CNS Stimulants

10

I. OVERVIEW

This chapter describes two groups of drugs that act primarily to stimulate the central nervous system (CNS) (Figure 10.1). The first group, the psychomotor stimulants, cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity. The second group, psychotomimetic drugs or hallucinogens, produce profound changes in thought patterns and mood, with little effect on the brainstem and spinal cord. As a group, the CNS stimulants have few clinical uses, but they are important as drugs of abuse, along with the CNS depressants described in Chapter 9, and the narcotics described in Chapter 14 (Figure 10.2).

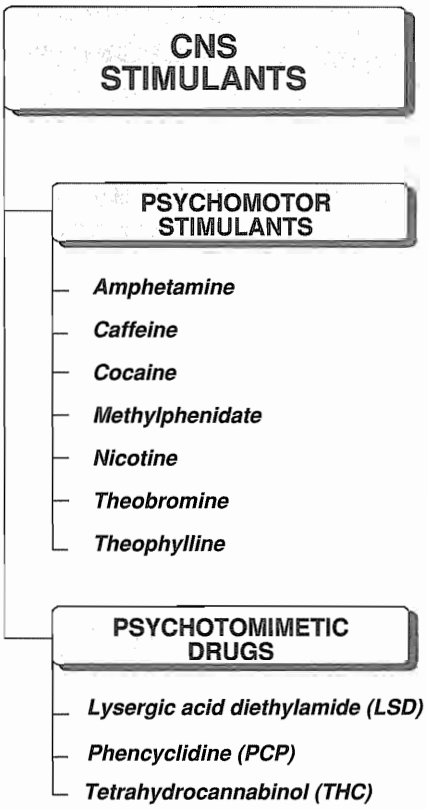

Figure 10.1
Summary of CNS stimulants.

II. PSYCHOMOTOR STIMULANTS

A. Methylxanthines

Methylxanthines include *theophylline* [thee OFF i lin] found in tea, *theobromine* [thee o BRO min] found in cocoa, and *caffeine* [kaf EEN]. *Caffeine*, the most widely consumed stimulant in the world, is found in highest concentration in coffee but is also present in tea, cola drinks, chocolate candy, and cocoa.

1. **Mechanism of action:** The methylxanthines may act by several mechanisms, including translocation of extracellular calcium, increase in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) caused by inhibition of phosphodiesterase, and blockade of adenosine receptors.

2. **Actions:**

   a. **Central nervous system:** The *caffeine* contained in one to two cups of coffee (100 to 200 mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain. Consumption of 1.5 grams of *caffeine* (12 to 15 cups of coffee) produces anxiety and tremors. The spinal cord is stimulated only by very high doses (2 to 5 g) of *caffeine*.

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by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
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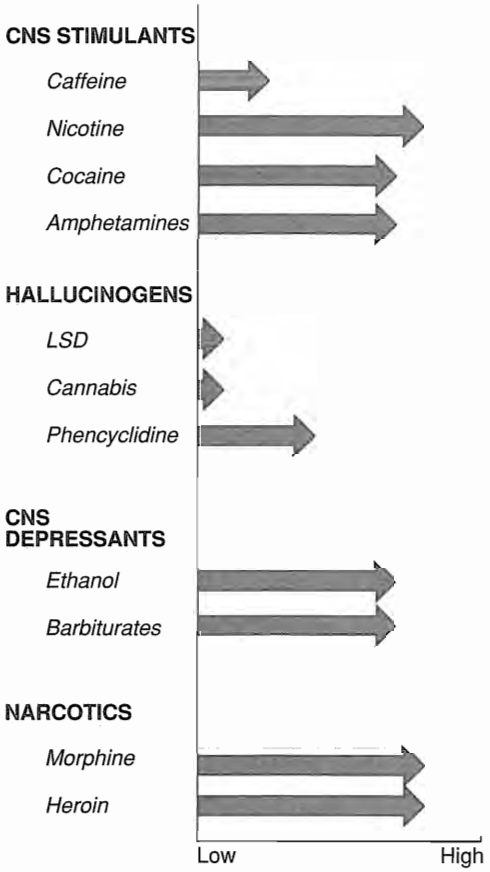

Figure 10.2
Relative potential for dependence for commonly abused substances.

b. **Cardiovascular system:** A high dose of *caffeine* has positive inotropic and chronotropic effects on the heart. [Note: Increased contractility can be harmful to patients with angina pectoris. Accelerated heart rate can trigger premature ventricular contractions in others.]

c. **Diuretic action:** *Caffeine* has a mild diuretic action that increases urinary output of sodium, chloride, and potassium.

d. **Gastric mucosa:** Since all methylxanthines stimulate secretion of hydrochloric acid (HCl) from the gastric mucosa, individuals with peptic ulcers should avoid beverages containing methylxanthines.

3. **Therapeutic uses:** *Caffeine* and its derivatives relax the smooth muscles of the bronchioles. Previously the main-stay of asthma therapy, *theophylline* has been largely replaced with β-agonists and corticosteroids (see p. 220).

4. **Pharmacokinetics:** The methylxanthines are well absorbed orally. *Caffeine* distributes throughout the body, including the brain. The drugs cross the placenta to the fetus and are secreted into the mother's milk. All the methylxanthines are metabolized in the liver, and the metabolites are then excreted in the urine.

5. **Adverse effects:** Moderate doses of *caffeine* cause insomnia, anxiety, and agitation. A high dosage is required to show toxicity, which is manifested by emesis and convulsions. The lethal dose is about 10 g for *caffeine* (about 100 cups of coffee), which induces cardiac arrhythmias; death from *caffeine* is thus highly unlikely. Lethargy, irritability, and headache occur in users who have routinely consumed more than 600 mg of *caffeine* per day (roughly 6 cups of coffee/day) and then suddenly stop.

B. Nicotine

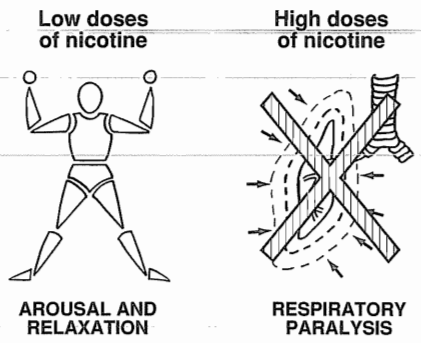

Figure 10.3
Actions of nicotine on the central nervous system.

Nicotine [NIC o teen] is the active ingredient in tobacco. Although this drug is not currently used therapeutically (except in smoking cessation therapy, see p. 101), *nicotine* remains important because it is second only to *caffeine* as the most widely used CNS stimulant and is second to alcohol as the most abused drug. In combination with the tars and carbon monoxide found in cigarette smoke, *nicotine* represents a serious risk factor for lung and cardiovascular disease, various cancers, as well as other illnesses.

1. **Mechanism of action:** In low doses, *nicotine* causes ganglionic stimulation by depolarization. At high doses, *nicotine* causes ganglionic blockade (see p. 49). *Nicotine* receptors exist in the CNS where similar actions occur. (See nicotinic receptors, p. 39.)

2. **Actions:**

a. **CNS:** *Nicotine* is highly soluble in lipid and readily crosses the blood-brain barrier. Cigarette smoking or administration of low doses of *nicotine* produces some degree of euphoria, and

arousal, as well as relaxation, and improves attention, learning, problem solving, and reaction time. High doses of *nicotine* result in central respiratory paralysis and severe hypotension caused by medullary paralysis (Figure 10.3).

b. **Peripheral effects:** The peripheral effects of *nicotine* are complex. Stimulation of sympathetic ganglia as well as the adrenal medulla increases blood pressure and heart rate. Thus use of tobacco is particularly harmful in hypertensive patients. Many patients with peripheral vascular disease experience an exacerbation of symptoms with smoking. For example, *nicotine*-induced vasoconstriction can decrease coronary blood flow, adversely affecting the patient with angina. Stimulation of parasympathetic ganglia also increases motor activity of the bowel. At higher doses, blood pressure falls and activity ceases in both the gastrointestinal tract and bladder musculature as a result of a *nicotine*-induced block of parasympathetic ganglia.

3. **Pharmacokinetics:** *Nicotine* is highly-lipid soluble. Thus, absorption readily occurs via the oral mucosa, lungs, gastrointestinal mucosa, and skin. *Nicotine* crosses the placental membrane and is secreted in the milk of lactating women. Most cigarettes contain 6 to 8 mg of *nicotine*; the acute lethal dose is 60 mg. Over 90% of *nicotine* inhaled in smoke is absorbed. Clearance of *nicotine* involves metabolism in the lung and the liver, and urinary excretion. Tolerance to the toxic effects of *nicotine* develops rapidly, often within days after beginning usage.

4. **Adverse effects:** The CNS effects of *nicotine* include irritability and tremors. *Nicotine* may also cause intestinal cramps, diarrhea, and increased heart rate and blood pressure. In addition, cigarette smoking increases the rate of metabolism of a number of drugs. [Note: It is not known which of the over 3,000 components of cigarette smoke are responsible for this phenomenon, although the benzopyrenes have been implicated.]

5. **Withdrawal syndrome:** As with the other drugs in this class, *nicotine* is an addictive substance; physical dependence on *nicotine* develops rapidly and is severe. Withdrawal is characterized by irritability, anxiety, restlessness, difficulty in concentrating, headaches, and insomnia. Appetite is affected and gastrointestinal pain often occurs. [Note: Smoking cessation programs that combine pharmacologic and behavioral therapy are the most successful in helping individuals to stop smoking. The transdermal patch and chewing gum containing *nicotine* have been shown to reduce *nicotine*-withdrawal symptoms and to help smokers stop smoking. For example, the blood concentration of *nicotine* obtained from chewing gum is typically about one-half of the peak level observed with smoking (Figure 10.4).]

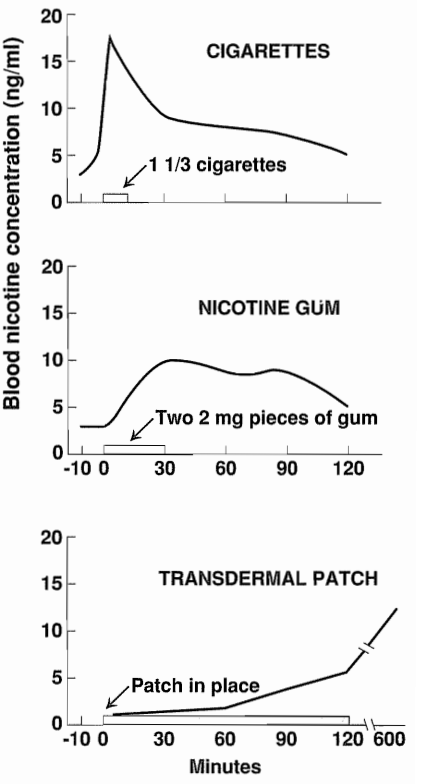

Figure 10.4
Blood concentrations of nicotine in individuals who smoked cigarettes, chewed nicotine gum or received nicotine by transdermal patch.

C. Cocaine

Cocaine [koe KANE] is an inexpensive, widely available, and highly addictive drug that is currently abused daily by over 3 million people in the United States.

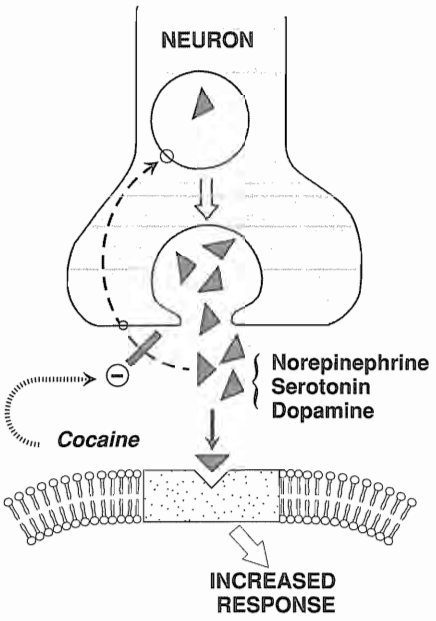

Figure 10.5
Mechanism of action of *cocaine*.

1. **Mechanism of action:** The primary mechanism of action underlying *cocaine*'s central and peripheral effects is blockade of norepinephrine, serotonin, and dopamine re-uptake into the presynaptic terminals from which these transmitters are released (Figure 10.5). This block potentiates and prolongs the CNS and peripheral actions of these catecholamines. In particular, the prolongation of dopaminergic effects in the brain's pleasure system (limbic system), produces the intense euphoria that *cocaine* initially causes. Chronic intake of *cocaine* depletes dopamine. This depletion triggers the vicious cycle of craving for *cocaine* that temporarily relieves severe depression.

2. **Actions:**

   a. **Central nervous system:** The behavioral effects of *cocaine* result from powerful stimulation of the cortex and brainstem. *Cocaine* acutely increases mental awareness and produces a feeling of well-being and euphoria that is similar to that caused by *amphetamine*. Like *amphetamine*, *cocaine* can produce hallucinations, delusions, and paranoia. *Cocaine* increases motor activity, and at high doses causes tremors and convulsions, followed by respiratory and vasomotor depression.

   b. **Sympathetic nervous systems:** Peripherally, *cocaine* potentiates the action of norepinephrine and produces the "fight or flight" syndrome characteristic of adrenergic stimulation. This is associated with tachycardia, hypertension, pupillary dilation, and peripheral vasoconstriction.

3. **Therapeutic uses:** *Cocaine* has a local anesthetic action that represents the only current rationale for the therapeutic use of *cocaine*; *cocaine* is applied topically as a local anesthetic during eye, ear, nose, and throat surgery. While the local anesthetic action of *cocaine* is due to a block of voltage-activated sodium channels, an interaction with potassium channels may contribute to *cocaine's* ability to cause cardiac arrhythmias. [Note: *Cocaine* is the only local anesthetic that causes vasoconstriction. This effect is responsible for the necrosis and perforation of the nasal septum seen in association with chronic inhalation of *cocaine* powder.]

4. **Pharmacokinetics:** *Cocaine* is self-administered by chewing, intranasal snorting, smoking, and intravenous (IV) injection. Peak effect occurs at 15 to 20 minutes after intranasal intake of *cocaine* powder, and the high disappears in 1 to 1.5 hours. Rapid but short-lived effects are achieved following IV injection of *cocaine*, or by smoking the free base form of the drug ("crack"). Because the onset of action is most rapid, the potential for overdosage and dependence is greatest with IV injection and crack smoking.

5. **Adverse effects:**

   a. **Anxiety:** The toxic response to acute *cocaine* ingestion can precipitate an anxiety reaction that includes hypertension, tachycardia, sweating, and paranoia.

b. Depression: Like all stimulant drugs, *cocaine* stimulation of the CNS is followed by a period of mental depression. Addicts withdrawing from *cocaine* exhibit physical and emotional depression as well as agitation. These symptoms can be treated with benzodiazepines (see p. 89) or phenothiazines (see p. 127).

c. Heart disease: *Cocaine* can induce seizures as well as fatal cardiac arrhythmias (Figure 10.6). Intravenous *diazepam* (see p. 89) and *propranolol* (see p. 74) may be required to control *cocaine*-induced seizures and cardiac arrhythmias, respectively. The incidence of myocardial infarction in *cocaine* users is unrelated to dose, to duration of use, or to route of administration. There is no marker to identify those individuals who may have life-threatening cardiac effects after taking *cocaine*.

D. Amphetamine

Amphetamine shows neurologic and clinical effects that are quite similar to those of *cocaine*.

1. **Mechanism of action:** As with *cocaine*, the effects of *amphetamine* on the CNS and peripheral nervous system are indirect; that is, they depend upon an elevation of the level of catecholamine transmitters in synaptic spaces. *Amphetamine*, however, achieves this effect by releasing intracellular stores of catecholamines (Figure 10.7). Since *amphetamine* also blocks monoamine oxidase (MAO), high levels of catecholamines are readily released into synaptic spaces. Despite different mechanisms of action, the behavioral effects of *amphetamine* are similar to those of *cocaine*.

2. **Actions:**

   a. Central nervous system: The major cause of the behavioral effects of *amphetamine*s is probably due to release of dopamine rather than release of norepinephrine. *Amphetamine* stimulates the entire cerebrospinal axis, cortex, brain stem, and medulla. This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia. In high doses, convulsions can ensue. These CNS stimulant effects of *amphetamine* and its derivatives have led to their use in the therapy of depression, hyperactivity in children, narcolepsy, and appetite control.

   b. Sympathetic nervous system: In addition to its marked action on the CNS, *amphetamine* acts on the adrenergic system, indirectly stimulating the receptors through norepinephrine release (see p. 68).

3. **Therapeutic uses:** Factors that limit the therapeutic usefulness of *amphetamine* include psychological and physiological dependence similar to those with *cocaine*, and the development of tolerance to the euphoric and anorectic effects with chronic use. [Note: Less tolerance to the toxic CNS effects (for example, convulsions) develops.]

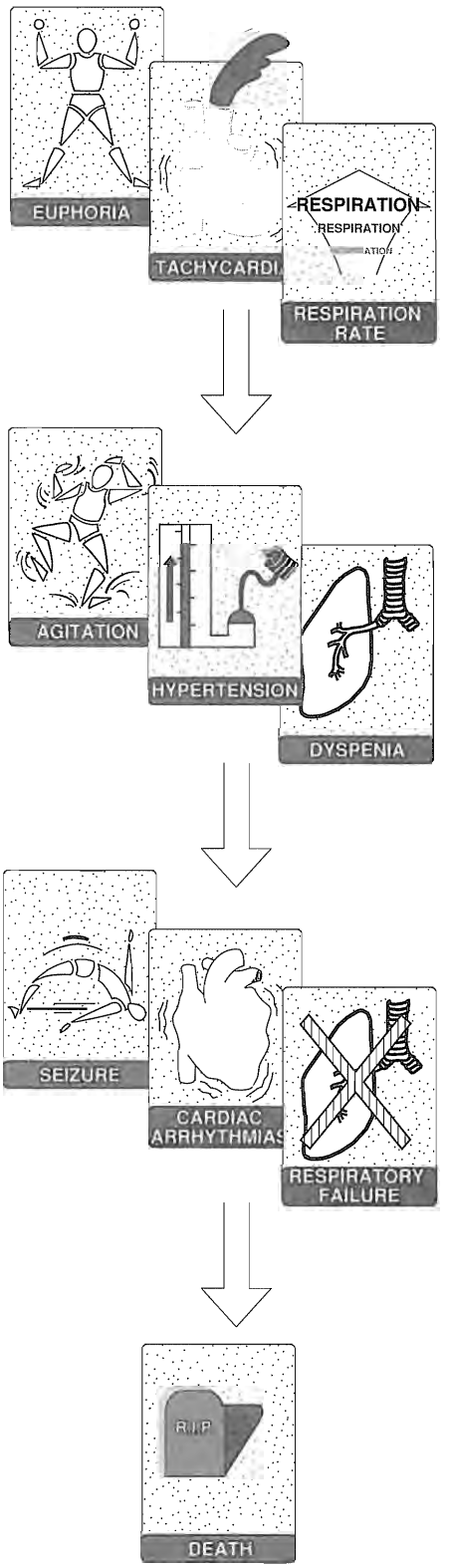

Figure 10.6
Major effects of *cocaine* use.

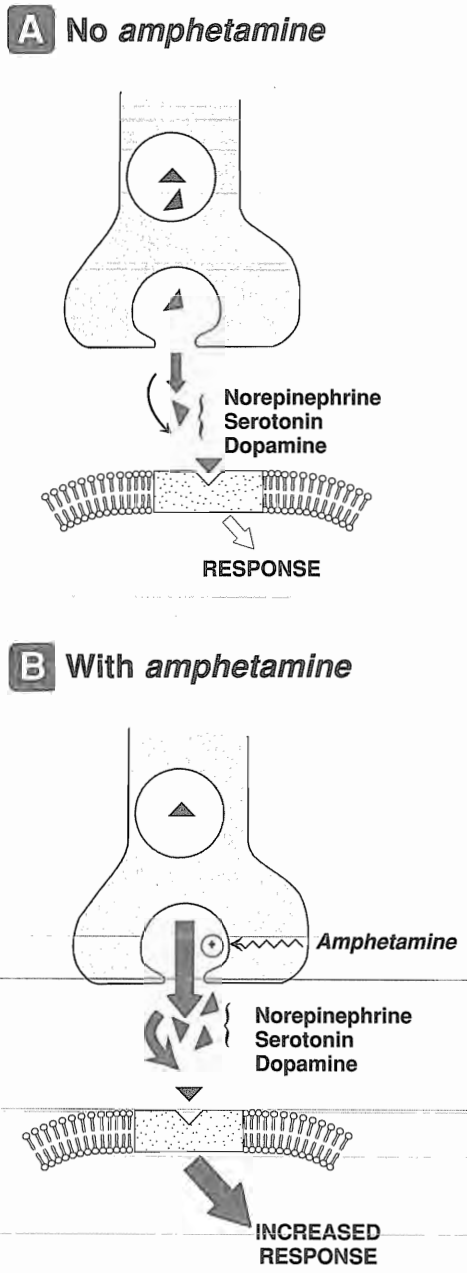

Figure 10.7
Mechanism of action of *amphetamine*.

a. **Attention deficit syndrome:** Some young children are hyperkinetic and lack the ability to be involved in any one activity for longer than a few minutes. *Amphetamine,* and more recently the *amphetamine* derivative *methylphenidate* [meth ill FEN i date], alleviate many of the behavioral problems associated with this syndrome, and reduce the hyperkinesia that the children demonstrate. Their attention is thus prolonged, allowing them to function better in a school atmosphere.

b. **Narcolepsy:** *Methylphenidate* is used to treat narcolepsy, a disorder marked by an uncontrollable desire for sleep.

4. **Pharmacokinetics:** Amphetamines are completely absorbed from the gastrointestinal tract, metabolized by the liver, and excreted in the urine. Amphetamine abusers often administer the drugs by intravenous injection and by smoking. The euphoria caused by *amphetamine* lasts 4 to 6 hours, or 4 to 8 times longer than the effects of *cocaine*. The amphetamines produce addiction—dependence, tolerance and drug-seeking behavior.

5. **Adverse effects:**

a. **Central effects:** Undesirable side effects of *amphetamine* usage include insomnia, irritability, weakness, dizziness, tremor, and hyperactive reflexes (Figure 10.8). *Amphetamine* can also cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients. Chronic *amphetamine* use produces a state of "*amphetamine* psychosis" that resembles an acute schizophrenic attack. While *amphetamine* is associated with psychic and physical dependence, tolerance to its effects may occur within a few weeks. Overdoses of *amphetamine* are treated with *chlorpromazine* (see p. 127), which relieves the CNS symptoms as well as the hypertension because of its α-blocking effects.

b. **Cardiovascular effects:** In addition to its CNS effects, *amphetamine* causes palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse. Headache, chills, and excessive sweating may also occur. Because of its cardiovascular effects, *amphetamine* should not be given to patients with cardiovascular disease or those receiving MAO inhibitors.

c. **Gastrointestinal system effects:** *Amphetamine* acts on the gastrointestinal system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea.

