined as necrosis of the myocardium (heart muscle) resulting from local ischemia (deficient blood flow). The underlying cause is partial or complete blockage of a coronary artery. When blockage is complete, the area of infarction is much larger than when the blockage is partial. In this chapter, discussion is limited to acute MI caused by *complete* interruption of regional myocardial blood flow. This class of MI is called *ST-elevation MI* (STEMI), because it causes elevation of the ST segment on the electrocardiogram (ECG). Management of STEMI differs from management of non–ST-elevation MI, which occurs when blockage of blood flow is only partial.

In the United States, STEMI strikes about 500,000 people each year and is the most common cause of death. Between 20% and 30% of STEMI victims die before reaching the hospital, another 9.9% die in the hospital, and 7.1% die within a year of hospital discharge. Risk factors for STEMI include advanced age, a family history of MI, sedentary lifestyle, obesity, high serum cholesterol, hypertension, smoking, and diabetes. The objectives of this chapter are to describe the pathophysiology of STEMI and to discuss interventions that can help reduce morbidity and mortality.

PATHOPHYSIOLOGY OF STEMI

Acute MI occurs when blood flow to a region of the myocardium is stopped owing to platelet plugging and thrombus formation in a coronary artery—almost always at the site of a fissured or ruptured atherosclerotic plaque. Myocardial injury is ultimately the result of an imbalance between oxygen demand and oxygen supply.

In response to local ischemia, a dramatic redistribution of ions takes place. Hydrogen ions accumulate in the myocardium and calcium ions become sequestered in mitochondria. The resultant acidosis and functional calcium deficiency alter the distensibility of cardiac muscle. Sodium ions accumulate in myocardial cells and promote edema. Potassium ions are lost from myocardial cells, thereby setting the stage for dysrhythmias.

Local metabolic changes begin rapidly following coronary arterial occlusion. Within seconds, metabolism shifts from aerobic to anaerobic. High-energy stores of ATP and creatine phosphate become depleted. As a result, contraction ceases in the affected region.

If blood flow is not restored, cell death begins within 20 minutes. Clear indices of cell death—myocyte disruption, coagulative necrosis, elevation of cardiac proteins in serum—are present by 24 hours. By 4 days, monocyte infiltration and removal of dead myocytes weaken the infarcted area, making it vulnerable to expansion and rupture. Structural integrity is partially restored with deposition of collagen, which begins in 10 to 12 days, and ends with dense scar formation by 4 to 6 weeks.

Myocardial injury also triggers ventricular remodeling, a process in which ventricular mass increases and the chambers change in volume and shape. Remodeling is driven in part by local production of angiotensin II. Ventricular remodeling increases the risk of heart failure and death.

The degree of residual cardiac impairment depends on how much of the myocardium was damaged. With infarction of 10% of left ventricular (LV) mass, the ejection fraction is reduced. With 25% LV infarction, cardiac dilation and heart failure (HF) occur. With 40% LV infarction, cardiogenic shock and death are likely.

DIAGNOSIS OF STEMI

Acute STEMI is diagnosed by the presence of chest pain, characteristic ECG changes, and elevated serum levels of myocardial cellular components (troponin, creatine kinase). Other symptoms include sweating, weakness, and a sense of impending doom. About 20% of people with STEMI experience no symptoms.

Chest Pain.

Patients undergoing STEMI typically experience severe substernal pressure that they characterize as unbearable crushing or constricting pain. The pain often radiates down the arms and up to the jaw. STEMI can be differentiated from angina pectoris in that pain caused by STEMI lasts longer (20 to 30

minutes) and is not relieved by nitroglycerin. Some patients confuse the pain of STEMI with indigestion.

ECG Changes.

Acute STEMI produces changes in the ECG. Why? Because conduction of electrical impulses through the heart becomes altered in the region of injury. Elevation of the ST segment, which defines STEMI, occurs almost immediately in response to acute ischemia (Fig. 52-1).

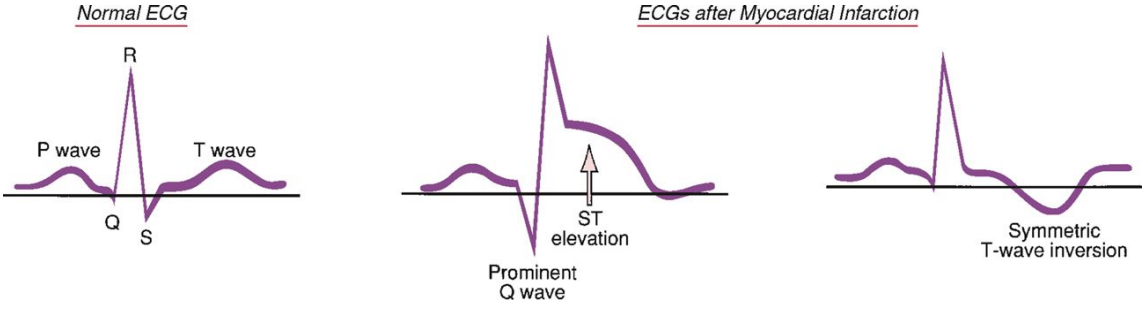

Figure 52-1 ECG changes associated with ST-elevation myocardial infarction.

Following a period of ST-segment elevation, a prominent Q wave (more than 0.04-second duration) develops in the majority of patients. (Q waves are small or absent in the normal ECG.) Over time, the ST segment returns to baseline, after which a symmetric inverted T wave appears. This T wave inversion may resolve within weeks to months. Q waves may resolve over a period of years.

Biochemical Markers for MI.

When myocardial cells undergo necrosis, they release intracellular proteins (eg, cardiac troponins, creatine kinase). Hence, elevations in these proteins in blood can be diagnostic of STEMI.

Today, cardiac-derived troponins—*cardiac troponin I* and *cardiac troponin T*—are considered the best serum markers for STEMI. These proteins are components of the sarcomere, and are distinct from their counterparts in skeletal muscle. Under normal conditions, troponin I and troponin T are undetectable in blood. However, when STEMI occurs, their levels rise dramatically, often to 100-fold or more above the lower limits of detection. Cardiac troponins become detectable 2 to 4 hours after symptom onset, peak in 10 to 24 hours, and return to

undetectable in 5 to 14 days. Measurements of troponin I and troponin T are more sensitive than measurements of other biochemical markers for STEMI, and produce fewer false-positive or false-negative results.

Before cardiac troponins became the preferred biomarkers for STEMI, clinicians relied on measurement of the MB isozyme of creatine kinase (CK-MB). Since CK-MB is found primarily in cardiac muscle rather than skeletal muscle, an increase in serum CK-MB is highly suggestive of cardiac injury. Following MI, serum levels of CK-MB begin to rise in 4 to 8 hours, peak in 24 hours, and return to baseline in 36 to 72 hours. In some patients, the increase in CK-MB may be too small to allow a definitive diagnosis, even though significant myocardial injury has occurred.

MANAGEMENT OF STEMI

The acute phase of management refers to the interval between the onset of symptoms and discharge from the hospital (usually 6 to 10 days). The goal is to bring cardiac oxygen supply back in balance with oxygen demand. This can be accomplished by reperfusion therapy, which restores blood flow to the myocardium, and by reducing myocardial oxygen demand. The first few hours of treatment are most critical. The major threats to life during acute STEMI are ventricular dysrhythmias, cardiogenic shock, and HF.

In 2004 and again in 2007, the American College of Cardiology (ACC), in conjunction with the American Heart Association (AHA), issued revised guidelines for the management of acute MI. These guidelines—*ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction* and *2007 Focused Update of ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction*—are available online at www.acc.org and www.americanheart.org. The discussion below reflects recommendations in these documents.

Routine Drug Therapy

When a patient presents with suspected STEMI, several interventions should be started immediately. The objective is to minimize possible myocardial necrosis while waiting for a clear diagnosis. Once STEMI has been diagnosed, more definitive therapy—reperfusion—can be implemented (see below).

Oxygen

Supplemental oxygen, administered by nasal cannula, can increase arterial oxygen saturation, and thereby increase oxygen delivery to the ischemic myocardium. Accordingly, oxygen should be given to all patients with reduced arterial oxygen saturation (below 90%), and may be given to all other patients with suspected STEMI as well.

Aspirin

Aspirin suppresses platelet aggregation, producing an immediate antithrombotic effect. In the Second International Study of Infarct Survival (ISIS-2), aspirin caused a substantial reduction in mortality. Moreover, benefits were synergistic with fibrinolytic drugs: mortality was 13.2% with thrombolytics alone, and dropped to 8% with the addition of aspirin. Because of these benefits, virtually all patients with evolving STEMI should get aspirin. Therapy should begin immediately after onset of symptoms, and should continue indefinitely. The first dose (162 to 325 mg) should be chewed to allow rapid absorption across the buccal mucosa. Prolonged therapy (with 81 to 162 mg/day) reduces the risk of reinfarction, stroke, and death.

Nonaspirin NSAIDs

According to the 2007 guideline updates, routine use of nonsteroidal drugs (NSAIDs) other than aspirin should be *discontinued*. Why? Because, unlike aspirin, these agents increase the risk of mortality, reinfarction, hypertension, HF, and myocardial rupture.

Morphine

Intravenous morphine is the treatment of choice for STEMI-associated pain. In addition, morphine can improve hemodynamics. By promoting venodilation, the drug reduces cardiac preload. By promoting modest arterial dilation, morphine may cause some reduction in afterload. The combined reductions in preload and afterload lower cardiac oxygen demand, thereby helping preserve the ischemic myocardium.

Beta Blockers

When given to patients undergoing acute STEMI, beta blockers (eg, atenolol, metoprolol) reduce cardiac pain, infarct size, and short-term mortality. Recurrent ischemia and reinfarction are also decreased. Reduction in myocardial wall tension may decrease the risk of myocardial rupture. Continued use of an oral beta blocker increases long-term survival. Unfortunately, although nearly all patients can benefit from beta blockers, many don't get them.

Benefits result from several mechanisms. As STEMI evolves, traffic along sympathetic nerves to the heart increases greatly, as does the number of beta receptors in the heart. As a result, heart rate and force of contraction rise substantially, thereby increasing cardiac oxygen demand. By preventing beta receptor activation, beta blockers reduce heart rate and contractility, and thereby reduce oxygen demand. They reduce oxygen demand further by lowering blood pressure. By prolonging diastolic filling time, beta blockers increase coronary blood flow and myocardial oxygen supply. Additional benefits derive from antidysrhythmic actions.

Beta blockers should be used routinely in the absence of specific contraindications (eg, asthma, bradycardia, significant LV dysfunction). The initial dose may be oral or IV; oral dosing is used thereafter. Treatment with an oral beta blocker should begin within 24 hours and should continue for at least 2 to 3 years, and perhaps longer. Beta blockers are especially good for patients with reflex tachycardia, systolic hypertension, atrial fibrillation, and atrioventricular conduction abnormalities. Contraindications include overt severe HF, pronounced bradycardia, persistent hypotension, advanced heart block, and cardiogenic shock. The basic pharmacology of the beta blockers is presented in Chapter 18.

Nitroglycerin

In patients with STEMI, nitroglycerin has several beneficial effects: It can (1) reduce preload, and thereby reduce oxygen demand; (2) increase collateral blood flow in the ischemic region of the heart; (3) control hypertension caused by STEMI-associated anxiety; and (4) limit infarct size and improve LV function. However, despite these useful effects, nitroglycerin does not reduce mortality. Nonetheless, since the drug is easily administered, offers hemodynamic benefits, and helps relieve ischemic chest pain, it continues to be used. According to the current guidelines, patients with ongoing ischemic discom-

fort should be given sublingual nitroglycerin (0.4 mg) every 5 minutes for a total of three doses, and then be assessed to determine whether IV nitroglycerin should be given. Indications for IV therapy include persisting ischemic discomfort, hypertension, and pulmonary congestion. Nitroglycerin should be avoided in patients with hypotension (systolic pressure below 90 mm Hg), severe bradycardia (heart rate below 50 bpm), marked tachycardia (heart rate above 100 bpm), or suspected right ventricular infarction. In addition, nitroglycerin should be avoided in men who have taken sildenafil or vardenafil for erectile dysfunction within the last 24 hours, or tadalafil within the last 48 hours.

Reperfusion Therapy

The goal of reperfusion therapy is to restore blood flow through the blocked coronary artery. Reperfusion is the most effective way to preserve myocardial function and limit infarct size. How do we accomplish reperfusion? Either with fibrinolytic drugs (also known as thrombolytic drugs) or with percutaneous coronary intervention (PCI), usually balloon angioplasty. Both options are very effective. However, PCI is generally preferred. The relative advantages of fibrinolytic therapy and primary PCI are summarized in Table 52-1. With either intervention, rapid implementation is essential.

Advantages of Fibrinolytic Therapy
• More universal access
• Shorter time to treatment
• Results less dependent on physician experience
• Lower system cost
Advantages of Primary PCI
• Higher initial reperfusion rates
• Less residual stenosis
• Lower recurrence rates of ischemia/infarction
• Does not promote intracranial bleeding
• Defines coronary anatomy and LV function
• Can be used when fibrinolytic therapy is contraindicated
LV = left ventricular, PCI = percutaneous coronary intervention.

TABLE 52-1 Comparison of Fibrinolytic Therapy with Primary PCI

Primary Percutaneous Coronary Intervention

The term *primary PCI* refers to the use of angioplasty, rather than fibrinolytic therapy, to recanalize an occluded coronary artery. In the most common type of angioplasty, a catheter containing a deflated balloon is worked into the affected coronary artery, and then the balloon is inflated. This opens the vessel,

allowing blood to flow. Placement of a stent (a small mesh tube) in the artery helps prevent reocclusion. Under current guidelines, the institutional goal is to implement PCI within 90 minutes of initial patient contact. As discussed below, all patients undergoing PCI should receive an anticoagulant (IV heparin) and antiplatelet drugs (aspirin plus clopidogrel, and probably a glycoprotein IIb/IIIa inhibitor).

The success rate with primary PCI is somewhat higher than with fibrinolytic therapy. Moreover, studies indicate that the benefits of PCI last longer. After 30 days, the rate of death, reinfarction, or disabling stroke following PCI is 9.6%, versus 13.6% following fibrinolytic therapy with tissue plasminogen activator (tPA). After 5 years, the rate of all-cause mortality following PCI is 13%, versus 24% with streptokinase—the difference being due entirely to lower cardiovascular mortality in PCI-treated patients. Benefits of primary PCI over fibrinolytic therapy are greatest in high-risk patients.

Fibrinolytic Therapy

Fibrinolytic drugs dissolve clots. How? By converting plasminogen into plasmin, a proteolytic enzyme that digests the fibrin meshwork that holds clots together. Five fibrinolytic drugs are available: *alteplase (tPA), reteplase, streptokinase, tenecteplase*, and *urokinase*. The basic pharmacology of these drugs is presented in Chapter 51. Discussion here is limited to their use in STEMI.

Fibrinolytic therapy is most effective when presentation is early. When thrombolytics are given soon enough, the occluded artery can be opened in 80% of patients. Current guidelines suggest a target of 30 minutes or less for the elapsed time between entering the emergency department and starting fibrinolysis. Clinical trials have shown that timely therapy improves ventricular function, limits infarct size, and reduces mortality. Restoration of blood flow reduces or eliminates chest pain, and often reduces ST elevation. Current guidelines restrict fibrinolytic therapy to patients with ischemic pain that has been present no more than 12 hours. Patients for whom fibrinolytic therapy is contraindicated are listed in Table 52-2.

Absolute Contraindications

- Any prior intracranial hemorrhage
- Known structural cerebral vascular lesion
- Ischemic stroke within last 3 months *except* ischemic stroke within 3 hours
- Known intracranial neoplasm
- Active internal bleeding (other than menses)
- Suspected aortic dissection

Relative Contraindications/Cautions

- Severe, uncontrolled hypertension on presentation (blood pressure above 180/110 mm Hg)
- History of chronic, severe, poorly controlled hypertension
- History of prior ischemic stroke, dementia, or known intracerebral pathology not covered in contraindications
- Current use of anticoagulants in therapeutic doses (INR 2–3 or greater); known bleeding diathesis
- Traumatic or prolonged (more than 10 minutes) CPR or major surgery (less than 3 weeks ago)
- Recent internal bleeding (within 2–4 weeks)
- Noncompressible vascular punctures
- For streptokinase: prior exposure (more than 5 days ago) or prior allergic reaction
- Pregnancy
- Active peptic ulcer

Adapted from Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction: A report of the

TABLE 52-2 Contraindications and Cautions Regarding Fibrinolytic Use for Myocardial Infarction

Under *typical* conditions, all of the available fibrinolytics are equally beneficial. However, under ideal conditions (ie, treatment within 4 to 6 hours of pain onset), alteplase is most effective, especially in patients under age 75 (see discussion of the GUSTO-I trial in Chapter 51). Unfortunately, alteplase is also very expensive. With streptokinase, neutralizing antibodies may develop within 5 days of initial use. These antibodies prevent streptokinase from acting, and hence a different agent must be used if fibrinolytic therapy must be repeated.

The major complication of fibrinolytic therapy is bleeding, which occurs in 1% to 5% of patients. Intracranial hemorrhage (ICH) is the greatest concern. ICH has an incidence of 0.5% to 1%, and is most likely in the elderly. Nonetheless, the benefits of fibrinolysis generally outweigh the risks. ICH is slightly more common with alteplase than with streptokinase.

As discussed below, all patients undergoing fibrinolytic therapy should receive an anticoagulant (IV heparin) plus antiplatelet drugs (aspirin plus clopidogrel—but not a glycoprotein IIb/IIIa inhibitor [eg, abciximab]).

Adjuncts to Reperfusion Therapy

Heparin

Heparin is a parenteral anticoagulant that was used widely to treat MI before fibrinolytics and primary PCI became available. The drug was shown to decrease mortality, reinfarction, stroke, pulmonary embolism, and deep vein thrombosis. Today, heparin is used in conjunction with fibrinolytics and PCI to reduce the risk of thrombosis. The main complication of heparin is bleeding.

Heparin is recommended for all STEMI patients undergoing fibrinolytic therapy or PCI. For those receiving fibrinolytic drugs, treatment should begin prior to giving the fibrinolytic, and should continue for at least 48 to 72 hours after. For patients undergoing PCI, heparin is given once, immediately before the procedure.

As discussed in Chapter 51, heparin is available as the intact (unfractionated) drug and in low-molecular-weight (LMW) forms. When heparin is used as an adjunct to fibrinolytic therapy, selection of a heparin product depends on dur-

ation of its use. For treatment lasting less than 48 hours, *unfractionated* heparin can be employed. However, for treatment lasting more than 48 hours, an *LMW* heparin should be chosen. Why? Because prolonged use of unfractionated heparin poses a risk of heparin-induced thrombocytopenia.

Antiplatelet Drugs

Clopidogrel.

Clopidogrel [Plavix] is an antiplatelet drug that works by blocking receptors for adenosine diphosphate (see Chapter 51). The drug is recommended for all MI patients undergoing reperfusion therapy, and even for those who do not undergo reperfusion. In all cases, clopidogrel should be *combined* with aspirin. In patients undergoing PCI, dosing should continue for 1 to 12 months, and in patients undergoing fibrinolytic therapy, dosing should continue at least 14 days.

Glycoprotein (GP) IIb/IIIa Inhibitors.

As discussed in Chapter 51, the GP IIb/IIIa inhibitors (eg, abciximab [ReoPro]) are powerful, intravenous antiplatelet drugs that inhibit the final step in platelet aggregation. These drugs are recommended for patients undergoing PCI, but not for those undergoing fibrinolytic therapy. Of the three GP IIb/IIIa inhibitors available, abciximab is preferred. Treatment should begin as soon as possible before PCI and should continue for 12 hours after.

Aspirin.

As discussed above, *low-dose* aspirin (81 to 162 mg/day) should be taken indefinitely by all people who have had an MI. In addition, *higher-dose* aspirin (162 to 325 mg/day) is recommended for patients who have undergone PCI combined with stent implantation. How long should the higher dose be taken? For at least 1 month by those with a *bare-metal* stent, at least 3 months by those with a *sirolimus-eluting* stent, and at least 6 months by those with a *paclitaxel-eluting* stent—after which all patients should switch to low-dose aspirin and take it indefinitely.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

When used following acute STEMI, angiotensin-converting enzyme (ACE) inhibitors (eg, captopril, lisinopril) decrease short-term mortality in all patients, and long-term mortality in patients with reduced LV function. Benefits derive from reducing preload and afterload, promoting water loss, and favorably altering ventricular remodeling. Because of their benefits, ACE inhibitors are recommended for all STEMI patients in the absence of specific contraindications. Treatment should start within 24 hours of symptom onset and should continue for 6 weeks in all patients, and indefinitely in patients with LV dysfunction. The possibility that long-term therapy may also benefit patients who do not have LV dysfunction is being evaluated in large-scale trials. The major adverse effects of ACE inhibitors are hypotension and cough. Contraindications to ACE inhibitors are hypotension, bilateral renal artery stenosis, renal failure, and a history of ACE inhibitor–induced cough or angioedema. The basic pharmacology of the ACE inhibitors is presented in Chapter 43.

Therapy with angiotensin II receptor blockers (ARBs) in STEMI patients has not been studied as extensively as has therapy with ACE inhibitors. However, one major trial—Valsartan in Acute Myocardial Infarction Trial (VALIANT)—demonstrated that, in patients with post-MI HF or LV dysfunction, valsartan (an ARB) was as effective as captopril (an ACE inhibitor) at reducing short-term and long-term mortality. In the current guidelines, ARBs are recommended for STEMI patients who are intolerant of ACE inhibitors and have HF or reduced LV function.

Calcium Channel Blockers

Because of their antianginal, vasodilatory, and antihypertensive actions, calcium channel blockers (CCBs) were presumed beneficial for patients with acute STEMI, and hence were once used widely. However, in large-scale controlled trials, these drugs failed to decrease mortality either during or after acute STEMI. Accordingly, CCBs are not recommended for routine use. However, since the effects of CCBs on the heart are nearly identical to those of beta blockers, current guidelines state that it is reasonable to use two CCBs—verapamil or diltiazem—when beta blockers are either ineffective or contraindicated to relieve ongoing ischemia or control a rapid ventricular rate

caused by atrial fibrillation or atrial flutter. These drugs should not be used if the patient has HF, LV dysfunction, or atrioventricular block.

Magnesium

Magnesium has several potential cardioprotective effects. The drug decreases platelet aggregation, increases coronary blood flow, reduces cardiac afterload, and lowers the risk of serious ventricular dysrhythmias. In several small trials, magnesium infusion decreased mortality from MI. However, in ISIS-4, a trial involving over 58,000 patients, adding magnesium to fibrinolytic therapy failed to reduce mortality—and actually *increased* the incidence of bradycardia, HF, and death from cardiogenic shock. Accordingly, magnesium is not recommended for routine use. However, if magnesium deficiency is present, it should be corrected.

COMPLICATIONS OF STEMI

Myocardial infarction predisposes the heart and vascular system to serious complications. Among the most severe are ventricular dysrhythmias, cardiogenic shock, and HF.

Ventricular Dysrhythmias.

These develop frequently and are the major cause of death following MI. Sudden death from dysrhythmias occurs in 15% of patients during the first hour. Ultimately, ventricular dysrhythmias cause 60% of infarction-related deaths. Acute management of ventricular fibrillation consists of defibrillation followed by IV lidocaine for 24 to 48 hours. Programmed ventricular stimulation with guided antidysrhythmic therapy may be lifesaving for some patients.

Attempts to prevent dysrhythmias by giving antidysrhythmic drugs *prophylactically* have failed to reduce mortality. Worse yet, attempted prophylaxis of ventricular dysrhythmias with two drugs—encainide and flecainide—actually increased mortality. Similarly, when quinidine was employed to prevent supraventricular dysrhythmias, it too increased mortality. Therefore, since prophylaxis with antidysrhythmic drugs does not reduce mortality—and may in fact increase mortality—antidysrhythmic drugs should be withheld until a dysrhythmia actually occurs.

Cardiogenic Shock.

Shock results from greatly reduced tissue perfusion secondary to impaired cardiac function. Shock develops in 7% to 15% of patients during the first few days after MI and has a mortality rate of up to 90%. Patients at highest risk are those with large infarcts, a previous infarct, a low ejection fraction (less than 35%), diabetes, and advanced age. Drug therapy includes inotropic agents (eg, dopamine, dobutamine) to increase cardiac output and vasodilators (nitroglycerin, nitroprusside) to improve tissue perfusion and reduce cardiac work and oxygen demand. Unfortunately, although these drugs can improve hemodynamic status, they do not seem to reduce mortality. Restoration of cardiac perfusion with PCI or coronary artery bypass grafting may be of value.

Heart Failure.

HF secondary to acute MI can be treated with a combination of drugs. A diuretic (eg, furosemide) is given to decrease preload and pulmonary congestion. Inotropic agents (eg, digoxin) increase cardiac output by enhancing contractility. Vasodilators (eg, nitroglycerin, nitroprusside) improve hemodynamic status by reducing preload, afterload, or both. ACE inhibitors (or ARBs), which reduce both preload and afterload, can be especially helpful. Beta blockers may also improve outcome. Drug therapy of heart failure is discussed at length in Chapter 47.

Cardiac Rupture.

Weakening of the myocardium predisposes the heart wall to rupture. Following rupture, shock and circulatory collapse develop rapidly. Death is often immediate. Fortunately, cardiac rupture is relatively rare (less than 2% incidence). Patients at highest risk are those with a large anterior infarction. Cardiac rupture is most likely within the first days after MI. Early treatment with vasodilators and beta blockers may reduce the risk of wall rupture.

SECONDARY PREVENTION OF STEMI

As a rule, patients who survive the acute phase of STEMI can be discharged from the hospital after 6 to 10 days. However, they are still at risk of reinfarction (5% to 15% incidence within the first year) and other complications (eg,

dysrhythmias, heart failure). Outcome can be improved with risk factor reduction, exercise, and long-term therapy with drugs.

Reduction of risk factors for MI can increase long-term survival. Patients who smoke must be encouraged to quit; the goal is total cessation. Patients with high serum cholesterol should be given an appropriate dietary plan and, if necessary, treated with a cholesterol-lowering drug (usually one of the statins); the goal is an LDL cholesterol level substantially below 100 mg/dL. Patients with high triglyceride levels (200 mg/dL or higher) should be given niacin or a "fibrate" (eg, gemfibrozil). Overweight patients should reduce; the goal is a body mass index of 18.5 to 29.4 kg/m^2 (see Chapter 81) and a waist circumference under 35 inches (for women) or under 40 inches (for men). Hypertension and diabetes increase the risk of mortality and must be controlled. For patients with hypertension, blood pressure should be decreased to below 140/90 mm Hg (or below 130/80 mm Hg for those with chronic kidney disease or diabetes). For patients with diabetes, the goal is a level of hemoglobin A$_{1c}$ below 7%.

Exercise training can be valuable for two reasons: (1) it reduces complications associated with prolonged bed rest and (2) it accelerates return to an optimal level of functioning. The goal is 30 minutes of exercise at least 3 to 4 days a week, and preferably 7. Although exercise is safe for most patients, there is concern about cardiac risk and impairment of infarct healing in patients whose infarct is large.

All post-MI patients should take three drugs: (1) a beta blocker, (2) an ACE inhibitor or an ARB, and (3) an antiplatelet drug (aspirin or clopidogrel) or an anticoagulant (warfarin). All three should be taken indefinitely.

Estrogen therapy for postmenopausal women is not effective as secondary prevention, and hence should not be initiated post-MI.

KEY POINTS

- Myocardial infarction (MI) is defined as necrosis of the myocardium secondary to acute occlusion of a coronary artery. The usual cause is platelet

plugging and thrombus formation at the site of a ruptured atherosclerotic plaque.

- ST-elevation MI (STEMI) is diagnosed by the presence of chest pain, characteristic ECG changes, and elevated serum levels of cardiac troponins.
- Aspirin suppresses platelet aggregation, and thereby decreases mortality, reinfarction, and stroke. All patients should chew a 162- to 325-mg dose upon hospital admission, and should take 81 to 162 mg/day indefinitely after discharge. A higher dose (162 to 325 mg/day) should be used short term (1 to 6 months) by patients who received a stent during PCI.
- In patients undergoing acute STEMI, beta blockers reduce cardiac pain, infarct size, short-term mortality, recurrent ischemia, and reinfarction. Continued use increases long-term survival. All patients should receive a beta blocker in the absence of specific contraindications.
- In addition to aspirin and a beta blocker, three other drugs—oxygen, morphine, and nitroglycerin—are considered routine therapy for suspected STEMI. They should be started, as appropriate, soon after symptom onset.
- Reperfusion therapy, which restores blood flow through blocked coronary arteries, is the most beneficial treatment for STEMI.
- Reperfusion can be accomplished with PCI or with fibrinolytic drugs. Both approaches are highly effective—but PCI is now generally preferred.
- The most common PCI procedure is balloon angioplasty, with or without stent implantation.
- Fibrinolytic drugs dissolve clots by converting plasminogen into plasmin, an enzyme that digests the fibrin meshwork that holds clots together.
- Under typical conditions, all fibrinolytic drugs are equally effective. However, when treatment is initiated within 4 to 6 hours of pain onset, alteplase is most effective (but also very expensive).
- The major complication of fibrinolytic therapy is bleeding. Intracranial hemorrhage is the greatest concern.
- Heparin (an anticoagulant) is recommended for all patients undergoing fibrinolytic therapy or PCI.

- Clopidogrel (an antiplatelet drug) *combined* with aspirin (also an antiplatelet drug) is recommended for all patients undergoing reperfusion therapy, either with PCI or with a fibrinolytic drug.
- Glycoprotein IIb/IIIa inhibitors (eg, abciximab) are powerful IV antiplatelet drugs that can enhance the benefits of primary PCI.
- In patients with acute MI, ACE inhibitors decrease mortality, severe heart failure, and recurrent MI. All patients should receive an ACE inhibitor in the absence of specific contraindications. For patients who cannot tolerate ACE inhibitors, an ARB may be used instead.
- To lower the risk of a second MI, all patients should decrease cardiovascular risk factors (eg, smoking, hypercholesterolemia, hypertension, obesity, diabetes); exercise for 30 minutes at least 3 or 4 days a week; and undergo long-term therapy with three drugs: (1) a beta blocker, (2) an ACE inhibitor or an ARB, and (3) an antiplatelet drug (aspirin or clopidogrel) or warfarin (an anticoagulant).

53 Drugs for Hemophilia

Hemophilia is a genetically based bleeding disorder seen almost exclusively in males. About 70% of cases result from inheriting a defective gene from the mother; the other 30% result from a spontaneous gene mutation.

Hemophilia has two forms: hemophilia A and hemophilia B. In hemophilia A, there is a deficiency of clotting factor VIII (aka antihemophilic factor). In hemophilia B, there is a deficiency of clotting factor IX (aka Christmas factor, named for Stephen Christmas, the first boy diagnosed with the disease). Hemophilia A is about 6 times more prevalent than hemophilia B, occurring in 1 of every 5000 males, compared with 1 of every 30,000 for hemophilia B.

When hemophilia is managed well, the prognosis is good. Patients starting treatment today can live healthy, near-normal lives. The foundation of treatment is clotting factor replacement, which may be given on a regular schedule (to prevent bleeds from occurring) or "on demand" (to stop an ongoing bleed). Unfortunately, although treatment is highly effective, it is also very expensive: For patients undergoing prophylactic treatment, the cost for clotting factors alone is about $300,000 a year.

BASIC CONSIDERATIONS

Pathophysiology

In people with hemophilia, there is a failure of hemostasis, the process by which bleeding is normally stopped. As discussed in Chapter 51, hemostasis occurs in two stages: (1) formation of a platelet plug followed by (2) production of fibrin, a protein that reinforces the platelet plug. In patients with hemophilia, platelet aggregation proceeds normally, but fibrin production does not. The underlying problem is a deficiency of clotting factors—specifically, factor VIII (in hemophilia A) and factor IX (in hemophilia B). As indicated in Figure 53-1, both factors are part of the contact-activation (intrinsic) coagulation pathway, and both—in their activated forms—are needed to catalyze the conversion of factor X to *its* active form (factor Xa), which in turn catalyzes the conversion of prothrombin to thrombin, which catalyzes the formation of fibrin. If either

factor VIII or factor IX is deficient, the contact-activation pathway will not work properly, causing clot formation to be delayed. As a result, bleeding will continue longer than in the population at large.

It should be noted that the degree of factor deficiency—and hence the tendency for bleeding to be prolonged—depends on the nature of the underlying gene mutation. In some patients, the mutation produces a severe deficiency, resulting in a high probability of prolonged bleeding; in others, the mutation causes mild deficiency, and hence the tendency to bleed is low.

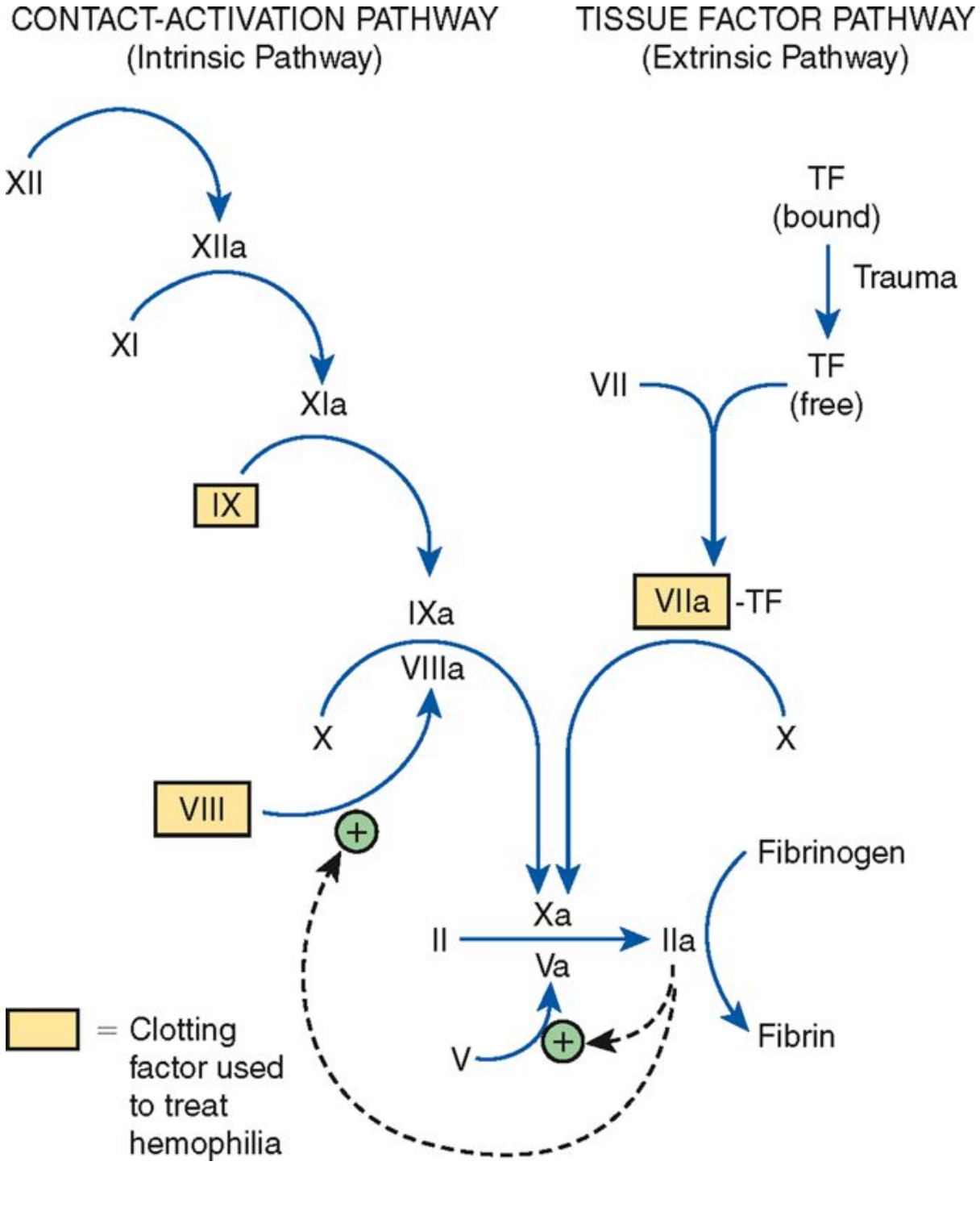
CONTACT-ACTIVATION PATHWAY
(Intrinsic Pathway)
TISSUE FACTOR PATHWAY
(Extrinsic Pathway)
XII
XIIa
XI
XIa
IX
IXa
VIIIa
X
VIII
TF
(bound)
Trauma
TF
(free)
VII
VIIa -TF
X
Xa
II
IIa
Va
V
Fibrinogen
Fibrin
= Clotting factor used to treat hemophilia

Figure 53-1 Outline of the coagulation cascade showing clotting factors used to treat hemophilia. TF = tissue factor. Common names for factors shown in roman numerals: II = prothrombin, IIa = thrombin, VII = proconvertin, VIII = antihemophilic factor, IX = Christmas factor, X = Stuart factor, XI = plasma thromboplastin antecedent, and XII = Hageman factor. The letter "a" after a factor's name (eg, factor VIIIa) indicates the active form of the factor. Note that factors VIII and IX, which are deficient in hemophilia A and B respectively, are part of the contact-activation (intrinsic) coagulation pathway. The symbol indicates acceleration of the reaction.

Inheritance Pattern

The genes for factors VIII and IX are *recessive,* and both are carried on the X chromosome. Because males have only one X chromosome, a male with a defective gene will have hemophilia. In contrast, a female with a defective gene on one X chromosome will usually be an asymptomatic carrier, since she still has a functioning gene on her other X chromosome. Please be aware, however, that although females are usually asymptomatic carriers, there are two situations in which females *can* have hemophilia: (1) a female could be born with defective genes on *both* X chromosomes, which is rare; and (2) a female who was born with one defective gene could experience *inactivation* of the good gene. Boys whose mothers are carriers have a 1 in 2 chance of inheriting the disease. Girls whose mothers are carriers have a 1 in 2 chance of being carriers themselves. Males with hemophilia cannot pass the disease on to their sons, but all of their daughters will be carriers. The risk of acquiring hemophilia is shared by all races and ethnic groups.

Clinical Features

Hemophilia may be severe, moderate, or mild, depending on the degree of clotting factor deficiency. Patients with severe hemophilia may experience life-threatening hemorrhage in response to minor trauma, whereas those with mild hemophilia may experience little or no excessive bleeding. The defining characteristics of severe, moderate, and mild hemophilia are summarized in Table 53-1.

	Disease Severity		
Disease Parameter	**Severe**	**Moderate**	**Mild**
Clotting factor level (VIII or IX)	Less than 1% of normal	Between 1% and 5% of normal	Between 6% and 24% of normal
Bleeding tendency	Can bleed with very mild injury	Can bleed with moderate injury	Can bleed with severe injury, surgery, or invasive procedures
Bleeding frequency	May bleed once or twice a week	May bleed once a month	May never have a bleeding episode
Occurrence of joint bleeding	Frequent	Less frequent	Infrequent, but can occur in response to severe injury

TABLE 53-1 Clinical Classification of Hemophilia Severity

Severe Hemophilia.

In patients with severe hemophilia, the concentration of clotting factor VIII or IX is very low—less than 1% of normal. As a result, these patients experience frequent bleeds within joints and soft tissues, especially muscle. Trauma or surgery can cause profuse hemorrhage. Joint bleeding occurs most often in the knee, followed in turn by the elbow, ankle, shoulder, and hip. Bleeding in these joints causes swelling and intense pain. With recurrent episodes, permanent injury to the joint develops. In addition to joints, bleeding may occur in muscles, mucous membranes (eg, nosebleeds), the GI and urinary tracts, near the pharynx (which can cause life-threatening restriction of airflow), and within the skull (which carries a 30% risk of death). Among patients with hemophilia A, about 60% have severe disease. In contrast, among patients with hemophilia B, only 20% to 45% have severe disease. Although severe hemophilia can be devastating, most patients can live normal and productive lives, thanks to the availability of safe factor concentrates for replacement therapy.

Moderate Hemophilia.

In patients with moderate hemophilia, the concentration of factor VIII or factor IX is between 1% and 5% of normal. Excessive bleeding in response to minor trauma is unlikely. However, it can be induced by significant trauma, tooth extractions, and surgery. Joint bleeding may occur, but the frequency is much lower than with severe hemophilia.

Mild Hemophilia.

In patients with mild hemophilia, the concentration of clotting factors is between 6% and 24% of normal. Joint bleeding is uncommon, but can be induced by severe injury or surgery.

Overview of Therapy

Whenever possible, treatment should be guided by a team of specialists at a hemophilia treatment center. Typically, the team consists of a hematologist, orthopedist, dietitian, psychologist, physical therapist, occupational therapist, genetics counselor, infectious disease specialist, social worker, and nurse coordinator.

The cornerstone of treatment is *replacement therapy* with factor VIII (hemophilia A) or factor IX (hemophilia B). Traditionally, factor replacement was performed only to terminate an ongoing bleeding episode. Today, however, there is increasing emphasis on primary prophylaxis, especially for young children. Why? Because, by minimizing bleeding episodes, prophylaxis can minimize long-term damage to joints.

For some patients with mild *hemophilia A,* bleeding can be stopped with *desmopressin,* a drug that promotes release of factor VIII from the vascular endothelium. Desmopressin has the advantage of being much cheaper than factor VIII, and can be administered by nasal spray as well as by IV infusion. Keep in mind, however, that repeated use of desmopressin can deplete stored factor VIII, making the drug ineffective until more factor VIII is made.

Antifibrinolytic drugs (ie, drugs that prevent the breakdown of fibrin) can be used as adjuncts to factors VIII and IX in special situations, such as tooth extractions. Two antifibrinolytic drugs are currently available: aminocaproic acid and tranexamic acid.

In some patients receiving factor VIII or factor IX, antibodies against the factor develop. These antibodies, referred to as inhibitors, prevent the factor from working. When inhibitors are present, bleeding can be stopped by infusing *activated factor VII*. Other treatments are also available, as discussed below under *Managing Patients with Inhibitors*.

Pain Management

How should we manage bleeding-related pain? For mild pain, *acetaminophen* [Tylenol, others] is the drug of choice. For severe pain, an *opioid analgesic* may be needed. Regardless of pain severity, *aspirin should be avoided!* Why? First, aspirin causes irreversible inhibition of platelet aggregation, and can thereby increase bleeding risk. Second, aspirin can induce GI ulceration and bleeding, an obvious problem.

Can we use nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin? As a rule, these agents should also be avoided. Why? First, like aspirin, most NSAIDs inhibit platelet aggregation (although the inhibition is reversible rather than irreversible). Second, like aspirin, most NSAIDs can promote GI ulceration and bleeding (although the risk is somewhat lower than with aspirin).

What about the second-generation NSAIDs, known as cyclooxygenase-2 (COX-2) inhibitors? As discussed in Chapter 70, the COX-2 inhibitors (eg, celecoxib) do not suppress platelet aggregation, and they cause less GI ulceration and bleeding than traditional NSAIDs. Accordingly, these agents are clearly preferred to traditional NSAIDs, although their safety in hemophilia has not been proved.

Immunization

Children with hemophilia should undergo the normal immunization schedule (see Chapter 67). Some clinicians inject vaccines subQ (rather than IM) to avoid muscle hemorrhage. However, since the efficacy of subQ vaccination is not certain, and since most patients tolerate IM injections without bleeding, IM vaccination is generally preferred. The risk of bleeding after IM injection can be reduced by prolonged application of pressure.

To minimize the risk of hepatitis (see below), all patients with newly diagnosed hemophilia should be vaccinated for hepatitis A and hepatitis B, as

should all other patients with hemophilia who are not seropositive for hepatitis A or B. Family members who administer clotting factors at home should also be immunized, provided they test negative for hepatitis.

PREPARATIONS USED TO TREAT HEMOPHILIA

Factor VIII Concentrates

Factor VIII concentrates are the mainstay of hemophilia A treatment. What's a concentrate? It's simply a powdered formulation in which the amount of factor VIII is very high. When treatment is needed, the powder is dissolved in a sterile solution and administered IV.

All factor VIII concentrates available today are very safe. They carry essentially no risk of HIV/AIDS, and little or no risk of hepatitis.

Production Methods and Product Safety

Factor VIII concentrates are made in two basic ways: (1) purification from human plasma and (2) production in cell culture using recombinant DNA technology. Recombinant factor VIII is somewhat safer than plasma-derived factor VIII, but is also more expensive. All factor VIII products, whether recombinant or plasma derived, are equally effective. Currently available products are listed in Table 53-2.

Type of Preparation	Factor VIII	Factor IX
Recombinant		
Third generation	Advate	BeneFix
	Xyntha	
Second generation	Helixate FS	
	Kogenate FS	
	ReFacto	
First generation	Recombinate	
	Bioclate	
Plasma-Derived		
Ultrapure	Hemofil-M	AlphaNine SD
	Monoclate-P	Mononine Profilnine SD
Intermediate and high purity	Alphanate	
	Koate-DVI	
	Humate-P*	

TABLE 53-2 Some Factor VIII and Factor IX Concentrates

* Factor VIII complexed with von Willebrand factor.

Plasma-Derived Factor VIII.

Prior to 1985, factor VIII produced from donor plasma often contained viral contaminants. As a result, nearly all people with hemophilia developed hepatitis and/or HIV/AIDS. Today, however, the risk of viral contamination is exceedingly low. Why? First, donated plasma is now screened for viral pathogens—specifically, human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), and parvovirus B19. Second, techniques for inactivating *lipid-coated* viruses (HIV, HBV, and HCV) are now employed. Unfortunately, viruses that lack a lipid coat, such as HAV and parvovirus B19, are not eliminated. Nonetheless, no case of virus transmission has been reported with any of the products now used in the United States.

There is one additional concern: prions. These strange proteins, which are responsible for Creutzfeldt-Jakob disease (CJD, the human form of "mad cow disease"), are not susceptible to any known inactivation technique. Hence, the possibility of transmitting CJD remains.

As indicated in Table 53-2, plasma-derived factor VIII is available in varying degrees of purity. The ultrapure products (eg, Hemofil-M) are prepared using monoclonal antibodies.

Recombinant Factor VIII.

Recombinant factor VIII is produced in culture, using hamster cells that have been genetically transformed. All recombinant factor VIII products are very safe, and hence are considered the agents of choice for treating hemophilia A. During the manufacturing process, most recombinant factor VIII products are exposed to bovine serum albumin (BSA), human serum albumin (HSA), or both. Because BSA or HSA could, in theory, be a source of viruses or prions, manufacturing processes that reduce the use of BSA and HSA have been developed. As a result, we now have three "generations" of recombinant products:

- *First-generation products*—Bioclate and Recombinate—are made using BSA in the cell culture, and they contain HSA as a stabilizer in the vial.
- *Second-generation products*—Helixate FS, Kogenate FS, and ReFacto—are made using HSA in the cell culture, but they contain neither BSA nor HSA in the vial.
- *Third-generation products*—Advate and Xyntha—are not exposed to BSA or HSA during cell culture, and they contain neither BSA nor HSA in the vial.

Theoretically, the third-generation products—Advate and Xyntha—which are never exposed to any proteins of animal or human origin, are safer than the first- or second-generation products. However, there are no published data showing this is the case. With all three generations, the risk of human viral contamination is essentially zero. Transmission of HIV, HBV, or HCV has not been reported.