III. HALLUCINOGENS

A few drugs have as their primary action the ability to induce altered perceptual states reminiscent of dreams. Many of these altered states are accompanied by bright, colorful changes in the environment and by

a plasticity of constantly changing shapes and color. The individual under the influence of these drugs is incapable of normal decision making, since the drug interferes with rational thought. These compounds are known as hallucinogens or psychotomimetic drugs.

A. Lysergic acid diethylamide (LSD)

Multiple sites in the CNS are affected by *LSD*. The drug shows serotonin (5-HT) agonist activity at presynaptic receptors in the midbrain, binding to both 5-HT_1 and 5-HT_2 receptors. Activation of the sympathetic nervous system occurs, which causes pupillary dilation, increased blood pressure, piloerection, and increased body temperature. Taken orally, low doses of *LSD* can induce hallucinations with brilliant colors, and mood alteration occurs. Tolerance and physical dependence have occurred, but true dependence is rare. Adverse effects include hyperreflexia, nausea, and muscular weakness. Sometimes high doses produce long-lasting psychotic changes in susceptible individuals. *Haloperidol* (see p. 127) and other neuroleptics can block the hallucinatory action of *LSD* and quickly abort the syndrome.

B. Tetrahydrocannabinol

The main alkaloid contained in marijuana is *dronabinol* [droe NAB i nol], also called Δ^9-*tetrahydrocannabinol* [tet ra hi dro can NAB i nol] (*THC*). *Dronabinol* produces euphoria that is followed by drowsiness and relaxation, depending on the social situation. *THC* impairs short-term memory and mental activity. It decreases muscle strength and impairs highly skilled motor activity, such as that required to drive a car. It increases appetite, causes xerostomia, visual hallucinations, delusions, and enhancement of sensory activity. Although THC-receptors have been identified in the CNS, the mechanism of action of *THC* is unknown. *THC* effects show immediately after smoking, but maximal effects take about 20 minutes. By 3 hours, the effects largely disappear. Adverse effects include an increased heart rate, decreased blood pressure, and a reddening of the conjunctiva. At high doses, a toxic psychosis develops. Tolerance and mild physical dependence occur with continued frequent use of the drug. *THC* is sometimes given for the severe emesis caused by some cancer chemotherapeutic agents (see p. 243).

C. Phencyclidine (PCP)

Phencyclidine [fen SYE kli deen] ("angel dust") inhibits the re-uptake of dopamine, 5-HT, and norepinephrine. It also has anticholinergic activity, but surprisingly produces hypersalivation. *Phencyclidine*, an analog of *ketamine* (see p. 117), causes dissociative anesthesia (insensitivity to pain, without loss of consciousness) and analgesia. In this state, it produces numbness of extremities, staggered gait, slurred speech, and muscular rigidity. Sometimes hostile and bizarre behavior occurs. In increased dosage, anesthesia, stupor, or coma result, but strangely, the eyes may remain open. Increased sensitivity to external stimuli exists, and the CNS actions may persist for a week. Tolerance often develops with continued use.

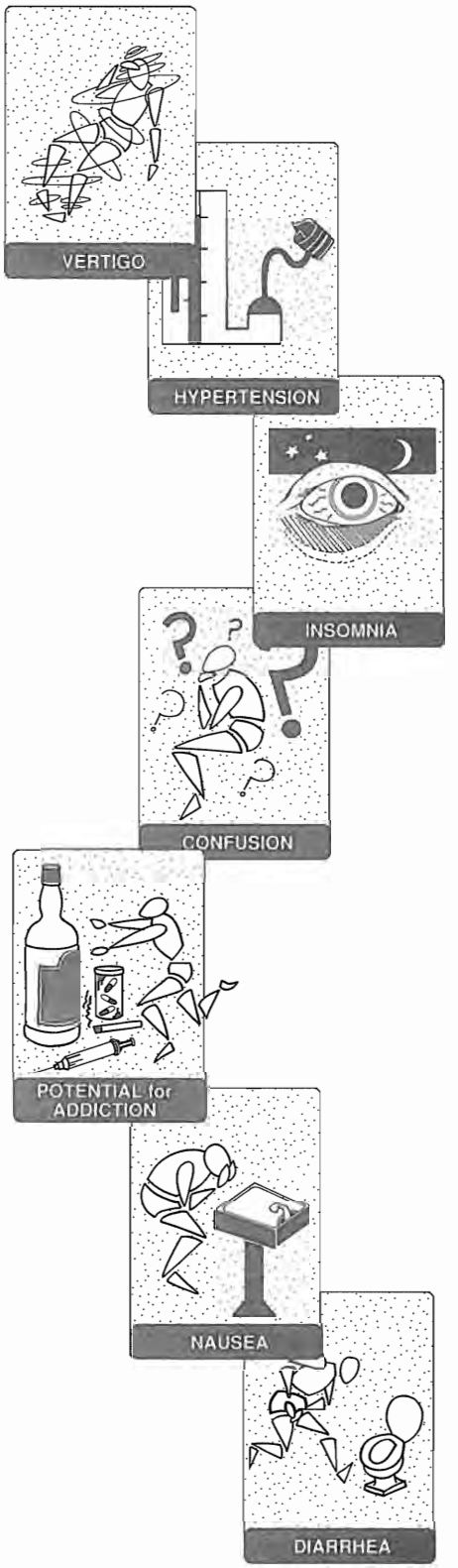

Figure 10.8
Adverse effects of amphetamines.

Choose the ONE best answer.

10.1 Which of the following is NOT characteristic of cocaine overdosage?

A. Dilation of the pupil.
B. Euphoria.
C. Tachycardia.
D. Peripheral vasodilation.
E. Hallucinations.

Correct choice = D. Cocaine causes peripheral vasoconstriction.

10.2 Which of the following statements about amphetamine is INCORRECT?

A. Overdosage of amphetamine can be managed with chlorpromazine.
B. Amphetamine is used as an adjunct with MAO inhibitors in the treatment of depression.
C. Amphetamine has a longer duration of action than cocaine.
D. Amphetamine depresses the hunger center in the hypothalamus.
E. Amphetamine acts on α- and β-adrenergic presynaptic terminals.

Correct choice = B. Amphetamines should not be used in patients receiving MAO inhibitors, since amphetamine itself weakly inhibits MAO. Chlorpromazine relieves the CNS symptoms and the hypertension because of its α-blocking effects. The euphoria caused by amphetamine lasts 4 to 6 hours, or 4 to 8 times longer than the effects of cocaine.

10.3 Which of the following statements concerning tetrahydrocannabinol (THC) is CORRECT?

A. THC decreases heart rate.
B. THC increases muscle strength.
C. THC decreases appetite.
D. THC causes hypotension.
E. THC has antiemetic action.

Correct answer = E. THC is sometimes used to treat the severe emesis caused by cancer chemotherapeutic agents.

10.4 Which one of the following drugs is INCORRECTLY paired with its toxic effects?

A. Amphetamine: Paranoid psychosis
B. Nicotine (low dose): Decreased heart rate and blood pressure
C. Cocaine: Anxiety and depression
D. LSD: Hallucinations
E. Caffeine: Insomnia and agitation

Correct answer = B. Nicotine activates the sympathetic nervous system and causes hypertension and tachycardia.

10.5 A very agitated young male was brought to the emergency room by the police. Psychiatric examination revealed that he had snorted cocaine several times in the past few days, the last time being 10 hours previously. He was given a drug which sedated him and he fell asleep. The drug very likely used to counter this patient's apparent cocaine withdrawal was:

A. Phenobarbital
B. Lorazepam
C. Cocaine
D. Hydroxyzine
E. Fluoxetine

Correct answer = B. The anxiolytic properties of benzodiazepines, such as lorazepam, make them the drugs of choice in treating the anxiety and agitation of cocaine withdrawal. Lorazepam also has hypnotic properties. Phenobarbital has hypnotic properties but it's anxiolytic properties are inferior to those of the benzodiazepines. Cocaine itself could counteract the agitation of withdrawal but its use would not be proper therapy. Hydroxyzine, an antihistaminic, is effective as an hypnotic and is sometimes used to deal with anxiety especially if emesis is a problem. Fluoxetine is an antidepressant with no immediate effects on anxiety.

Anesthetics

11

I. OVERVIEW

General anesthesia is essential to surgical practice because it renders patients analgesic, amnesic, and unconscious while causing muscle relaxation and suppression of undesirable reflexes. No single drug is capable of achieving these effects rapidly and safely. Rather, several different categories of drugs are utilized to produce "balanced anesthesia" (Figure 11.1). For example, adjuncts to anesthesia consist of preanesthetic medication and skeletal muscle relaxants. Preanesthetic medication serves to calm the patient, relieve pain, and protect against undesirable effects of the subsequently administered anesthetic or the surgical procedure. Skeletal muscle relaxants facilitate intubation and suppress muscle tone to the degree required for surgery. Potent general anesthetics are delivered via inhalation or intravenous injection. With the exception of *nitrous oxide*, modern inhaled anesthetics are all volatile, halogenated hydrocarbons that derive from early research and clinical experience with *diethyl ether* and *chloroform*. On the other hand, intravenous general anesthetics consist of a number of chemically unrelated drug types that are commonly used for the rapid induction of anesthesia. For some patients and surgical procedures, co-administration of local anesthetics and low doses of general anesthetics produces discreet analgesia, while minimizing the undesirable actions of the less selective agents.

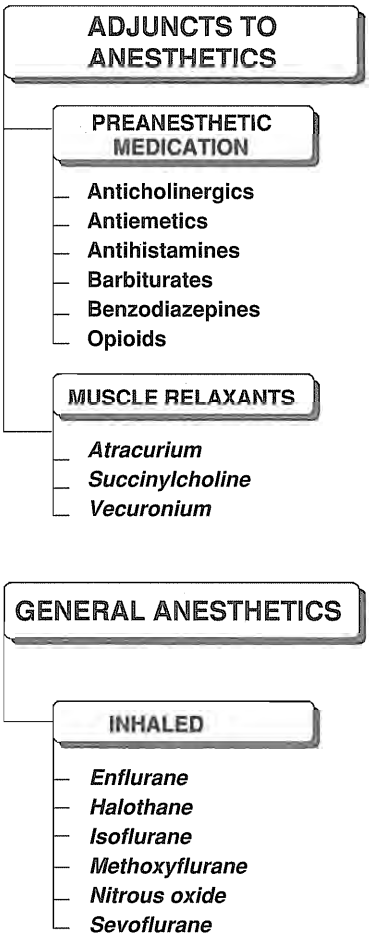

Figure 11.1
Summary of anesthetics.
(Figure continues on next page.)

II. PATIENT FACTORS IN SELECTION OF ANESTHESIA

During the preoperative phase, the anesthesiologist selects drugs that provide a safe and efficient anesthetic regimen based on the nature of the surgical procedure as well as the patient's physiologic and pharmacologic state.

A. Status of organ systems

1. **Liver and kidney:** Since the liver and kidney not only influence the long-term distribution and clearance of anesthetic agents, but also

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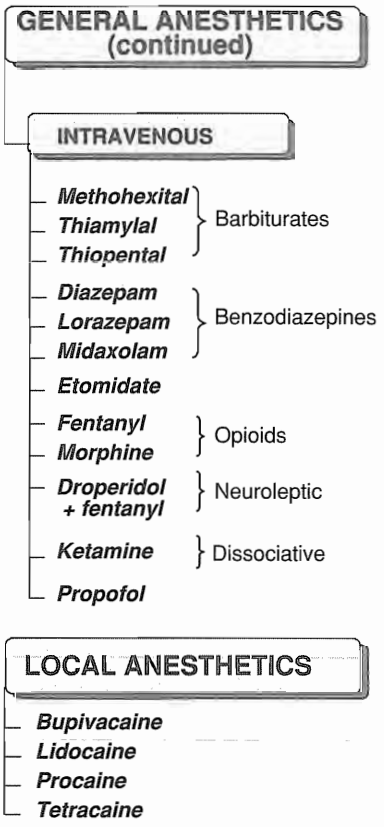

Figure 11.1 (continued)
Summary of anesthetics.

frequently serve as the target organs for toxic effects, the physiologic status of these organs must be considered. Of particular concern, release of fluoride, bromide, and other metabolic products of halogenated hydrocarbons can affect these organs, especially if these metabolites accumulate with repeated anesthetic administration.

2. **Respiratory system:** The condition of the respiratory system must be considered if inhalation anesthetics are indicated. For example, asthma, or ventilation or perfusion abnormalities complicate control of an inhalation anesthetic.

3. **Cardiovascular system:** While the hypotensive effect of most anesthetics is sometimes desirable, ischemic injury of tissues could follow reduced perfusion pressure. Should a hypotensive episode during a surgical procedure necessitate treatment, a vasoactive substance must be selected after considering the possibility that the anesthetic present may sensitize the heart to the arrhythmogenic effects of sympathomimetic agents.

4. **Nervous system:** The existence of neurologic disorders (for example, epilepsy, myasthenia gravis) influences the selection of an anesthetic. So, too, would a patient history suggestive of a genetically-determined sensitivity to halogenated hydrocarbon-induced malignant hyperthermia (see p. 113).

B. Concomitant use of drugs

1. **Multiple adjunct agents:** Quite often, surgical patients receive one or more of the following preanesthetic medications: benzodiazepines (for example, *diazepam*, see p. 89) to relieve anxiety and facilitate amnesia; barbiturates (for example, *pentobarbital*, see p. 94) for sedation; antihistamines for prevention of allergic reactions (for example, *diphenhydramine*, see p. 422) or to reduce gastric acidity (*cimetidine*, see p. 236); antiemetics (for example, *droperidol*, see p. 242); opioids (for example, *fentanyl*, see p. 139) for analgesia; and/or anticholinergics (for example, *scopolamine*, see p. 48) to prevent bradycardia and secretion of fluids into the respiratory tract (Figure 11.2). These agents facilitate smooth induction of anesthesia, and when continuously administered, they also lower the dose of anesthetic required to maintain the desired level of surgical (Stage III) anesthesia. However, such co-administration can also enhance undesirable anesthetic effects (for example, hypoventilation) and may produce negative effects not observed when the same drugs are given alone.

2. **Concomitant use of additional nonanesthetic drugs:** Surgery patients may be chronically exposed to agents for the treatment of the underlying disease, as well as to drugs of abuse that alter the response to anesthetics. For example, alcoholics have elevated levels of hepatic microsomal enzymes involved in the metabolism of barbiturates, and drug abusers may be overly tolerant of the anesthetic, since drugs of abuse and anesthetics can act on the same biochemical pathway(s).

III. INDUCTION, MAINTENANCE AND RECOVERY FROM ANESTHESIA

Anesthesia can be divided into three stages: induction, maintenance, and recovery. Induction is defined as the period of time from onset of administration of the anesthetic to the development of effective surgical anesthesia in the patient. Maintenance provides a sustained surgical anesthesia. Recovery is the time from discontinuation of administration of anesthesia until consciousness is regained. Induction of anesthesia depends on how fast effective concentrations of the anesthetic drug reach the brain; recovery is the reverse of induction and depends on how fast the anesthetic drug is removed from the brain.

A. Induction

During induction it is essential to avoid the dangerous excitatory phase (Stage II delirium) characterizing the slow onset of action of some anesthetics (see below). Thus, general anesthesia is normally induced with an intravenous anesthetic like *thiopental*; unconsciousness results within 25 seconds after injection. At that time, additional inhalation or intravenous drugs comprising the selected anesthetic may be given to produce the desired depth of surgical (Stage III) anesthesia. [Note: This often includes co-administration of an intravenous skeletal muscle relaxant to facilitate intubation and relaxation. Currently used muscle relaxants include *vecuronium*, *atracurium*, and *succinylcholine* (see p. 52).]

B. Maintenance of anesthesia

Maintenance is the time during which the patient is surgically anesthetized. After administering the selected anesthetic mixture, the anesthesiologist monitors the patient's vital signs and response to various stimuli throughout the surgical procedure in order to carefully balance the amount of drug inhaled and/or infused with the depth of anesthesia. Anesthesia is usually maintained by the administration of gases or volatile anesthetics, since these agents offer good minute-to-minute control over the depth of anesthesia.

C. Recovery

Postoperatively, the anesthesiologist withdraws the anesthetic mixture and monitors the immediate return of the patient to consciousness. For most anesthetic agents, recovery is the reverse of induction; that is, redistribution from the site of action rather than metabolism underlies recovery. The anesthesiologist continues to monitor the patient to be sure that there are no delayed toxic reactions, for example, diffusion hypoxia for *nitrous oxide*, and hepatotoxicity with halogenated hydrocarbons.

D. Depth of anesthesia

The depth of anesthesia can be divided into a series of four sequential stages; each is characterized by increased CNS depression that is caused by accumulation of the anesthetic drug in the brain. With

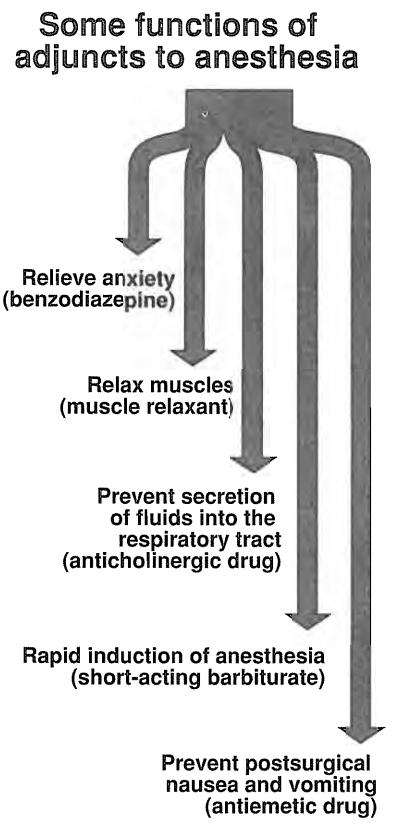

Figure 11.2
Components of balanced anesthesia.

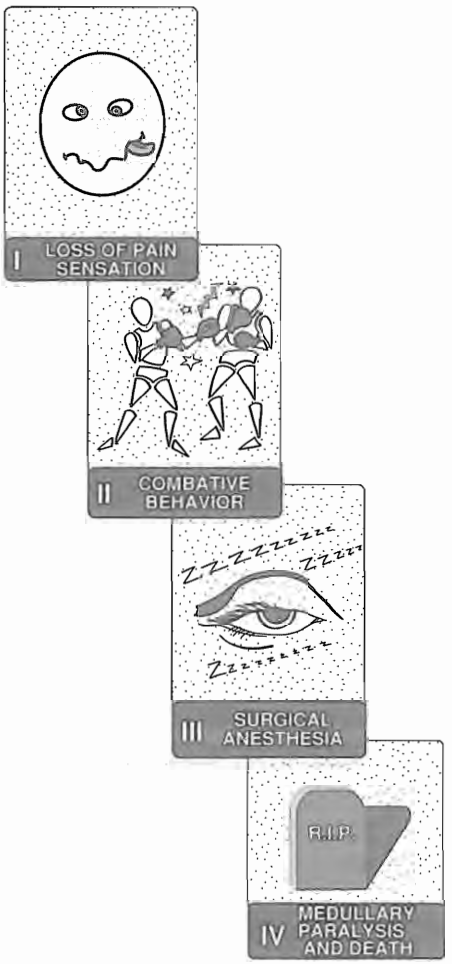

Figure 11.3
Stages of anesthesia.

ether, which produces a slow onset of anesthesia, all the stages are discernible (Figure 11.3). However, with *halothane* and many other commonly used anesthetics, the stages are difficult to clearly characterize because of the rapidity of onset of anesthesia.

1. **Stage I—analgesia:** Loss of pain sensation results from interference with sensory transmission in the spinothalamic tract. The patient is conscious and conversational. A reduced awareness of pain occurs as Stage II is approached.

2. **Stage II—excitement:** The patient experiences delirium and violent combative behavior. There is a rise and irregularity in blood pressure. The respiratory rate may be increased. To avoid this stage of anesthesia, a short-acting barbiturate, such as *sodium pentothal*, is given intravenously before inhalation anesthesia is administered.

3. **Stage III—surgical anesthesia:** Regular respiration and relaxation of the skeletal muscles occur in this stage. Eye reflexes decrease progressively, until the eye movements cease and the pupil is fixed. Surgery may proceed during this stage.

4. **Stage IV—medullary paralysis:** Severe depression of the respiratory center and vasomotor center occur during this stage. Death can rapidly ensue.

IV. INHALATION ANESTHETICS

Inhaled gases are the mainstay of anesthesia and are primarily used for the maintenance of anesthesia after administration of an intravenous agent. Inhalation anesthetics have a benefit that is not available with intravenous agents, since the depth of anesthesia can be rapidly altered by changing the concentration of the inhaled anesthetic. Because most of these agents are rapidly eliminated from the body, they do not cause postoperative respiratory depression.

A. Common features of inhaled anesthestics

Modern inhalation anesthetics are nonexplosive agents that include the gas *nitrous oxide* as well as a number of volatile halogenated hydrocarbons. As a group, these agents decrease cerebrovascular resistance, resulting in increased perfusion of the brain. They cause bronchodilation and decrease minute ventilation. Their clinical potency cannot be predicted by their chemical structure, but potency does correlate with their solubility in lipid. The movement of these agents from the lungs to the different body compartments depends upon their solubility in blood and various tissues. Recovery from their effects is due to redistribution from the brain.

B. Potency

The potency of inhaled anesthetics is defined quantitatively as the minimum alveolar concentration (MAC), which is the concentration of anesthetic gas needed to eliminate movement among 50% of patients challenged by a standardized skin incision. The MAC is

usually expressed as the percent of gas in a mixture required to achieve the effect. Numerically, MAC is small for potent anesthetics, such as *halothane*, and large for less potent agents, such as *nitrous oxide*. Therefore, the inverse of MAC is an index of potency of the anesthetic. The MAC values are useful in comparing pharmacologic effects of different anesthetics (Figure 11.4). The more lipid-soluble an anesthetic, the lower the concentration of anesthetic needed to produce anesthesia.

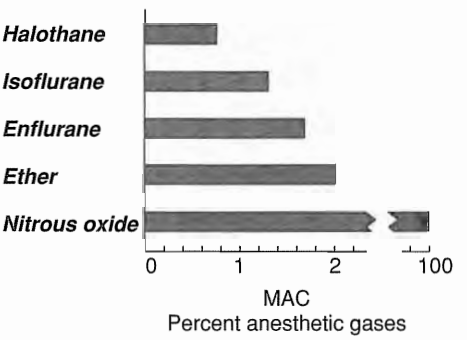

Figure 11.4
Minimal alveolar concentrations (MAC) for anesthetic gases.

C. Uptake and Distribution of Inhalation Anesthetics

The partial pressure of an anesthetic gas at the origin of the respiratory pathway is the driving force that moves the anesthetic into the alveolar space and thence into the blood, which delivers the drug to the brain and various other body compartments. Since gases move from one compartment to another within the body according to partial pressure gradients, a steady state is achieved when the partial pressure in each of these compartments is equivalent to that in the inspired mixture. The time course for attaining this steady state is determined by the following three factors:

1. **Alveolar wash-in:** This term refers to the replacement of the normal lung gases with the inspired anesthetic mixture. The time required for this process is directly proportional to the functional residual capacity of the lung, and inversely proportional to the ventilatory rate; it is independent of the physical properties of the gas. Once the partial pressure builds within the lung, anesthetic uptake from the lung begins.