Adverse Effects: Allergic Reactions

Factor VIII concentrates can cause allergic reactions, which can range from mild to severe. Symptoms of a mild reaction include hives, rash, urticaria, stuffy nose, and fever. These can be managed with an antihistamine (eg, di-

phenhydramine [Benadryl]). Rarely, anaphylaxis may develop. Symptoms of this potentially fatal reaction include wheezing, tightness in the throat, shortness of breath, and swelling in the face. The treatment of choice is epinephrine, injected subQ.

Dosage and Administration

On-Demand Therapy.

On-demand therapy is indicated for patients who are bleeding or about to undergo surgery. As a rule, administration is by slow IV push over a period of 5 to 10 minutes. Continuous infusion may also be done, but only by a clinician with special training.

Dosage depends primarily on the site and severity of the bleed. Table 53-3 indicates approximate dosages for a variety of bleeding situations. The dosing target is expressed as a percentage of normal factor VIII activity. For example, when treating a joint bleed, the dosing target is 40% of the normal activity level.

Type of Hemorrhage	Factor VIII (Hemophilia A)		Factor IX (Hemophilia B)	
	Target Activity Level*	Dose (units/kg)	Target Activity Level*	Dose (units/kg)
Joint	40%	20	40%	40
Muscle (except the iliopsoas muscle)	40%	20	40%	40
Iliopsoas muscle†				
Initial	80%–100%	40–50	80%–100%	80–100
Maintenance	50%	25	50%	50
CNS/head				
Initial	80%–100%	40–50	80%–100%	80–100
Maintenance	50%	25	50%	50
Throat and neck				
Initial	80%–100%	40–50	80%–100%	80–100
Maintenance	50%	25	50%	50
Gastrointestinal				
Initial	80%–100%	40–50	80%–100%	80–100
Maintenance	50%	25	50%	50
Ophthalmic	80%–100%	40–50	80%–100%	80–100
Renal	50%	25	50%	50
Deep laceration	50%	25	50%	50
Surgical				
Initial	80%–100%	40–50	80%–100%	80–100
Maintenance	50%	25	50%	50

Data are from Hemophilia of Georgia: Protocols for the Treatment of Hemophilia and von Willebrand Disease. Atlanta: Hemophilia of Georgia (available online as of October 11, 2008, at www.wfh.org/2/docs/Publications/Diagnosis_and_Treatment/TOH-14_English_von_Willebrand.pdf).

CNS = central nervous system.

TABLE 53-3 Estimated Dosages for Factor VIII and Factor IX

* Target activity levels are expressed as a percentage of the normal activity level.

† The iliopsoas is a compound muscle consisting of the iliacus and psoas major muscles, located in the groin region.

How can we calculate dosage? By knowing that, *for each unit of factor VIII we give per kilogram of body weight, we will raise factor VIII activity in plasma by 2%*. Hence, to calculate dosage, we simply multiply the patient's weight by the target activity level for factor VIII and then divide by 2, as in this example:

$$\frac{50(\text{kg body weight}) \times 40(\text{target \%})}{2} = 1000(\text{units of factor VIII})$$

To help guide dosing, factor VIII activity can be measured before and after treatment. However, although knowledge of factor VIII activity is helpful, dosage is ultimately determined by the clinical response.

Prophylactic Therapy.

For prophylaxis, factor VIII is administered on a regular schedule. The goal is to *prevent* bleeding, and thereby prevent life-threatening hemorrhage and long-term injury to joints. Children with severe hemophilia are the primary candidates for prophylaxis. Treatment is often done at home. The goal is to maintain factor VIII activity above 1% of normal. As a rule, this can be achieved by infusing factor VIII concentrate 3 times a week. However, dosing just once or twice a week may work for some patients. Recombinant factor VIII products are generally preferred, although plasma-derived products, which are just as effective and much less expensive, may also be used.

To facilitate frequent IV administration, a central venous access device can be installed. Options include an external catheter (eg, Hickman catheter) or an implanted venous port (eg, Port-A-Cath). Both types of device are intended for long-term use, and can remain in place several years. It should be noted, however, that although these devices make prophylaxis much easier, they do carry risks, infection and thrombosis being the greatest concerns.

Factor IX Concentrates

Therapeutic Use, Production, and Safety

Factor IX concentrates are the mainstay of treatment for hemophilia B. The pharmacology of these concentrates is nearly identical to that of the factor VIII concentrates. Like the factor VIII concentrates, the factor IX concentrates are made either by extraction from donor plasma or by recombinant DNA technology (see Table 53-2). None of the products in current use poses a risk of HIV/AIDS. However, the plasma-derived products may carry a very small risk of hepatitis A, parvovirus B19, or CJD—although there have been no reports of transmitting any of these infections with current products. Because recombinant factor IX [BeneFIX] is, in theory, safer than plasma-derived factor IX [AlphaNine SD, Mononine, Profilnine SD], recombinant factor IX is considered the preparation of choice. Like factor VIII, factor IX can cause allergic reactions.

Dosage and Administration

On-Demand Therapy.

On-demand therapy, administered by IV push, should be initiated at the earliest sign of bleeding. As with factor VIII, dosage is determined primarily by the site and severity of bleeding (see Table 53-3). However, factors VIII and IX differ in that, on a unit-per-kilogram (unit/kg) basis, we need twice as much factor IX to achieve an equivalent increase in plasma factor level. Hence, with factor IX, *for each unit we give per kilogram of body weight, we will raise the plasma activity level by 1%* (compared with 2% for each unit/kg of factor VIII). To calculate dosage, we simply multiply the patient's weight by the target factor IX activity level (expressed as a percentage of normal factor IX activity level), as in this example:

$$50(\text{ kg body weight }) \times 40(\text{ target } \%) = 2000(\text{ units of factor IX})$$

As with factor VIII therapy, plasma levels of factor IX activity can be measured to guide treatment—although the dose depends ultimately on the clinical response.

Prophylactic Therapy.

As with factor VIII, prophylaxis is done to prevent bleeding, and thereby prevent injury to joints. The dosing goal is to maintain factor IX levels above 1% of normal. Because factor IX has a longer half-life than factor VIII (18 to 24 hours

vs. 8 to 12 hours), prophylaxis can be done less often (twice a week rather than 3 times a week). The usual dose is 20 to 40 units/kg.

Desmopressin

Therapeutic Use.

Desmopressin [DDAVP, Stimate], an analog of antidiuretic hormone, can stop or prevent bleeding in patients with *mild* hemophilia A. The drug works by releasing stored factor VIII from the vascular endothelium. Levels of factor VIII begin to rise within 30 minutes of drug administration, and peak within 90 to 120 minutes. Desmopressin can be used to stop episodes of trauma-induced bleeding, and can be given preoperatively to maintain hemostasis during surgery. Desmopressin does not release factor IX, and hence cannot be used to treat hemophilia B. Principal adverse effects are fluid retention and hyponatremia. The basic pharmacology of desmopressin, along with its use in hypothalamic diabetes insipidus, is discussed in Chapter 58 (Drugs Related to Hypothalamic and Pituitary Function).

Preparations, Dosage, and Administration.

For treatment of hemophilia A, desmopressin may be administered IV or by intranasal spray. An oral formulation is available, but is not indicated for hemophilia.

For *intravenous therapy,* desmopressin [DDAVP] is formulated in a concentrated solution (4 mcg/mL) that must be diluted in physiologic saline. The usual dosage is 0.3 mcg/kg infused over 15 to 30 minutes.

For *intranasal therapy,* desmopressin is available under two trade names: *DDAVP,* which delivers 10 mcg/spray, and *Stimate,* which delivers 150 mcg/spray. Only Stimate is used for hemophilia. For patients who weigh 50 kg or more, the dosage is 150 mcg/nostril, for a total of 300 mcg; for patients who weigh less than 50 kg, the dosage is one spray (150 mcg) in just one nostril.

Antifibrinolytic Agents

Antifibrinolytic agents inhibit the normal process of fibrin breakdown. As discussed in Chapter 51, when a clot is no longer needed, an enzyme called *plas-*

min dissolves the fibrin meshwork that holds the clot together, and thereby promotes clot removal. Unfortunately, in people with hemophilia, fibrin breakdown can lead to a resumption of bleeding. Accordingly, by preserving fibrin with an antifibrinolytic drug, we can help keep bleeding under control. Because of their mechanism, antifibrinolytic drugs are most useful for *preventing recurrent* bleeding; they are less useful for stopping an ongoing bleed.

Two antifibrinolytic drugs are currently available: *aminocaproic acid* [Amicar] and *tranexamic acid* [Cyklokapron]. Both agents act primarily by preventing the formation of plasmin from its precursor (plasminogen). These drugs are most useful for controlling bleeding in mucous membranes (of the nose, mouth, and throat) as well as bleeding caused by dental extractions—presumably because fibrinolytic activity at all of these sites is especially high.

Aminocaproic acid is available in solution (250 mg/mL) for IV use, and in tablets (500 and 1000 mg) and a syrup (250 mg/mL) for oral use. Dosages to prevent or treat serious bleeding are as follows:

- *Oral therapy, adults*—give 5 gm for the first hour, then 1 or 1.25 gm every hour
- *IV therapy, adults*—infuse 4 to 5 gm over the first hour, then infuse at a rate of 1 gm/hr
- *Oral therapy, children*—give 100 mg/kg for the first hour, then 33.3 mg/kg every hour
- *IV therapy, children*—infuse 100 mg/kg over the first hour, then infuse at a rate of 33.3 mg/kg/hr

In all cases, continue dosing for 8 hours or until bleeding stops.

Tranexamic acid is available in tablets (500 mg) for oral use and in solution (100 mg/mL) for IV use. To control bleeding associated with dental extractions, the recommended dosage is 10 mg/kg IV immediately before the extraction, followed by 25 mg/kg PO every 6 to 8 hours for 2 to 8 days. Dosage should be decreased in patients with renal impairment.

Managing Patients with Inhibitors

Patients receiving factor VIII or factor IX can develop antibodies against the factor. These antibodies, referred to as inhibitors, neutralize the clotting

factor, and thereby render factor replacement ineffective. In most cases, the antibodies develop early, typically after only 9 to 12 courses of treatment.

Some patients are more likely to develop inhibitors than others. Among patients with *severe* hemophilia A, between 20% and 30% develop antibodies to factor VIII, compared with 3% to 13% of those with *mild* hemophilia A. Among patients with severe hemophilia B, between 2% and 12% develop antibodies to factor IX. The risk of inhibitor development among African American and Hispanic patients is unusually high (up to 50%).

The titer of inhibitors to factor VIII is measured using the Bethesda assay. In this procedure, serial dilutions of patient plasma are mixed with an equal volume of normal plasma, after which factor VIII activity in the mixture is measured. The dilution that inhibits 50% of factor VIII activity defines the inhibitor titer. For example, if the 1:40 dilution inhibits 50% of the factor VIII activity, the patient is said to have a titer of 40 *Bethesda units* (BU) of factor VIII inhibitor.

For some patients, *immune tolerance therapy* (ITT) can eliminate inhibitor production. The procedure involves repeated administration of factor replacement products over an extended time. The success rate is high (63% to 83%) for patients with hemophilia A, and very low for those with hemophilia B. A low antibody titer (less than 5 BU) increases the chances of success. If ITT fails to stop antibody production, then hemostasis must be achieved with drugs, as discussed immediately below.

Drugs for Patients with Factor VIII Inhibitors

To control bleeding in patients with inhibitors to factor VIII, the preferred treatments are (1) activated factor VII and (2) anti-inhibitor coagulant complex. Neither option is clearly superior to the other. Accordingly, selection between them is based on previous response and physician preference.

Activated Factor VII (Factor VIIa).

Factor VIIa [NovoSeven RT], manufactured by recombinant DNA technology, can control bleeding in patients with inhibitors to factor VIII or factor IX. As indicated in Figure 53-1, factor VIIa has the same action as factors VIII and IX. That is, it catalyzes the conversion of factor X to its active form. Hence,

by giving factor VIIa, we can bypass neutralization of factors VIII and IX, and thereby allow clotting to proceed normally.

Factor VIIa is generally well tolerated. No human proteins are used in making this agent, and hence there is no risk of transmitting a human virus. Rarely, thrombotic events have occurred, including venous thrombosis, cerebral sinus thrombosis, and myocardial infarction (MI). In most cases, these events were seen when NovoSeven was used off-label to stop bleeding in nonhemophiliacs, including patients with acute intracerebral hemorrhage.

Factor VIIa is supplied as a powder in single-use vials (1.2, 2.4, and 4.8 mg) and must be reconstituted in sterile water prior to use. Administration is by IV bolus. The usual dosage is 90 mcg/kg, repeated every 2 hours until bleeding is stopped. However, some patients require much higher doses (eg, 300 mcg/kg). Treatment is very expensive: A single 90-mcg/kg dose for a 70-kg patient costs about $10,000. The drug should be stored under refrigeration.

Anti-inhibitor Coagulant Complex (AICC).

AICC [Autoplex T, Feiba VH Immuno*], made from pooled human plasma, contains variable amounts of clotting factors II, VII, IX, and X—in both their activated and nonactivated forms. AICC is indicated for patients with inhibitors to factor VIII or factor IX who are bleeding or about to undergo surgery. Benefits are believed to derive from factors VIIa and Xa, which bypass factors VIII and IX in the coagulation cascade (see Fig. 53-1).

Because AICC is made from human plasma, there is a theoretical risk of transmitting viral or prion disease. However, there have been no reports of transmitting CJD, HIV, or hepatitis A, B, or C with these products as currently formulated.

Because AICC contains multiple coagulation factors, it poses a risk of thrombotic complications, specifically, MI and disseminated intravascular coagulation (DIC). Fortunately, these events are very rare. The risk of MI or DIC is increased with repeated dosing and by liver disease.

Preparations of Feiba VH Immuno are standardized in *Immuno units*. The usual dosage is 50 to 100 Immuno units/kg, infused IV at a rate no faster than 2 Immuno units/kg/min. Dosing can be repeated every 6 hours, but the total daily dose must not exceed 200 Immuno units/kg.

Preparations of Autoplex T are standardized in *Hyland factor VII correctional units*. The usual dosage is 25 to 100 Hyland correctional units/kg, infused IV. Dosing may be repeated in 6 hours.

* FYI: *Feiba* stands for *factor VIII inhibitor bypassing activity*.

Factor VIII Concentrate.

If the inhibitor titer is very low (less than 5 BU), we may be able to overcome inhibition with high doses of factor VIII itself. However, if the inhibitor titer is high, then factor VIII will not work, and the agents discussed above must be employed.

Porcine Factor VIII.

Porcine factor VIII [Hyate: C] can establish hemostasis in patients with hemophilia A who have developed antibodies to human factor VIII. The product, a highly purified form of factor VIII, is extracted from the blood of pigs. The donor animals live in a carefully maintained environment and undergo frequent screening for several viruses. Transmission of porcine viruses to humans receiving the product has never been documented. However, allergic reactions, including anaphylaxis, have occurred, especially with recurrent use. The incidence is about 5%. Rarely, patients develop acute thrombocytopenia. Like all other factor VIII preparations, porcine factor VIII is administered IV. The recommended initial dosage is 100 to 150 factor VIII units/kg. The product should be stored at –15°C to –20°C (5°F to –4°F).

Antibodies to human factor VIII can cross-react with porcine factor VIII. However, the degree of cross-reactivity is low. Accordingly, if the antibody titer is not too high (less than 50 BU/mL), porcine factor VIII is likely to work. If the titer exceeds 50 BU/mL, significant neutralization of the porcine factor can occur. To determine if Hyate: C will work in a patient with a high titer, we need to directly measure the ability of a plasma sample to neutralize the drug.

Drugs for Patients with Factor IX Inhibitors

Treatment options for patients with factor IX inhibitors are limited. In contrast to factor VIII inhibitors, which may be overcome with large doses of human factor VIII or porcine factor VIII, factor IX inhibitors are difficult to overcome with any preparation of factor IX available. Furthermore, elimination of

factor IX inhibitors with ITT often fails. Currently, factor VIIa and AICC are the treatments of choice. Both options are effective because they bypass the blockade caused by the inhibitor.

KEY POINTS

- Hemophilia is a bleeding disorder seen almost exclusively in males. The underlying cause is a genetically based deficiency of clotting factors.
- Hemophilia has two forms: hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency).
- Hemophilia may be severe, moderate, or mild, depending on the degree of clotting factor deficiency.
- Patients with severe hemophilia may experience life-threatening hemorrhage in response to minor trauma, whereas those with mild hemophilia may experience little or no excessive bleeding.
- Repeated bleeding in the knee and other joints can cause permanent joint damage.
- The cornerstone of hemophilia treatment is replacement therapy with factor VIII (hemophilia A) or factor IX (hemophilia B).
- Replacement therapy may be done prophylactically (to prevent bleeding and thereby prevent joint injury) or on demand (to stop an ongoing bleed or prevent excessive bleeding during surgery).
- Clotting factor products are made in two basic ways: extraction from donor plasma and production in cell culture using recombinant DNA technology.
- All clotting factor concentrates, whether plasma derived or recombinant, are equally effective.
- All clotting factor concentrates in use today are very safe: They carry no risk of transmitting HIV/AIDS, and little or no risk of transmitting hepatis or CJD. However, because recombinant factors are, in theory, slightly safer than plasma-derived factors, recombinant factors are considered the treatment of choice.

- As a rule, clotting factors are given by slow IV push. Continuous infusion may also be done, but only by a clinician with special training.
- Clotting factor dosage depends primarily on the site and severity of the bleed.
- A dose of 1 unit of factor VIII/kg will raise the plasma level of factor VIII activity by 2%, whereas 1 unit of factor IX/kg will raise the plasma level of factor IX activity by only 1%.
- Although we can monitor the activity of clotting factors in blood to help guide treatment, dosage is ultimately determined by the clinical response.
- For prophylaxis, clotting factor concentrates are administered on a regular schedule, usually 3 times a week for factor VIII and twice a week for factor IX. With both factors, the goal is to maintain plasma levels above 1% of normal.
- To facilitate frequent IV administration during prophylaxis, a central venous access device can be installed.
- Clotting factor concentrates can cause allergic reactions. Mild reactions can be managed with an antihistamine (eg, diphenhydramine [Benadryl]). The most severe reaction—anaphylaxis—is treated with subQ epinephrine.
- For some patients with mild hemophilia A, bleeding can be stopped with desmopressin, a drug that promotes release of stored factor VIII. Desmopressin does not release factor IX, and hence cannot treat hemophilia B.
- Two drugs—aminocaproic acid and tranexamic acid—can suppress fibrinolysis (by blocking production of plasmin) and can thereby promote hemostasis in hemophilia A and hemophilia B. These antifibrinolytic agents are more effective for preventing recurrent bleeding than for stopping an ongoing bleed.
- Development of inhibitors (antibodies that neutralize factor VIII or factor IX) is a serious complication of hemophilia therapy.
- Activated factor VII (factor VIIa) and AICC are preferred agents for controlling bleeding when inhibitors of factor VIII or factor IX are present.
- People with hemophilia should avoid aspirin and other traditional NSAIDs because these agents suppress platelet aggregation and promote GI ulcera-

tion and bleeding. Second-generation NSAIDs (COX-2 inhibitors) are *probably* safe.

Summary of Major Nursing Implications*

FACTOR VIII AND FACTOR IX CONCENTRATES

Preadministration Assessment

Therapeutic Goal

Factor VIII is indicated for replacement therapy in patients with hemophilia A, and factor IX is indicated for replacement therapy in patients with hemophilia B.

Both factors may be given prophylactically (to prevent bleeding and subsequent joint injury) or "on demand" (to stop ongoing bleeding or prevent excessive bleeding during anticipated surgery).

Baseline Data

Obtain a baseline level for activity of factor VIII or factor IX.

Identifying High-Risk Patients

Use with *caution* in patients with a history of allergic reactions to the factor concentrate.

Implementation: Administration

Route

Intravenous.

Administration

Administer by slow IV push or continuous infusion.

Record the following each time you give a factor concentrate:

- Time and date
- Infusion site and rate
- Total dose
- Manufacturer, trade name, lot number, and expiration date of the factor concentrate

Teach home caregivers about

- The **importance of having an assistant, who can give aid or call for help if complications arise**
- The **importance and proper method of hand washing**
- **Making dosage calculations**
- **Reconstituting the powdered factor concentrate**
- **Infusion technique**
- **Cleanup and waste disposal**
- **Recording the time, date, and other information listed above**

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Success is indicated by preventing bleeding (during prophylactic therapy) or controlling bleeding (during on demand therapy). With both forms of therapy, monitoring activity levels of factor VIII or factor IX can help guide treatment.

Minimizing Adverse Effects

Allergic Reactions.

Clotting factor concentrates can cause allergic reactions, ranging from mild to severe. **Inform patients about symptoms of mild reactions (eg, hives, rash, urticaria, stuffy nose, fever), and advise them to take an antihistamine (eg, diphenhydramine) if these occur. Inform patients about symptoms of anaphylaxis (wheezing, tightness in the throat, shortness of breath, swelling in the face), and instruct them to seek immediate emergency care if these develop.** The treatment of choice is epinephrine, injected subQ.

Minimizing Adverse Interactions

Aspirin.

Warn patients not to use aspirin, a drug that inhibits platelet aggregation and can cause GI ulceration and bleeding.

NSAIDs Other Than Aspirin.

Advise patients that first-generation NSAIDs (eg, ibuprofen, naproxen) have actions similar to those of aspirin, and hence should be avoided.

Advise patients that second-generation NSAIDs (eg, celecoxib), which do not inhibit platelets and cause minimal GI effects, are *probably* safe.

54 Drugs for Deficiency Anemias

Anemia is defined as a decrease in the number, size, or hemoglobin content of erythrocytes (red blood cells [RBCs]). Causes include blood loss, hemolysis, bone marrow dysfunction, and deficiencies of substances essential for RBC formation and maturation. Most deficiency anemias result from deficiency of iron, vitamin B*12*, or folic acid. Accordingly, this chapter focuses on anemias caused by these three deficiencies. To facilitate discussion, we begin by reviewing RBC development.

RED BLOOD CELL DEVELOPMENT

RBCs begin developing in the bone marrow and then mature in the blood. As developing RBCs grow and divide, they evolve through four stages (Fig. 54-1). In their earliest stage, RBCs lack hemoglobin and are known as *proerythroblasts*. In the next stage, they gain hemoglobin and are called *erythroblasts*. Both the erythroblasts and the proerythroblasts reside in bone marrow. After the erythroblast stage, RBCs evolve into *reticulocytes* (immature erythrocytes) and enter the systemic circulation. Following the reticulocyte stage, circulating RBCs reach full maturity and are referred to as *erythrocytes*.

Development of RBCs requires the cooperative interaction of several factors: the bone marrow must be healthy; erythropoietin (a stimulant of RBC maturation) must be present; iron must be available for hemoglobin synthesis; and other factors, including vitamin B*12* and folic acid, must be available to support synthesis of DNA. If any of these is absent or amiss, anemia will result.

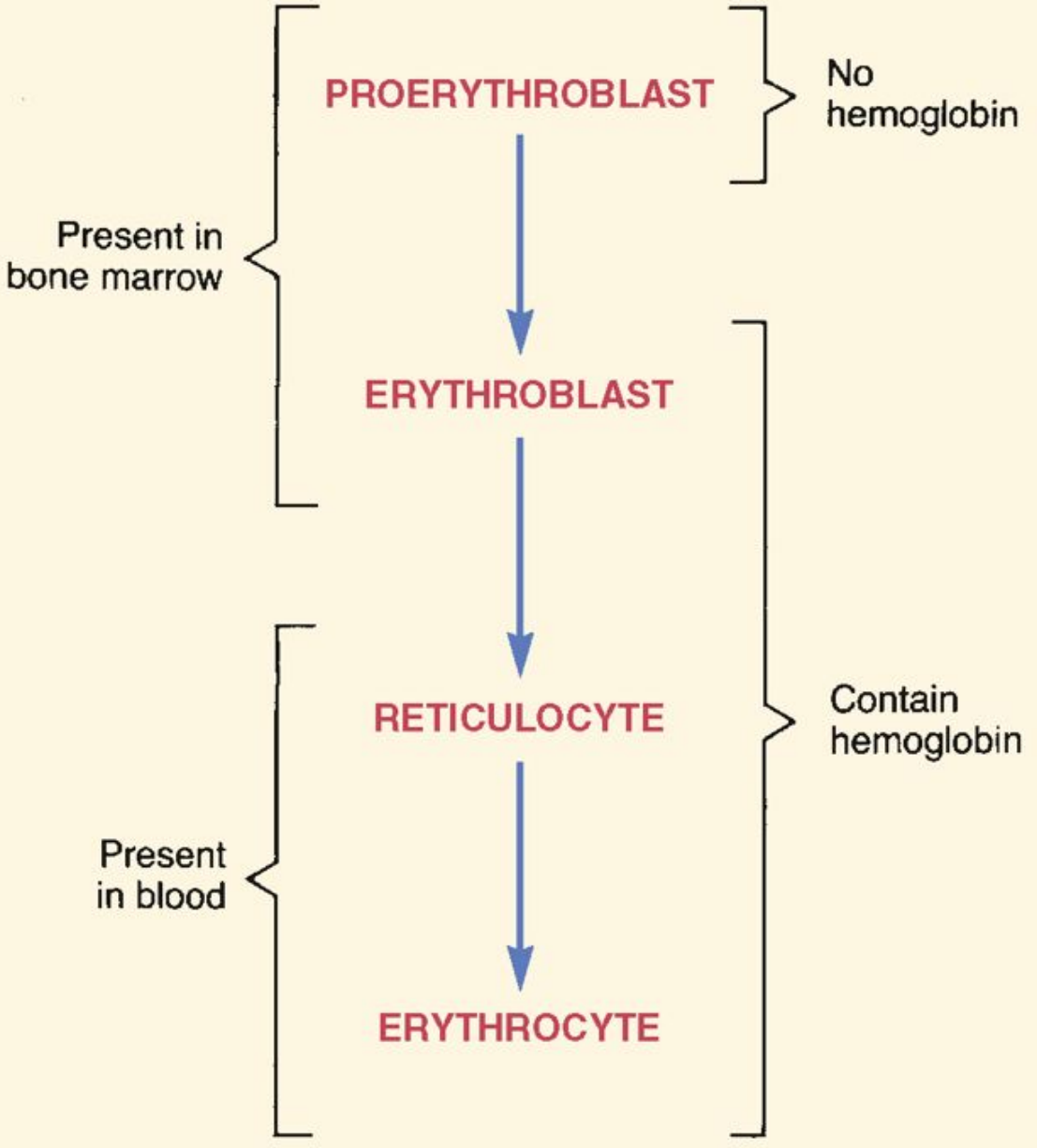
PROERYTHROBLAST
No hemoglobin
Present in bone marrow
ERYTHROBLAST
RETICULOCYTE
Contain hemoglobin
Present in blood
ERYTHROCYTE

Figure 54-1 Stages of red blood cell development.

IRON DEFICIENCY

Iron deficiency is the most common nutritional deficiency, and the most common cause of nutrition-related anemia. Worldwide, people with iron deficiency number in the hundreds of millions. In the United States, about 5% of the population is iron deficient.

Biochemistry and Physiology of Iron

In order to understand the consequences of iron deficiency as well as the rationale behind iron therapy, we must first understand the biochemistry and physiology of iron. This information is reviewed below.

Metabolic Functions

Iron is essential to the function of hemoglobin, myoglobin (the oxygen-storing molecule of muscle), and a variety of iron-containing enzymes. Most (70% to 80%) of the body's iron is present in hemoglobin. A much smaller amount (10%) is present in myoglobin and iron-containing enzymes.

Fate in the Body

The major pathways for iron movement and utilization are shown in Figure 54-2. In the discussion below, the numbers in parentheses refer to the circled numbers in the figure.

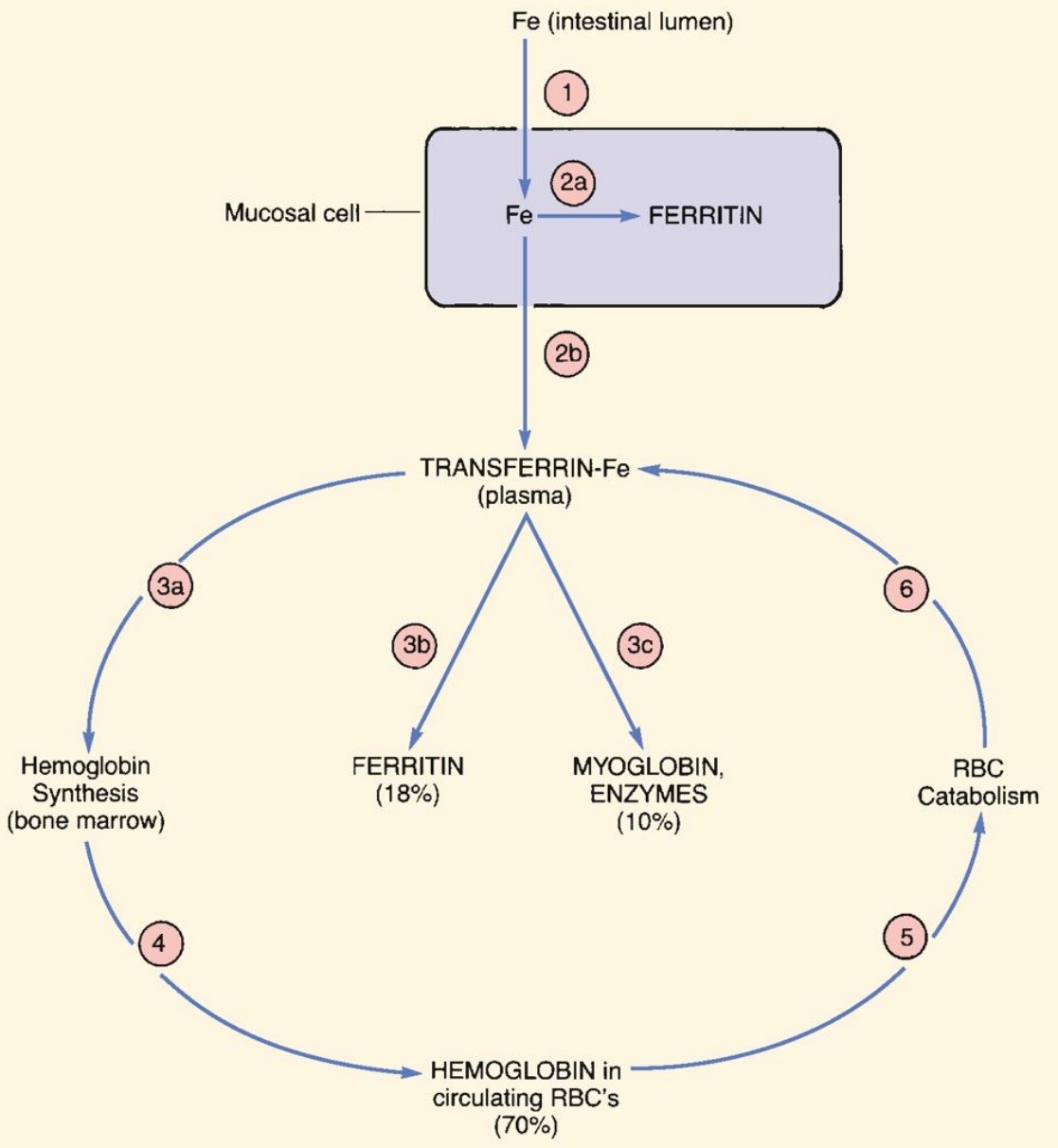
Fe (intestinal lumen)
1
Mucosal cell
2a
Fe
FERRITIN
2b
TRANSFERRIN-Fe
(plasma)
3a
3b
3c
6
Hemoglobin
Synthesis
(bone marrow)
FERRITIN
(18%)
MYOGLOBIN,
ENZYMES
(10%)
RBC
Catabolism
4
5
HEMOGLOBIN in
circulating RBC's
(70%)

Figure 54-2 Fate of iron in the body. Pathways labeled with circled numbers are explained in the text. Values in parentheses indicate percentage of total body stores. Elimination of iron is not shown, because most iron is rigidly conserved. (Fe = iron, RBC = red blood cell.)

Uptake and Distribution.

The life cycle of iron begins with (1) uptake of iron into mucosal cells of the small intestine. These cells absorb between 5% and 20% of dietary iron. Their maximum absorptive capacity is 3 to 4 mg/day. Iron in the ferrous form (Fe^{++}) is absorbed more readily than iron in the ferric form (Fe^{+++}). Food greatly reduces absorption.

Following uptake, iron can either (2a) undergo storage within mucosal cells in the form of *ferritin* (a complex consisting of iron plus a protein used to store iron) or (2b) undergo binding to *transferrin* (the iron transport protein) for distribution throughout the body.

Utilization and Storage.

Iron that is bound to transferrin can undergo one of three fates. The majority of transferrin-bound iron (3a) is taken up by cells of the bone marrow for incorporation into hemoglobin. Small amounts (3b) are taken up by the liver and other tissues for storage as ferritin. Lastly (3c), some of the iron in plasma is taken up by muscle (for production of myoglobin) and some is taken up by all tissues (for production of iron-containing enzymes).

Recycling.

As Figure 54-2 depicts, iron associated with hemoglobin undergoes continuous recycling. After hemoglobin is made in bone marrow, iron re-enters the circulation (4) as a component of hemoglobin in erythrocytes. (The iron in circulating erythrocytes accounts for about 70% of total body iron.) After 120 days of useful life, RBCs are catabolized (5). Iron released by this process re-enters the plasma bound to transferrin (6), and then the cycle begins anew.

Elimination.

Excretion of iron is minimal. Under normal circumstances, only 1 mg of iron is excreted each day. At this rate, if none of the lost iron were replaced, body stores would decline by only 10% a year.

Iron leaves the body by several routes. Most excretion occurs via the bowel. Iron in ferritin is lost as mucosal cells slough off, and iron also enters the bowel in bile. Small amounts are excreted in urine and sweat.

It should be noted that, although very little iron leaves the body as a result of excretion (ie, normal physiologic loss), substantial amounts can leave because of blood loss. Hence, menorrhagia (excessive menstrual flow), hemorrhage, and blood donations can all cause iron deficiency.

Regulation of Body Iron Content.

The amount of iron in the body is regulated through control of intestinal absorption. As noted, most of the iron that enters the body stays in the body. Hence, if all dietary iron were readily absorbed, body iron content would rapidly accumulate to toxic levels. However, *excessive buildup is prevented through control of iron uptake: As body stores rise, uptake of iron declines; conversely, as body stores become depleted, uptake increases*. For example, when body stores of iron are high, only 2% to 3% of dietary iron is absorbed. In contrast, when body stores are depleted, as much as 20% may be absorbed.

Daily Requirements

Requirements for iron are determined largely by the rate of erythrocyte production. When RBC production is low, iron needs are low too. Conversely, when RBC production is high, iron needs rise. Accordingly, among infants and children—individuals whose rapid growth rate requires massive RBC synthesis—iron requirements are high (relative to body weight). In contrast, the daily iron needs of adults are relatively low. Adult males need only 10 mg of dietary iron each day. Adult females need somewhat more, so as to replace iron lost through menstruation.

During pregnancy, requirements for iron increase dramatically, owing to (1) expansion of maternal blood volume and (2) production of RBCs by the fetus. In most cases, the iron needs of pregnant women are too great to be met by

diet alone. Consequently, iron supplements (about 30 mg/day) are recommended during pregnancy and for 2 to 3 months after parturition.

Table 54-1 summarizes the recommended dietary allowances (RDAs) of iron as a function of age. For each age, the table presents two iron values. The first is the actual physiologic need for iron; the second is the RDA. Note that RDA values are about 10 times greater than the values for physiologic need. Why? Because, on average, only 10% of dietary iron is absorbed. Hence, if physiologic requirements are to be met, the diet must contain 10 times more iron than we actually need.

	Age (yr)	Physiologic Requirement for Iron (mg/day)	RDA* for Iron (mg/day)
Infants	0–0.5	0.6	6
	0.5–1	1	10
Children	1–10	1	10
Males	11–18	1.2	12
	18†	1	10
Females	11–50	1.5	15
	50†	1	10
Pregnant and 2–3 mo postpartum	—	5	30†

TABLE 54-1 Recommended Dietary Allowances (RDAs) for Iron

* Because only a small fraction of dietary iron is absorbed, the RDA is higher than the actual physiologic need.

† Iron requirements during pregnancy cannot be met through dietary sources alone; supplements are recommended.

Dietary Sources

Iron is available in foods of plant and animal origin. Foods especially rich in iron include liver, egg yolk, brewer's yeast, and wheat germ. Other foods with a high iron content include muscle meats, fish, fowl, cereal grains, beans, and green leafy vegetables. Foods that do not provide much iron include milk and most non-green vegetables. Since iron can be extracted from cooking utensils, using iron pots and pans can augment dietary iron. Except for individuals who have very high iron requirements (infants, pregnant women, those undergoing chronic blood loss), the average diet is sufficient to meet iron needs.

Iron Deficiency: Causes, Consequences, and Diagnosis

Causes

Iron deficiency results when there is an imbalance between iron uptake and iron demand. As a rule, the imbalance results from increased demand—not from reduced uptake. The most common causes of increased iron demand (and resulting iron deficiency) are (1) blood volume expansion during pregnancy coupled with RBC synthesis by the growing fetus; (2) blood volume expansion during infancy and early childhood; and (3) chronic blood loss, usually of GI or uterine origin. Rarely, iron deficiency results from reduced iron uptake; potential causes include gastrectomy and sprue.

Consequences

Iron deficiency has multiple effects, the most conspicuous being *iron deficiency anemia*. In the absence of iron for hemoglobin synthesis, red blood cells become *microcytic* (small) and *hypochromic* (pale). The reduced oxygen-carrying capacity of blood results in listlessness, fatigue, and pallor of the skin and mucous membranes. If tissue oxygenation is severely compromised, tachycardia, dyspnea, and angina may result. In addition to causing anemia, iron deficiency impairs myoglobin production and synthesis of iron-containing enzymes. In young children, iron deficiency can cause developmental problems, and in school-age children, iron deficiency may impair cognition.

Diagnosis

The hallmarks of iron deficiency anemia are (1) the presence of microcytic, hypochromic erythrocytes, and (2) the absence of hemosiderin (aggregated fer-

ritin) in bone marrow. Additional laboratory data that can help confirm a diagnosis include reduced RBC count, reduced reticulocyte hemoglobin content, reduced hemoglobin and hematocrit values, reduced serum iron content, and increased serum iron-binding capacity (IBC).*

When a diagnosis of iron deficiency anemia is made, it is imperative that the underlying cause be determined. This is especially true when the suspected cause is GI-related blood loss. Why? Because GI blood loss may be indicative of peptic ulcer disease or GI cancer, conditions that demand immediate treatment.

* Serum IBC measures iron binding by transferrin. An *increase* in IBC indicates an increase in the amount of transferrin that is *not* carrying any iron, and hence signals reduced iron availability.

Oral Iron Preparations I: Iron Salts

Three oral iron salts are available: ferrous sulfate, ferrous gluconate, and ferrous fumarate. All three are equally effective, and with all three, GI disturbances are the major adverse effect.

Ferrous Sulfate

Ferrous sulfate is the least expensive oral iron preparation and the standard against which the others are measured. Accordingly, ferrous sulfate will be our prototype for the group.

Indications.

Ferrous sulfate is the drug of choice for treating iron deficiency anemia. It is also the preferred drug for *preventing* deficiency when iron needs cannot be met by diet alone (eg, during pregnancy or chronic blood loss).

Adverse Effects.

GI Disturbances.

The most significant adverse effects involve the GI tract. These effects, which are dose dependent, include nausea, pyrosis (heartburn), bloating, constipation, and diarrhea. Gastrointestinal reactions are most intense during initial therapy, and become less disturbing with continued drug use. Because of their

GI effects, oral iron preparations can aggravate peptic ulcers, regional enteritis, and ulcerative colitis. Accordingly, patients with these disorders should not take iron by mouth. In addition to its other GI effects, oral iron may impart a dark green or black color to stools. This effect is harmless and should not be interpreted as a sign of bleeding.

Staining of Teeth

Liquid iron preparations can stain the teeth. This can be prevented by (1) diluting liquid preparations with juice or water, (2) administering the iron through a straw or with a dropper, and (3) rinsing the mouth after administration.

Toxicity.

Iron in large amounts is toxic. Poisoning is almost always the result of accidental or intentional overdose, not from therapeutic doses. Death from iron ingestion is rare in adults. By contrast, in young children, iron-containing products are a leading cause of poisoning fatalities. For children, the lethal dose of elemental iron is 2 to 10 gm. To reduce the risk of pediatric poisoning, iron should be stored in childproof containers and kept out of reach.

Symptoms.

The effects of iron poisoning are complex. Early reactions include nausea, vomiting, diarrhea, and shock. These are followed by acidosis, gastric necrosis, hepatic failure, pulmonary edema, and vasomotor collapse.

Diagnosis and Treatment.

With rapid diagnosis and treatment, mortality from iron poisoning is low (about 1%). Serum iron should be measured and the intestine x-rayed to determine if unabsorbed tablets are present. Gastric lavage will remove iron from the stomach. Acidosis and shock should be treated as required.

If the plasma level of iron is high (above 350 to 500 mcg/dL), it should be lowered with parenteral *deferoxamine* [Desferal]. A new oral drug—*deferasirox* [Exjade]—is indicated for patients with chronic iron overload caused by blood transfusions. Both agents—deferoxamine and deferasirox—adsorb iron and

thereby prevent toxic effects. The pharmacology of these drugs is discussed in Chapter 108 (Management of Poisoning).

Drug Interactions.

Interaction of iron with other drugs can alter the absorption of iron, the other drug, or both. *Antacids* reduce the absorption of iron. Coadministration of iron with tetracyclines decreases absorption of both. *Ascorbic acid* (vitamin C) promotes iron absorption but also increases its adverse effects. Accordingly, attempts to enhance iron uptake by combining iron with ascorbic acid offer no advantage over a simple increase in iron dosage.

Formulations.

Ferrous sulfate is available in several formulations. Sustained-release products (eg, Slow FE) are designed to reduce gastric disturbances. Unfortunately, although side effects may be lowered, these formulations have disadvantages. First, iron may be released at variable rates, causing variable and unpredictable absorption. Second, these preparations are expensive. Ordinary tablets do not share these drawbacks.

Dosage and Administration.

General Considerations.

Dosing with oral iron can be complicated in that oral iron salts differ from one another with regard to percentage of elemental iron (Table 54-2). Ferrous *sulfate,* for example, contains 20% iron by weight. In contrast, ferrous **gluconate** contains only 11.6% iron by weight. Consequently, in order to provide equivalent amounts of elemental iron, we must use different doses of these iron preparations. For example, if we want to provide 100 mg of elemental iron using ferrous *sulfate,* we need to administer a 500-mg dose. To provide this same amount of elemental iron using ferrous *fumarate,* the dose would be only 300 mg. In the discussion below, dosage values refer to milligrams of *elemental iron,* and not to milligrams of any particular iron preparation needed to provide that amount of elemental iron.

Iron Preparation	% Iron (by weight)	Dose Providing 100 mg Iron
Iron Salts		
Ferrous sulfate	20	500 mg
Ferrous sulfate (dried)	~30	330 mg
Ferrous fumarate	33	300 mg
Ferrous gluconate	11.6	860 mg
Elemental Iron		
Carbonyl iron	100	100 mg

TABLE 54-2 Oral Iron Preparations

Food affects therapy in two ways. First, food helps protect against iron-induced GI distress. Second, food decreases iron absorption by 50% to 70%. Hence, we have a dilemma: *Absorption is best* when iron is taken *between meals*, but *side effects are lowest* when iron is taken *with meals*. As a rule, iron should be administered between meals, thereby maximizing absorption. If necessary, the dosage can be lowered to render GI effects more acceptable.

For two reasons, it may be desirable to take iron *with* food during *initial* therapy. First, since the GI effects of iron are most intense when treatment commences, the salving effects of food can be especially beneficial. Second, by reducing GI discomfort during the early phase of therapy, administration with food can help promote adherence.

Use in Iron Deficiency Anemia

Dosing with oral iron represents a compromise between a desire to replenish lost iron rapidly and a desire to keep GI effects to a minimum. For most adults, this compromise can best be achieved by giving 65 mg 3 times a day, yielding a total daily dose of about 200 mg. Since there is a ceiling to intestinal absorption of iron, doses above this amount provide only a modest increase in therapeutic effect. On the other hand, at dosages greater than 200 mg/day, GI disturbances become disproportionately high. Hence, elevation of the daily dosage above 200 mg would augment adverse effects without offering a signi-

ficant increase in benefits. When treating iron deficiency in infants and children, a typical dosage is 5 mg/kg/day administered in three or four divided doses.

Timing of administration is important: Doses should be spaced evenly throughout the day. This schedule provides the bone marrow with a continuous iron supply, thereby maximizing RBC production.

Duration of therapy is determined by the therapeutic objective. If correction of anemia is the sole objective, a few months of therapy is sufficient. However, if the objective also includes replenishing ferritin, treatment must continue 4 to 6 months longer. It should be noted, however, that drugs are usually unnecessary for ferritin replenishment; in most cases, diet alone can do the job. Accordingly, once anemia has been corrected, pharmaceutical iron can usually be discontinued.

Prophylactic Use

Pregnant women are the principal candidates for prophylactic therapy. A total daily dose of 30 mg, taken between meals, is recommended. Other candidates include infants, children, and women experiencing menorrhagia.

Ferrous Gluconate and Ferrous Fumarate

In addition to ferrous sulfate, two other oral iron salts are available: ferrous gluconate [Fergon] and ferrous fumarate [Ferro-Sequels, others]. Except for differences in percentage of iron content (see Table 54-2), all of these preparations are equivalent. Hence, when dosage is adjusted to provide equal amounts of elemental iron, ferrous gluconate and ferrous fumarate produce pharmacologic effects identical to those of ferrous sulfate. All three agents produce equivalent therapeutic responses, and all three cause the same degree of GI distress. Patients who fail to respond to one will not respond to the others. Patients who cannot tolerate the GI effects of one agent will find the others intolerable too.

Oral Iron Preparations II: Carbonyl Iron

Carbonyl iron is pure, elemental iron in the form of microparticles. Because of these microparticles, the iron has good bioavailability. Therapeutic efficacy

of carbonyl iron equals that of the iron salts. Carbonyl iron is reputed to be less toxic than the iron salts, and hence should pose less risk to children in the event of poisoning. Four formulations are available: (1) 45-mg tablets, marketed as *Feosol*; (2) 65-mg tablets, marketed as *Ircon*; (3) 15-mg chewable tablets, marketed as *Icar*; and (4) a suspension (15 mg/1.25 mL), also marketed as *Icar*. Because these products contain 100% iron, rather than an iron salt, there should be no confusion about dosage: 100 mg of either product provides 100 mg of elemental iron. The usual dosage is 50 mg 3 times a day.

Parenteral Iron I: Iron Dextran

Iron dextran [INFeD, DexFerrum] is the most frequently used parenteral iron preparation. The drug is a complex consisting of ferric hydroxide and dextrans (polymers of glucose). The rate of response to parenteral iron is equal to that of oral iron. Iron dextran is dangerous—fatal anaphylactic reactions have occurred—and hence should be used only when circumstances demand.