2. **Solubility in blood:** The first compartment that the anesthetic gas encounters is the blood. Solubility in blood is determined by a physical property of the anesthetic molecule called the blood/gas partition coefficient, which is the ratio of the total amount of gas in the blood relative to the gas equilibrium phase (Figure 11.5). Drugs with low versus high solubility in blood differ in their speed of induction of anesthesia. For example, when an anesthetic gas with low blood solubility, such as *nitrous oxide*, diffuses from the alveoli into the circulation, little of the anesthetic dissolves in the blood. Therefore, the equilibrium between the inhaled anesthetic and arterial blood occurs rapidly, and relatively few additional molecules of anesthetic are required to raise arterial tension (that is, steady-state is rapidly achieved). In contrast, an anesthetic gas with high blood solubility, such as *halothane*, dissolves more completely in the blood, and greater amounts of the anesthetic and longer periods of time are required to raise arterial tension. This results in increased times of induction and recovery, and slower changes in the depth of anesthesia in response to changes in the concentration of the inhaled drug.

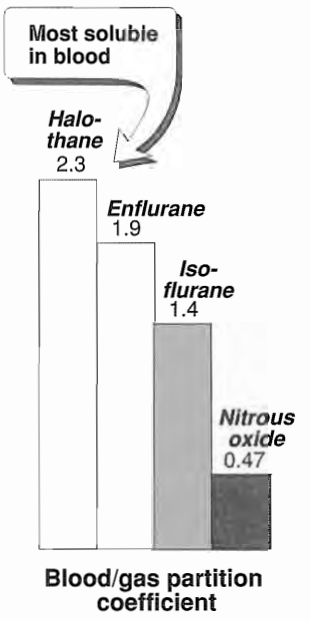

Figure 11.5
Blood/gas partition coefficients for the inhalation anesthetics.

3. **Tissue uptake:** The arterial circulation distributes the anesthetic to various tissues, and the pressure gradient drives free anesthetic gas into tissues. The time required for a particular tissue to achieve a steady-state with the partial pressure of an anesthetic gas in the inspired mixture is inversely proportional to the blood flow to that tissue (faster flow results in a more rapidly achieved steady-state), and directly proportional to the capacity to store anesthetic (larger

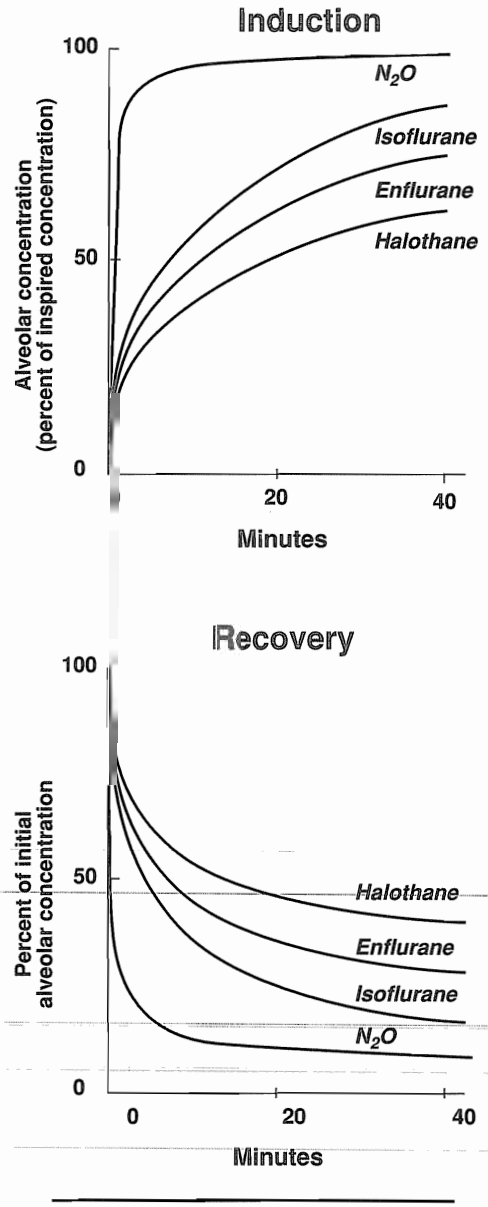

Figure 11.6
Changes in the alveolar blood concentration of the inhalation anesthetics with time.

capacity results in a longer time to achieve steady-state). Capacity, in turn, is directly proportional to the tissue's volume, and the tissue/blood solubility coefficient of the anesthetic molecule. On the basis of these considerations, four major compartments determine the time course of anesthetic uptake:

a. **Brain, heart, liver, kidney, endocrine glands:** These highly perfused tissues rapidly attain a steady-state with the partial pressure of the anesthetic in blood.

b. **Skeletal muscles:** These are poorly perfused during anesthesia. This and the fact that they have a large volume, prolong the time required to achieve steady-state.

c. **Fat:** This tissue is also poorly perfused. However, potent general anesthetics are very lipid soluble. Therefore, fat has a large capacity to store anesthetic. This combination of slow delivery to a high capacity compartment prolongs the time required to achieve steady state.

d. **Bone, ligaments, and cartilage:** These are poorly perfused and have a relatively low capacity to store anesthetic. Therefore, these tissues have only a slight impact on the time course of anesthetic distribution in the body.

4. **Return of gas-depleted blood to the lung:** As the venous circulation returns blood depleted of anesthetic to the lung, more gas moves into the blood from the lung according to the partial pressure difference. Over time, the partial pressure in the alveolar space closely approximates the partial pressure in the inspired mixture; that is, there is no further anesthetic uptake from the lung.

5. **Uptake curves for inhaled anesthetics:** Figure 11.6 illustrates the uptake curves for four inhalation anesthetics. The solubility in blood, as well as tissues, is in the following order: *halothane* > *enflurane* > *isoflurane* > *nitrous oxide*. Because of its low solubility, the partial pressure of *nitrous oxide* in the inspired mixture and the body most rapidly achieves a steady-state.

6. **Washout:** When the administration of an inhalation anesthetic is discontinued, the body now becomes the "source" that drives the anesthetic into the alveolar space. The same factors that influence attainment of steady-state with an inspired anesthetic determine the time course of clearance of the drug from the body. Thus, *nitrous oxide* exits the body faster than *halothane*.

C. Mechanism of Action

Inhalation anesthetics are nonselective in their action. That is, in addition to their clinically important effect on the central nervous system (CNS), they also alter the function of various peripheral cell types. The fact that chemically unrelated molecules produce a state of general anesthesia argues against a specific anesthetic receptor. Further, whereas anesthetics alter the function of receptors for neurotransmitters (for example, γ-aminobutyric acid, glutamate),

they do so nonselectively. Thus, the fact that CNS regions, like the reticular activating system and cortex, represent important sites of anesthetic action is apparently unrelated to the presence of a specific receptor in a particular region, but rather to the role of the CNS in controlling the overall state of consciousness and response to sensory stimuli.

D. Specific inhalation anesthetics

Each of the halogenated gases has characteristics beneficial for selected clinical applications. No one anesthetic is superior to another under all circumstances. [Note: In a very small population of patients, all of the halogenated hydrocarbon anesthetics have the potential to induce malignant hyperthermia. While the etiology of this condition is unknown, it appears to be inherited. Thus, asking whether a family member responded adversely to gaseous anesthesia could provide the warning needed to avoid a rare encounter with this pathology. Should a patient exhibit the hyperthermia and muscle rigidity characteristic of malignant hyperthermia, *dantrolene* is given as the anesthetic mixture is withdrawn.]

1. **Halothane:** This agent is the prototype to which newer agents in this series of anesthetics are compared. While *halothane* [hal loe thane] is a potent anesthetic, it is a relatively weak analgesic. Thus, *halothane* is usually co-administered with *nitrous oxide*, opioids, or local anesthetics. Like other halogenated hydrocarbons, *halothane* is vagomimetic and will cause *atropine*-sensitive bradycardia. In addition, *halothane* has the undesirable property of causing cardiac arrhythmias. These are especially serious if hypercapnia (increased arterial carbon dioxide tension) develops due to reduced alveolar ventilation, or if the plasma concentration of catecholamines increases. The latter fact is of particular significance since *halothane* produces hypotension. Should it become necessary to counter excessive hypotension during *halothane* anesthesia, it is recommended that a direct-acting vasoconstrictor (for example, *phenylephrine*, see p. 66) be given. *Halothane* is oxidatively metabolized in the body to tissue-toxic hydrocarbons (for example, trifluroethanol) and bromide ion. These substances may be responsible for the toxic reactions that some patients (especially females) develop after *halothane* anesthesia. This reaction begins as fever, anorexia, nausea, and vomiting, and patients may exhibit signs of hepatitis. Although the incidence of this reaction is low—approximately 1 in 10,000 individuals—50% of such patients will die of hepatic necrosis. To avoid this condition, a *halothane* anesthesia is not repeated at intervals less than 2 to 3 weeks. [Note: *Halothane* is not hepatotoxic in pediatric patients and that, combined with its pleasant odor, make it the agent of choice in children.]

2. **Enflurane:** This gas is less potent than *halothane*, but it produces rapid induction and recovery. About 2% of the agent is metabolized to fluoride ion, which is excreted by the kidney. Therefore, *enflurane* [EN floo rane] is contraindicated in patients with kidney failure. *Enflurane* anesthesia exhibits the following differences from *halothane*: fewer arrhythmias, less sensitization of the heart to catecholamines, and greater potentiation of muscle relaxants

due to a more potent "curare-like" effect. A disadvantage of *enflurane* is that it causes CNS excitation at twice the MAC and at lower doses if hyperventilation reduces the pCO_2.

3. **Isoflurane:** This is a newer halogenated anesthetic that has low biotransformation and low organ toxicity. Unlike the other halogenated anesthetic gases, *isoflurane* [ey soe FLURE ane] does not induce cardiac arrhythmias and does not sensitize the heart to the action of catecholamines. *Isoflurane* is a very stable molecule that undergoes little metabolism, as a result of which, less fluoride is produced. *Isoflurane* is not currently believed to be tissue toxic.

4. **Methoxyflurane:** This agent is the most potent inhalation anesthetic because of its high solubility in lipid. Prolonged administration of *methoxyflurane* [meth ox ee FLURE ane] is associated with the metabolic release of fluoride, which is toxic to the kidneys. Therefore, *methoxyflurane* is rarely used outside of obstetric practice. It finds use in child-birth because it does not relax the uterus when briefly inhaled.

5. **Nitrous oxide:** Whereas *nitrous oxide* [nye truss OX ide] (N_2O or "laughing gas") is a potent analgesic, it is a weak general anesthetic. Thus, it is frequently combined with other more potent agents. Because it moves very rapidly into and out of the body, *nitrous oxide* can increase the volume (pneumothorax) or pres-

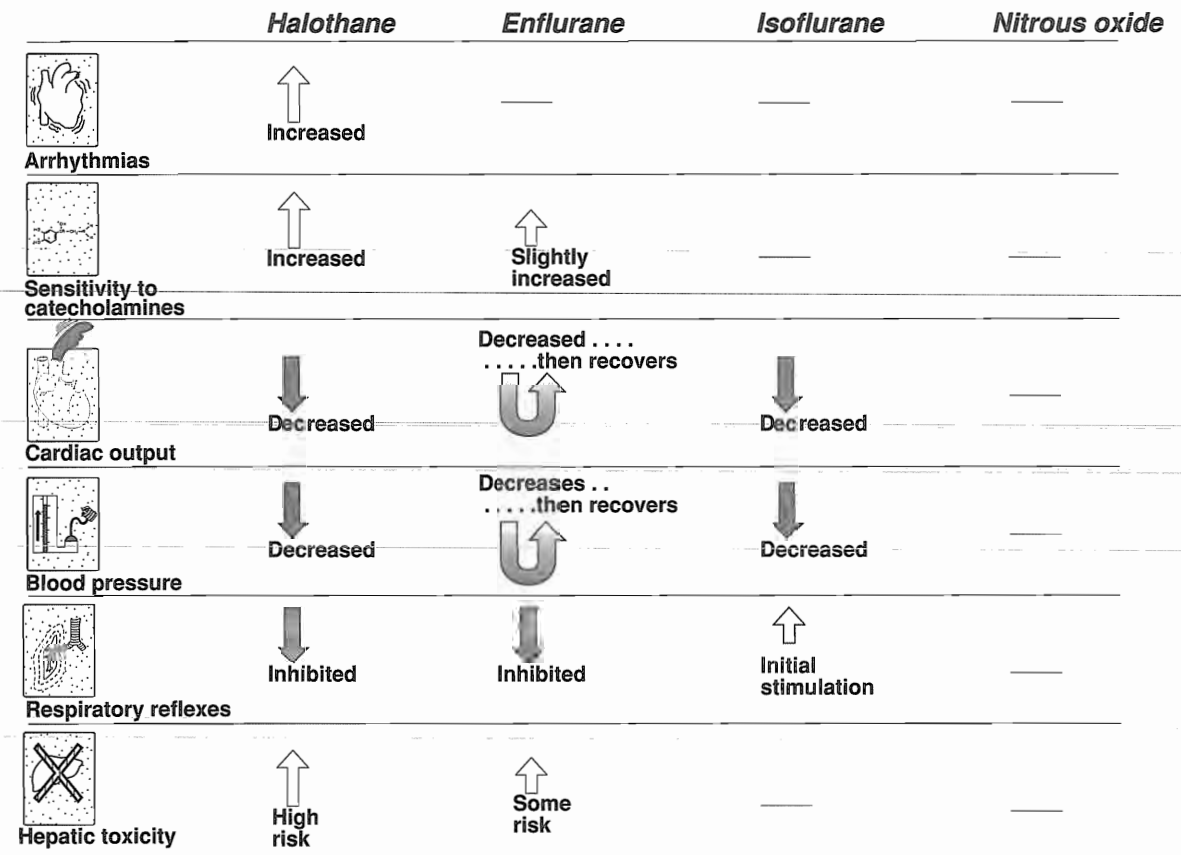

Figure 11.7
Characteristics of some inhalation anesthetics.

sure (sinuses) within closed body compartments. Furthermore, its speed of movement allows *nitrous oxide* to retard oxygen uptake during recovery, thus causing diffusion hypoxia. This anesthetic does not depress respiration nor does it produce muscle relaxation. It also has the least effect on the cardiovascular system and on increasing cerebral blood flow, and is the least hepatotoxic of the inhalation anesthetics. It is therefore probably the safest of these anesthetics, provided that at least 20% oxygen is always administered at the same time. [Note: *Nitrous oxide* at 80% (without other adjunct agents) cannot produce surgical anesthesia.] *Nitrous oxide* is often employed at concentrations of 30% in combination with oxygen for analgesia, particularly in dental surgery.

6. **Sevoflurane:** This fluorocarbon has recently been approved for induction and maintenance of general anesthesia. *Sevoflurane* has low pungency, allowing rapid uptake without irritating the airway during induction and making it suitable for induction through a mask in children. The drug has low solubility in blood and shows a rapid uptake and excretion. Some characteristics of the inhaled anesthetics are summarized in Figure 11.7

V. INTRAVENOUS ANESTHETICS

Intravenous anesthetics are often used for the rapid induction of anesthesia, which is then maintained with an appropriate inhalation agent. They rapidly induce anesthesia, and must therefore be injected slowly. Recovery from intravenous anesthestics is due to redistribution from sites in the CNS.

A. Barbiturates

Thiopental (see p. 94) is a potent anesthetic and a weak analgesic. It is the most widely used intravenously administered general anesthetic. It is an ultra-short-acting barbiturate and has a high lipid solubility. When agents such as *thiopental*, *thiamylal* [thye AM i lal], and *methohexital* [meth oh HEX i tal] are administered intravenously, they quickly enter the CNS and depress function, often in less than 1 minute. However, diffusion out of the brain can occur very rapidly as well, because of redistribution of the drug to other body tissues, including skeletal muscle and ultimately adipose tissue (Figure 11.8). This latter site serves as a reservoir of drug from which the agent slowly leaks out and is metabolized and excreted. The short duration of anesthetic action is due to the decrease of its concentration in the brain to a level below that necessary to produce anesthesia. These drugs may remain in the body for relatively long periods of time after their administration, since only about 15% of the dose of barbiturate entering the circulation is metabolized by the liver per hour. Thus, metabolism of *thiopental* is much slower than tissue redistribution. The barbiturates are not significantly analgesic and require some type of supplementary analgesic administration during anesthesia, otherwise objectionable changes in blood pressure and autonomic function may ensue. *Thiopental* has minor effects on the

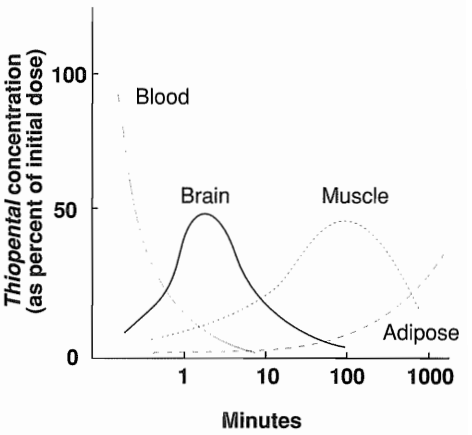

Figure 11.8
Redistribution of *thiopental* from brain to muscle and adipose tissue.

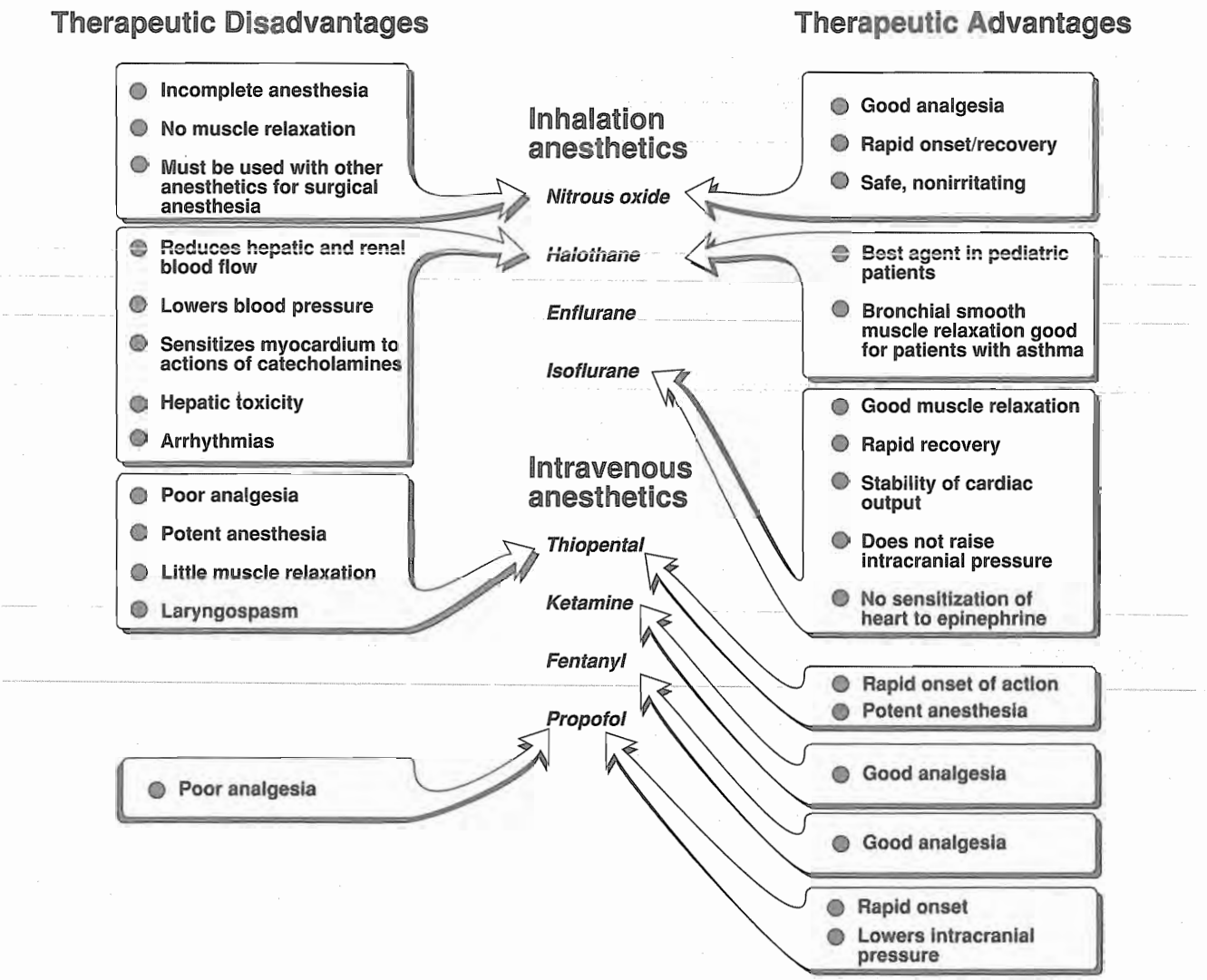

Figure 11.9
Therapeutic disadvantages and advantages of some anesthetic agents.

cardiovascular system, but it may contribute to severe hypotension in hypovolemic or shock patients. All barbiturates can cause apnea, coughing, chest wall spasm, laryngospasm, and bronchospasm; this is a concern for asthmatic patients. Barbiturates are contraindicated in patients with acute intermittent or variegate porphyria.

B. Benzodiazepines

Although *diazepam* (see p. 89) is the prototype benzodiazepine, *lorazepam* and *midazolam* are more potent. All three facilitate amnesia while causing sedation. *Etomidate* [e TOE mi date] is a hypnotic substance lacking analgesic properties that can cause uncontrolled skeletal muscle activity.

C. Opioids

Because of their analgesic property, opioids are frequently used together with other anesthetics; for example, the combination of

morphine (see p. 135) and *nitrous oxide* provide good anesthesia for cardiac surgery. However, opioids are not good amnesics and they can all cause hypotension, respiratory depression, and muscle rigidity as well as postanesthetic nausea and vomiting. *Fentanyl* (see p. 139) is more frequently used than *morphine.* Opioid effects can be antagonized by *naloxone* (see p. 141).

D. Neuroleptanesthesia

The combination of *droperidol* and *fentanyl* is a fixed ratio preparation called INNOVAR. Since *droperidol* is a neuroleptic substance, INNOVAR is said to produce neurolept analgesia; if combined with a more potent anesthetic, INNOVAR produces neuroleptic anesthesia. A neuroleptic has adrenergic blocking as well as sedative, antiemetic, and anticonvulsant properties. Since INNOVAR can cause extrapyramidal muscle movements, it is contraindicated in Parkinson's patients.

E. Ketamine

Ketamine [KET a meen], a short-acting nonbarbiturate anesthetic, induces a dissociated state in which the patient appears awake but is unconscious and does not feel pain. This dissociative anesthesia provides sedation, amnesia, and immobility. *Ketamine* stimulates the central sympathetic outflow, which in turn, causes stimulation of the heart and increased blood pressure and cardiac output. It also increases plasma catecholamine levels and increases blood flow. *Ketamine* is therefore used when circulatory depression is undesirable. On the other hand, these effects mitigate against the use of *ketamine* in hypertensive or stroke patients. The drug is lipophilic and enters the brain circulation very quickly, but like the barbiturates, it can redistribute to other organs and tissues. It is metabolized in the liver, but small amounts can be excreted unchanged. *Ketamine* is employed mainly in children and young adults for short procedures, but it is not widely used, because it increases cerebral blood flow and induces postoperative hallucinations ("nightmares").

F. Propofol

Propofol [pro POF ol] is an IV sedative/hypnotic used in the induction or maintenance of anesthesia. Onset is smooth and occurs within about 40 seconds of administration. Supplemenation with narcotics for analgesia is required. While *propofol* facilitates depression in the CNS, high plasma levels can cause excitation. *Propofol* decreases blood pressure without depressing the myocardium. It also reduces intracranial pressure.

Some therapeutic advantages and disadvantages of the anesthetic agents are summarized in Figure 11.9.

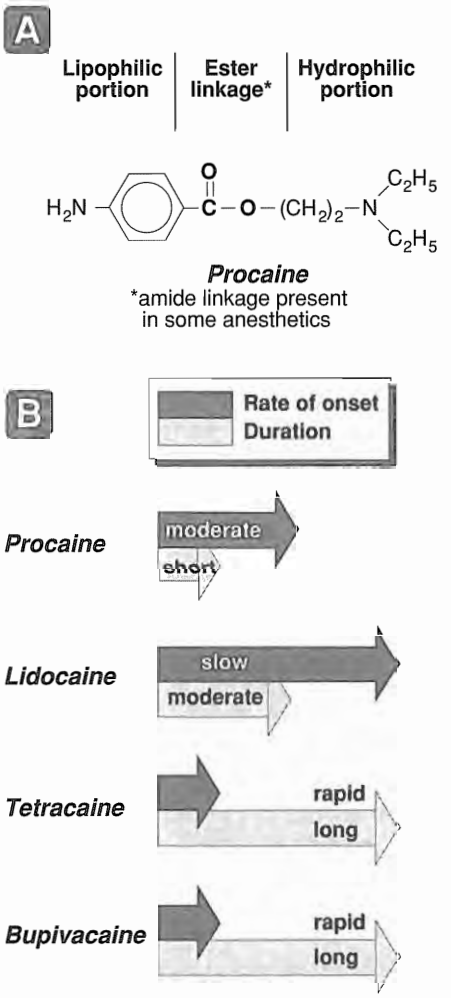

Figure 11.10
A. Structural formula of *procaine.*
B. Pharmacokinetic properties of local anesthetics.

VI. LOCAL ANESTHETICS

These drugs are applied locally and block nerve conduction of sensory impulses from the periphery to the CNS. Local anesthetics abolish sensation (and in higher concentrations, motor activity) in a limited area of

the body without producing unconsciousness. They inhibit sodium channels of the nerve membrane. The small, unmyelinated nerve fibers, that conduct impulses for pain, temperature, and autonomic activity, are most sensitive to actions of local anesthetics. All of the local anesthetics consist of a hydrophilic amino group linked through a connecting group of variable length to a lipophilic aromatic residue (Figure 11.10). Both potency and toxicity of the local anesthetics increase as the connecting group becomes longer. Adverse effects result from systemic absorption of toxic amounts of the locally applied anesthetic. Seizures are the most significant of these systemic effects. By adding the vasoconstrictor *epinephrine* to the local anesthetic, the rate of absorption is decreased (see p. 63). This both minimizes systemic toxicity and increases the duration of action.

Study Questions

Questions 11.1 – 11.7

Given the following drugs:

A. Methoxyflurane
B. Succinylcholine
C. Diazepam
D. Halothane
E. Nitrous oxide
F. Thiopental
G. Innovar®
H. Ketamine
I. Etomidate
K. Isoflurane

Match the most appropriate anesthetic or adjunct from the list above with the following descriptions:

11.1 Acts at the neuromuscular junction to cause initial muscle excitation.

Correct answer = B (Succinylcholine).

11.2 Contains tissue toxic bromide.

Correct answer = D (Halothane).

11.3 Potent analgesic; weak anesthetic.

Correct answer = E (Nitrous oxide).

11.4 Potent anesthetic; weak analgesic.

Correct answer = F (Thiopental).

11.5 Drug combination producing neurolept analgesia.

Correct answer = G (Innovar®).

11.6 Used solely in obstetric practice.

Correct answer = A (Methoxyflurane).

11.7 Facilitates surgical amnesia.

Correct answer = C (Diazepam).

Choose the ONE best answer

11.8 Which one of the following is most likely to require administration of a muscle relaxant?

A. Ethyl ether
B. Halothane
C. Methoxyflurane
D. Benzodiazepines
E. Nitrous oxide

Correct answer = E. Nitrous oxide has virtually no muscle relaxing properties. Ether, methoxyflurane, and benzodiazepine produce good muscle relaxation; halothane produces moderate muscle relaxation.

Antidepressant Drugs

12

I. OVERVIEW

Major depresssion and bipolar disorder are pervasive mood altering illnesses affecting energy, sleep, appetite, libido and the ability to function. Depression is different from schizophrenia, which produces disturbances in thought. The symptoms of depression are intense feelings of sadness, hopelessness, despair, and the inability to experience pleasure in usual activities. Mania is characterized by the opposite behavior, that is, enthusiasm, rapid thought and speech patterns, and extreme self-confidence and impaired judgment. All clinically useful antidepressant drugs (also called thymoleptics) potentiate, either directly or indirectly, the actions of norepinephrine, dopamine, and/or serotonin in the brain. (See Figure 12.1 for a summary of the antidepressant agents.) This, along with other evidence, led to the biogenic amine theory, which proposes that depression is due to a deficiency of monoamines such as norepinephrine and serotonin at certain key sites in the brain. Conversely, mania is envisioned as caused by an overproduction of these neurotransmitters.The amine theory of depression is probably overly simplistic, since it is now known that the antidepressant drugs, particularly the tricyclic antidepressants, affect many biological systems in addition to neurotransmitter uptake. It is not known which of these neurochemical systems is most responsible for the antidepressant activity.

II. TRICYCLIC/POLYCYCLIC ANTIDEPRESSANTS

The tricyclic and polycyclic antidepressants block norepinephrine, and serotonin uptake into the neuron. Prolonged therapy probably leads to alterations in selected central nervous system (CNS) receptors. The important drugs in this group are *imipramine* ([im IP ra meen], the prototype), *amitriptyline* [a mee TRIP ti leen], *desipramine* ([dess IP ra meen], a demethylated derivative of *imipramine*), *nortriptyline* [nor TRIP ti leen], *protriptyline* [proe TRIP te leen], and *doxepin* [DOX e pin]. *Amoxapine* [a MOX a peen] and *maprotiline* [ma PROE ti leen] are termed "second generation" to distinguish them from the older tricyclic antidepressants. [Note: These second generation drugs have actions similar to *imipramine*, although they exhibit slightly different pharmacokinetics.] All the tricyclic antidepressants (TCAs) have similar therapeutic efficacy, and the choice of drug depends on tolerance of side effects and duration of action. Patients who do not respond to one TCA may benefit from a different drug in this group.

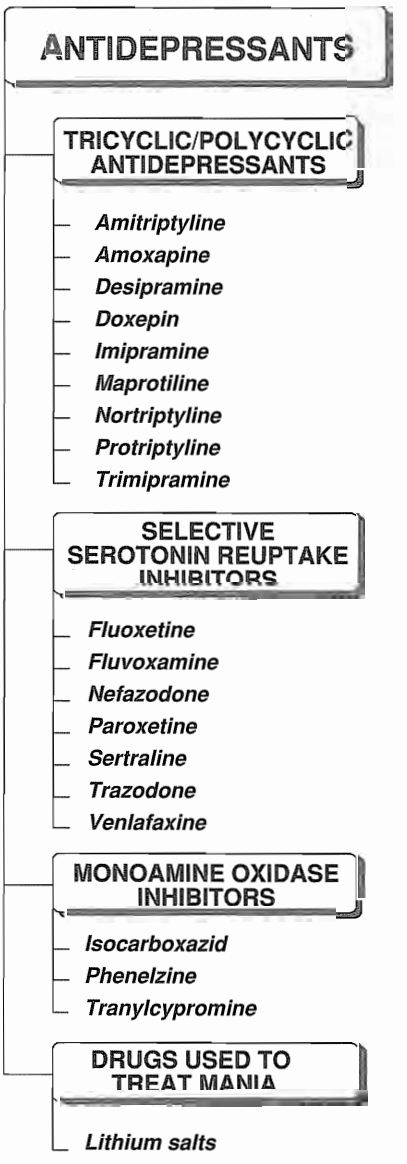

Figure 12.1
Summary of antidepressants.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

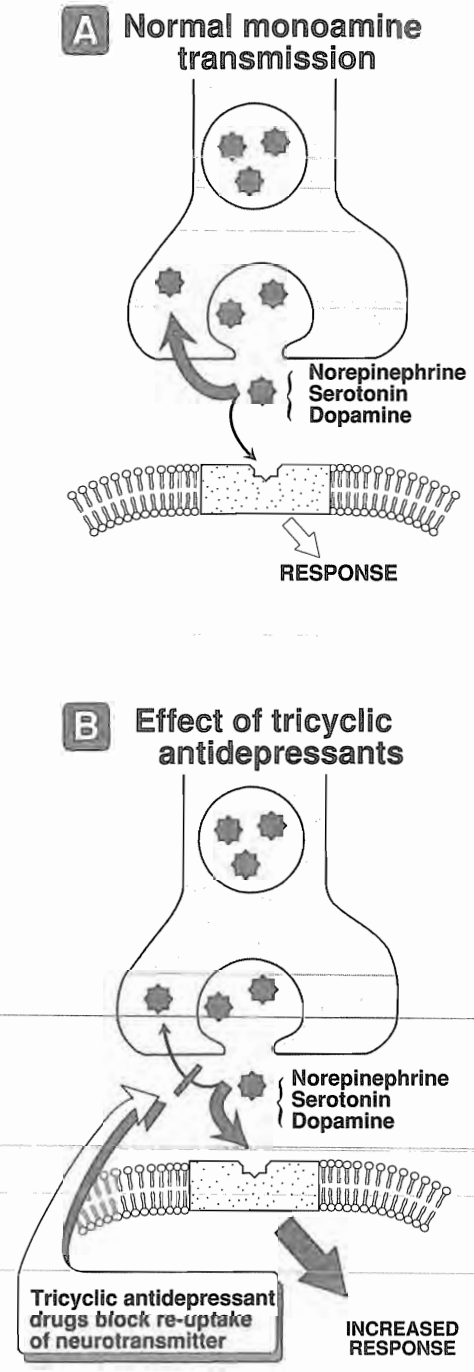

Figure 12.2
Mechanisms of action of tricyclic and polycyclic antidepressant drugs.

A. Mode of action

1. **Inhibition of neurotransmitter uptake:** TCAs inhibit the neuronal reuptake of norepinephrine, and serotonin into presynaptic nerve terminals (Figure 12.2). By blocking the major route of neurotransmitter removal, the TCAs lead to increased concentrations of monoamines in the synaptic cleft, resulting in antidepressant effects. This theory has been discounted by some because of several observations. For example, the potency of the TCA in blocking neurotransmitter uptake often does not correlate with clinically observed antidepressant effects. Further, blockade of reuptake of neurotransmitter occurs immediately after administration of the drug, but the antidepressant effect of the TCA requires several weeks of continued treatment. This suggests that decreased uptake of neurotransmitter is only an initial event that may not be related to the antidepressant effects. It has been suggested that monoamine receptor densities in the brain may change over a 2 to 4 week period with drug use and may be important in the onset of activity.

2. **Blocking of receptors:** The TCAs also block serotonergic, α-adrenergic, histamine, and muscarinic receptors (Figure 12.3). It is not known which, if any, of these accounts for the therapeutic benefit.

B. Actions

TCAs elevate mood, improve mental alertness, increase physical activity, and reduce morbid preoccupation in 50 to 70% of individuals with major depression. The onset of the mood-elevation is slow, requiring 2 weeks or longer (Figure 12.4). These drugs do not produce CNS stimulation or mood elevation in normal individuals. Tolerance to the anticholinergic properties of the TCAs develops within a short time. Some tolerance to the autonomic effects of TCAs develops. Physical and psychological dependence have been reported. The drugs can be used for prolonged treatment of depression without loss of effectiveness.

C. Therapeutic uses

The tricyclic antidepressants are effective in treating severe major depression. Some panic disorders also respond to TCAs. *Imipramine* has been used to control bed-wetting in children (older than 6 years) by causing contraction of the internal sphincter of the bladder. At present it is used cautiously, because of the inducement of cardiac arrhythmias and other serious cardiovascular problems.

D. Pharmacokinetics

1. **Absorption and distribution:** The TCAs are well absorbed upon oral administration, and because of their lipophilic nature, are widely distributed and readily penetrate into the CNS. This lipid solubility also causes these drugs to have long half-lives, for example, 4 to 17 hours for *imipramine*. As a result of their variable first pass metabolism in the liver, TCAs have low and inconsistent bioavailability. Therefore the patient's response is

DRUG	UPTAKE INHIBITION		RECEPTOR AFFINITIES		
	Norepinephrine	Serotonin	Muscarinic	Histaminergic	Adrenergic
Tricyclic antidepressant *Imipramine*	++	+++	++	+	+
Selective serotonin reuptake inhibitor *Fluoxetine*	0	++++	0	0	0

Figure 12.3
Relative receptor specificity of some antidepressant drugs.

used to adjust dosage. The initial treatment period is typically 4 to 8 weeks. The dosage can be gradually reduced unless relapse occurs.

2. **Fate:** These drugs are metabolized by the hepatic microsomal system (see p. 14) and conjugated with glucuronic acid. Ultimately, the TCAs are excreted as inactive metabolites via the kidney.

E. Adverse effects

1. **Antimuscarinic effects:** Blockade of acetylcholine receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, constipation, and aggravation of glaucoma and epilepsy.

2. **Cardiovascular:** Increased catecholamine activity results in cardiac overstimulation, which can be life-threatening if an overdose of one of the drugs is taken. The slowing of atrioventricular conduction among depressed elderly patients is of particular concern.

3. **Orthostatic hypotension:** TCAs block α-adrenergic receptors, causing orthostatic hypotension and reflex tachycardia. In clinical practice this is the most serious problem in the elderly.

4. **Sedation:** Sedation may be prominent, especially during the first several weeks of treatment.

5. **Precautions:** The tricyclic antidepressants should be used with caution in manic-depressive patients, since they may unmask manic behavior. The tricyclic antidepressants have a narrow therapeutic index; for example, 5 to 6 times the maximal daily dose of *imipramine* can be lethal. Depressed patients who are suicidal should be given only limited quantities of these drugs and should be monitored closely. Drug interactions with the tricyclic antidepressants are shown in Figure 12.5.

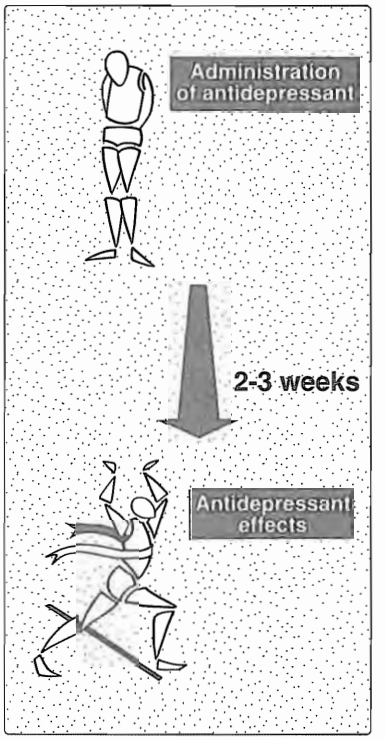

Figure 12.4
Onset of therapeutic effects of the major antidepressant drugs (tricyclic antidepressants, serotonin reuptake inhbitors, and monoamine oxidase inhibitors) requires several weeks.

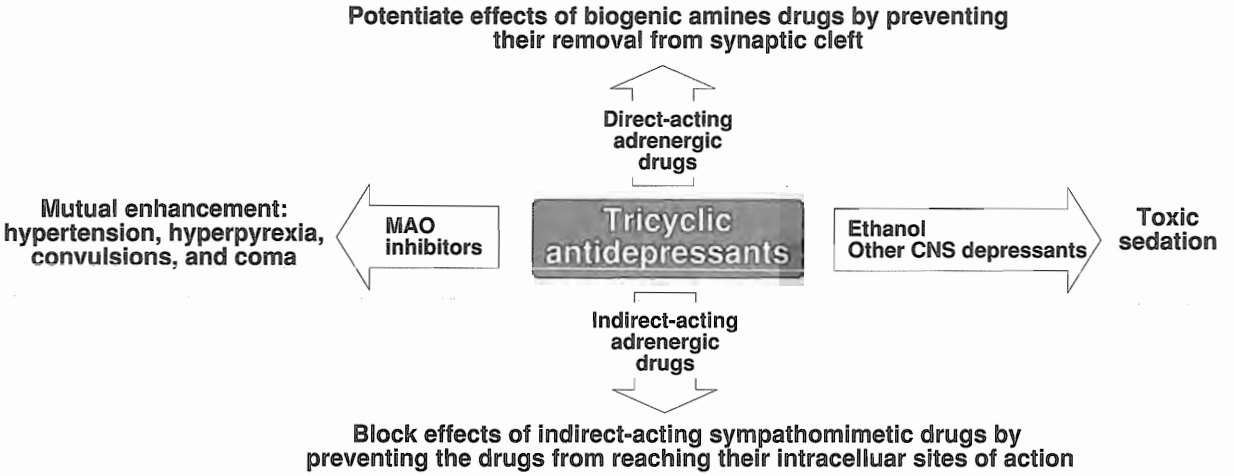

Figure 12.5
Drugs interacting with tricyclic antidepressants.

III. SELECTIVE SEROTONIN-REUPTAKE INHIBITORS

The selective serotonin-reuptake inhibitors (SSRI) are a new group of chemically unique antidepressant drugs that specifically inhibit serotonin reuptake (see Figure 12.3). This contrasts with the tricyclic antidepressants that nonselectively inhibit the uptake of norepinephrine, and serotonin, and block muscarinic, H_1-histaminic and α_1-adrenergic receptors. Compared with tricyclic antidepressants, the SSRIs cause fewer anticholinergic effects and lower cardiotoxicity. However, the newer serotonin reuptake inhibitors should be used cautiously until their long-term effects have been evaluated.

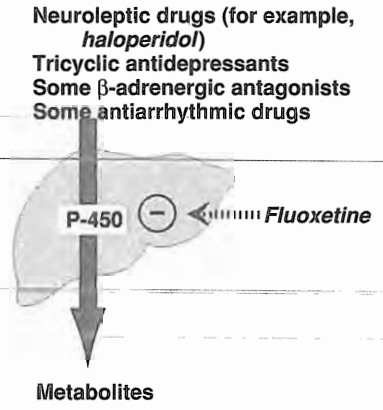

Figure 12.6
Fluoxetine inhibition of P-450 drug metabolism.

A. Fluoxetine

1. **Actions:** *Fluoxetine* [Floo OX e teen] is the prototype of antidepressant drugs that selectively inhibit serotonin reuptake. *Fluoxetine* is as effective in the treatment of major depression as tricyclic antidepressants. The drug is free of most of the troubling side effects of tricyclic antidepressants, including anticholinergic effects, orthostatic hypotension, and weight gain. *Fluoxetine* is preferred over tricyclic antidepressants by nonspecialists who write most of the prescriptions for antidepressant drugs. As a result *fluoxetine* is now the most widely prescribed antidepressant in the United States.

2. **Therapeutic uses:** The primary indication for *fluoxetine* is depression, where it is as effective as the tricyclic antidepressants. *Fluoxetine* is effective in treating bulimia nervosa and obsessive-compulsive disorder. The drug has been used for a variety of other indications, including anorexia nervosa, panic disorder, pain associated with diabetic neuropathy, and for premenstrual syndrome.

3. **Pharmacokinetics:** *Fluoxetine* is available therapeutically as a mixture of the R and the more active S enantiomers. Both com-

pounds are demethylated to the active metabolite, norfluoxetine. *Fluoxetine* and norfluoxetine are slowly cleared from the body, with a 1 to 10 day half-life for the parent compound, and 3 to 30 days for the active metabolite. *Fluoxetine* is administered orally; with a constant dose, a steady-state plasma concentration of the drug is achieved after several weeks of treatment. *Fluoxetine* is a potent inhibitor of a hepatic cytochrome P-450 isoenzyme responsible for the elimination of tricyclic antidepressant drugs, neuroleptic drugs, and some antiarrhythmic and β-adrenergic anatagonist drugs (Figure 12.6). [Note: About 7% of the white population lack this P-450 enzyme and therefore metabolize *fluoxetine* very slowly.]

4. **Adverse affects:** Commonly observed adverse effects of *fluoxetine* are summarized in Figure 12.7. Loss of libido, delayed ejaculation and anorgasmia are probably under-reported side effects often noted by clinicians but are not prominently featured in the list of standard side effects. Overdoses of *fluoxetine* do not cause cardiac arrhythmias but can cause seizures. For example, in a report of patients who took an overdose of *fluoxetine* (up to 1200 mg compared with 20 mg/day as a therapeutic dose) about half of the patients had no symptoms.

B. Other selective serotonin reuptake inhibitors

Other antidepressant drugs that primarily affect serotonin reuptake include *trazodone* [TRAZ oh done], *fluvoxamine* [floo VOX a meen], *nefazodone* [ne FAZ oh don], *paroxetine* [pah ROX a teen], *sertraline* [SIR trah leen], and *venlafaxine* [vin lah FACKS in]. These SSRIs differ from *fluoxetine* in their relative effects on the reuptake of serotonin and norepinephrine. They do not seem to be more efficacious than *fluoxetine,* but their profiles of side effects are somewhat different. There is a high variability among patients in the rate of elimintion of these drugs (including *fluoxetine*), and failure to tolerate one drug should not preclude a trial of another SSRI.

IV. MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase (MAO) is a mitochondrial enzyme found in neural and other tissues, such as the gut and liver. In the neuron, MAO functions as a "safety valve" to oxidatively deaminate and inactivate any excess neurotransmitter molecules (norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest. The MAO inhibitors may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitter molecules to escape degradation and therefore to both accumulate within the presynaptic neuron and to leak into the synaptic space. This causes activation of norepinephrine and serotonin receptors, and may be responsible for the antidepressant action of these drugs. Three MAO inhibitors are currently available for treatment of depression: *phenelzine* [FEN el zeen], *isocarboxazid* [eye soe kar BOX a zid], and *tranylcypromine* [tran ill SIP roe meen]; no one drug is a prototype. Use of MAO inhibitors is now limited because of the complicated dietary restrictions required of patients taking MAO inhibitors.