Indications

Iron dextran is reserved for patients with a clear diagnosis of iron deficiency and for whom oral iron is either ineffective or intolerable. Primary candidates for parenteral iron are patients who, because of intestinal disease, are unable to absorb iron taken orally. Iron dextran is also indicated when blood loss is so great (500 to 1000 mL/wk) that oral iron cannot be absorbed fast enough to meet hematopoietic needs. Parenteral iron may also be employed when there is concern that oral iron might exacerbate pre-existing disease of the stomach or bowel. Lastly, parenteral iron can be given to the rare patient for whom the GI effects of oral iron are intolerable.

Adverse Effects

Anaphylactic Reactions.

Potentially fatal anaphylaxis is the most serious adverse effect. These reactions are triggered by dextran in the product, not by the iron. Although anaphylactic reactions are rare, their possibility demands that iron dextran be used only when clearly required. Whenever iron dextran is administered, in-

jectable epinephrine and facilities for resuscitation should be at hand. Furthermore, each full dose should be preceded by a small test dose.

Other Adverse Effects.

Hypotension is common in patients receiving parenteral iron. In addition, iron dextran can cause headache, fever, urticaria, and arthralgia. More serious reactions—circulatory failure and cardiac arrest—may also occur. When administered IM, iron dextran can cause persistent pain and prolonged, localized discoloration. Very rarely, tumors develop at sites of IM injection. Intravenous administration may result in lymphadenopathy and phlebitis.

Preparations, Dosage, and Administration

Preparations.

Iron dextran [INFeD, DexFerrum] is available in single-dose vials (1 and 2 mL) that contain 50 mg/mL of elemental iron.

Dosage.

Dosage determination is complex. Dosage depends on the degree of anemia, the weight of the patient, and the presence of persistent bleeding. For patients with iron deficiency anemia who are not losing blood, the equation in Figure 54-3 provides a guideline for estimating total iron dosage.

$$\text{mg iron} = 0.66 \times \text{kg body weight} \times \left(100 - \frac{\text{hemoglobin value in g/dL}}{14.8}\right)$$

Figure 54-3 Formula for estimating total dosage of parenteral iron dextran.

Administration.

Iron dextran may be administered IM or IV. Intravenous administration is preferred. This route is just as effective as IM administration but causes fewer anaphylactic reactions and other adverse effects.

Intravenous.

To minimize anaphylactic reactions, intravenous iron dextran should be administered by the following protocol: (1) administer a small test dose (25 mg over 5 minutes) and observe the patient for at least 15 minutes; (2) if the test dose appears safe, slowly administer a larger dose (500 mg over a 10- to 15-minute interval); and (3) if the 500-mg dose is uneventful, additional doses may be given as needed.

Intramuscular.

Intramuscular iron dextran has significant drawbacks and should be avoided. Disadvantages include persistent pain and discoloration at the injection site, possible development of tumors, and a greater risk of anaphylaxis. When IM administration must be performed, iron dextran should be injected deep into each buttock using the Z-track technique. (Z-track injection keeps the iron dextran deep in the muscle, thereby minimizing leakage and surface discoloration.) As with IV iron dextran, a small test dose should precede the full therapeutic dose.

Parenteral Iron II: Sodium–Ferric Gluconate Complex and Iron Sucrose

Iron sucrose and sodium–ferric gluconate complex (SFGC) represent alternatives to iron dextran for parenteral iron therapy. With both drugs, the risk of anaphylaxis is very low, and hence there is much less need for giving test doses. As a result, both drugs are more convenient than iron dextran. Indications for these drugs are limited to treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).

Sodium–Ferric Gluconate Complex

SFGC, sold under the trade name *Ferrlecit*, is a parenteral iron product indicated for iron deficiency anemia in patients with CKD who are undergoing chronic hemodialysis. The drug is always used in conjunction with erythropoietin, an agent that stimulates RBC production (see Chapter 55). SFGC can cause transient flushing and hypotension, associated with lightheadedness, malaise, fatigue, weakness, and severe pain in the chest, back, flanks, or groin. This reaction can be minimized by infusing the drug slowly. In contrast to iron dextran, SFGC poses little risk of anaphylaxis. Accordingly, *repeated* test doses are unnecessary—although a test dose *is* required the first time the drug is used.

SFGC is supplied in 5-mL ampules that contain 62.5 mg of elemental iron. Dilution is not required (but may be done) before the infusion. For most patients, a single dose consists of 125 mg (contents of 2 ampules) infused slowly (over 10 minutes or more). The typical patient requires a cumulative dose of 1 gm (eight 125-mg infusions on separate days). A small test dose (25 mg infused over 60 minutes) should precede the first full dose. Every time the drug is administered, facilities for cardiopulmonary resuscitation should be immediately available.

Iron Sucrose

Like SFGC, iron sucrose [Venofer] is a parenteral form of iron indicated for iron deficiency anemia in patients with CKD. However, in contrast to SFGC, whose indications are limited to CKD patients undergoing hemodialysis in conjunction with erythropoietin therapy, iron sucrose is indicated for a broader range of CKD patients, specifically

- Non–dialysis-dependent (NDD) patients receiving erythropoietin
- NDD patients *not* receiving erythropoietin
- Hemodialysis-dependent (HDD) patients receiving erythropoietin
- Peritoneal dialysis–dependent (PDD) patients receiving erythropoietin

The most common adverse effects of iron sucrose are hypotension (36%) and cramps (23%). The drug has also been associated with heart failure, sepsis, and taste perversion. Life-threatening hypersensitivity reactions are very rare: No cases were observed during clinical trials, and only 27 cases (out of 450,000 patients) were reported during postmarketing surveillance. Nonetheless, facilities for cardiopulmonary resuscitation should be available during administration. However, in contrast to iron dextran, test doses are not needed.

Iron sucrose is supplied in 5-mL single-dose vials that contain 100 mg of elemental iron. Administration is IV, either by (1) slow injection (1 mL/min) or (2) infusion (dilute iron sucrose in up to 100 mL of 0.9% saline and infuse over 15 minutes or longer). Iron sucrose should not be mixed with other drugs or with peripheral nutrition solutions. All patients should receive a *total* dose of 1000 mg, but the dosing schedule and administration technique depend on the patient as follows:

- HDD patients—Give ten 100-mg doses during each of 10 consecutive dialysis sessions. Administer by slow IV injection or IV infusion.
- NDD patients—Give five 200-mg doses on separate occasions over a 14-day span. Administer by slow IV injection.
- PDD patients—Give two 300-mg doses 14 days apart, then one 400-mg dose 14 days later. Administer by slow IV infusion.

Guidelines for Treating Iron Deficiency

Assessment.

Prior to starting therapy, the cause of iron deficiency must be determined. Without this information, appropriate treatment is not possible. Potential causes of deficiency include pregnancy, bleeding, inadequate diet, and, rarely, reduced intestinal absorption.

The objective is to increase production of hemoglobin and erythrocytes. When therapy is successful, reticulocytes will increase within 4 to 7 days; within 1 week, increases in hemoglobin and the hematocrit will be apparent; and within 1 month, hemoglobin levels will rise by at least 2 gm/dL. If these responses fail to occur, the patient should be evaluated for (1) compliance, (2) continued bleeding, (3) inflammatory disease (which can interfere with hemoglobin production), and (4) malabsorption of oral iron.

Routes of Administration.

Iron preparations are available for oral, IV, and IM administration. Oral iron is preferred. Why? Because oral iron is safer than parenteral iron and just as effective. Parenteral iron should be used only when oral iron is ineffective or intolerable. Of the two parenteral routes, IV is safer and preferred.

Duration of Therapy.

Therapy with oral iron should be continued until hemoglobin levels become normal (about 15 gm/dL). This phase of treatment may require 1 to 2 months. After this, continued treatment can help replenish stores of ferritin. However, for most patients, dietary iron alone is sufficient.

Therapeutic Combinations.

As a rule, combinations of antianemic agents should be avoided. Combining oral iron with parenteral iron can lead to iron toxicity. Accordingly, use of oral iron should cease prior to giving iron injections. Combinations of iron with vitamin B*12* or folic acid should be avoided; as discussed in the following sections, these combinations can confuse interpretation of hematologic responses.

VITAMIN B*12* DEFICIENCY

The term *vitamin B12* refers to a group of compounds that have similar structures. These compounds are large molecules that contain an atom of cobalt. Because of the cobalt atom, members of the vitamin B*12* family are known as *cobalamins*.

The most prominent consequences of vitamin B*12* deficiency are *anemia* and *injury to the nervous system*. Anemia reverses rapidly following vitamin B*12* administration. Neurologic damage takes longer to repair and, in some cases, may never fully resolve. Additional effects of B*12* deficiency include GI disturbances and impaired production of white blood cells and platelets.

Biochemistry and Physiology of Vitamin B*12*

In order to understand the consequences of vitamin B*12* deficiency and the rationale behind therapy, we must first understand the normal biochemistry and physiology of B*12*. This information is reviewed below.

Metabolic Function

Vitamin B*12* is essential for synthesis of DNA, and hence is required for the growth and division of virtually all cells. The mechanism by which the vitamin influences DNA synthesis is depicted in Figure 54-4. As indicated, vitamin B*12* helps catalyze the conversion of folic acid to its active form. Active folic acid then participates in several reactions essential for DNA synthesis. Hence, *it is by permitting utilization of folic acid that vitamin B12 influences cell growth and division*—and it is the absence of usable folic acid that underlies the blood cell abnormalities seen during B*12* deficiency.

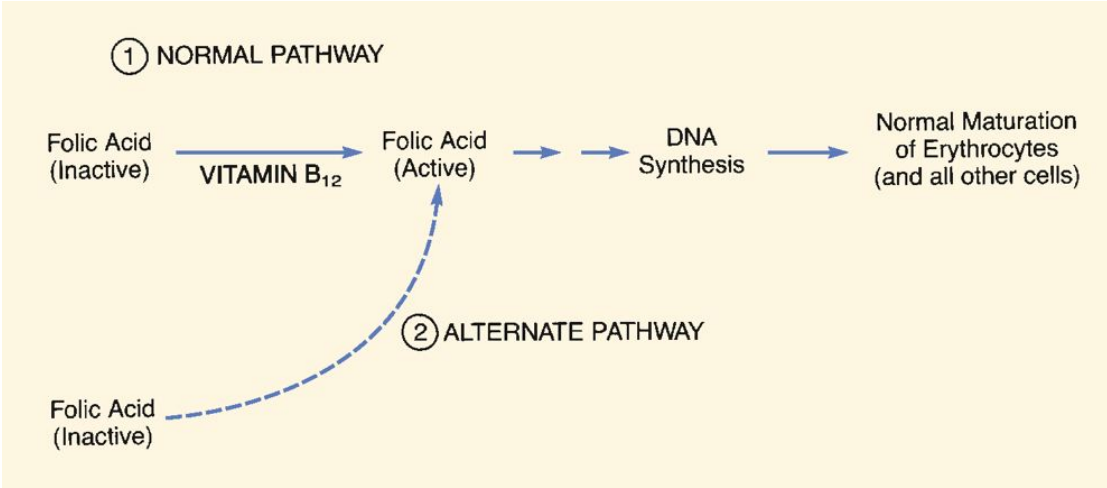

Figure 54-4 Relationship of folic acid and vitamin B12 to DNA synthesis and cell maturation. Folic acid requires activation to be of use. Normally, activation occurs via a vitamin B12–dependent pathway. However, when folic acid is present in large amounts, activation can occur via an alternate pathway, thereby bypassing the need for B12.

Fate in the Body

Absorption.

Efficient absorption of B***12*** requires *intrinsic factor*, a compound secreted by parietal cells of the stomach. Following ingestion, vitamin B***12*** forms a complex with intrinsic factor. Upon reaching the ileum, the B***12***–intrinsic factor complex interacts with specific receptors on the intestinal wall, causing the complex to be absorbed. In the absence of intrinsic factor, absorption of vitamin B***12*** is greatly reduced. However, about 1% of the amount present can still be absorbed by passive diffusion; no intrinsic factor is required.

Distribution and Storage.

Following absorption, the vitamin B***12***–intrinsic factor complex dissociates. Free B***12*** then binds to *transcobalamin II* for transport to tissues. Most vitamin B***12*** goes to the liver and is stored. Total body stores of B***12*** are minute, ranging from 2 to 3 mg by most estimates.

Elimination.

Excretion of vitamin B*12* takes place very slowly: Daily losses are about 0.1% of total body stores. Because B*12* is excreted so slowly, years are required for B*12* deficiency to develop—even with no replenishment of lost B*12* taking place.

Daily Requirements

Because very little vitamin B*12* is excreted, and because body stores are small to begin with, daily requirements for this vitamin are minuscule. The average adult needs about 2.4 mcg of B*12* per day. Children need even less.

Dietary Sources

The ability to biosynthesize vitamin B*12* is limited to microorganisms; higher plants and animals can't make it. The microorganisms that make B*12* reside in the soil, sewage, and the intestines of humans and other animals. Unfortunately, vitamin B*12* produced in the human GI tract is unavailable for absorption. Consequently, humans must obtain the majority of their B*12* by consuming animal products. Liver and dairy products are especially good sources. Between 10% and 30% of adults over age 50 are unable to absorb vitamin B*12* found naturally in foods. Accordingly, these people should meet their requirements by consuming B*12*-fortified foods or a B*12*-containing vitamin supplement.

Vitamin B*12* Deficiency: Causes, Consequences, and Diagnosis

Causes

In the majority of cases, vitamin B*12* deficiency is the result of *impaired absorption*. Insufficient B*12* in the diet is rarely a cause of deficiency. Potential causes of poor absorption include (1) regional enteritis, (2) celiac disease (a malabsorption syndrome involving abnormalities in the intestinal villi), and (3) development of antibodies directed against the vitamin B*12*–intrinsic factor complex. In addition, because stomach acid is required to release vitamin B*12* from foods, it cannot be absorbed if acid secretion is significantly reduced, as often happens in the elderly and in those taking acid-suppressing drugs.

Most frequently, impaired absorption of vitamin B***12*** occurs secondary to a lack of intrinsic factor. The usual causes are atrophy of gastric parietal cells and surgery of the stomach (total gastric resection).

When vitamin B***12*** deficiency is caused by an absence of intrinsic factor, the resulting syndrome is called *pernicious anemia*—a term suggesting a highly destructive or fatal condition. Pernicious anemia is an old term that refers back to the days when, for most patients, vitamin B***12*** deficiency had no effective therapy. Hence, the condition was uniformly fatal. Today, vitamin B***12*** deficiency secondary to lack of intrinsic factor can be managed successfully. Hence, the label *pernicious* no longer bears its original ominous connotation.

Consequences

Many of the consequences of B***12*** deficiency result from disruption of DNA synthesis. The tissues affected most are those with a high proportion of cells undergoing growth and division. Accordingly, B***12*** deficiency has profound effects on the bone marrow (the site where blood cells are produced) and the epithelial cells lining the mouth and GI tract.

Megaloblastic Anemia.

The most conspicuous consequence of B***12*** deficiency is an anemia in which large numbers of *megaloblasts* (oversized erythroblasts) appear in the bone marrow, and in which *macrocytes* (oversized erythrocytes) appear in the blood. These strange cells are produced because of impaired DNA synthesis: lacking sufficient DNA, growing cells are unable to divide; hence, as erythroblasts mature and their division is prevented, oversized cells result. Most megaloblasts die within the bone marrow; only a few evolve into the macrocytes that can be seen in the blood. Because of these unusual cells, the anemia associated with vitamin B***12*** deficiency is often referred to as either *megaloblastic* or *macrocytic* anemia.

Severe anemia is the principal cause of mortality from B***12*** deficiency. Anemia produces peripheral and cerebral hypoxia. Heart failure and dysrhythmias are the most frequent cause of death.

It is important to note that the hematologic effects of vitamin B***12*** deficiency can be reversed with large doses of *folic acid*. As indicated in Figure 54-4, when

folic acid is present in large amounts, some of it can be activated by an alternate pathway that is independent of vitamin B*12*. This pathway bypasses the metabolic block caused by B*12* deficiency, thereby permitting DNA synthesis to proceed.

Neurologic Damage.

Deficiency of vitamin B*12* causes demyelination of neurons, primarily in the spinal cord and brain. A variety of signs and symptoms can result. Early manifestations include paresthesias (tingling, numbness) of the hands and feet and a reduction in deep tendon reflexes. Late-developing responses include loss of memory, mood changes, hallucinations, and psychosis. If vitamin B*12* deficiency is prolonged, neurologic damage can become permanent.

The precise mechanism by which B*12* deficiency results in neuronal damage is unknown. We do know, however, that *neuronal damage is not related to effects on folic acid or DNA*. That is, the mechanism that underlies neuronal damage is different from the mechanism that underlies disruption of hematopoiesis. Consequently, although administering large doses of folic acid can correct the hematologic consequences of B*12* deficiency, folic acid will not affect the neurologic picture.

Other Effects.

As noted, vitamin B*12* deficiency can adversely affect virtually all tissues in which a high proportion of cells are undergoing growth and division. Hence, in addition to disrupting the production of erythrocytes, lack of B*12* also prevents the bone marrow from making leukocytes (white blood cells) and thrombocytes (platelets). Loss of these blood elements can lead to infection and spontaneous bleeding. Disruption of DNA synthesis can also suppress division of the cells that form the epithelial lining of the mouth, stomach, and intestine, thereby causing oral ulceration and a variety of GI disturbances.

Diagnosis

When megaloblastic anemia occurs, it may be due to vitamin B*12* deficiency or other causes, especially a lack of folic acid. Hence, if therapy is to be appropriate, a definitive diagnosis must be made. Two tests are particularly helpful. The first is obvious: measurement of plasma B*12* content. The second proced-

ure, known as the Schilling test, measures vitamin B*12* absorption. The combination of megaloblastic anemia plus low plasma vitamin B*12* plus evidence of B*12* malabsorption permits a clear diagnosis of vitamin B*12* deficiency.

Vitamin B*12* Preparations: Cyanocobalamin

Cyanocobalamin is a purified, crystalline form of vitamin B*12*. This compound is the drug of choice for all forms of B*12* deficiency.

Adverse Effects

Cyanocobalamin is generally devoid of serious adverse effects. One potential response, *hypokalemia*, may occur as a natural consequence of increased erythrocyte production. Erythrocytes incorporate significant amounts of potassium. Hence, as large numbers of new erythrocytes are produced, levels of free potassium may fall.

Preparations, Dosage, and Administration

Cyanocobalamin can be given orally, intranasally, and by IM or subQ injection. Most pharmacology texts, including prior editions of this one, will tell you that oral therapy is appropriate only for people who absorb B*12* well; all others (ie, those with impaired absorption) should use intranasal or parenteral therapy. However, this statement is not correct. Although it *is* true that various conditions—including lack of intrinsic factor, low gastric acidity, and regional enteritis—severely impair B*12* absorption, these conditions do not prevent absorption entirely. Hence, even people with impaired absorption can still be treated orally; the only catch is that doses must be very high. Is there any advantage to oral therapy compared with parenteral therapy? Yes. First, oral therapy is more comfortable (injections sometimes hurt). Second, oral therapy is more convenient (because it avoids regular trips to the physician for shots).

Oral.

Oral cyanocobalamin is appropriate for most people with mild to moderate B*12* deficiency, regardless of the cause. (The principal exception is patients with severe neurologic involvement.) If the B*12* deficiency is due to malabsorption, dosages must be high—ranging between 1000 and 10,000 mcg/day.

To ensure that absorption has been adequate, B*12* levels should be measured periodically.

In addition to treating patients with B*12* deficiency, oral cyanocobalamin can be used as a dietary supplement. The usual dosage is 6 mcg/day.

Three oral formulations are available: standard tablets (100, 500, 1000, and 5000 mg), sold as *Big Shot B-12*; sublingual tablets (1000 mg); and lozenges (50, 100, 250, and 500 mg).

Parenteral.

Parenteral cyanocobalamin [Crystamine, Cyanoject, others] can be administered by *IM or deep subQ injection. Cyanocobalamin must NOT be given IV*. Intramuscular and subQ injections are generally well tolerated, although they occasionally cause pain and other local reactions.

Parenteral administration is indicated for patients with impaired B*12* absorption—although most of these people can be treated with oral cyanocobalamin instead. If the cause of malabsorption is irreversible (eg, parietal cell atrophy, total gastrectomy), therapy must continue lifelong. A typical dosing schedule for megaloblastic anemia is 30 mcg/day for 5 to 10 days followed by 100 to 200 mcg monthly until remission is complete. After anemia has been corrected, doses of 100 mcg are administered monthly for life.

Intranasal.

Intranasal cyanocobalamin [Nascobal, CaloMist] represents a convenient alternative to IM or subQ injection for people who cannot take cyanocobalamin by mouth. Efficacy of intranasal cyanocobalamin has not been determined for patients with nasal congestion, allergic rhinitis, or upper respiratory infections. Accordingly, until more is known, patients with these disorders should not use this formulation until symptoms subside. Hot foods or liquids can increase nasal secretions, which might flush cyanocobalamin gel from the nose. Accordingly, hot foods should not be eaten within 1 hour before or 1 hour after administering the drug.

Intranasal cyanocobalamin is available in two metered-dose formulations: Nascobal and CaloMist. Nascobal delivers 500 mg/actuation; CaloMist delivers only 25 mcg/actuation. The dosing schedule with Nascobal is 500 mcg in one

nostril once a week. The dosing schedule with CaloMist is 25 mcg in each nostril once a day.

Guidelines for Treating Vitamin B*12* Deficiency

Route of B*12* Administration.

As discussed above, oral therapy can be used for most patients, including those with conditions that impair B*12* absorption. The major exception is patients with severe neurologic deficits caused by B*12* deficiency. For these people, parenteral cyanocobalamin is indicated.

Treatment of Moderate B*12* Deficiency.

The primary manifestations of moderate B*12* deficiency are megaloblasts in the bone marrow and macrocytes in peripheral blood. Moderate deficiency does not cause leukopenia, thrombocytopenia, or neurologic complications. Moderate deficiency can be managed with vitamin B*12* alone; no other measures are required.

Treatment of Severe B*12* Deficiency.

Severe deficiency produces multiple effects, all of which must be attended to. Unlike mild deficiency, in which erythrocytes are the only blood cells affected, severe deficiency disrupts production of all blood cells. Loss of erythrocytes leads to hypoxia, cerebrovascular insufficiency, and heart failure. Loss of leukocytes encourages infection, and loss of thrombocytes promotes bleeding. In addition to causing serious hematologic deficits, severe B*12* deficiency has adverse effects on the nervous system and GI tract.

Treatment of severe deficiency involves the following: (1) IM injection of vitamin B*12* and folic acid (the folic acid accelerates recovery of hematologic deficits); (2) administration of 2 to 3 units of packed RBCs (to correct anemia quickly); (3) transfusion of platelets (to suppress bleeding); and (4) therapy with antibiotics if infection has developed.

Following treatment with vitamin B*12* plus folic acid, recovery from anemia occurs quickly. Within 1 to 2 days, megaloblasts disappear from the bone marrow; within 3 to 5 days, reticulocyte counts become elevated; by day 10, the

hematocrit begins to rise; and within 14 to 21 days, the hematocrit becomes normal.

Recovery from neurologic damage is slow and depends on how long the damage had been present. When deficits have been present for only 2 to 3 months, recovery is relatively fast. When deficits have been present for many months or for years, recovery is slow: Months may pass before any improvement is apparent, and complete recovery may never occur.

Long-Term Treatment.

For patients who lack intrinsic factor or who suffer from some other permanent cause of vitamin B***12*** malabsorption, lifelong treatment is required. Traditional therapy consists of monthly IM or subQ injections. However, *large* daily oral doses can be just as effective, as can intranasal doses (weekly with Nascobal or daily with CaloMist). During prolonged therapy, treatment should be periodically assessed: plasma levels of vitamin B***12*** should be measured every 3 to 6 months, blood samples should be examined for the return of macrocytes, and blood counts should be performed.