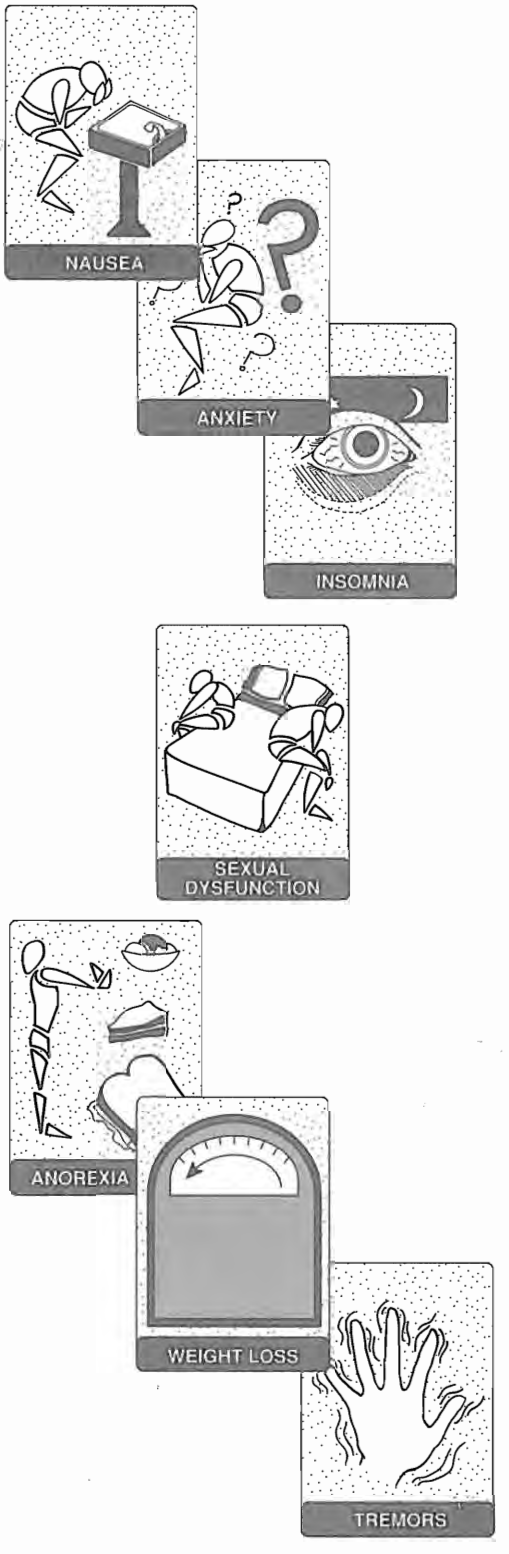

Figure 12.7
Some commonly oberved adverse effect of *fluoxetine.*

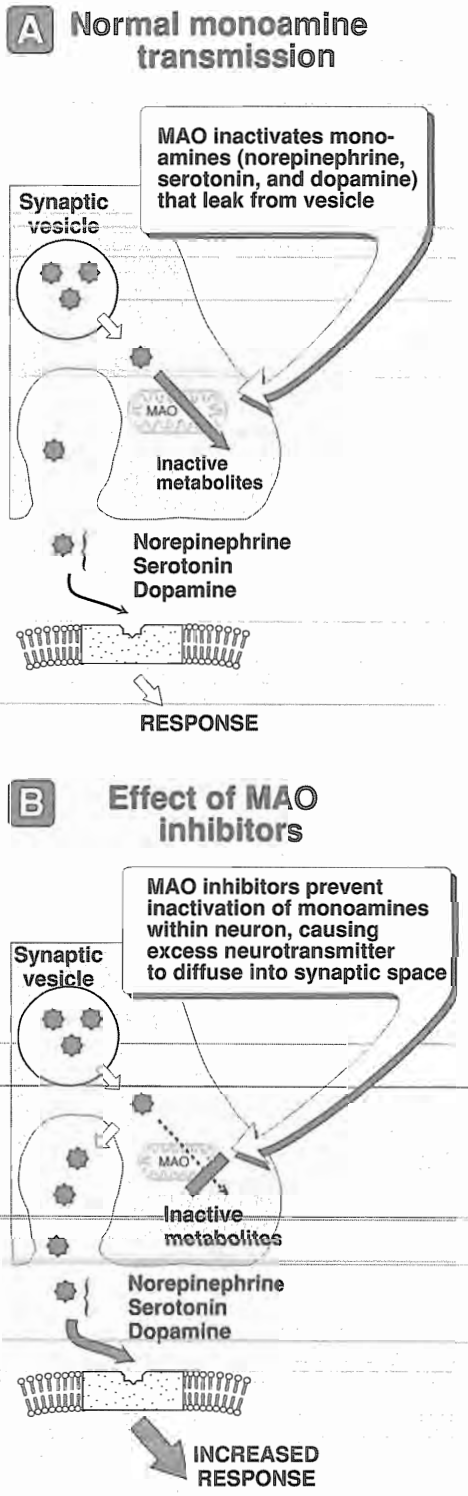

Figure 12.8
Mechanism of action of MAO inhibitors.

A. Mode of action

Most MAO inhibitors, such as *isocarboxazid*, form stable complexes with the enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin and dopamine within the neuron, and subsequent diffusion of excess neurotransmitter into the synaptic space (Figure 12.8).These drugs inhibit not only MAO in brain, but oxidases that catalyze oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods. The MAO inhibitors therefore show a high incidence of drug-drug and drug-food interactions (see "Adverse effects").

B. Actions

Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAO inhibitors, like that of the TCAs (see p. 119), is delayed several weeks. *Phenelzine* and *tranylcypromine* have a mild amphetamine-like stimulant effect.

C. Therapeutic uses

MAO inhibitors are indicated for depressed patients who are unresponsive or allergic to tricyclic antidepressants or who experience strong anxiety. Patients with low psychomotor activity may benefit from the stimulant properties of MAO inhibitors. These drugs are also useful in the treatment of phobic states. A special subcategory of depression, called atypical depression, may respond to MAOIs. Atypical depresssion is characterized by labile mood, rejection sensitivity and appetite disorders.

D. Pharmacokinetics

These drugs are well absorbed on oral administration, but antidepressant effects require 2 to 4 weeks of treatment. Enzyme regeneration, when irreversibly inactivated, varies but usually occurs several weeks after termination of the drug. Thus, when switching antidepressant agents, a minimum of 2 weeks delay must be allowed after termination of MAO-inhibitor therapy. MAO inhibitors are metabolized and excreted rapidly in the urine.

E. Adverse effects

Severe and often unpredictable side effects limit the widespread use of MAO inhibitors. For example, tyramine, contained in certain foods, such as aged cheeses, chicken liver, beer, and red wines, is normally inactivated by MAO in the gut. Individuals receiving a MAO inhibitor are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in headache, tachycardia, nausea, hypertension, cardiac arrhythmias, and stroke. Patients must therefore be educated to avoid tyramine-containing foods. *Phentolamine* (see p. 72) or *prazosin* (see p. 73) are helpful in the management of tyramine-induced hypertension. [Note: Treatment with MAO inhibitors may be dangerous in severely depressed patients with suicidal tendencies. Purposeful consumption of tyramine-containing foods is a possibility.] Other possible

side effects of treatment with MAO inhibitors include drowsiness, orthostatic hypotension, blurred vision, dryness of the mouth, dysuria, and constipation. MAO inhibitors and SSRIs should not be co-administered due to the risk of life-threatening "serotonin-syndrome". Both drugs require washout periods of 6 weeks before administering the other

V. LITHIUM SALTS

Lithium salts are used prophylactically in treating manic-depressive patients and in the treatment of manic episodes. They are also effective in treating 60 to 80% of patients exhibiting mania and hypomania. Although many cellular processes are altered by treatment with *lithium salts*, the mode of action is unknown. [Note: It is currently proposed that *lithium* acts by altering the cellular concentration of the second messenger, inositol triphosphate (IP_3), see p. 33).] *Lithium* is given orally, and the ion is excreted by the kidney. *Lithium salts* are very toxic. Their safety factor and therapeutic index are extremely low—comparable to those of *digitalis* (see p.161). Adverse effects include ataxia, tremors, confusion, and convulsions. *Lithium* causes no noticeable effect on normal individuals. It is not a sedative, euphoriant or depressant. Figure 12.9 summarizes the therapeutic disadvantages and advantages of the antidepressant drugs.

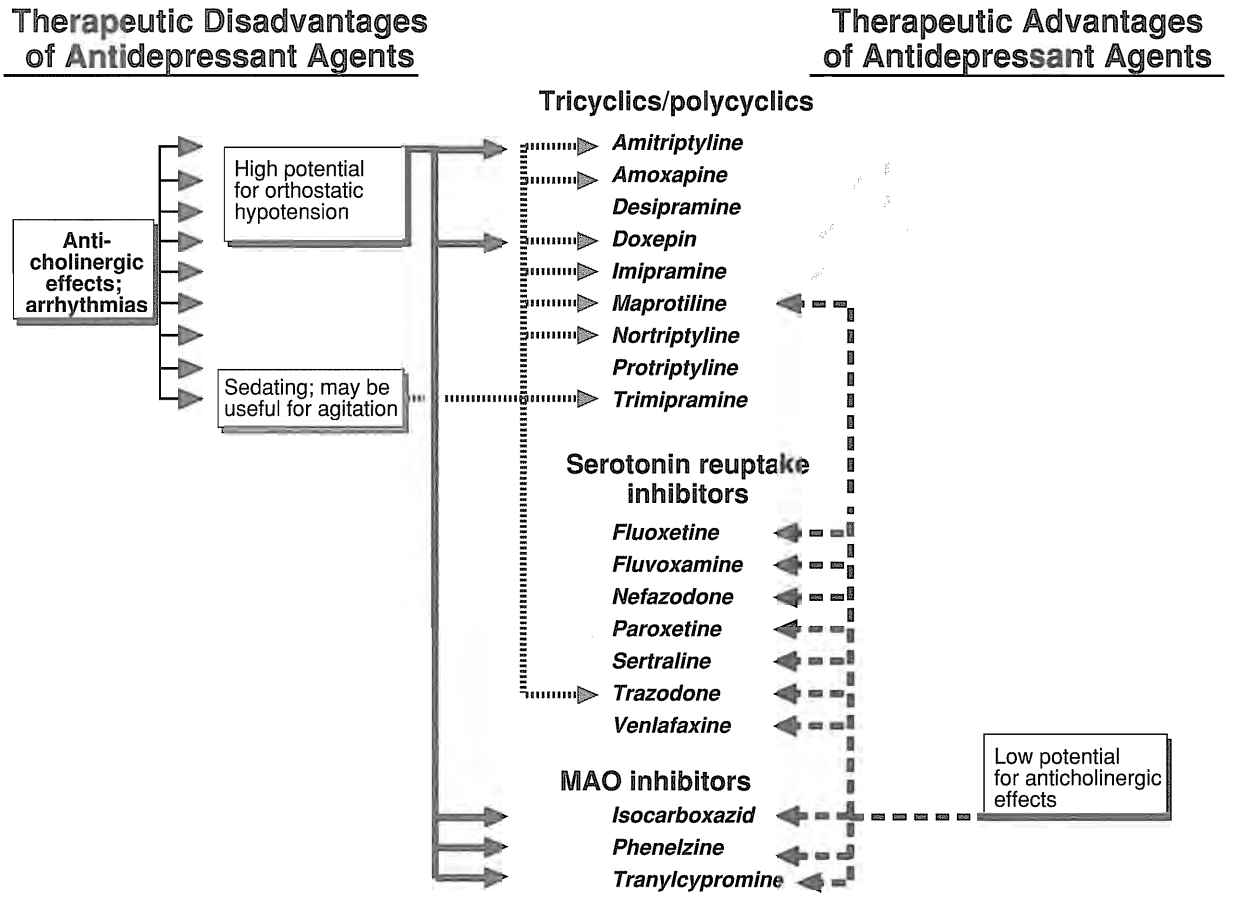

Figure 12.9
Therapeutic disadvantages and advantages of some drugs used to treat depression.

Choose the ONE best answer.

12.1 Which one of following is an appropriate therapeutic use for imipramine?

A. Insomnia
B. Epilepsy
C. Bed-wetting in children
D. Glaucoma
E. Mania

Correct answer = C. Imipramine can be used with caution to contract the internal sphincter of the bladder.

12.2 MAO inhibitors are contraindicated with all of the following EXCEPT:

A. indirect adrenergic agents, such as ephedrine.
B. tricyclic antidepressants.
C. beer and cheese.
D. aspirin.
E. dopamine.

Correct answer = D. MAO inhibitors and aspirin can be taken concurrently. Hypertensive crisis may result from use (concurrently or within 2 weeks) of MAO inhibitors and indirect sympathomimetic amines, such as ephedrine. Concomitant use of MAO inhibitors and tricyclic antidepressants may result in mutual enhancement of effects with the possibility of hyperpyrexia, hypertension, seizures and death. Tyramine-containing foods, such as aged cheeses and beer, may precipitate a hypertensive crisis because of the accumulation and release of stored catecholamines from nerve endings. MAO inhibitors may lead to an exaggerated response to dopamine.

12.3 Which of the following statements concerning tricyclic antidepressants is correct?

A. All of the tricyclic antidepressants show similar therapeutic efficacy.
B. Hypertension is a common adverse effect.
C. The tricyclic antidepressants selectively inhibit uptake of norepinephrine into the neuron.
D. These drugs show an immediate therapeutic effect.
E. These drugs must be administered intramuscularly.

Correct choice = A. The choice of tricyclic antidepressants depends on the tolerance of side effects and the desired duration of action. Orthostatic hypotension (not hypertension) is a side effect of the tricyclic drugs. The tricyclic antidepressants nonspecifically block the uptake of norepinephrine and serotonin; the onset of action requires 2 weeks or longer. These drugs are usually given orally.

12.4 Which of the following is common to the tricyclic antidepressants and MAO inhibitors?

A. They can produce sedation.
B. They produce physical dependence.
C. They show strong interaction with certain foods.
D. They can produce postural hypotension.
E. They decrease availability of epinephrine and serotonin in the synaptic cleft

Correct answer = D.

12.5 Which of the following antidepressant agents exhibits an amphetamine-like CNS stimulation?

A. Imipramine
B. Doxepin
C. Tranylcypromine
D. Trazodone
E. Lithium salts

Correct answer = C.

12.6 A very upset mother brings in her 10 year old son to ask help in dealing with his bed-wetting. Which of the following drugs might alleviate this problem?

A. Fluoxetine
B. Imipramine
C. Tranylcypromine
D. Trazodone

The correct answer = B. The tricyclic antidepressants and especially imipramine are effective in this condition because it contracts the internal sphincter of the bladder. Fluoxetine and trazodone act at serotonin receptors and have no effect on bladder function. Tranylcypromine is an MAO inhibitor with serious side effects.

Neuroleptic Drugs

13

I. OVERVIEW

Neuroleptic drugs (also called antischizophrenic drugs, antipsychotic drugs, or major tranquilizers) are used primarily to treat schizophrenia but are also effective in other psychotic states, such as manic states and delirium. The traditional neuroleptic drugs are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of dopamine receptors. These drugs vary in their potency, but no one drug is clinically more effective than another. In contrast, the newer "atypical" antipsychotic drugs appear to owe their unique activity to blockade of serotonin receptors. Therapy has tended toward the use of high potency drugs, such as *thiothixene* [thye oh THIX een], *haloperidol* [ha loe PER i dole], and *fluphenazine* [floo FEN a zeen]. *Chlorpromazine* [klor PROE ma zeen], the prototype of the neuroleptic agents, is used infrequently because of its high incidence of serious side effects. Neuroleptic drugs are not curative and do not eliminate the fundamental thinking disorder, but often do permit the psychotic patient to function in a supportive environment.

II. SCHIZOPHRENIA

Schizophrenia is a particular type of psychosis, that is, a mental disorder caused by some inherent dysfunction of the brain. It is characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances. This mental disorder is a common affliction, occurring among about 1% of the population, or at about the same incidence as diabetes mellitus. The illness often initially affects people during adolescence and is a chronic and disabling disorder. Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly an overactivity of the mesolimbic dopaminergic neurons.

III. NEUROLEPTIC DRUGS

The neuroleptic drugs can be divided into five major classifications based on the structure of the drug (Figure 13.1). This classification is of modest importance, because within each chemical group, different side chains have profound effects on the potencies of the drugs. The management of

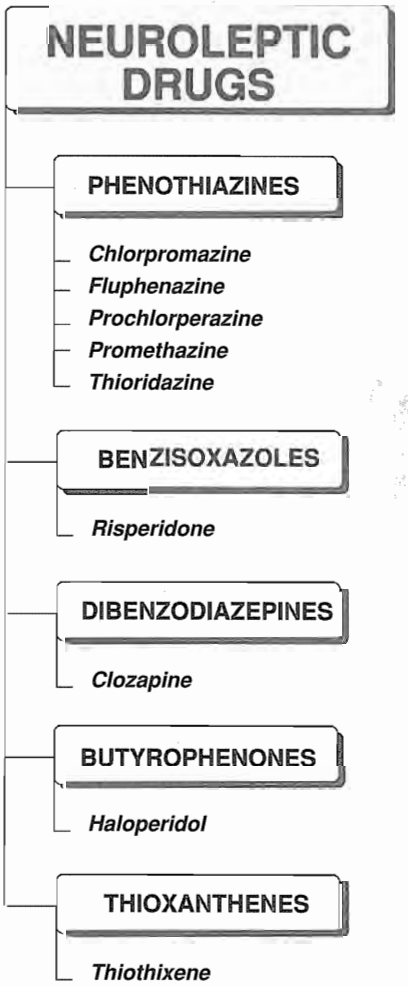

Figure 13.1
Summary of neuroleptic agents.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997

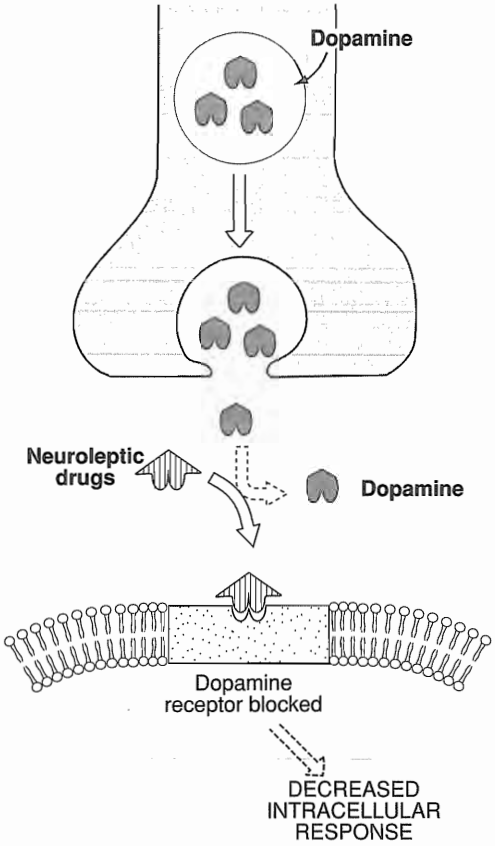

Figure 13.2
Dopamine-blocking actions of neuroleptic drugs.

psychotic disorders can typically be achieved by familiarity with the effects of one or two drugs in each class.

A. Mode of action

1. **Dopamine receptor-blocking activity in brain:** All of the neuroleptic drugs block dopamine receptors in the brain and in the periphery (Figure 13.2). Five types of dopamine receptors have been identified: D_1 and D_5 receptors activate adenylyl cyclase, whereas D2, D_3 and D_4 receptors inhibit adenylyl cyclase. The neuroleptic drugs bind to these receptors to varying degrees; however, the clinical efficacy of the traditional neuroleptic drugs correlates closely with their relative ability to block D_2 receptors in the mesolimbic system of the brain. The actions of the neuroleptic drugs are antagonized by agents that raise dopamine concentration, for example, *L-dopa* (see p. 84) and amphetamines (see p. 103).

2. **Serotonin receptor-blocking activity in brain:** The newer "atypical" agents appear to exert part of their unique action through inhibition of serotonin (S) receptors. Thus, *clozapine* [KLOE za peen] has high affinity for D_1 and D_4, S_2, muscarinic and α-adrenergic receptors, but it is also a dopamine D_2-receptor antagonist. Another new agent, *risperidone* [ris PEER i dohn], blocks S_2 receptors to a greater extent than it does D_2 receptors. Both of these drugs exhibit a low incidence of extrapyramidal side effects.

B. Actions

The antipsychotic actions of neuroleptic drugs reflect blockade at dopamine and/or serotonin receptors. However, many of these agents also block cholinergic, adrenergic, and histamine receptors, causing a variety of side effects (Figure 13.3).

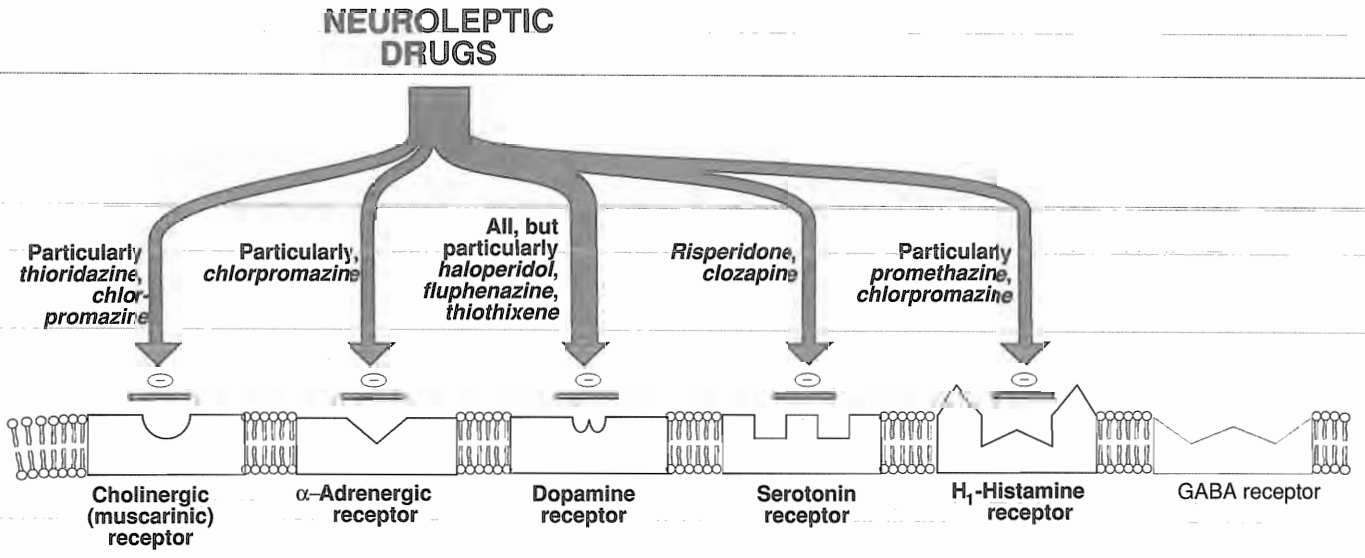

Figure 13.3
Neuroleptic drugs block at dopaminergic and serotonergic receptors as well as at adrenergic, cholinergic, and histamine-binding receptors. GABA = γ-aminobutyric acid.