Potential Hazard of Folic Acid.

Treatment with folic acid can exacerbate the neurologic consequences of B***12*** deficiency. Recall that folic acid, by itself, can reverse the *hematologic* effects of B***12*** deficiency—but will not alleviate *neurologic* deficits. Hence, by correcting the most obvious manifestation of B***12*** deficiency (anemia), folic acid can mask the fact that deficiency of B***12*** still exists. As a result, *use of folic acid can lead to undertreatment with B**12** itself*, and can thereby permit neurologic damage to progress. Clearly, folic acid is not a substitute for vitamin B***12***, and vitamin B***12*** deficiency should never be treated with folic acid alone. Whenever folic acid is employed during treatment of vitamin B***12*** deficiency, extra care must be taken to ensure that B***12*** dosage is adequate.

FOLIC ACID DEFICIENCY

In one respect, folic acid deficiency is identical to vitamin B***12*** deficiency: In both states, *megaloblastic anemia* is the most conspicuous pathology. However, in other important ways, folic acid deficiency and vitamin B***12*** deficiency are dissimilar (Table 54-3 provides a summary). Consequently, when a patient

presents with megaloblastic anemia, it is essential to determine whether the cause is deficiency of folic acid, vitamin B12, or both.

	Vitamin B_{12} Deficiency	Folic Acid Deficiency
Usual cause	Vitamin B_{12} malabsorption from lack of intrinsic factor	Low dietary folic acid
Primary hematologic effect	Megaloblastic anemia	Megaloblastic anemia
Neurologic effect	Damage to brain and spinal cord	None*
Diagnosis	Low plasma vitamin B_{12}; low B_{12} absorption (Schilling test)	Low plasma folic acid
Treatment (usual route)	Cyanocobalamin (IM)	Folic acid (PO)
Usual duration of therapy	Lifelong	Short term

TABLE 54-3 Vitamin B12 Deficiency Versus Folic Acid Deficiency

* Folic acid deficiency in pregnancy can cause neural tube defects in the fetus.

Physiology and Biochemistry of Folic Acid

Metabolic Function

As noted when we discussed vitamin B12, folic acid (also known as *folate*) is an essential factor for DNA synthesis. Without folic acid, DNA replication and cell division cannot proceed.

In order to be usable, dietary folic acid must first be converted to an active form. Under normal conditions, activation occurs through a pathway employing vitamin B12 (see Fig. 54-4). However, when large amounts of folate are ingested, some can be activated through an alternate pathway—one that does not employ vitamin B12. Hence, even in the absence of vitamin B12, if suffi-

cient amounts of folic acid are consumed, active folate will be available for DNA synthesis.

Fate in the Body

Folic acid is absorbed in the early segment of the small intestine, and then is transported to the liver and other tissues, where it is either used or stored.

Folic acid in the liver undergoes extensive enterohepatic recirculation. That is, folate from the liver is excreted into the intestine, after which it is reabsorbed and then returned to the liver through the hepatic-portal circulation. This enterohepatic recirculation helps salvage up to 200 mcg of folate per day. Accordingly, the process is an important way to maintain folic acid stores.

In contrast to vitamin B***12***, folic acid is not conserved rigidly: every day, significant amounts are excreted. As a result, if intake of folic acid were to cease, signs of deficiency would develop rapidly (within weeks if body stores were already low).

Daily Requirements

The RDA of folic acid is now 400 mcg for adult males and females. RDAs during pregnancy and lactation are 600 mcg and 500 mcg, respectively. Individuals with malabsorption syndromes (eg, tropical sprue) may require as much as 2000 mcg (2 mg) per day; at these high doses, folate will be taken up in sufficient quantity despite impaired absorption.

Dietary Sources

Folic acid is present in all foods. Good sources include liver, peas, lentils, oranges, whole-wheat products, asparagus, beets, broccoli, and spinach. Also, many grain products (eg, cereals, bread, pasta, rice, flour) are now fortified with folic acid.

Folic Acid Deficiency: Causes, Consequences, and Diagnosis

Causes

Folic acid deficiency has two principal causes: (1) poor diet (especially as seen in alcoholics), and (2) malabsorption secondary to intestinal disease. Rarely, certain drugs may cause folate deficiency.

Alcoholism.

Alcoholism, either acute or chronic, may be the most common cause of folate deficiency. Deficiency results for two reasons: (1) insufficient folic acid in the diet and (2) derangement of enterohepatic recirculation secondary to alcohol-induced injury to the liver. Fortunately, with improved diet and reduced alcohol consumption, alcohol-related folate deficiency can often be reversed.

Sprue.

Sprue is an intestinal malabsorption syndrome that decreases folic acid uptake. Since sprue does not block folate absorption entirely, deficiency can be corrected by giving large doses of folic acid orally.

Consequences

All People.

With the important exception that folic acid deficiency does not injure the nervous system, the effects of folate deficiency are identical to those of vitamin B***12*** deficiency. Hence, as with B***12*** deficiency, the most prominent consequence of folate deficiency is *megaloblastic anemia*. In addition, like B***12*** deficiency, lack of folic acid may result in leukopenia, thrombocytopenia, and injury to the oral and GI mucosa. Since we already noted that many of the consequences of vitamin B***12*** deficiency result from depriving cells of active folic acid, the similarities between folate deficiency and vitamin B***12*** deficiency should be no surprise.

The Developing Fetus.

Folic acid deficiency *very early* in pregnancy can cause neural tube defects (eg, spina bifida, anencephaly). Accordingly, it is imperative that all women of reproductive age ensure adequate folate levels *before* pregnancy occurs. Because folate present naturally in foods has relatively low bioavailability, women capable of becoming pregnant should consume 400 mcg/day of *synthetic* folate

(either from fortified foods, supplements, or both). If pregnancy occurs, folate intake should increase to 600 mcg/day.

Other Consequences.

As discussed in Chapter 80 (Vitamins), folic acid deficiency may increase the risk of colorectal cancer and atherosclerosis.

Diagnosis

When patients present with megaloblastic anemia, it is essential to distinguish between folic acid deficiency and vitamin B***12*** deficiency as the cause. How? By comparing plasma levels of folate and vitamin B***12***. If folic acid levels are low and vitamin B***12*** levels are normal, a diagnosis of folic acid deficiency is suggested. Conversely, if folate levels are normal and B***12*** is low, B***12*** deficiency would be the likely diagnosis. A decision against folic acid deficiency would be strengthened if neurologic deficits were observed.

Folic Acid Preparations

Nomenclature

Nomenclature regarding folic acid preparations can be confusing and deserves comment. Two forms of folic acid are available. One form is inactive as administered (but undergoes activation after being absorbed). The second form is active to start with. Both forms have several generic names: the *inactive* form is referred to as *folacin, folate, pteroylglutamic acid*, or *folic acid*; the *active* form is referred to as *leucovorin calcium, folinic acid*, or *citrovorum factor*. The inactive form is by far the most commonly used preparation.

Folic Acid (Pteroylglutamic Acid)

Chemistry.

Folic acid is inactive as administered and cannot support DNA synthesis. Activation takes place rapidly following absorption.

Indications.

Folic acid has three uses: (1) treatment of megaloblastic anemia resulting from folic acid deficiency; (2) prophylaxis of folate deficiency, especially during pregnancy and lactation; and (3) initial treatment of severe megaloblastic anemia resulting from vitamin B***12*** deficiency.

Adverse Effects.

Oral folic acid is nontoxic. Massive dosages (eg, as much as 15 mg/day) have been taken with no ill effects.

Warning.

If taken in sufficiently large doses, folic acid can correct the hematologic consequences of vitamin B***12*** deficiency, thereby masking the fact that a deficiency in vitamin B***12*** still exists. Since folic acid will not prevent the neurologic consequences of B***12*** deficiency (despite correcting the hematologic picture), this masking effect may allow the development of irreversible damage to the nervous system. To reduce the chances of this problem, folate should not be used indiscriminately: Unless specifically indicated, consumption of folic acid should not exceed 1000 mcg/day. Furthermore, whenever folic acid is given to patients known to have a deficiency in vitamin B***12***, special care must be taken to ensure that the vitamin B***12*** dosage is adequate.

Formulations and Routes of Administration.

Folic acid is available in tablets (0.4, 0.8, and 1 mg) for oral use and in a 5-mg/mL solution [Folvite] for IM, IV, or subQ injection. As a rule, injections are reserved for patients with severely impaired GI absorption.

Dosage.

For treatment of folate-deficient megaloblastic anemia in adults, the usual oral dosage is 1000 to 2000 mcg/day. Once symptoms have resolved, the maintenance dosage is 400 mcg/day. For prophylaxis during pregnancy and lactation, doses up to 1000 mcg/day may be used.

Leucovorin Calcium (Folinic Acid)

Leucovorin calcium is an active form of folic acid used primarily as an adjunct to cancer chemotherapy (see Chapter 101). Leucovorin is not used routinely

to correct folic acid deficiency. Why? Because folic acid is just as effective and cheaper.

Guidelines for Treating Folic Acid Deficiency

Choice of Treatment Modality.

The modality for treating folic acid deficiency should be matched with the cause. If folic acid deficiency is due to poor diet, the deficiency should be corrected by dietary measures—not with drugs (except for women who may become pregnant). Ingestion of one serving of a fresh vegetable or one glass of fruit juice a day will often suffice. In contrast, when folate deficiency is the result of malabsorption, diet alone cannot correct the deficiency, and hence pharmaceutical folate will be needed.

Route of Administration.

Oral administration is preferred for most patients. Unlike vitamin B***12***, folic acid is rarely administered by injection. Even in the presence of intestinal disease, oral folic acid can be effective, providing the dosage is big enough.

Prophylactic Use of Folic Acid.

Folic acid should be taken prophylactically only when clearly appropriate. The principal indications are pregnancy and lactation. Since folic acid may mask vitamin B***12*** deficiency, indiscriminate use of folate should be avoided.

Treatment of Severe Deficiency.

Folic acid deficiency can produce severe megaloblastic anemia. To ensure a rapid response, therapy should be initiated with an IM injection of folic acid and vitamin B***12***. (Because of the metabolic interrelationship between folic acid and vitamin B***12***, combining these agents accelerates recovery.) After the initial injection, treatment should be continued with folic acid alone. Folic acid should be given orally in a dosage of 1000 to 2000 mcg/day for 1 to 2 weeks. After this, maintenance doses of 400 mcg/day may be required.

Therapy is evaluated by monitoring the hematologic picture. When treatment has been effective, megaloblasts will disappear from the bone marrow within

48 hours; the reticulocyte count will increase measurably within 2 to 3 days; and the hematocrit will begin to rise in the second week.

KEY POINTS

- The principal cause of iron deficiency is increased iron demand secondary to (1) maternal and fetal blood volume expansion during pregnancy; (2) blood volume expansion during infancy and early childhood; or (3) chronic blood loss, usually of GI or uterine origin.
- The major consequence of iron deficiency is microcytic, hypochromic anemia.
- Ferrous sulfate, given PO, is the drug of choice for iron deficiency.
- Iron-deficient patients who cannot tolerate or absorb oral ferrous salts are treated with parenteral iron—usually iron dextran administered IV.
- The major adverse effects of ferrous sulfate are GI disturbances. These are best managed by reducing the dosage (rather than by administering the drug with food, which would greatly reduce absorption).
- Parenteral iron dextran carries a significant risk of fatal anaphylactic reactions. The risk is much lower with other parenteral iron products (eg, iron sucrose).
- The principal cause of vitamin B***12*** deficiency is impaired absorption secondary to lack of intrinsic factor.
- The principal consequences of B***12*** deficiency are megaloblastic (macrocytic) anemia and neurologic injury.
- Vitamin B***12*** deficiency caused by malabsorption is treated lifelong with cyanocobalamin. Traditional treatment consists of IM injections administered monthly. However, large oral doses administered daily are also effective, as are intranasal doses (administered weekly with Nascobal or daily with CaloMist).
- For initial therapy of severe vitamin B***12*** deficiency, parenteral folic acid is given along with cyanocobalamin.

- When folic acid is combined with vitamin B*12* to treat B*12* deficiency, it is essential that the dosage of B*12* be adequate. Why? Because folic acid can mask continued B*12* deficiency (by improving the hematologic picture), while allowing the neurologic consequences of B*12* deficiency to progress.
- The principal causes of folic acid deficiency are poor diet (usually in alcoholics) and malabsorption secondary to intestinal disease.
- The principal consequences of folic acid deficiency are megaloblastic anemia and neural tube defects in the developing fetus.
- To prevent neural tube defects, all women who may become pregnant should ingest 400 mcg of folate daily, in the form of folate supplements or folate-fortified foods.

Summary of Major Nursing Implications*

IRON PREPARATIONS

Carbonyl iron

Ferrous fumarate

Ferrous gluconate

Ferrous sulfate

Iron dextran

Iron sucrose

Sodium–ferric gluconate complex (SFGC)

Except where indicated, the implications summarized below apply to all iron preparations.

Preadministration Assessment

Therapeutic Goal

Prevention or treatment of iron deficiency anemias.

Baseline Data

Prior to treatment, assess the degree of anemia. Fatigue, listlessness, and pallor indicate mild anemia; dyspnea, tachycardia, and angina suggest severe anemia. Laboratory findings indicative of anemia are subnormal hemoglobin levels, subnormal hematocrit, subnormal hemosiderin in bone marrow, and the presence of microcytic, hypochromic erythrocytes.

The cause of iron deficiency (eg, pregnancy, occult bleeding, menorrhagia, inadequate diet, malabsorption) must be determined.

Identifying High-Risk Patients

All iron preparations are *contraindicated* for patients with anemias other than iron deficiency anemia.

Parenteral preparations are *contraindicated* for patients who have had a severe allergic reaction to them in the past.

Use *oral* preparations with *caution* in patients with peptic ulcer disease, regional enteritis, and ulcerative colitis.

Implementation: Administration

Routes

Oral.

Ferrous sulfate, ferrous fumarate, ferrous gluconate, carbonyl iron.

Parenteral.

Iron dextran, SFGC, iron sucrose.

Oral Administration

Food reduces GI distress from oral iron but also greatly reduces absorption. **Instruct patients to administer oral iron between meals to maximize uptake.** If GI distress is intolerable, the dosage may be reduced. If absolutely necessary, oral iron may be administered with meals.

Liquid preparations can stain the teeth. **Instruct patients to dilute liquid preparations with juice or water, administer them through a straw, and rinse the mouth after.**

Warn patients not to crush or chew sustained-release preparations.

Warn patients against ingesting iron salts together with antacids or tetracyclines.

Inform patients that oral iron preparations differ and warn them against switching from one to another.

Parenteral Administration: Iron Dextran

Iron dextran may be given IV or IM. Intravenous administration is safer and preferred.

Intravenous.

To minimize anaphylactic reactions, follow this protocol: (1) Infuse 25 mg as a test dose and observe the patient for at least 15 minutes. (2) If the test dose appears safe, infuse 500 mg over 10 to 15 minutes. (3) If the 500-mg dose proves uneventful, give additional doses as needed.

Intramuscular.

Intramuscular injection can cause significant adverse reactions (anaphylaxis, persistent pain, localized discoloration, promotion of tumors) and is generally avoided. Make injections deep into each buttock using the Z-track technique. Give a 25-mg test dose and wait 1 hour before giving the full therapeutic dose.

Parenteral Administration: SFGC

To minimize adverse reactions, precede the first full dose with a test dose (25 mg infused IV over 60 minutes). Administer therapeutic doses by slow IV infusion (no faster than 12.5 mg/min).

Parenteral Administration: Iron Sucrose

Hemodialysis-Dependent Patients.

Administer iron sucrose directly into the dialysis line. Do not mix with other drugs or with parenteral nutrition solutions. Administer by either (1) slow injection (1 mL/min) or (2) infusion (dilute iron sucrose in up to 100 mL of 0.9% saline and infuse over 15 minutes or longer).

Peritoneal Dialysis–Dependent Patients.

Administer by slow infusion.

Non–Dialysis-Dependent Patients.

Administer by slow injection.

Implementation: Measures to Enhance Therapeutic Effects

If the diet is poor in iron, advise the patient to increase consumption of iron-rich foods (eg, liver, egg yolks, brewer's yeast, wheat germ, muscle meats, fish, fowl).

Ongoing Evaluation and Interventions

Evaluating Therapeutic Responses

Evaluate treatment by monitoring hematologic status. Reticulocyte counts should increase within 4 to 7 days, hemoglobin content and the hematocrit should begin to rise within 1 week, and hemoglobin levels should rise by at least 2 gm/dL within 1 month. If these responses do not occur, evaluate the patient for adherence, persistent bleeding, inflammatory disease, and malabsorption.

Minimizing Adverse Effects

GI Disturbances.

Forewarn patients about possible GI reactions (nausea, vomiting, constipation, diarrhea) and inform them these will diminish over time. If GI distress is severe, the dosage may be reduced, or, if absolutely necessary, iron may be administered with food.

Inform patients that iron will impart a harmless dark green or black color to stools.

Anaphylactic Reactions.

Parenteral iron dextran (and, rarely, SFGC and iron sucrose) can cause potentially fatal anaphylaxis. Before giving parenteral iron, ensure that inject-

able epinephrine and facilities for resuscitation are immediately available. After administration, observe the patient for 60 minutes. Give test doses as described above. Precede all doses of iron dextran and the first dose of SFGC with a test dose; test doses are unnecessary with iron sucrose.

Managing Acute Toxicity.

Iron poisoning can be fatal to young children. **Instruct parents to store iron out of reach and in childproof containers.** If poisoning occurs, rapid treatment is imperative. Use gastric lavage to remove iron from the stomach. Administer deferoxamine if plasma levels of iron exceed 500 mcg/mL. Manage acidosis and shock as required.

CYANOCOBALAMIN (VITAMIN B*12*)

Preadministration Assessment

Therapeutic Goal

Correction of megaloblastic anemia and other sequelae of vitamin B*12* deficiency.

Baseline Data

Assess the extent of vitamin B*12* deficiency. Record signs and symptoms of anemia (eg, pallor, dyspnea, palpitations, fatigue). Determine the extent of neurologic damage. Assess GI involvement.

Baseline laboratory data include plasma vitamin B*12* levels, erythrocyte and reticulocyte counts, and hemoglobin and hematocrit values. Bone marrow may be examined for megaloblasts. A Schilling test may be ordered to assess vitamin B*12* absorption.

Identifying High-Risk Patients

Use with *caution* in patients receiving folic acid.

Implementation: Administration

Routes and Administration

Administration may be IM, subQ, oral, or intranasal. For most patients, lifelong treatment is required. Traditional therapy consists of IM or subQ injections administered monthly. However, treatment can be just as effective with large daily oral doses or with intranasal doses (administered weekly with Nascobal or daily with CaloMist). **Inform patients that intranasal doses should not be administered within 1 hour before or 1 hour after consuming hot foods or hot liquids.**

Implementation: Measures to Enhance Therapeutic Effects

Promoting Adherence

Patients with permanent impairment of B*12* absorption require lifelong B*12* therapy. To promote adherence, **educate patients about the nature of their condition and impress upon them the need for monthly injections, daily oral therapy, or daily or weekly intranasal therapy.** Schedule appointments for injections at convenient times.

Improving Diet

When B*12* deficiency is not due to impaired absorption, a change in diet may accelerate recovery. **Advise the patient to increase consumption of B*12*-rich foods (eg, muscle meats, dairy products).**

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Assess for improvements in hematologic and neurologic status. Over a period of 2 to 3 weeks, megaloblasts should disappear, reticulocyte counts should rise, and the hematocrit should normalize. Neurologic damage may take months to improve; in some cases, full recovery may never occur.

For patients receiving long-term therapy, vitamin B*12* levels should be measured every 3 to 6 months, and blood counts should be performed.

Minimizing Adverse Effects

Hypokalemia may develop during the first days of therapy. Monitor serum potassium levels and observe the patient for signs of potassium insufficiency.

Teach patients the signs and symptoms of hypokalemia (eg, muscle weakness, irregular heartbeat) and instruct them to report these immediately.

Minimizing Adverse Interactions

Folic acid can mask hematologic symptoms of vitamin B*12* deficiency, resulting in undertreatment and progression of neurologic injury caused by low B*12*. When folic acid and cyanocobalamin are used concurrently, special care must be taken to ensure that the cyanocobalamin dosage is adequate.

FOLIC ACID (FOLACIN, FOLATE, PTEROYLGLUTAMIC ACID)

Preadministration Assessment

Therapeutic Goal

Folic acid is used for (1) treatment of megaloblastic anemia resulting from folic acid deficiency, (2) initial treatment of severe megaloblastic anemia resulting from vitamin B*12* deficiency, and (3) prevention of folic acid deficiency (especially during pregnancy).

Baseline Data

Assess the extent of folate deficiency. Record signs and symptoms of anemia (eg, pallor, dyspnea, palpitations, fatigue). Determine the extent of GI damage.

Baseline laboratory data include serum folate levels, erythrocyte and reticulocyte counts, and hemoglobin and hematocrit values. In addition, bone marrow may be evaluated for megaloblasts. To rule out vitamin B*12* deficiency, vitamin B*12* determinations and a Schilling test may be ordered.

Identifying High-Risk Patients

Folic acid is *contraindicated* for patients with pernicious anemia (except during the acute phase of treatment). Inappropriate use of folic acid by these patients can mask signs of vitamin B*12* deficiency, thereby allowing further neurologic deterioration.

Implementation: Administration

Routes

Oral, subQ, IV, and IM.

Oral administration is most common and preferred. Injections are employed only when intestinal absorption is severely impaired.

Implementation: Measures to Enhance Therapeutic Effects

Improving Diet

If the diet is deficient in folic acid, advise the patient to increase consumption of folate-rich foods (eg, green vegetables, liver). If alcoholism underlies dietary deficiency, counseling should be offered.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Monitor hematologic status. Within 2 weeks, megaloblasts should disappear, reticulocyte counts should increase, and the hematocrit should begin to rise.

55 Hematopoietic Growth Factors

Hematopoiesis is the process by which the body makes red blood cells, white blood cells, and platelets. The process is regulated in part by hematopoietic growth factors—naturally occurring hormones that stimulate the proliferation and differentiation of hematopoietic stem cells, and enhance function in the mature forms of those cells. In a laboratory setting, hematopoietic growth factors can cause stem cells to form colonies of mature blood cells. Because of this action, some hematopoietic growth factors are also known as *colony-stimulating factors*. Therapeutic applications of hematopoietic growth factors include (1) acceleration of neutrophil and platelet repopulation after cancer chemotherapy, (2) acceleration of bone marrow recovery after an autologous bone marrow transplantation (BMT), and (3) stimulation of erythrocyte production in patients with chronic renal failure (CRF).

The names used for the hematopoietic growth factors are a potential source of confusion. Why? Because each product has a biologic name, a generic name, and one or more proprietary (trade) names. The biologic, generic, and proprietary names for available products are listed in Table 55-1.

	Pharmacologic Names	
Biologic Name	**Generic Name**	**Trade Name**
Erythropoietic Growth Factors		
Erythropoietin	Darbepoetin alfa	Aranesp
	Epoetin alfa	Epogen, Procrit
	MPEG–epoetin beta*	Mircera
Leukopoietic Growth Factors		
Granulocyte colony-stimulating factor (G-CSF)	Filgrastim	Neupogen
	Pegfilgrastim	Neulasta
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Sargramostim	Leukine
Thrombopoietic Growth Factor		
Interleukin-11	Oprelvekin	Neumega

TABLE 55-1 Nomenclature for Hematopoietic Growth Factors

* MPEG–epoetin beta = methoxy polyethylene glycol–epoetin beta.