1. **Antipsychotic actions:** The neuroleptic drugs reduce the hallucinations and agitation associated with schizophrenia by blocking dopamine receptors in the mesolimbic system of the brain. These drugs also have a calming effect and reduce spontaneous physical movement. In contrast to the central nervous system (CNS) depressants, such as barbiturates, the neuroleptics do not depress intellectual function of the patient, and motor incoordination is minimal. The antipsychotic effects usually take several weeks to occur, suggesting that the therapeutic effects are related to secondary changes in the corticostriatal pathways.

2. **Extrapyramidal effects:** Parkinsonian symptoms, akathisia (motor restlessness), and tardive dyskinesia (inappropriate postures of the neck, trunk, and limbs) occur with chronic treatment. Blocking of dopamine receptors in the nigrostriatal pathway probably causes these unwanted parkinsonian symptoms. *Clozapine* and *risperidone* exhibit a low incidence of these symptoms.

3. **Antiemetic effect:** With the exception of *thioridazine* [thye oh RID a zeen], most of the neuroleptic drugs have antiemetic effects that are mediated by blocking D_2 dopaminergic receptors of the chemoreceptor trigger zone of the medulla (see p. 241 for a discusssion of emesis). Figure 13.4 summarizes the antiemetic uses of neuroleptic agents, along with the therapeutic applications of other drugs that combat nausea.

4. **Antimuscarinic effects:** All of the neuroleptics, particularly *thioridazine* and *chlorpromazine*, cause anticholinergic effects, including blurred vision, dry mouth, sedation, confusion, and inhibition of gastrointestinal and urinary smooth muscle, leading to constipation and urinary retention.

5. **Other effects:** Blockade of α-adrenergic receptors causes orthostatic hypotension and lightheadedness. The neuroleptics also alter temperature-regulating mechanisms and can produce poikilothermia (body temperature varies with the environment). In the pituitary, neuroleptics block D_2 receptors, leading to an increase in prolactin release.

C. Therapeutic uses

1. **Treatment of schizophrenia:** The neuroleptics are the only efficacious treatment for schizophrenia. Not all patients respond, and complete normalization of behavior is seldom achieved. The traditional neuroleptics are most effective in treating positive symptoms of schizophrenia (delusions, hallucinations and thought disorders). The newer agents with serotonin blocking activity are effective in many patients resistant to the traditional agents, especially in treating negative symptoms of schizophrenia (withdrawal, blunted emotions, reduced ability to relate to people).

2. **Prevention of severe nausea and vomiting:** The neuroleptics, (most commonly *prochlorperazine*), are useful in the treatment of drug-induced nausea (see p. 241). Nausea arising from emotion

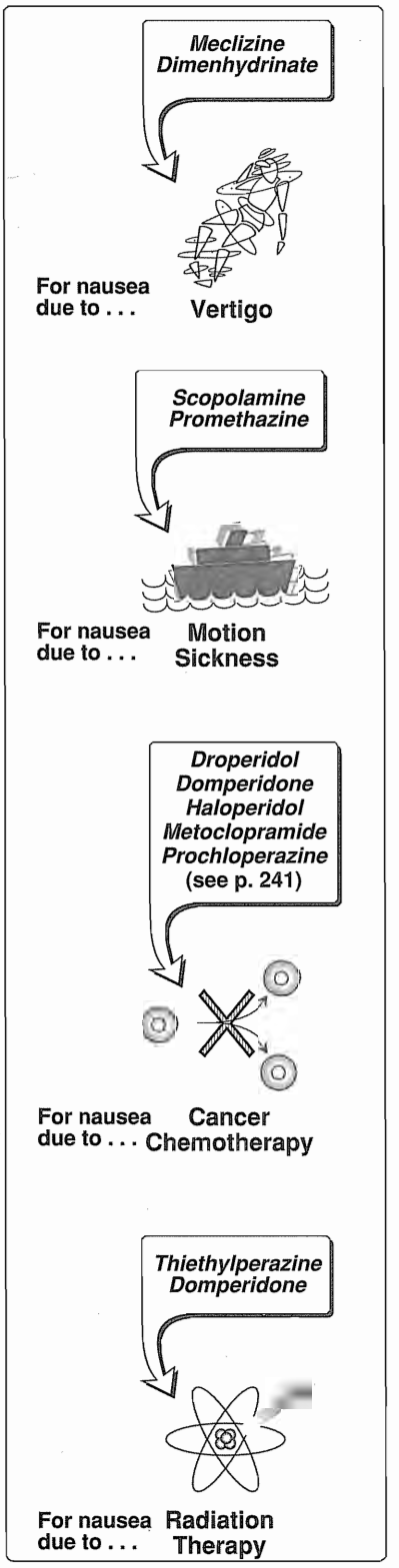

Figure 13.4
Therapeutic application of antiemetic agents.

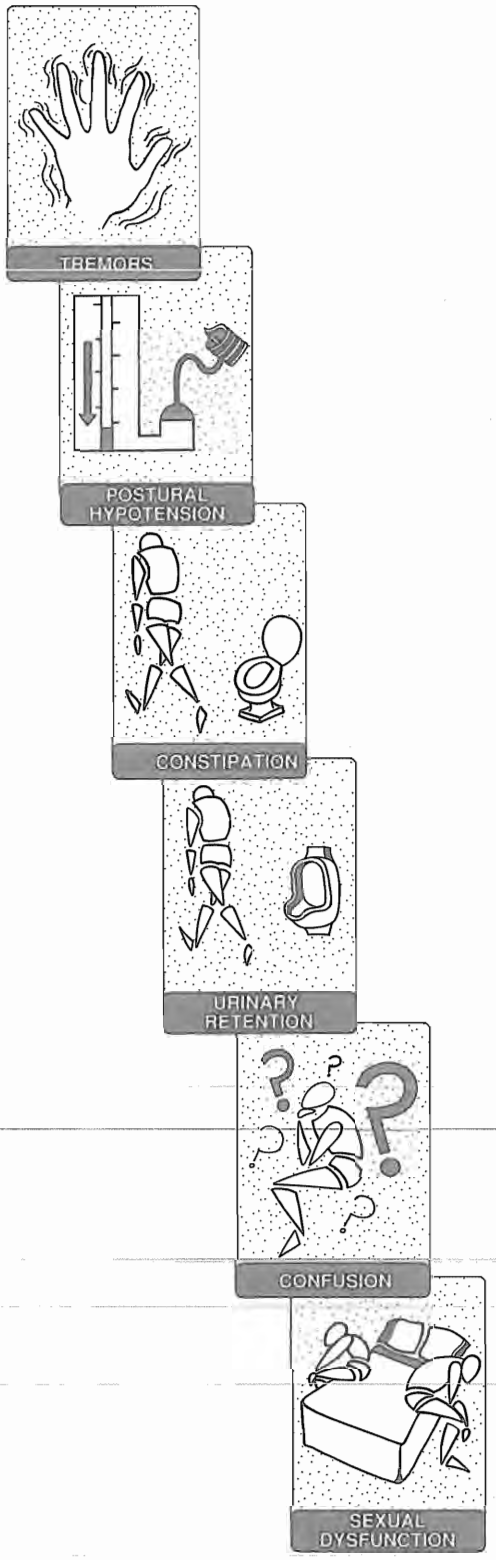

Figure 13.5
Adverse effects commonly observed in individuals treated with neuroleptic drugs.

should be treated with sedatives and antihistamines, rather than with these powerful drugs. *Scopolamine* (see p. 48) is the drug of choice for treatment of motion sickness.

3. **Other uses:** The neuroleptic drugs may be used as tranquilizers to manage agitated and disruptive behavior. Neuroleptics are used in combination with narcotic analgesics for treatment of chronic pain with severe anxiety. *Chlorpromazine* is used to treat intractable hiccups. *Droperidol* [droe PER i dole] is a component of neuroleptanesthesia (see p. 117). *Promethazine* [proe METH a zeen] is not a good antipsychotic drug, but the agent is used in treating pruritus because of its antihistaminic properties (see p. 422).

D. Absorption and metabolism

The neuroleptics show variable absorption after oral administration. These agents readily pass into the brain, have a large volume of distribution, bind well to plasma proteins, and are metabolized to many different substances by the P-450 system in the liver. *Fluphenazine decanoate* and *haloperidol decanoate* are slow release (up to 3 weeks) formulations of neuroleptics, administered by intramuscular injection. These drugs are increasingly used in treating outpatients and individuals who are noncompliant. However, about 30% of these patients develop extrapyramidal symptoms. The neuroleptic drugs produce some tolerance but little physical dependence.

E. Adverse effects

Adverse effects of the neuroleptic drugs occur in practically all patients and are significant in about 80% (Figure 13.5). Although antipsychotic drugs have an array of adverse effects, their therapeutic index is high.

1. **Parkinsonian effects:** The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence and resulting in extrapyramidal motor effects.

   a. **Effect of anticholinergic drugs:** If cholinergic activity is also blocked, a new, more nearly normal balance is restored, and extrapyramidal effects are minimized. This can be achieved by administration of an anticholinergic drug, such as *benztropine*. The therapeutic tradeoff is fewer extrapyramidal effects in exchange for the side effects of parasympathetic blockade. [Note: Often, the parkinsonian actions persist, despite the anticholinergic drugs.] Those drugs that exhibit strong anticholinergic activity, such as *thioridazine*, show few extrapyramidal disturbances, since the cholinergic activity is strongly dampened. This contrasts with *haloperidol* and *fluphenazine*, which have low anticholinergic activity and produce extrapyramidal effects because of the preferential blocking of dopaminergic transmission without the blocking of cholinergic activity.

b. Clozapine and risperidone: These drugs have a low potential for causing extrapyramidal symptoms and lower risk of tardive dyskinesia. These drugs appear to be superior to *haloperidol* and *chlorpromazine* in treating the symptoms of schizophrenia, especially the negative symptoms. *Risperidone* should be included among the first-line antipsychotic drugs, whereas *clozapine* should be reserved for severely schizophrenic patients who are refractory to traditional therapy. *Clozapine* can produce bone marrow suppression and cardiovascular side effects. The risk of severe agranulocytosis necessitates frequent monitoring of white blood cell count. Figure 13.6 summarizes the receptor-binding properties of *clozapine*, *chlorpromazine*, and *haloperidol*.

2. **Tardive dyskinesia:** Long-term treatment with neuroleptics can cause this motor disorder. Patients display involuntary movements, including lateral jaw movements and "fly-catching" motions of the tongue. A prolonged holiday from neuroleptics may cause the symptoms to diminish or disappear within 3 months. However, in many individuals, dyskinesia is irreversible and persists after discontinuation of therapy. Tardive dyskinesia is postulated to result from an increased number of dopamine receptors that are synthesized in response to long-term dopamine receptor blockade. This makes the neuron supersensitive to the actions of dopamine and allows the dopaminergic input to this structure to overpower the cholinergic input, causing excess movement in the patient.

3. **Other effects:** Drowsiness occurs due to CNS depression, usually during the first 2 weeks of treatment. Confusion is sometimes encountered.The neuroleptics often produce dry mouth, urinary retention, constipation, and loss of accommodation. They block α-adrenergic receptors, resulting in lowered blood pressure and orthostatic hypotension. The neuroleptics depress the hypothalamus, causing amenorrhea, galactorrhea, infertility, and impotence.

4. **Cautions and contraindications:** Acute agitation accompanying withdrawal from alcohol or other drugs may be aggravated by the neuroleptics. Stabilization with a simple sedative, such as a benzodiazepine (see p. 89), is the preferred treatment. *Chlorpromazine* is contraindicated in patients with seizure disorders, since this drug can lower seizure threshold. The neuroleptics can also aggravate epilepsy. The high incidence of agranulocytosis with *clozapine* may limit its use to patients resistant to other drugs.

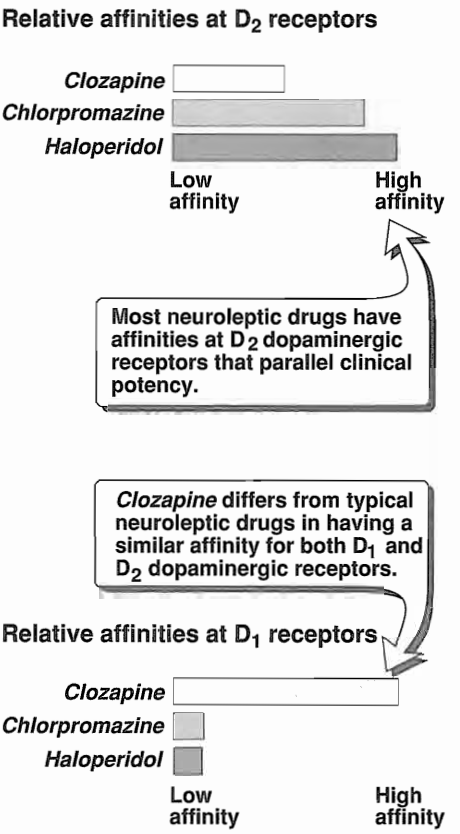

Figure 13.6
Relative affinity of *clozapine, chlorpromazine* and *haloperidol* at D_1 and D_2 dopaminergic receptors

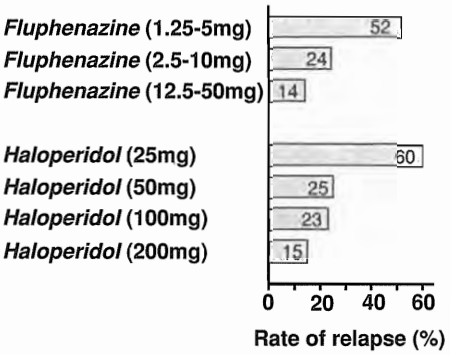

Figure 13.7
Cumulative rates of relapse among patients with schizophrenia after one year of maintenance therapy with either *fluphenazine* or *haloperidol*.

F. Maintenance treatment

Patients who have had two or more schizophrenic episodes should receive maintenance therapy for at least five years, and some experts prefer indefinite therapy. Low doses of antipsychotic drugs are not as effective in preventing relapse as higher dose maintenance therapy (Figure 13.7). Figure 13.8 summarizes the therapeutic uses of the neuroleptic drugs.

Drug	Therapeutic notes
Haloperidol	Little adrenergic or muscarinic activity. Available as slow release depot form
Fluphenazine	Available as slow release depot form
Thiothixene	
Thioridazine	Strong muscarinic antagonist
Chlorpromazine	Used infrequently because of adverse effects
Clozapine	Few extrapyramidal effects; causes a potentially fatal agranulcytosis in 1-2% of patients.
Risperidone	Minimal sedation, low potential for extrapyramidal effects.

Sedation and cardiovascular effects commonly seen with agents in the lower portion of table

Parkinsonian effects commonly seen with agents in the upper portion of table

Figure 13.8
Summary of neuroleptic agents.

Study Questions

Choose the ONE best answer.

13.1 The neuroleptic drugs:

A. are equally effective against the positive and negative symptoms of schizophrenia.
B. can cause blurred vision, urinary retention and other signs of muscarinic blockade.
C. bind selectively to D_2-dopaminergic receptors.
D. have antiparkinsonism effects similar to levodopa.
E. have a rapid onset of antipsychotic action.

Correct answer = B. The traditional neuroleptics are most effective in treating positive symptoms of schizophrenia (delusions, hallucinations and thought disorders). The newer agents with serotonin blocking activity are effective in many patients resistant to the traditional agents, especially in treating negative symptoms of schizophrenia (withdrawal, blunted emotions, reduced ability to relate to people). Most of the neuroleptic drugs block both D_1 and D_2 dopaminergic receptors. Most neuroleptic drugs cause parkinsonism effects. The antipsychotic effects occur after several weeks of administration.

13.2 All of the following statements about the extrapyramidal effects of neuroleptics are correct EXCEPT:

A. They are caused by blockade of dopamine receptors.
B. They are less likely to be produced by clozapine than by fluphenazine.
C. They can be countered to some degree by antimuscarinic drugs.
D. Haloperidol does not cause extrapyramidal disturbances.
E. Neuroleptics may cause tardive dyskinesia.

Correct choice = D. Tardive dyskinesia appears to be produced to the same degree and frequency by all the neuroleptic drugs when used in equieffective antipsychotic doses.

13.3 All of the following are observed in patients taking neuroleptic agents EXCEPT:

A. sexual dysfunction.
B. increased blood pressure.
C. altered endocrine function.
D. constipation.
E. orthostatic hypotension.

Correct choice = B. The neuroleptics block α-adrenergic receptors resulting in lowered blood pressure and orthostatic hypotension.

Opioid Analgesics and Antagonists

14

I. OVERVIEW

Opioids are natural or synthetic compounds that produce morphine-like effects. The term opiates is reserved for drugs, such as *morphine* and *codeine*, obtained from the juice of the opium poppy. All drugs in this category act by binding to specific opioid receptors in the central nervous system (CNS) to produce effects that mimic the action of endogenous peptide neurotransmitters, the opiopeptins (for example, the endorphins, and the enkephalins). Although the opioids have a broad range of effects, their primary use is to relieve intense pain and the anxiety that accompanies it, whether it be from surgery or as a result of injury or a disease, such as cancer. However, their widespread availability has led to abuse of those opioids with euphoric properties. Antagonists that can reverse the actions of opioids are also very important clinically in cases of overdose. (See Figure 14.1 for a summary of the opioid agonists and antagonists.)

II. OPIOID RECEPTORS

Opioids interact stereospecifically with protein receptors on the membranes of certain cells in the CNS, on nerve terminals in the periphery, and on cells of the gastrointestinal tract. The major effects of the opioids are mediated by 4 families of receptors, designated by the Greek letters, μ, κ, σ and δ, each of which exhibits a different specificity for the drug(s) it binds (Figure 14.2). In general, binding potency correlates with analgesia. The analgesic properties of the opioids are primarily mediated by the μ receptors; however, the κ receptors in the dorsal horn also contribute. The enkephalins interact more selectively with the δ receptors in the periphery. Other receptors for the opioids, such as the σ receptor, have been shown to be less specific; for example, the σ receptor also binds nonopioid agents, such as the hallucinogen *phencyclidine* (see p. 105). The σ receptor may be responsible for the hallucinations and dysphoria sometimes associated with opioids. [Note: *Naloxone* [nal OX own] does not antagonize binding at this receptor as it does at the others.] All opioid receptors are coupled to inhibitory G proteins, and inhibit adenylyl cyclase. They may also be associated with ion channels to increase K^+ efflux (hyperpolarization) or reduce Ca^{++} influx, thus impeding neuronal firing and transmitter release.

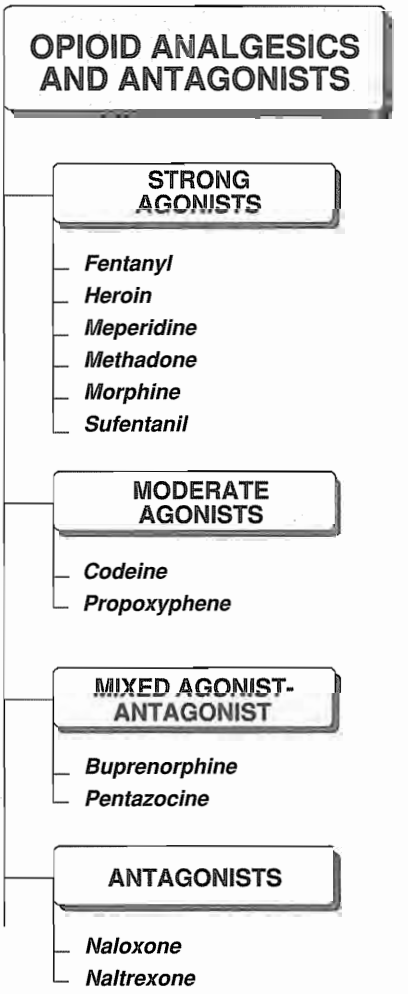

Figure 14.1
Summary of opioid analgesics and antagonists.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

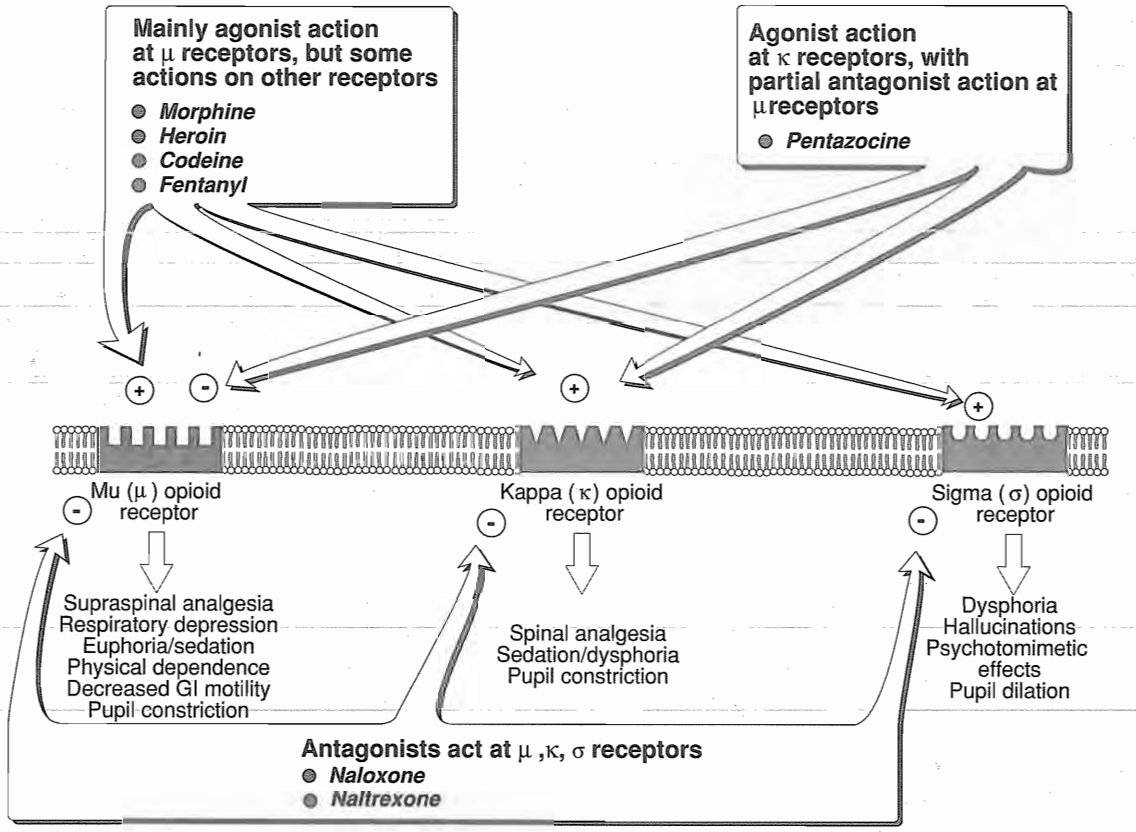

Figure 14.2
Actions of agonists and antagonists at opioid receptors.