ERYTHROPOIETIC GROWTH FACTORS

Erythropoietic growth factors—also known as *erythropoiesis stimulating agents* or ESAs—stimulate production of erythrocytes (red blood cells, RBCs). Because they increase RBC production, ESAs represent an alternative to infusions for patients with low RBC counts, including patients with CRF and cancer patients undergoing chemotherapy or radiation treatment. Unfortunately, data gathered in recent years have shown that, for many cancer patients, ESAs can shorten time to tumor progression and reduce overall survival. Also, these drugs can increase the risk of deep vein thrombosis when used prior to elective surgery. Currently, three ESA preparations are available: epoetin alfa (erythropoietin), darbepoetin alfa (a long-acting form of erythropoietin), and

methoxy polyethylene glycol–epoetin beta (a very-long-acting form of erythropoietin).

Epoetin Alfa (Erythropoietin)

Epoetin alfa [Epogen, Procrit] is a growth factor produced by recombinant DNA technology. Chemically, the compound is a glycoprotein containing 165 amino acids. The protein portion of epoetin alfa is identical to that of human erythropoietin, a naturally occurring hormone. Epoetin alfa is used to maintain erythrocyte counts in (1) patients with CRF, (2) HIV-infected patients taking zidovudine, and (3) patients with nonmyeloid malignancies who have anemia secondary to chemotherapy. In addition, the drug can be used to elevate erythrocyte counts in anemic patients prior to elective surgery.

Physiology

Erythropoietin is a glycoprotein hormone that stimulates production of red blood cells in the bone marrow. The hormone is produced by peritubular cells in the proximal tubules of the kidney. In response to anemia or hypoxia, circulating levels of erythropoietin rise dramatically, triggering an increase in erythrocyte synthesis. However, because production of erythrocytes requires iron, folic acid, and vitamin B***12***, the response to erythropoietin is minimal if any of these is deficient.

Evidence gathered over the last decade shows that erythropoietin has significant physiologic effects outside the hematopoietic system. Animal studies indicate that erythropoietin is secreted by cells of many organs, including the brain, bone marrow, liver, heart, kidney, uterus, testes, and blood vessels—and that receptors for erythropoietin are present at most of these sites. Actions of the hormone include modulation of angiogenesis (blood vessel formation) and maintenance of cellular integrity (by inhibiting apoptotic mechanisms of cell injury). In the future, these actions may be exploited to treat a variety of disorders, including stroke, diabetic nephropathy, multiple sclerosis, myocardial infarction (MI), and heart failure (HF).

Therapeutic Uses

Anemia of Chronic Renal Failure.

Epoetin alfa can reverse anemia associated with CRF. The drug can benefit patients on dialysis as well as those who do not yet require dialysis. Effective treatment virtually eliminates the need for transfusions. Initial effects can be seen within 1 to 2 weeks. Hemoglobin reaches target levels (10 to 12 gm/dL) in 2 to 3 months. Patients experience an improved quality of life and increased energy levels. Unfortunately, treatment does not prevent progressive renal deterioration.

For therapy to be effective, iron stores must be adequate. Transferrin saturation should be at least 20%, and ferritin concentration should be at least 100 ng/mL. If pretreatment assessment indicates these values are low, they must be restored with iron supplements.

HIV-Infected Patients Taking Zidovudine.

Epoetin alfa is approved for treating anemia caused by therapy with zidovudine (AZT) in patients with AIDS. For these patients, treatment can maintain or elevate erythrocyte counts and reduce the need for transfusions. However, if endogenous levels of erythropoietin are at or above 500 milliunits/mL, raising them further with epoetin is unlikely to help.

Chemotherapy-Induced Anemia.

Epoetin alfa is used to treat chemotherapy-induced anemia in patients with *nonmyeloid malignancies,* thereby reducing or eliminating the need for periodic transfusions. Since transfusions require hospitalization, whereas epoetin can be self-administered at home, epoetin therapy can spare patients considerable inconvenience. Because epoetin works slowly (the hematocrit may take 2 to 4 weeks to recover), transfusions are still indicated when rapid replenishment of red blood cells is required. Please note that epoetin is not approved for patients with *leukemias* and *other myeloid malignancies*. Why? Because the drug may stimulate proliferation of these cancers.

Anemia in Patients Facing Surgery.

Epoetin may be given to increase erythrocyte levels in anemic patients scheduled for elective surgery. The drug should be used only when significant blood loss is anticipated—but should not be used prior to cardiac or vascular surgery. For surgical patients, epoetin offers two benefits: (1) it decreases the

need for transfusions, and (2) by increasing erythrocyte synthesis, it allows patients to predeposit more blood in anticipation of transfusion needs.

Pharmacokinetics

Epoetin alfa is administered parenterally (IV or subQ). The drug cannot be given orally because, being a glycoprotein, it would be degraded in the GI tract. The plasma half-life is highly variable and unchanged by dialysis.

Adverse Effects and Interactions

Epoetin alfa is generally well tolerated. Although the drug is a protein, no serious allergic reactions have been reported. The most significant adverse effect is hypertension. There are no significant drug interactions. As discussed below under *Warnings,* improper use of epoetin alfa has been associated with serious cardiovascular events, tumor progression, and deaths.

Hypertension.

In patients with CRF, epoetin is frequently associated with an increase in blood pressure. The extent of hypertension is directly related to the rate of rise in the hematocrit. To minimize risk, blood pressure should be monitored and, if necessary, controlled with antihypertensive drugs. If hypertension cannot be controlled, epoetin dosage should be reduced. In patients with pre-existing hypertension (a common complication of CRF), it is imperative that blood pressure be under control prior to epoetin use. About 30% of dialysis patients receiving epoetin require an adjustment in their antihypertensive therapy once the hematocrit has been normalized.

Cardiovascular Events.

Epoetin has been associated with an increase in cardiovascular events. Among these are cardiac arrest, hypertension, HF, and thrombotic events, including stroke and MI. Risk is greatest when (1) the hemoglobin level exceeds 12 gm/dL or (2) the rate of rise in hemoglobin exceeds 1 gm/dL in any 2-week interval. Accordingly, dosage should be reduced when hemoglobin approaches 12 gm/dL or when the rate of rise exceeds 1 gm/dL in 2 weeks—and dosing should be temporarily stopped if hemoglobin rises to 13 gm/dL or more. To prevent

clotting in the artificial kidney, CRF patients on dialysis may need increased anticoagulation with heparin.

Autoimmune Pure Red-Cell Aplasia.

Very, very rarely, treatment with epoetin leads to pure red-cell aplasia (PRCA), a condition characterized by severe anemia and a complete absence of erythrocyte precursor cells in bone marrow. The cause is production of neutralizing antibodies directed against epoetin itself as well as any native erythropoietin the body is still able to produce. In the absence of epoetin and erythropoietin, production of red blood cells ceases. Because patients can no longer make erythrocytes, transfusions are required for survival. If evidence of PRCA develops, epoetin should be discontinued and blood should be assessed for neutralizing antibodies.

Warnings

Excessive Dosage.

To minimize the risk of serious adverse events, the dosage of epoetin alfa and all other ESAs should be the lowest needed to gradually raise hemoglobin content to the lowest level sufficient to eliminate the need for RBC transfusions. In all cases, hemoglobin level should not exceed 12 gm/dL. Why? Because when ESAs are administered in doses sufficient to raise hemoglobin above this level, there is an increased risk of serious cardiovascular events and death.

Cancer Patients.

Postmarketing reports indicate that ESAs can accelerate tumor progression and shorten life in certain cancer patients—especially when hemoglobin has been driven above 12 gm/dL. In patients with advanced head and neck cancer who are undergoing radiation therapy, ESAs have shortened the time to tumor progression. In patients with metastatic breast cancer who are receiving chemotherapy, ESAs have shortened overall survival and increased deaths from tumor progression. Also, ESAs have increased the risk of death in patients with active malignant disease who are not receiving either radiation or chemotherapy, and hence ESAs are contraindicated for this group.

Renal Failure Patients.

In patients with anemia of chronic renal failure, ESAs can increase the risk of serious cardiovascular events and death if hemoglobin levels are driven too high. Accordingly, dosage should be individualized to produce hemoglobin levels in the range of 10 to 12 gm/dL.

Preoperative Patients.

When given to preoperative patients to reduce the need for RBC transfusion, ESAs have increased the risk of deep vein thrombosis—but only in patients who were not given an anticoagulant. Accordingly, anticoagulant therapy should be considered for all preoperative patients receiving an ESA.

Monitoring

Hemoglobin level should be measured at baseline and twice weekly thereafter until the target level (10 to 12 gm/dL) has been reached and a maintenance dose established. Complete blood counts with a differential should be done routinely. Blood chemistry—blood urea nitrogen (BUN), uric acid, creatinine, phosphorus, and potassium—should be monitored. Iron should be measured periodically and maintained at an adequate level.

Preparations, Dosage, and Administration

Preparations.

Epoetin alfa [Epogen, Procrit] is supplied in 1-mL vials (2000, 3000, 4000, 10,000, 20,000, and 40,000 units) for subQ and IV injection. Vials should not be shaken (because epoetin is a protein that can be denatured by agitation). Don't mix epoetin with other drugs. Store at 2°C to 8°C; don't freeze.

General Dosing Guidelines.

Use the lowest dosage needed to gradually increase the hemoglobin concentration to the lowest level sufficient to eliminate the need for RBC transfusion. For most patients, the treatment goal is a hemoglobin level of 10 to 12 gm/dL. *Regimens that raise hemoglobin above 12 gm/dL are associated with an increased risk of serious cardiovascular events and death.* Accordingly, dosage should be reduced when hemoglobin approaches 12 gm/dL, or when hemoglobin increases by more

than 1 gm/dL in any 2-week interval. If hemoglobin rises above 13 gm/dL, withhold treatment until hemoglobin drops below 12 gm/dL. When treatment resumes, decrease the dose by 25%, and then titrate upward as needed.

Dosing in Patients with Chronic Renal Failure.

Route.

Administration may be IV or subQ. Initially, IV administration was preferred, in part because subQ administration was reputedly painful, and in part because bioavailability following subQ injection is reduced—although the half-life is prolonged. In 1998, a study comparing IV therapy with subQ therapy indicated that both produce equivalent effects. Furthermore, with subQ administration, 30% less epoetin is required, and reported discomfort at the injection site is minimal. Because epoetin is expensive, and because subQ therapy is equivalent to IV therapy and cheaper, it seems likely that subQ therapy will become the new standard.

Dosage.

The initial dosage is 50 to 100 units/kg 3 times a week. Administration is by IV bolus for dialysis patients and by IV bolus or subQ injection for nondialysis patients. Once the target hemoglobin level has been achieved, an individualized maintenance dosage should be established: For dialysis patients, the median maintenance dosage is 75 units/kg 3 times a week; for nondialysis patients, the median maintenance dosage is 75 to 100 units/kg once a week. If the hematocrit rises above 12 gm/dL, epoetin should be temporarily withheld.

Dosing in HIV-Infected Patients Taking Zidovudine.

Prior to treatment, measure the endogenous erythropoietin level. If this level is already at or above 500 milliunits/mL, epoetin alfa is unlikely to help.

The initial dosage is 100 units/kg (IV or subQ injection) 3 times/wk for 8 weeks. If the response is insufficient, the dosage may be increased by increments of 50 to 100 units/kg until a maximum of 300 units/kg 3 times a week has been reached.

Dosing in Patients Receiving Cancer Chemotherapy.

Two dosing schedules may be used: once weekly or thrice weekly.

Once-Weekly Dosing.

The initial dosage is 40,000 units subQ each week. If, after 4 weeks of therapy, hemoglobin has not increased by at least 1 gm/dL, the dosage should be increased to 60,000 units once weekly. If hemoglobin has not increased by 1 gm/dL after 4 weeks, treatment should stop, since further increases are not likely to succeed.

Thrice-Weekly Dosing.

The initial dosage is 150 units/kg subQ 3 times a week. If the response is inadequate by 8 weeks, the dosage may be increased to 300 units/kg 3 times a week.

Dosing in Anemic Patients Scheduled for Surgery.

The recommended dosage is 300 units/kg/day subQ for 15 days starting 10 days before surgery.

Darbepoetin Alfa (Erythropoietin, Long Acting)

Actions and Therapeutic Use

Darbepoetin alfa [Aranesp], also known as novel erythrocyte stimulation protein (NESP), is a long-acting analog of epoetin alfa [Epogen, Procrit]. Both drugs act on erythroid progenitor cells to stimulate production of erythrocytes. Darbepoetin differs structurally from epoetin in that it has two additional carbohydrate chains. Because of these chains, darbepoetin is cleared more slowly than epoetin, and hence has a longer half-life (49 hours vs. 18 to 24 hours). As a result, darbepoetin can be administered less frequently, and thus is more convenient. Darbepoetin is approved for maintaining erythrocyte counts in (1) patients with CRF and (2) patients with nonmyeloid malignancies who have anemia secondary to chemotherapy. As discussed above, epoetin has additional indications.

Adverse Effects and Warnings

Darbepoetin is generally well tolerated. As with epoetin, the most common problem is hypertension. The risk can be minimized by ensuring that the rate of rise in hemoglobin does not exceed 1 gm/dL every 2 weeks. If hypertension develops, it should be controlled with antihypertensive drugs. Patients already taking antihypertensive drugs may need to increase their dosage.

Like epoetin alfa, darbepoetin increases the risk of PRCA, MI, HF, stroke, cardiac arrest, and other cardiovascular events, especially when the hemoglobin level exceeds 12 gm/dL or when the rate of rise in hemoglobin exceeds 1 gm/dL in 2 weeks.

Like epoetin alfa, darbepoetin can promote tumor progression and shorten survival in some cancer patients.

Monitoring

When initiating darbepoetin or changing dosage, the hemoglobin level should be measured weekly until it stabilizes. Thereafter, hemoglobin should be measured at least once a month.

Preparations, Dosage, Administration, and Monitoring

Preparations and Storage.

Darbepoetin alfa [Aranesp] is available in 1-mL, single-dose vials (25, 40, 60, 100, 200, 300, and 500 mcg/mL) for subQ and IV injection. Don't dilute darbepoetin or mix it with other drugs. Because darbepoetin is a protein that can be denatured by agitation, don't shake the vials. Discard preparations that are discolored or contain particles. Store at 2°C to 8°C; don't freeze.

General Dosing Guidelines.

The treatment goal is to increase hemoglobin to a maximum of 12 gm/dL. Dosage should be reduced when hemoglobin approaches 12 gm/dL, or when hemoglobin increases by more than 1 gm/dL in any 2-week interval. If hemoglobin rises to 13 gm/dL or higher, withhold treatment until hemoglobin drops below 12 gm/dL.

Dosing in Patients with Chronic Renal Failure.

The initial dosage is 0.45 mcg/kg, given either IV or subQ once a week. The target hemoglobin level is 12 gm/dL. Because responses develop gradually, dosage should be adjusted no more than once every 4 weeks. Quite often, the maintenance dosage is less than the initial dosage.

When switching from epoetin to darbepoetin, the new dosage and dosing frequency are based on the existing epoetin usage. For example, patients receiving 5000 to 11,000 units of epoetin each week should be given 25 mcg of darbepoetin each week. If the epoetin dosing frequency was 2 to 3 times a week, darbepoetin should be given once a week; if epoetin was given once a week, darbepoetin should be given once every 2 weeks.

Dosing in Patients Undergoing Cancer Chemotherapy.

The initial dosage is 2.25 mcg/kg injected subQ once a week. If the increase in hemoglobin is less than 1 gm/dL after 6 weeks, dosage should be increased to 4.5 mcg once a week. If the increase in hemoglobin exceeds 1 gm/dL in 2 weeks, or if hemoglobin rises above 12 gm/dL, dosage should be reduced by 25%.

Methoxy Polyethylene Glycol–Epoetin Beta (Erythropoietin, Very Long Acting)

Description and Therapeutic Use

Methoxy polyethylene glycol (MPEG)–epoetin beta [Mircera], approved in 2007, is a long-acting derivative of erythropoietin. Like the natural hormone, MPEG–epoetin beta acts on erythroid progenitor cells to stimulate production of red blood cells.

MPEG–epoetin beta has a unique structure, created by conjugating one molecule of epoetin beta (a recombinant form of erythropoietin) to one molecule of methoxy propylene glycol. Because of this structure, MPEG–epoetin beta has a very long half-life (about 135 hours)—about 6 times that of darbepoetin alfa and 27 times that of epoetin alfa. Because it stays in the body so long, MPEG–epoetin beta can be dosed less frequently than the other two ESAs, making treatment more convenient.

MPEG–epoetin beta is indicated only for anemia associated with CRF. The drug is not approved for use by cancer patients. Why? Because in clinical trials, there were more deaths among patients taking MPEG–epoetin beta than among patients taking a comparator ESA.

As of this writing, MPEG–epoetin beta cannot be marketed in the United States. Why? Because there is an ongoing patent dispute between Hoffman LaRoche, the company that makes Mircera, and Amgen, the company that makes two other ESAs (Aranesp and Epogen).

Adverse Effects and Warnings

Adverse effects are like those of other ESAs. Hypertension is the most common (11%). The risk can be minimized by keeping the rate of rise in hemoglobin below 1 gm/dL every 2 weeks. If hypertension develops, it should be controlled with antihypertensive drugs.

Like other ESAs, MPEG–epoetin beta increases the risk of serious cardiovascular events, including PRCA, MI, HF, stroke, and cardiac arrest. Risk is greatest when the hemoglobin level exceeds 12 gm/dL or when the rate of rise in hemoglobin exceeds 1 gm/dL in 2 weeks.

More than other ESAs, MPEG–epoetin beta can promote tumor progression and shorten survival in some cancer patients. Accordingly, MPEG–epoetin beta is contraindicated for patients with cancer.

Monitoring

When initiating MPEG–epoetin beta or when changing the dosage, the hemoglobin level should be measured every 2 weeks until it stabilizes. Thereafter, hemoglobin should be measured every 2 to 4 weeks.

Preparations, Dosage, Administration, and Monitoring

Preparations and Storage.

MPEG–epoetin beta [Mircera] is available in single-use vials (50, 100, 200, 300, 400, 600, and 1000 mcg/mL) and in two sizes of single-use pre-filled syringes: 0.3 mL (containing 50, 75, 100, 150, 200, 250, or 300 mcg) and 0.6 mL (contain-

ing 400, 600, or 800 mcg). The syringes and vials should be stored cold (2°C to 8°C [36°F to 46°F]) and protected from light.

Administration.

Administration is by IV injection or subQ injection (into the abdomen, arm, or thigh).

Dosage.

Dosage differs for patients currently stabilized on another ESA versus patients not currently using an ESA.

Patients Not Currently Using an ESA.

The initial dosage is 0.6 mcg/kg once every 2 weeks. When the hemoglobin level reaches 10 to 12 gm/dL, dosing should be done every 4 weeks, using twice the dose that had been given every 2 weeks.

Patients Already Stabilized on Epoetin Alfa or Darbepoetin Alfa.

The dosage of MPEG–epoetin beta is based on the *total weekly* dosage of the current ESA as follows:

- *Less than 8000 units epoetin alfa* or *less than 40 mcg darbepoetin alfa*—give 60 mcg every 2 weeks or 120 mcg every month
- *8000 to 16,000 units epoetin alfa* or *40 to 80 mcg darbepoetin alfa*—give 100 mcg every 2 weeks or 200 mcg every month
- *More than 16,000 units epoetin alfa* or *more than 80 mcg darbepoetin alfa*—give 180 mcg every 2 weeks or 360 mcg every month

LEUKOPOIETIC GROWTH FACTORS

The leukopoietic growth factors stimulate production of leukocytes (white blood cells). Three preparations are available: filgrastim, pegfilgrastim, and sargramostim.

Filgrastim (Granulocyte Colony-Stimulating Factor)

Filgrastim [Neupogen] is a leukopoietic growth factor produced by recombinant DNA technology. The drug is essentially identical in structure and actions to human granulocyte colony-stimulating factor (G-CSF), a naturally occurring hormone. Filgrastim has two principal uses: elevation of neutrophil counts in cancer patients and treatment of severe chronic neutropenia.

Physiology

G-CSF acts on cells in bone marrow to increase production of neutrophils (granulocytes). In addition, it enhances phagocytic and cytotoxic actions of mature neutrophils. The hormone is produced by monocytes, fibroblasts, and endothelial cells in response to inflammation and allergic challenge, suggesting that its natural role is to help fight infection and cancer.

Therapeutic Uses

Cancer.

Patients Undergoing Myelosuppressive Chemotherapy.

Filgrastim is given to reduce the risk of infection in patients undergoing cancer chemotherapy. Many anticancer drugs act on the bone marrow to suppress production of neutrophils, thereby greatly increasing the risk of infection. By stimulating neutrophil production, filgrastim can decrease infection risk. Clinical trials have shown that treatment (1) reduces the incidence of severe neutropenia, (2) produces a dose-dependent increase in circulating neutrophils, (3) reduces the incidence of infection, (4) reduces the need for hospitalization, and (5) reduces the need for intravenous antibiotics. Unfortunately, this useful drug is very expensive: The cost for a single course of treatment is over $3500. Because filgrastim stimulates proliferation of bone marrow cells, it should be used with great caution in patients with cancers that originated in the marrow.

Patients Undergoing Bone Marrow Transplantation

Filgrastim is given to shorten the duration of neutropenia in patients who have undergone high-dose chemotherapy followed by BMT. As noted, the drug is not used when the cancer is of myeloid origin.

Harvesting of Peripheral Blood Progenitor Cells

Peripheral blood progenitor cells (PBPCs) are harvested prior to bone marrow ablation with high-dose chemotherapy. Following chemotherapy, the PBPCs are infused back into the patient to accelerate repopulation of the bone marrow. Treatment with filgrastim prior to harvesting increases the number of circulating PBPCs, and therefore facilitates collection.

Severe Chronic Neutropenia.

Filgrastim provides effective treatment for *congenital neutropenia* (Kostmann's syndrome), a condition characterized by pronounced neutropenia and frequent, severe infections. Therapy helps resolve existing infections and decreases the incidence of subsequent infections. Because treatment is chronic, the cost is very high. In addition to congenital neutropenia, filgrastim is used in patients with *idiopathic neutropenia* and *cyclic neutropenia*.

Investigational Uses.

Filgrastim can reverse *zidovudine-induced neutropenia* in HIV-infected patients. However, the drug does not reduce the incidence of opportunistic infections. In patients with *acute myelogenous leukemia,* filgrastim has been given to stimulate division of cancer cells, thereby making them more sensitive to chemotherapeutic agents. Filgrastim has also been employed in patients with *aplastic anemia* and *myelodysplasia*.

Pharmacokinetics

Administration is parenteral (IV or subQ). Filgrastim cannot be used orally because, being a protein, it would be destroyed in the GI tract. The drug is eliminated by renal excretion. Its serum half-life is about 3.5 hours.

Adverse Effects and Interactions

When used short-term, filgrastim is generally devoid of serious adverse effects. There are no drug interactions of note.

Bone Pain.

Filgrastim causes bone pain in about 25% of patients. Pain is dose related and usually mild to moderate. In most cases, relief can be achieved with a nonopioid analgesic (eg, acetaminophen). If not, an opioid may be tried.

Leukocytosis.

When administered in doses greater than 5 mcg/kg/day, filgrastim has caused white blood cell counts to rise above 100,000/mm3 in 2% of patients. Although no adverse effects were associated with this degree of leukocytosis, avoiding leukocytosis would nonetheless be prudent. Excessive white cell counts can be avoided by obtaining complete blood counts twice weekly during treatment and by reducing filgrastim dosage if leukocytosis develops.

Other Adverse Effects.

Treatment frequently causes elevation of plasma uric acid, lactate dehydrogenase, and alkaline phosphatase. Increases are usually moderate and reverse spontaneously. Long-term therapy has caused splenomegaly.

Preparations, Dosage, and Administration

Preparations and Storage.

Filgrastim [Neupogen] is supplied in solution (300 mcg/mL) in 1-mL and 1.6-mL single-dose vials. The drug is stored at 2°C to 8°C—not frozen.