A. Distribution of receptors

High densities of opioid receptors are present in five general areas of the CNS known to be involved in integrating information about pain. These pathways descend from the periacqueductal gray (PAG) through the dorsal horn of the spinal cord. They have also been identified in the periphery.

1. **Brainstem:** Opioid receptors mediate respiration, cough, nausea and vomiting, maintenance of blood pressure, pupillary diameter, and control of stomach secretions.

2. **Medial thalamus:** This area mediates deep pain that is poorly localized and emotionally influenced.

3. **Spinal cord:** Receptors in the substantia gelatinosa are involved with the receipt and integration of incoming sensory information, leading to the attenuation of painful afferent stimuli.

4. **Hypothalamus:** Receptors here affect neuroendocrine secretion.

5. **Limbic system:** The greatest concentration of opiate receptors in the limbic system is located in the amygdala. These receptors probably do not exert analgesic action, but they may influence emotional behavior.

6. **Periphery:** Opioids also bind to peripheral sensory nerve fibers and their terminals. As in the CNS, they inhibit Ca^{++}-dependent release of excitatory, proinflammatory substances (for example, substance P) from these nerve endings. It has been suggested that this may contribute to the antiinflammatory effects of opioids.

7. **Immune cells:** Opioid-binding sites have also been found on immune cells. The role of these receptors in nociception (response or sensitivity to painful stimuli) has not been determined.

III. STRONG AGONISTS

Morphine [MOR feen] is the major analgesic drug contained in crude opium and is the prototype agonist. *Codeine* [KOE deen] is present in lower concentrations and is inherently less potent. These drugs show a high affinity for μ receptors, varying affinities for δ and κ receptors, and low affinity for σ receptors.

A. Morphine

1. **Mechanism of action:** Opioids exert their major effects by interacting with opioid receptors in the CNS and the gastrointestinal tract. Opioids cause hyperpolarization of nerve cells, inhibition of nerve firing, and presynaptic inhibition of transmitter release. *Morphine* acts at μ receptors in lamina I and II of the substantia gelatinosa of the spinal cord, and decreases the release of substance P, which modulates pain perception in the spinal cord. *Morphine* also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.

2. **Actions:**

   a. **Analgesia:** *Morphine* causes analgesia (relief of pain without the loss of consciousness). Opioids relieve pain both by raising the pain threshold at the spinal cord level, and more importantly, by altering the brain's perception of pain. Patients treated with *morphine* are still aware of the presence of pain, but the sensation is not unpleasant. The maximum analgesic efficacy and the potential for addiction for representative agonists is shown in Figure 14.3.

   b. **Euphoria:** *Morphine* produces a powerful sense of contentment and well-being. Euphoria may be caused by stimulation of the ventral tegmentum.

   c. **Respiration:** *Morphine* causes respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide. This occurs with ordinary doses of *morphine* and

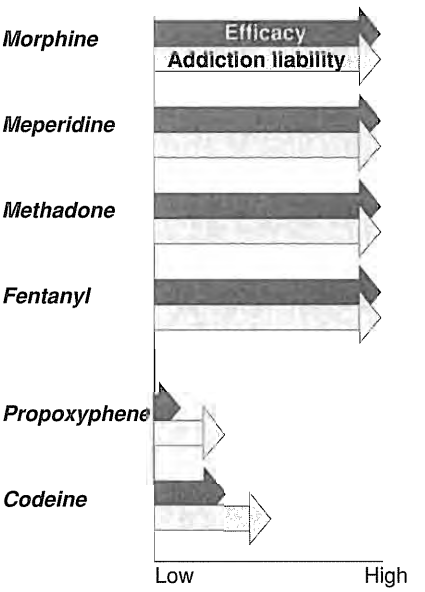

Figure 14.3
A comparison of the maximum efficacy and addiction/abuse liability of commonly used narcotic analgesics.

is accentuated as the dose increases until, ultimately, respiration ceases. Respiratory depression is the most common cause of death in acute opioid overdose.

d. Depression of cough reflex: *Morphine* and *codeine* have antitussive properties. In general, cough suppression does not correlate closely with analgesic and respiratory depressant properties of opioid drugs. The receptors involved in the antitussive action appear to be different than those involved in analgesia.

e. Miosis: The pinpoint pupil, characteristic of *morphine* use, results from stimulation of μ and κ receptors. *Morphine* excites the Edinger-Westphal nucleus of the oculomotor nerve, which causes enhanced parasympathetic stimulation to the eye. There is little tolerance to the effect, and all addicts demonstrate pin-point pupils. This is important diagnostically, because most other causes of coma and respiratory depression produce dilation of the pupil.

f. Emesis: *Morphine* directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting. However, the emesis does not produce unpleasant sensations.

g. Gastrointestinal tract: *Morphine* relieves diarrhea and dysentery. It decreases motility of smooth muscle and increases tone. It increases pressure in the biliary tract. *Morphine* also increases the tone of the anal sphincter. Overall, *morphine* produces constipation, with little tolerance developing.

h. Cardiovascular: *Morphine* has no major effects on the blood pressure or heart rate except at large doses, when hypotension and bradycardia may occur. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase the cerebrospinal fluid (CSF) pressure. Therefore, *morphine* is usually contraindicated in individuals with severe brain injury.

i. Histamine release: *Morphine* releases histamine from mast cells, causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, asthmatics should not receive the drug.

j. Hormonal actions: *Morphine* inhibits release of gonadotropin-releasing hormone and corticotropin-releasing hormone and decreases the concentration of luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone, and β-endorphin. Testosterone and cortisol levels decrease. *Morphine* increases prolactin and growth hormone release by diminishing dopaminergic inhibition. It increases antidiuretic hormone (ADH) and thus leads to urinary retention.

3. **Therapeutic uses:**

   a. **Analgesia:** Despite intensive research, few other drugs have been developed that are as effective in the treatment of pain. Opioids induce sleep, and in clinical situations when pain is present and sleep is necessary, opiates may be used to supplement the sleep-inducing properties of benzodiazepines, such as *flurazepam* (see p. 89) [Note: The sedative-hypnotic drugs are not usually analgesic, and may have diminished sedative effect in the presence of pain.]

   b. **Treatment of diarrhea:** *Morphine* decreases the motility of smooth muscle and increases tone.

   c. **Relief of cough:** *Morphine* suppresses the cough reflex; however, *codeine* or *dextromethorphan* (see p. 222) are more widely used. *Codeine* has greater antitussive action than *morphine*.

4. **Pharmacokinetics:**

   a. **Administration:** Absorption of *morphine* from the gastrointestinal tract is slow and erratic, and the drug is usually not given orally. *Codeine*, by contrast, is well absorbed when given by mouth. Significant first pass metabolism of *morphine* occurs in the liver; therefore, intramuscular, subcutaneous, or intravenous injections produce the most reliable responses. Opiates have been commonly taken for nonmedical purposes by inhalation of the smoke from burning crude opium, which provides a rapid onset of drug action.

   b. **Distribution:** *Morphine* rapidly enters all body tissues, including the fetuses of pregnant women, and should not be used for analgesia during labor. Infants born of addicted mothers show physical dependence on opiates and exhibit withdrawal symptoms if opioids are not administered. Only a small percentage of *morphine* crosses the blood-brain barrier, since *morphine* is the least lipophilic of the common opioids. This contrasts with the more fat-soluble opioids, such as *fentanyl* and *heroin*, which readily penetrate into the brain and rapidly produce an intense "rush" of euphoria.

   c. **Fate**: *Morphine* is metabolized in the liver to glucuronides. Morphine-6-glucuronide is a very potent analgesic, whereas the conjugate at the 3-position is inactive. The conjugates are excreted primarily in the urine, with small quantities appearing in the bile. The duration of action of *morphine* is 4 to 6 hours in naive individuals. [Note: Due to the low conjugating capacity in neonates, they should not receive *morphine*.]

5. **Adverse effects:** Severe respiratory depression occurs. Other effects include vomiting, dysphoria, and allergy-enhanced hypotensive effects (Figure 14.4). The elevation of intracranial pressure, particularly in head injury, can be serious. *Morphine* enhances cerebral and spinal ischemia. In prostatic hypertrophy, *morphine* may cause acute urinary retention. A serious action is stoppage of

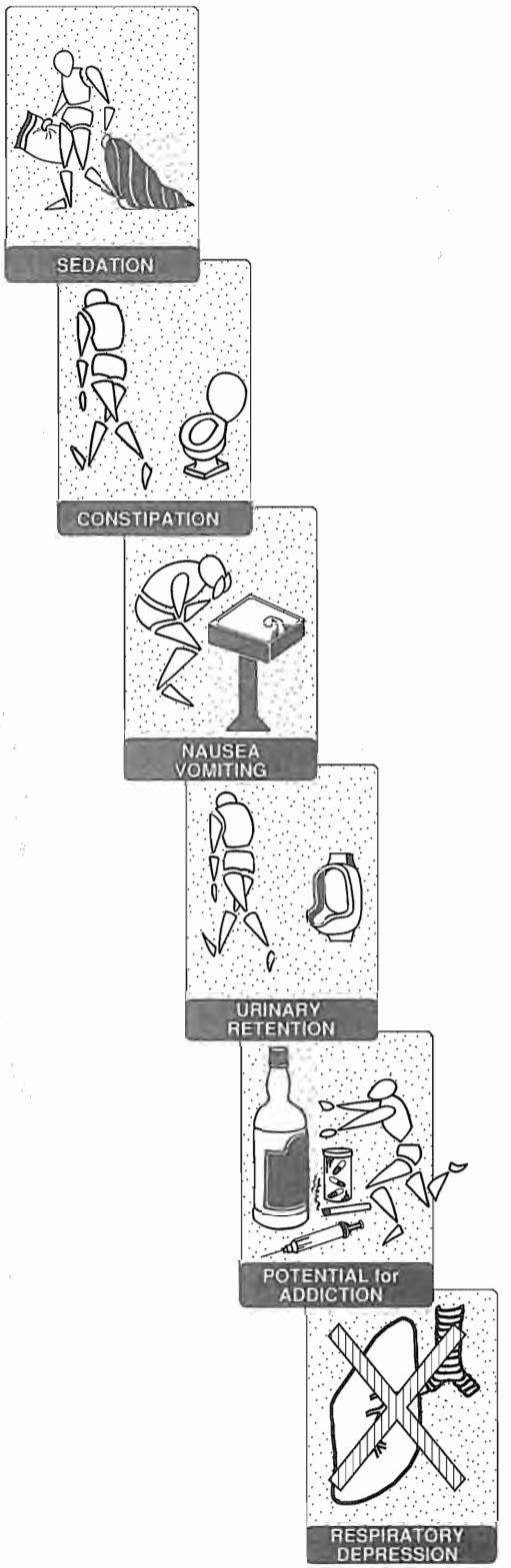

Figure 14.4
Adverse effects commonly observed in individuals treated with opioids.

respiratory exchange in emphysema or cor pulmonale patients. If employed in such individuals, respiration must be carefully watched. Patients with adrenal insufficiency or myxedema may experience extended and increased effects from the opioids.

6. **Tolerance and physical dependence:** Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, and sedative effects of *morphine*. However, tolerance usually does not develop to the pupil-constricting and constipating effects of the drug. Physical and psychologic dependence readily occur with *morphine* and with some of the other agonists to be described (see Figure 14.3). Withdrawal produces a series of autonomic, motor and psychological responses that incapacitate the individual and causes serious, almost unbearable symptoms. However, it is very rare that the effects are so profound as to cause death.

7. **Drug interactions:** The depressant actions of *morphine* are enhanced by phenothiazines (see p. 127), monoamine oxidase inhibitors (see p.123), and tricyclic antidepressants (see p. 119 and Figure 14.5). Low doses of *amphetamine* (see p. 103) strangely enhance analgesia. *Hydroxyzine* (see p. 422) also enhances analgesia.

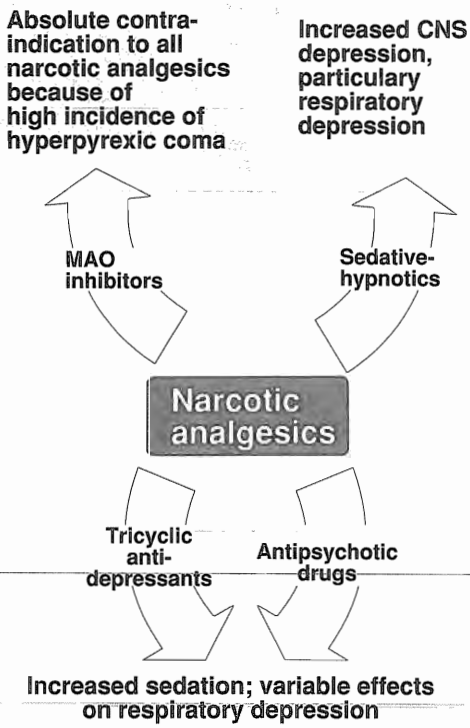

Figure 14.5
Drugs interacting with narcotic analgesics.

B. Meperidine

Meperidine [me PER i deen] is a synthetic opioid with a structure unrelated to *morphine*. It is used for acute pain.

1. **Mechanism of action:** *Meperidine* binds to opioid receptors, particularly κ receptors.

2. **Actions:** *Meperidine* causes a depression of respiration similar to that of *morphine*, but there is no significant cardiovascular action when the drug is given orally. On intravenous (IV) administration, *meperidine* produces a decrease in peripheral resistance and an increase in peripheral blood flow, and may cause an increase in cardiac rate. As with *morphine*, *meperidine* dilates cerebral vessels, increases cerebrospinal fluid pressure, and contracts smooth muscle (the latter to a lesser extent than does *morphine*). In the gastrointestinal tract, *meperidine* impedes motility, and chronic use results in constipation. *Meperidine* does not cause pinpoint pupils, but rather causes the pupils to dilate because of an *atropine*-like activity.

3. **Therapeutic uses:** *Meperidine* provides analgesia for any type of severe pain. Unlike *morphine*, *meperidine* is not clinically useful in the treatment of diarrhea or cough. *Meperidine* produces less of an increase in urinary retention than does *morphine*.

4. **Pharmacokinetics:** Unlike *morphine*, *meperidine* is well absorbed from the gastrointestinal tract and is useful when an orally-administered, potent analgesic is needed. However, *meperidine* is most often administered intramuscularly. The drug has a duration of action of 2 to 4 hours, which is shorter than that of *morphine* (see Figure 14.6). *Meperidine* is N-demethylated in the liver and is excreted in the urine. [Note: Because of its shorter action and dif-

ferent route of metabolism, *meperidine* is preferred for analgesia during labor.]

5. **Adverse effects:** Large doses of *meperidine* cause tremors, muscle twitches, and rarely, convulsions. The drug differs from opioids in that in large doses it dilates the pupil and causes hyperactive reflexes. Severe hypotension can occur when the drug is administered postoperatively. When used with major neuroleptics, depression is greatly enhanced. Administration to patients taking monoamine oxidase inhibitors (see p. 123) can provoke severe reactions such as convulsions and hyperthermia. *Meperidine* can cause dependence, and can substitute for *morphine* or *heroin* in use by addicts. Cross-tolerance with the other opioids occurs.

C. Methadone

Methadone [METH a don] is a synthetic, orally effective opioid that is approximately equal in potency to *morphine*, but induces less euphoria and has a longer duration of action.

1. **Mechanism of action:** *Methadone* has its greatest action on μ receptors.

2. **Actions:** The analgesic activity of *methadone* is equivalent to that of *morphine*. *Methadone* exhibits strong analgesic action when administered orally, in contrast to *morphine*, which is only partially absorbed from the gastrointestinal tract. The miotic and respiratory depressant actions of *methadone* have average half-lives of 24 hours. Like *morphine*, *methadone* increases biliary pressure, and is also constipating.

3. **Therapeutic uses:** *Methadone* is used in the controlled withdrawal of addicts from *heroin* and *morphine*. Orally administered, *methadone* is substituted for the injected opioid. The patient is then slowly weaned from *methadone*. *Methadone* causes a milder withdrawal syndrome, which also develops more slowly than that seen during withdrawal from *morphine*.

4. **Pharmacokinetics:** Readily absorbed following oral administration, *methadone* has a longer duration of action than does *morphine*. It accumulates in tissues, where it remains bound to protein from which it is slowly released. The drug is biotransformed in the liver and excreted in the urine, mainly as inactive metabolites.

5. **Adverse effects:** *Methadone* can produce dependence like that of *morphine*. The withdrawal syndrome is much milder but is more protracted (days to weeks) than with opiates.

D. Fentanyl

Fentanyl [FEN ta nil], which is chemically related to *meperidine,* has 80 times the analgesic potency of *morphine*, and is used in anesthesia. It has a rapid onset and short duration of action (15 to 30 minutes). When combined with *droperidol* (see p.117) it produces a dissociative anesthesia. *Sufentanil* [soo FEN ta nil], a related drug, is even more potent than *fentanyl*.

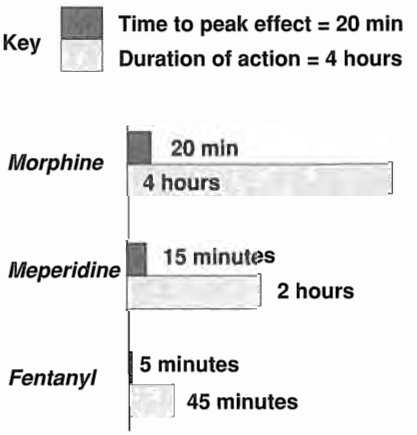

Figure 14.6
Time to peak effect and duration of action of several opioids administered intravenously.

E. Heroin

Heroin [HAIR o in] does not occur naturally but is produced by acetylation of *morphine*, which leads to a three-fold increase in its potency. Its greater lipid solubility allows it to cross the blood-brain barrier more rapidly than *morphine*, causing a more exaggerated euphoria when the drug is taken by injection. *Heroin* is converted to *morphine* in the body, but lasts about half as long. It has no accepted medical use in the United States.

IV. MODERATE AGONISTS

A. Propoxyphene

Propoxyphene [proe POX i feen] is a derivative of *methadone*. The dextro isomer is used as an analgesic to relieve mild to moderate pain. The levo isomer is not analgesic but has antitussive action. *Propoxyphene* is a weaker analgesic than *codeine,* requiring approximately twice the dose to achieve an equianalgesic effect as *codeine*. *Propoxyphene* is often used in combination with *aspirin* (see p. 403) or *acetaminophen* (see p. 412) for a greater analgesia than that obtained with either drug alone. It is well absorbed orally, with peak plasma levels occurring in 1 hour, and it is metabolized in the liver. *Propoxyphene* can produce nausea, anorexia, and constipation. In toxic doses, it can cause respiratory depression, convulsions, hallucinations and confusion. When toxic doses are taken, a very serious problem can arise in some individuals, with resultant cardiotoxicity and pulmonary edema. [Note: When used with alcohol and sedatives, a severe CNS depression is produced and death by respiratory depression and cardiotoxicity can result. The respiratory depression and sedation can be antagonized by *naloxone* (see p. 141), but the cardiotoxicity cannot.]

B. Codeine

Codeine [KOE deen] is a much less potent analgesic than *morphine*, but it has a higher oral efficacy. *Codeine* shows good antitussive activity at doses that do not cause analgesia. The drug has a lower abuse potential than *morphine* and rarely produces dependence. *Codeine* produces less euphoria than *morphine*. *Codeine* is often used in combination with *aspirin* or *acetaminophen*. [Note: In most nonprescription cough preparations, *codeine* has been replaced by newer drugs, such as *dextromethorphan* (see p. 222), a synthetic cough depressant that has no analgesic action and a low potential for abuse.] Figure 14.7 shows some of the actions of *codeine.*

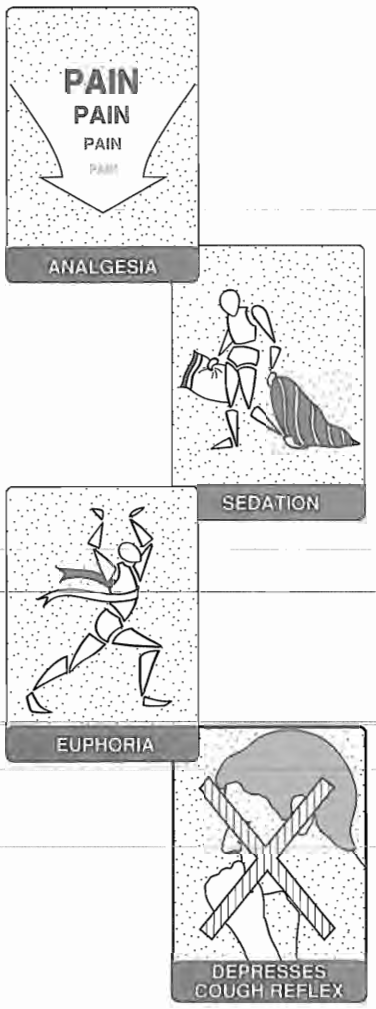

Figure 14.7
Some actions of *codeine*.

V. MIXED AGONIST-ANTAGONISTS

Drugs that stimulate one receptor but block another are termed mixed agonist-antagonists. The effects of these drugs depend on previous exposure to opioids. In individuals who have not recently received opioids,

mixed agonist-antagonists show agonist activity and are used to relieve pain. In the patient with opioid dependence, the agonist-antagonist drugs may show primarily blocking effects, that is, produce withdrawal symptoms. Most of the drugs in this group cause dysphoria, rather than euphoria, mediated by activation of σ receptors.

A. Pentazocine

Pentazocine [pen TAZ oh seen] acts as an agonist on κ receptors and is a weak antagonist at μ and δ receptors. It also binds to σ receptors, which may account for its dysphoric properties. *Pentazocine* promotes analgesia by activating receptors in the spinal cord, and is used to relieve moderate pain. It may be administered either orally or parenterally. *Pentazocine* produces less euphoria than does *morphine*. In higher doses, the drug causes respiratory depression and decreases the activity of the gastrointestinal tract. High doses increase blood pressure and can cause hallucinations, nightmares, tachycardia, and dizziness. In angina, *pentazocine* increases the mean aortic pressure and pulmonary arterial pressure and thus increases the work of the heart. The drug decreases renal plasma flow. Despite its antagonist action, *pentazocine* does not antagonize the respiratory depression of *morphine*, but it can precipitate a withdrawal syndrome in a *morphine* abuser. *Pentazocine* should not be used with agonists such as *morphine*, since the antagonist action of *pentazocine* may block the analgesic effects of *morphine*. Tolerance and dependence develop on repeated use.

B. Buprenorphine

Although *buprenorphine* [byou preh NOR feen] is classified as a partial agonist acting at the μ receptor, it behaves like *morphine* in naive patients. However, it can also antagonize *morphine*. *Buprenorphine* is administered parenterally and has a long duration of action because of its tight binding to the receptor. It is metabolized by the liver and excreted in the bile and urine. Adverse effects include respiratory depression, decrease (or, rarely, increase) in blood pressure, nausea and dizziness.