Dosage and Administration.

General Considerations.

Prior to administration, filgrastim can be kept at room temperature for up to 6 hours. It should not be agitated. Only one dose per vial should be used, and the vial should not be re-entered.

Cancer Chemotherapy.

The usual dosage is 5 mcg/kg once daily, given IV or subQ. Therapy should start no sooner than 24 hours after termination of chemotherapy, and should continue up to 2 weeks after the expected chemotherapy-induced nadir, or until the absolute neutrophil count has reached 10,000/mm3. Administer by

subQ bolus, short IV infusion, or continuous IV or subQ infusion. A complete blood count and platelet count should be obtained prior to treatment and twice weekly during treatment.

Bone Marrow Transplant.

The initial dosage is 10 mcg/kg/day, administered by slow IV or subQ infusion. During the period of neutrophil recovery, dosage is titrated against the neutrophil count.

Severe Chronic Neutropenia.

Dosage is 6 mcg/kg subQ administered twice a day every day.

Pegfilgrastim (Granulocyte Colony-Stimulating Factor, Long Acting)

Pegfilgrastim [Neulasta] is a long-acting derivative of filgrastim [Neupogen]. Both drugs stimulate myeloid cells to increase production of neutrophils. Pegfilgrastim is made by conjugating filgrastim with polyethylene glycol (PEG), in a process known as pegylation. Pegylation increases the size of filgrastim, and thereby delays its excretion by the kidneys. As a result, the drug's half-life is greatly increased—from 3.5 hours (for native filgrastim) up to about 17 hours. Because pegfilgrastim has a longer half-life than filgrastim, the drug is easier to use: A course of treatment consists of just one dose, rather than one dose every day for 2 weeks. At this time, pegfilgrastim has only one approved application: prevention of febrile neutropenia in patients undergoing chemotherapy of nonmyeloid malignancies. As discussed above, filgrastim has additional uses.

Adverse effects are much like those of filgrastim. Bone pain is the most common, occurring in 26% of patients. About 6% require an opioid analgesic for relief. Other side effects include reversible elevations of lactate dehydrogenase, alkaline phosphatase, and uric acid.

Preparations, Dosage, and Administration.

Pegfilgrastim [Neulasta] is available in solution (10 mg/mL) in pre-filled, single-dose syringes. For all patients, treatment consists of one 6-mg subQ

dose, injected 24 hours after each round of chemotherapy. Because stimulated myeloid cells are highly vulnerable to anticancer drugs, and because pegfilgrastim has a prolonged duration of action, at least 14 days must elapse between injecting pegfilgrastim and the next round of chemotherapy. Accordingly, if the scheduled interval between rounds of chemotherapy is less than 15 days (24 hours plus 14 days), pegfilgrastim cannot be used. Instead, filgrastim, with its shorter duration of action, should be employed. Pegfilgrastim has not been evaluated in infants, children, or adolescents who weigh less than 45 kg. Accordingly, the drug should not be used in these patients. Pegfilgrastim is expensive, costing over $3000 per dose. A comparable course of filgrastim costs about the same.

Sargramostim (Granulocyte-Macrophage Colony-Stimulating Factor)

Sargramostim [Leukine] is a hematopoietic growth factor produced by recombinant DNA technology. The drug is nearly identical in structure and actions to human granulocyte-macrophage colony-stimulating factor (GM-CSF), a naturally occurring hormone. Sargramostim is given to accelerate bone marrow recovery following bone marrow transplantation (BMT).

Physiology

GM-CSF acts on cells in bone marrow to increase production of neutrophils, monocytes, macrophages, and eosinophils. In addition, the hormone acts on the mature forms of these cells to enhance their function. For example, GM-CSF acts on neutrophils and macrophages to increase their chemotactic, antifungal, and antiparasitic actions. Also, the hormone acts on monocytes and polymorphonuclear leukocytes to enhance their actions against cancer cells. GM-CSF is synthesized by T lymphocytes, monocytes, fibroblasts, and endothelial cells. Like G-CSF, GM-CSF is produced in response to inflammation and allergic challenge, suggesting that its natural role is to help fight infection and cancer.

Therapeutic Uses

Adjunct to Autologous Bone Marrow Transplantation.

Sargramostim can accelerate myeloid recovery in cancer patients who have undergone autologous BMT following high-dose chemotherapy (with or without concurrent irradiation). The drug is approved for promoting myeloid recovery following BMT in patients with acute lymphoblastic leukemia, non-Hodgkin's lymphoma, and Hodgkin's disease. In these patients, sargramostim can (1) accelerate neutrophil engraftment, (2) reduce the duration of antibiotic use, (3) reduce the duration of infectious episodes, and (4) reduce the duration of hospitalization. Therapy is expensive: The cost for a 21-day course of sargramostim is more than $5000.

Treatment of Failed Bone Marrow Transplants.

Sargramostim is approved for patients in whom an autologous or allogenic bone marrow transplant has failed to take. For these patients, the drug can produce a significant increase in survival time.

Patients with Acute Myelogenous Leukemia (AML).

Sargramostim is given following induction chemotherapy in older patients with AML. The goal is to accelerate neutrophil recovery and reduce the incidence of life-threatening infections.

Investigational Uses.

In *HIV-infected patients,* sargramostim can reverse neutropenia caused by zidovudine (a drug that inhibits HIV replication) and by ganciclovir (a drug for cytomegalovirus retinitis).

In patients with *aplastic anemia* (a syndrome characterized by pancytopenia and high mortality from infection and bleeding), sargramostim can increase neutrophil counts and reduce the incidence and severity of infections.

Sargramostim is beneficial for patients with *myelodysplastic syndrome* (MDS), a chronic disorder characterized by greatly reduced hematopoiesis. Patients with MDS are neutropenic, thrombocytopenic, and anemic, putting them at high risk for serious infections and bleeding. The syndrome has a mortality rate of 66%—and those who survive often develop leukemia. Treatment with sargramostim can increase counts of neutrophils, eosinophils, and monocytes.

However, the premalignant clone still exists and may eventually cause leukemia.

Pharmacokinetics

Sargramostim is administered by IV infusion. Since the drug is a protein and hence would be degraded in the digestive tract, it cannot be administered by mouth. Other aspects of its kinetics are unremarkable.

Adverse Effects and Interactions

Sargramostim is generally well tolerated. A variety of acute reactions have been observed, including diarrhea, weakness, rash, malaise, and bone pain that can be managed with nonopioid analgesics (eg, acetaminophen). Pleural and pericardial effusions have occurred, but only when sargramostim dosage was massive (16 times the recommended dosage). There are no drug interactions of note.

Leukocytosis and Thrombocytosis.

Stimulation of the bone marrow can cause excessive production of white blood cells and platelets. Complete blood counts should be done twice weekly during therapy. If the white cell count rises above 50,000/mm^3, if the absolute neutrophil count rises above 20,000/mm^3, or if the platelet count rises above 500,000/mm^3, sargramostim should be interrupted or the dosage reduced.

Preparations, Dosage, and Administration

Preparations.

Sargramostim [Leukine] is available as a powder (250 mcg) to be reconstituted in 1 mL of sterile water for IV infusion. A solution formulation (500 mcg/mL) has been withdrawn from the market.

Dilution.

To prepare the final infusion solution, dilute the reconstituted powder in either (1) 0.9% sodium chloride (if the final concentration of sargramostim is to be 10 mcg/mL or more) or (2) 0.9% sodium chloride plus 0.1% albumin (if the final concentration is to be less than 10 mcg/mL). Since the solution con-

tains no antibacterial preservatives, it should be used as soon as possible—and no later than 6 hours after preparation.

Storage.

All sargramostim preparations should be stored at 2°C to 8°C (never frozen).

Dosage and Administration.

To accelerate myeloid recovery after autologous BMT, the recommended dosage is 250 mcg/m^2 (as a 2-hour IV infusion) administered once daily for 21 days beginning 2 to 4 hours after the bone marrow infusion.

For patients in whom an autologous or allogenic bone marrow transplant has failed or in whom engraftment has been delayed, the recommended dosage is 250 mcg/m^2 (as a 2-hour IV infusion) administered once daily for 14 days. After a 7-day hiatus, the 14-day series of infusions can be repeated if needed. After another 7-day hiatus, the 14-day series can be repeated once more if needed. If the graft still has not taken, further treatment is unlikely to help.

To accelerate neutrophil recovery following chemotherapy for AML, the recommended dosage is 250 mcg/m^2/day (as a 4-hour IV infusion), starting on day 11 (or 4 days after completing the course of chemotherapy). Continue daily infusions for 42 days or until the absolute neutrophil count exceeds 1500 cells/mm^3 on 3 consecutive days, whichever is less.

THROMBOPOIETIC GROWTH FACTOR

Thrombopoietic growth factors are compounds that stimulate production of thrombocytes (platelets). At this time, oprelvekin is the only thrombopoietic growth factor available.

Oprelvekin (Interleukin-11)

Oprelvekin [Neumega] is a thrombopoietic growth factor produced by recombinant DNA technology. The drug is a protein nearly identical in structure and actions to human *interleukin-11*, a cytokine produced in bone marrow. Oprelvekin is given to stimulate platelet production in patients undergoing myelosuppressive chemotherapy for nonmyeloid cancers.

Actions

Oprelvekin acts on platelet progenitor cells to increase platelet production. Specifically, it stimulates proliferation of hematopoietic stem cells and megakaryocyte progenitor cells, and thereby increases synthesis of megakaryocytes, the cells that synthesize platelets. In addition to promoting megakaryocyte *synthesis,* oprelvekin induces megakaryocyte *maturation*. The net result is increased platelet production. In patients treated with oprelvekin daily for 14 days, platelet counts begin to increase 5 to 9 days after the first injection, peak about 7 days after the last injection, and return to baseline 14 days after that.

Therapeutic Use

Oprelvekin is administered to patients undergoing myelosuppressive chemotherapy to minimize thrombocytopenia (platelet deficiency) and to decrease the need for platelet transfusions. Because it stimulates the bone marrow, oprelvekin should *not* be given to patients with cancers of myeloid origin.

In clinical trials, oprelvekin was effective for some patients but not others. To assess its benefits, oprelvekin was given to patients who had required platelet transfusions following earlier rounds of chemotherapy. Some patients were on moderately myelosuppressive regimens and some were on highly suppressive regimens. Among those on moderately suppressive regimens, 30% were spared the need for platelet transfusions by combining oprelvekin with chemotherapy. Among those on highly suppressive regimens, only 13% were spared the need for platelet transfusions. Hence, although oprelvekin can increase platelet counts and decrease the need for platelet transfusions, not all patients benefit equally. As these data indicate, the more myelosuppressive the regimen, the less effective oprelvekin is likely to be.

Pharmacokinetics

Oprelvekin is administered by subQ injection. (The drug is a protein and hence cannot be administered by mouth.) Serum levels peak about 3 hours after administration. Elimination is by hepatic and renal tubular metabolism, followed by excretion of the metabolites in urine. Children eliminate the drug faster than adults.

Adverse Effects

Fluid Retention.

Oprelvekin causes retention of sodium and water by the kidney. The result is *peripheral edema* and a 10% to 15% *expansion of plasma volume*. Expansion of plasma volume decreases both the hematocrit and hemoglobin concentration, thereby causing anemia. As a result, about 48% of patients experience dyspnea (shortness of breath on exertion). Because of fluid retention, oprelvekin should be used with caution in patients with a history of heart failure or pleural effusion. Fluid balance should be monitored throughout treatment. Following oprelvekin withdrawal, fluid balance normalizes within days.

Cardiac Dysrhythmias.

Tachycardia, atrial fibrillation, and atrial flutter are common. The incidence of tachycardia is higher in children (46%) than in adults. Conversely, atrial flutter and fibrillation are more likely in older adults. The cause of cardiac effects is unclear, although expansion of plasma volume is suspected. Oprelvekin does not affect the heart directly.

Severe Allergic Reactions.

Oprelvekin has been associated with severe allergic reactions, including anaphylaxis. Signs of oprelvekin-induced allergy include rash, urticaria, flushing, fever, hypotension, joint pain, chest pain, wheezing, shortness of breath, and edema of the face, tongue, and larynx. Patients and healthcare providers should be alert for these reactions and, if allergy is diagnosed, oprelvekin should be withdrawn and never used again.

Effects on the Eye.

Conjunctival injection is common. The incidence is 50% in children and 19% in adults. Other ophthalmic effects are transient visual blurring and papilledema (edema of the optic disk).

Sudden Death.

Two patients have died. Both had severe hypokalemia, and both had been treated with a diuretic and high doses of ifosfamide (an anticancer drug). Although oprelvekin is suspected, its precise role in these deaths is unknown.

Preparations, Dosage, and Administration

Preparation.

Oprelvekin [Neumega] is supplied as a powder in 5-mg single-dose vials. To reconstitute, add 1 mL of Sterile Water for Injection (supplied with the drug) and gently swirl; don't shake. Neither the powder nor the diluent contains preservatives, and hence the solution must be used within 3 hours to avoid infection. Oprelvekin and its diluent should be refrigerated at 2°C to 8°C.

Dosage and Administration.

Oprelvekin is administered by subQ injection into the abdomen, thigh, hip, or upper arm. The recommended adult dosage is 50 mcg/kg once daily; the pediatric dosage is 75 to 100 mcg/kg once daily. Dosing should begin 4 to 6 hours after chemotherapy and should continue until the platelet count rises above 50,000/mm***3***—but should not exceed 21 days. Treatment should cease 2 days before the next round of chemotherapy.

KEY POINTS

- Epoetin is given to increase red blood cell counts. Specific indications include anemia associated with (1) chronic renal failure, (2) zidovudine therapy in AIDS patients, and (3) cancer chemotherapy.
- By increasing the hematocrit, epoetin can cause or exacerbate hypertension.
- Epoetin increases the risk of cardiovascular events (eg, cardiac arrest, stroke, HF, MI), especially when the hemoglobin level exceeds 12 gm/dL or the rate of rise in hemoglobin exceeds 1 gm/dL in 2 weeks.
- In some cancer patients, epoetin can accelerate tumor progression and shorten life.
- Filgrastim is given to elevate neutrophil counts, and thereby reduce the risk of infection. Specific indications are chronic severe neutropenia and neutropenia associated with cancer chemotherapy or BMT.
- The principal adverse effects of filgrastim are bone pain and leukocytosis.

- Sargramostim is used to accelerate recovery from BMT, treat patients in whom a bone marrow transplant has failed, and accelerate neutrophil recovery in patients undergoing chemotherapy for AML.
- The principal adverse effect of sargramostim is leukocytosis.
- Oprelvekin is given to stimulate platelet production in patients undergoing myelosuppressive chemotherapy for nonmyeloid cancers. The goal is to minimize thrombocytopenia and platelet transfusions.
- The principal adverse effects of oprelvekin are fluid retention (which causes edema and anemia), cardiac dysrhythmias (tachycardia, atrial fibrillation, and atrial flutter), and severe allergic reactions, including anaphylaxis.
- Since epoetin alfa, filgrastim, sargramostim, and oprelvekin stimulate proliferation of bone marrow cells, these drugs should be used with great caution, if at all, in patients with cancers of bone marrow origin.

Summary of Major Nursing Implications*

EPOETIN ALFA (ERYTHROPOIETIN)

Preadministration Assessment

Therapeutic Goal

Epoetin is used to restore and maintain erythrocyte counts in (1) patients with chronic renal failure, (2) HIV-infected patients receiving zidovudine, (3) patients receiving cancer chemotherapy, and (4) anemic patients facing elective surgery. For most patients, the hemoglobin target level is 10 to 12 gm/dL, and should never exceed 12 gm/dL.

Baseline Data

All Patients.

Obtain blood pressure; blood chemistry (BUN, uric acid, creatinine, phosphorus, potassium); complete blood counts with differential and platelet count;

hemoglobin level; degree of transferrin saturation (should be at least 20%); and ferritin concentration (should be at least 100 ng/mL).

HIV-Infected Patients.

Obtain an erythropoietin level. If the level is above 500 milliunits/mL, epoetin is unlikely to help.

Identifying High-Risk Patients

Epoetin alfa is *contraindicated* for patients with uncontrolled hypertension or hypersensitivity to mammalian cell–derived products or albumin, and in cancer patients who are not undergoing either chemotherapy or radiation therapy.

Use with *caution* in patients with cancers of myeloid origin.

Implementation: Administration

Routes

IV and subQ.

Handling and Storage

Epoetin alfa is supplied in single-use and multi-use vials; don't re-enter the single-use vials. Don't agitate. Don't mix with other drugs. Store at 2°C to 8°C; don't freeze.

Administration

Chronic Renal Failure.

Administer by IV bolus or subQ injection.

Zidovudine-Induced Anemia.

Administer by IV or subQ injection.

Chemotherapy-Induced Anemia.

Administer by subQ injection.

Surgery Patients.

Administer by subQ injection.

Ongoing Evaluation and Interventions

Monitoring Summary

Measure hemoglobin level twice weekly until the target level (10 to 12 gm/dL) has been reached and a maintenance dosage established, and measure hemoglobin periodically thereafter. Obtain complete blood counts with a differential and platelet counts routinely. Monitor blood chemistry, including BUN, uric acid, creatinine, phosphorus, and potassium. Monitor iron stores and maintain at an adequate level. Monitor blood pressure.

Minimizing Adverse Effects

Hypertension.

Monitor blood pressure and, if necessary, control with antihypertensive drugs. If hypertension cannot be controlled, reduce epoetin dosage. In patients with pre-existing hypertension (a common complication of CRF), make certain that blood pressure is controlled prior to epoetin use.

Autoimmune Pure Red-Cell Aplasia.

Epoetin use may lead to pure red-cell aplasia (PRCA), owing to production of neutralizing antibodies directed against epoetin and native erythropoietin. If evidence of PRCA develops, epoetin should be discontinued and blood assessed for neutralizing antibodies. If PRCA is diagnosed, transfusions will be needed for life.

Cardiovascular Events.

Epoetin has been associated with an increase in cardiovascular events (eg, cardiac arrest, stroke, HF, and MI). Risk is greatest when the hemoglobin level exceeds 12 gm/dL or the rate of rise in hemoglobin exceeds 1 gm/dL in 2 weeks. To minimize risk, reduce dosage when hemoglobin approaches 12 gm/dL or when the rate of rise exceeds 1 gm/dL in 2 weeks, and temporarily stop dosing

if hemoglobin rises to 13 gm/dL or more. CRF patients on dialysis may need a higher dosage of heparin to prevent clotting in the artificial kidney.

For patients taking the drug prior to elective surgery, anticoagulant treatment can reduce the risk of deep vein thrombosis.

Cancer Patients: Tumor Progression and Shortened Survival.

Epoetin can accelerate tumor progression and shorten survival in some cancer patients. To reduce risk, dosage should be no higher than needed to bring hemoglobin gradually up to 12 gm/dL. Also, epoetin should be used only in cancer patients who are undergoing chemotherapy or radiation therapy. Those who are not receiving chemotherapy or radiation therapy should not get this drug.

FILGRASTIM (GRANULOCYTE COLONY-STIMULATING FACTOR)

Preadministration Assessment

Therapeutic Goal

Filgrastim is given to promote neutrophil recovery in cancer patients following myelosuppressive chemotherapy or BMT. The drug is also used to treat severe chronic neutropenia.

Baseline Data

Obtain complete blood counts and platelet counts.

Identifying High-Risk Patients

Filgrastim is *contraindicated* for patients with hypersensitivity to *Escherichia coli*–derived proteins.

Use with *caution* in patients with cancers of bone marrow origin.

Implementation: Administration

Routes

IV, subQ.

Handling and Storage

Filgrastim is supplied in single-use vials. Don't re-enter the vial; discard the unused portion. Don't agitate. Store at 2°C to 8°C; don't freeze. Prior to administration, filgrastim may be kept at room temperature for up to 6 hours.

Administration

Cancer Chemotherapy.

Administer by subQ bolus, short IV infusion, or continuous IV or subQ infusion.

Bone Marrow Transplantation.

Administer by slow IV or subQ infusion.

Chronic Severe Neutropenia.

Inject subQ twice daily every day.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects

Obtain complete blood counts twice weekly. Discontinue treatment when the absolute neutrophil count reaches 10,000/mm***3***.

Minimizing Adverse Effects

Bone Pain.

Evaluate for bone pain and treat with a nonopioid analgesic (eg, acetaminophen). Consider an opioid analgesic if the nonopioid is insufficient.

Leukocytosis.

Massive doses can cause leukocytosis (white blood cell counts above 100,000/mm3). If leukocytosis develops, reduce filgrastim dosage.

SARGRAMOSTIM (GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR)

Preadministration Assessment

Therapeutic Goal

Acceleration of myeloid recovery in cancer patients who have undergone autologous BMT following high-dose chemotherapy (with or without concurrent irradiation).

Treatment of patients for whom an autologous or allogenic bone marrow transplant has failed to take.

Acceleration of neutrophil recovery in older patients receiving induction chemotherapy for AML.

Baseline Data

Obtain complete blood counts with differential and platelet count.

Identifying High-Risk Patients

Sargramostim is *contraindicated* in the presence of hypersensitivity to yeast-derived products and excessive leukemic myeloid blasts in bone marrow or peripheral blood.

Exercise *caution* in patients with cardiac disease, hypoxia, peripheral edema, pleural or pericardial effusion, or cancers of bone marrow origin.

Implementation: Administration

Route

IV (by infusion).

Handling and Storage

Sargramostim is supplied in concentrated solution and as a powder, which must be reconstituted for IV infusion. To reconstitute the powder, add 1 mL of sterile water and gently swirl. Before infusing, dilute the concentrated solution or reconstituted powder. Administer as soon as possible after diluting—and no later than 6 hours after reconstitution. Store sargramostim (powder, reconstituted powder, final IV solution) at 2°C to 8°C until used.

Administration

Administer by 2-hour or 4-hour IV infusion.

Ongoing Evaluation and Interventions

Minimizing Adverse Effects

Leukocytosis and Thrombocytosis.

Obtain complete blood counts with a differential and platelet counts twice weekly. If the white blood cell count rises above 50,000/mm***3***, if the absolute neutrophil count rises above 20,000/mm***3***, or if the platelet count rises above 500,000/mm***3***, temporarily interrupt sargramostim or reduce the dosage.

OPRELVEKIN (INTERLEUKIN-11)

Preadministration Assessment

Therapeutic Goal

Oprelvekin is given to minimize thrombocytopenia and the need for platelet transfusions in patients undergoing myelosuppressive therapy for nonmyeloid cancers.

Baseline Data

Determine baseline blood cell counts and platelet count, hematocrit, and fluid and electrolyte status.

Identifying High-Risk Patients

Use with *caution* in patients with cancers of myeloid origin; patients taking diuretics or ifosfamide; and patients with a history of atrial dysrhythmias, heart failure, pleural effusion, or papilledema.

Implementation: Administration

Route

SubQ.

Handling and Storage

Oprelvekin is supplied in single-use vials; don't re-enter the vial. Don't agitate. Don't mix with other drugs. Store at 2°C to 8°C; don't freeze.

Administration

Administer once daily beginning 4 to 6 hours after chemotherapy. Continue for 21 days or until platelet counts exceed 50,000/mm***3***—whichever comes first.

Ongoing Evaluation and Interventions

Monitoring Summary

Monitor platelet counts from the time of the expected nadir until the count exceeds 50,000/mm***3***. Monitor blood cell counts, fluid status, and electrolyte status.

Minimizing Adverse Effects

Fluid Retention.

Fluid retention can result in edema, expanded plasma volume, anemia, and dyspnea. **Instruct patients with a history of congestive heart failure or pleural effusion to contact the prescriber if dyspnea worsens**.

Cardiac Dysrhythmias.

Oprelvekin can cause tachycardia, atrial flutter, and atrial fibrillation. Use caution in patients with a history of these disorders.