VI. ANTAGONISTS

The opioid antagonists bind with high affinity to opioid receptors but fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound effects in normal individuals. However, in patients addicted to opioids, antagonists rapidly reverse the effect of agonists, such as *heroin*, and precipitate the symptoms of opiate withdrawal.

A. Naloxone

Naloxone [nal OX own] is used to reverse the coma and respiratory depression of opioid overdose. It rapidly displaces all receptor-

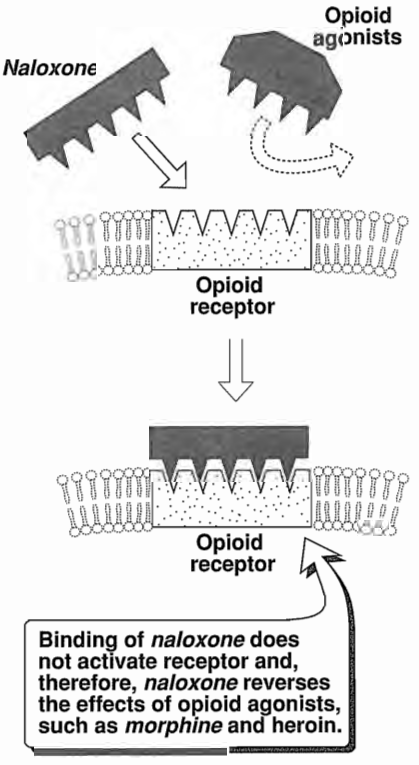

Figure 14.8
Competition of *naloxone* with opioid agonists.

bound opioid molecules and therefore is able to reverse the effect of a *heroin* overdose (Figure 14.8). Within 30 seconds of intravenous injection of *naloxone*, the respiratory depression and coma characteristic of high doses of *heroin* are reversed, causing the patient to be revived and alert. *Naloxone* has a half-life of 60 to 100 minutes. *Naloxone* is a competitive antagonist at μ, κ and δ, receptors, with a 10-fold higher affinity for μ receptors than for κ. This may explain why *naloxone* readily reverses respiratory depression with only minimal reversal of analgesia that results from agonist stimulation of κ receptors in the spinal cord. *Naloxone* produces no pharmacologic effects in normal individuals, but it precipitates withdrawal symptoms in *morphine* or *heroin* abusers.

B. Naltrexone

Naltrexone [nal TREX own] has actions similar to those of *naloxone*. This drug has a longer duration of action than *naloxone*, and a single oral dose of *naltrexone* blocks the effect of injected *heroin* for up to 48 hours. *Naltrexone* is used in opiate-dependence maintenance programs and may also be beneficial in treating chronic alcoholism.

Study Questions

Choose the ONE best answer.

14.1 All of the following statements concerning methadone are correct EXCEPT:

A. It has less potent analgesic activity than that of morphine.
B. It has a longer duration of action than that of morphine.
C. It is effective by oral administration.
D. It causes a milder withdrawal syndrome than morphine.
E. It has its greatest action on μ receptors

Correct choice = A. Methadone shows an analgesic action similar to that of morphine. Methadone is effective for 15 to 20 hr, whereas morphine acts for 4 to 6 hr. A major advantage of using methadone in the controlled withdrawal of heroin and morphine abusers is that it can be given orally.

14.2 Which of the following statements about pentazocine is INCORRECT?

A. It is a mixed agonist-antagonist.
B. It may be administered orally or parenterally.
C. It produces less euphoria than morphine.
D. It is often combined with morphine for maximal analgesic effects.
E. High doses of pentazocine increase blood pressure.

Correct choice = D. Pentazocine (a mixed agonist-antagonist) should not be used with agonists such as morphine, because it can block their actions. (Pentazocine acts as an agonist on κ receptors, but is an antagonist at μ and δ receptors.)

14.3 Which of the following statements about morphine is INCORRECT?

A. It is used therapeutically to relieve pain caused by severe head injury.
B. Its withdrawal symptoms can be relieved by methadone.
C. It causes constipation.
D. It is most effective by parenteral administration.
E. It rapidly enters all body tissues, including the fetus of a pregnant woman.

Correct choice = A. Morphine causes increased cerebrospinal fluid pressure secondary to dilation of cerebral vasculature. Methadone can relieve withdrawal symptoms because opioids show cross sensitivity. It is administered parenterally because absorption from the gastrointestinal tract is unreliable.

Drugs Used to Treat Epilepsy

15

I. OVERVIEW OF EPILEPSY

Epilepsy is widespread among the general population with over two million affected individuals in the United States. Epilepsy is not a single entity; it is a family of different recurrent seizure disorders that have in common the sudden, excessive and disorderly discharge of cerebral neurons. This results in abnormal movements or perceptions that are of short duration but that tend to recur. The site of the electrical discharge determines the symptoms that are produced. For example, epileptic seizures may cause convulsions if the motor cortex is involved. The seizures may include visual, auditory, or olfactory hallucinations if the parietal or occipital cortex plays a role. Drug therapy is the most widely effective mode of treatment for epilepsy. Seizures can be controlled completely in approximately 50% of epileptic patients, and meaningful improvement is achieved in at least one half of the remaining patients. (See Figure 15.1 for a summary of the antiepileptic drugs.)

A. Etiology

The neuronal discharge in epilepsy results from the firing of a small population of neurons in some specific area of the brain, referred to as the primary focus. Anatomically, this focal area may appear perfectly normal. There is usually no identifiable cause for epilepsy, although the focal areas that are functionally abnormal may be triggered into activity by changes in any of a variety of environmental factors, including alteration in blood gases, pH, electrolytes, or glucose availability.

1. **Primary epilepsy:** When no specific anatomic cause for the seizure, such as trauma or neoplasm, is evident the syndrome is called idiopathic or primary epilepsy. These seizures may be produced by an inherited abnormality in the central nervous system (CNS). Patients are treated chronically with antiepileptic drugs, often for life.

2. **Secondary epilepsy:** A number of reversible disturbances, such as tumors, head injury, hypoglycemia, meningeal infection, or rapid withdrawal of alcohol from an alcoholic, can precipitate seizures. Antiepileptic drugs are given until the primary cause of the seizures can be corrected. Seizures secondary to stroke or trauma may cause irreversible CNS damage.

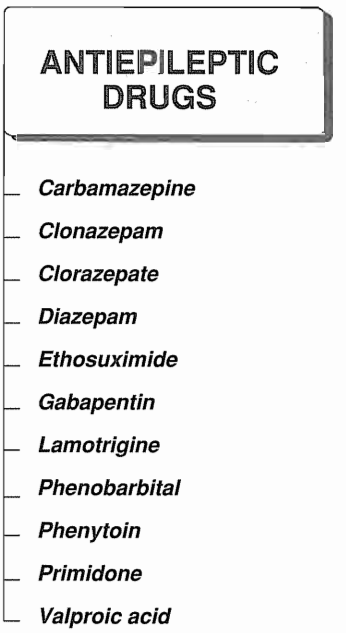

Figure 15.1
Summary of agents used in the treatment of epilepsy.

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by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
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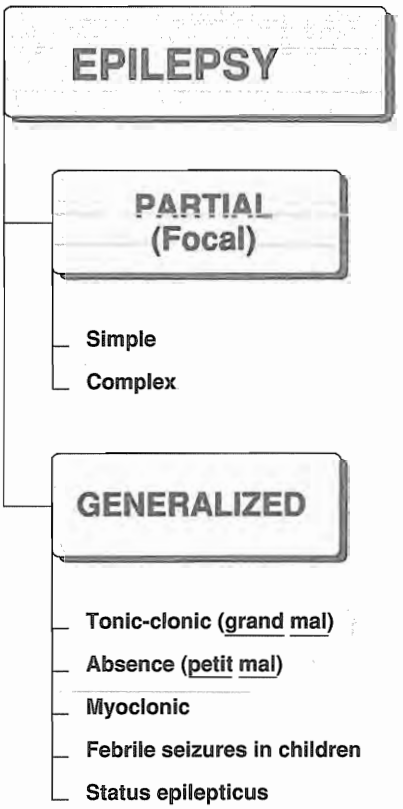

Figure 15.2
Classification of epilepsy.

B. Classification of epilepsy

Seizures have been classified into two broad groups, partial (or focal), and generalized. Choice of drug treatment is based on the classification of the epilepsy being treated (Figure 15.2).

1. **Partial:** The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons in the brain. Partial seizures may progress, becoming generalized tonic-clonic seizures.

   a. **Simple partial:** These seizures are caused by a group of hyperactive neurons exhibiting abnormal electrical activity and are confined to a single locus in the brain; the electrical disorder does not spread. The patient does not lose consciousness and often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain experiencing the disturbance. The patient may also show sensory distortions. Simple partial seizures may occur at any age.

   b. **Complex partial:** These seizures exhibit complex sensory hallucinations, mental distortion, and loss of consciousness. Motor dysfunction may involve chewing movements, diarrhea, urination. Most (80%) of individuals with complex partial epilepsy experience their initial seizures before 20 years of age.

2. **Generalized:** These seizures begin locally, but they rapidly spread, producing abnormal electrical discharge throughout both hemispheres of the brain. Generalized seizures may be convulsive or nonconvulsive; the patient usually has an immediate loss of consciousness.

   a. **Tonic-clonic (grand mal):** This is the most commonly encountered and the most dramatic form of epilepsy. Seizures result in loss of consciousness, followed by tonic, then clonic phases. The seizure is followed by a postictal period of confusion and exhaustion.

   b. **Absence (petit mal):** These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset occurs in patients at ages 3 to 5 years and lasts until puberty. The patient stares and exhibits rapid eye-blinking, which lasts for 3 to 5 seconds.

   c. **Myoclonic:** These seizures consist of short episodes of muscle contractions that may reoccur for several minutes. Myoclonic seizures are rare, occur at any age, and are often a result of permanent neurologic damage acquired as a result of hypoxia, uremia, encephalitis, or drug poisoning.

   d. **Febrile seizures:** Young children (3 months to 5 years of age) frequently develop seizures with illness accompanied by high fever. The febrile seizures consist of generalized tonic-clonic convulsions of short duration. Although febrile seizure may be frightening to observers, they are benign and do not cause death, neurologic damage, injury, or learning disorders, and they rarely require medication.

e. Status epilepticus: Seizures are rapidly recurrent.

C. Mechanism of action of antiepileptic drugs

Drugs that are effective in seizure reduction can either block the initiation of the electrical discharge from the focal area or, more commonly, prevent the spread of the abnormal electrical discharge to adjacent brain areas.

II. ANTIEPILEPTIC DRUGS

Initial drug treatment to suppress or reduce the incidence of seizures is based on the specific type of seizure (see Figure 15.3). Thus, tonic-clonic (grand mal) seizures are treated differently than absence seizures (petit mal). Several drugs may be equally effective, and the toxicity of the agent is often a major consideration in drug selection. Monotherapy is instituted with a single agent until seizures are controlled or toxic signs occur. When therapy with a single drug is ineffective, a second drug may be added to the therapeutic regimen. Antiepileptic therapy for tonic-clonic seizures should never be terminated abruptly, otherwise seizures may result.

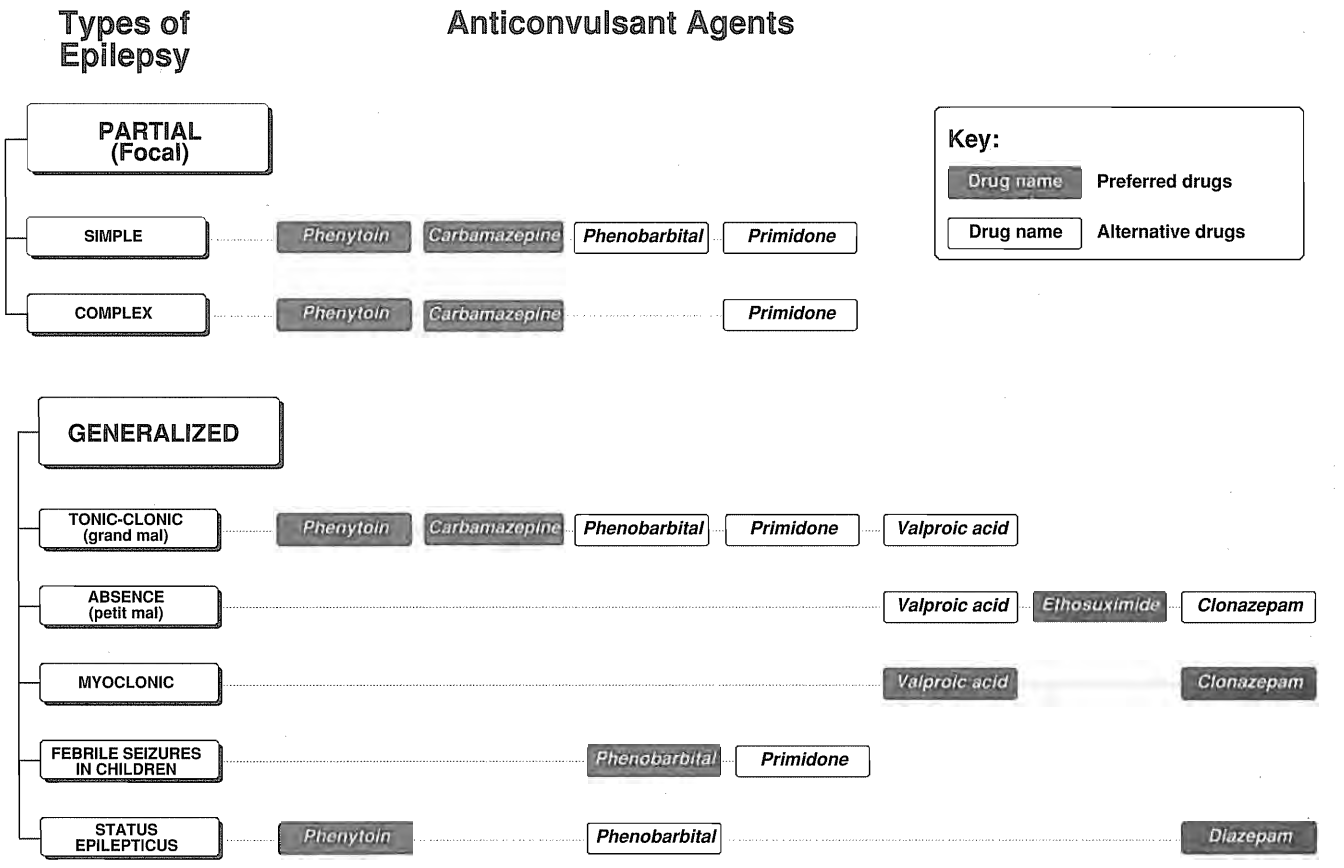

Figure 15.3
Therapeutic indications for anticonvulsant agents.

A. Phenytoin

Phenytoin [FEN i toy in] (formerly called *diphenylhydantoin*) is effective in suppressing tonic-clonic and partial seizures, and is a drug of choice for initial therapy, particularly in treating adults.

1. **Mechanism of action:** *Phenytoin* stabilizes neuronal membranes to depolarization by decreasing the flux of sodium ions in neurons in the resting state or during depolarization. It also reduces the influx of calcium ions during depolarization and suppresses repetitive firing of neurons.

2. **Actions:** *Phenytoin* is not a generalized CNS depressant like the barbiturates, but it does produce some degree of drowsiness and lethargy without progression to hypnosis. *Phenytoin* reduces the propagation of abnormal impulses in the brain.

3. **Therapeutic uses:** *Phenytoin* is highly effective for all partial seizures (simple and complex), for tonic-clonic seizures, and in the treatment of status epilepticus caused by recurrent tonic-clonic seizures (Figure 15.3). *Phenytoin* is not effective for absence seizures, which often may worsen if such a patient is treated with this drug.

4. **Absorption and Metabolism:** Oral absorption of *phenytoin* is slow, but once it occurs, distribution is rapid and brain concentrations are high. Chronic administration of *phenytoin* is always oral; in status epilepticus, it should be given intravenously. The drug is largely bound to plasma albumin. Less than 5% of a given dose is excreted unchanged in the urine. *Phenytoin* is metabolized by the hepatic hydroxylation system (see p. 14). At low doses the drug has a half-life of 24 hours, but as the dosage increases, the hydroxylation system becomes saturated. Thus, relatively small increases in each dose can produce large increases in the plasma concentration, resulting in drug-induced toxicity (Figure 15.4). Furthermore, large genetic variations in the rate of the drug's metabolism occur.

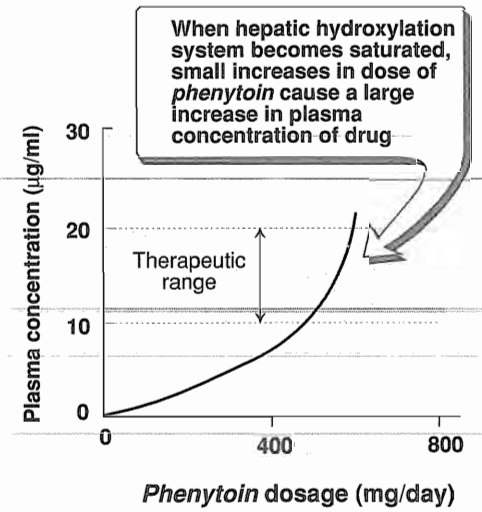

Figure 15.4
Nonlinear effect of *phenytoin* dosage on plasma concentration of drug.

5. **Adverse effects:** Depression of the CNS occurs particularly in the cerebellum and vestibular system, causing nystagmus and ataxia. Gastrointestinal problems (nausea, vomiting) are common. Gingival hyperplasia may cause the gums to grow over teeth, particularly in children. This hyperplasia slowly regresses after termination of drug therapy. Coarsening of facial features occurs in children. Megaloblastic anemia occurs because the drug interferes with vitamin B_{12} metabolism. Behavioral changes, such as confusion, hallucination, and drowsiness are common. Inhibition of antidiuretic hormone release occurs as well as hyperglycemia and glycosuria caused by inhibition of insulin secretion. *Phenytoin* is also an antiarrhythmic drug. Treatment with *phenytoin* should not be stopped abruptly.

6. **Teratogenic effects:** *Phenytoin* causes teratogenic effects in offspring of mothers given the drug during pregnancy. "Fetal hydantoin syndrome" includes cleft lip, cleft palate, congenital heart

disease, as well as slowed growth and mental deficiency. Almost half of untreated epileptic women have an increased seizure frequency during pregnancy. These seizures can lead to anoxic episodes, which yield a higher incidence of congenital birth defects. Antiepileptic drugs are given at the lowest possible dose to control seizures.

7. **Drug interactions:**

   a. **Inhibition of phenytoin metabolism:** Inhibition of microsomal metabolism of *phenytoin* in the liver is caused by *chloramphenicol*, *dicumarol*, *cimetidine*, sulfonamides, and *isoniazid*. When used chronically, these drugs increase the concentration of *phenytoin* in plasma by preventing its metabolism. A decrease in the plasma concentration of *phenytoin* is caused by *carbamazepine*, which enhances *phenytoin* metabolism (Figure 15.5).

   b. **Increase in metabolism of other drugs by phenytoin:** *Phenytoin* induces the P-450 system (see p. 14) which leads to an increase in the metabolism of other antiepileptics, anticoagulants, oral contraceptives, *quinidine*, *doxycycline*, *cyclosporine*, *mexiletine*, *methadone*, and *levodopa*.

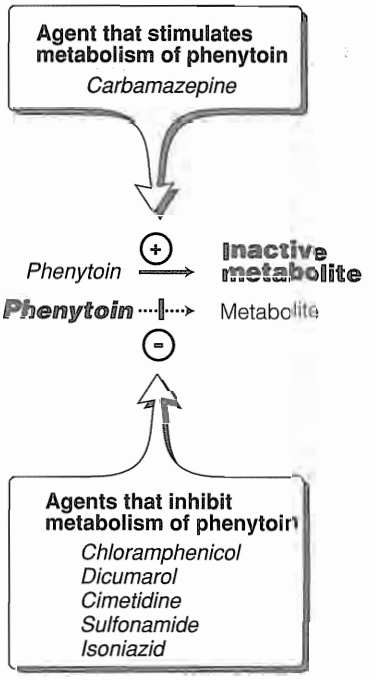

Figure 15.5
Drugs affecting the metabolism of *phenytoin*.

B. Carbamazepine

1. **Actions:** *Carbamazepine* [kar ba MAZ a peen] reduces the propagation of abnormal impulses in the brain by blocking sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus.

2. **Therapeutic uses:** *Carbamazepine* is highly effective for all partial seizures (simple and complex) and is often the drug of first choice. In addition the drug is highly effective for tonic-clonic seizures and is used to treat trigeminal neuralgia. It has occasionally been used in manic-depressive patients to ameliorate the symptoms.

3. **Absorption and metabolism:** *Carbamazepine* is absorbed slowly following oral administration. It enters the brain rapidly because of its high lipid solubility. *Carbamazepine* induces the drug metabolizing enzymes in the liver, and its half-life therefore decreases with chronic administration. The enhanced hepatic P-450 system activity also increases the metabolism of other antiepileptic drugs.

4. **Adverse effects:** Chronic administration of *carbamazepine* can cause stupor, coma, and respiratory depression, along with drowsiness, vertigo, ataxia, and blurred vision. The drug is irritating to the stomach, and nausea and vomiting may occur. Aplastic anemia, agranulocytosis, and thrombocytopenia have occurred in some patients. This drug has the potential for inducing serious liver toxicity. Therefore, anyone being treated with *carbamazepine* should have frequent liver function tests.

5. **Drug interactions:** The hepatic metabolism of *carbamazepine* is inhibited by several drugs (Figure 15.6). Toxic symptoms may arise if the dose is not adjusted.

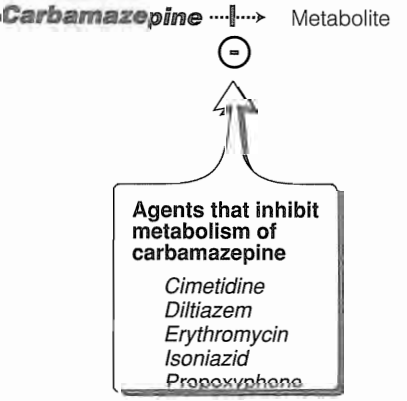

Figure 15.6
Drugs affecting the metabolism of *carbamazepine*.

C. Phenobarbital

1. **Actions:** *Phenobarbital* (see p. 94) has antiepileptic activity, limiting the spread of seizure discharges in the brain and elevating the seizure threshold. Its mechanism of action is unknown but may involve potentiation of the inhibitory effects of γ-aminobutyric acid (GABA)-mediated neurons. Doses required for antiepileptic action are lower than those that cause pronounced CNS depression.

2. **Therapeutic uses:** *Phenobarbital* provides a 50% favorable response rate for simple partial seizures, but it is not very effective for complex partial seizures. The drug has been regarded as the first choice in treating recurrent seizures in children, including febrile seizures. However, *phenobarbital* can depress cognitive performance in children treated for febrile seizures, and the drug should be used cautiously. *Phenobarbital* is also used to treat recurrent tonic-clonic seizures, especially in patients who do not respond to *diazepam* plus *phenytoin*. *Phenobarbital* is also used as a mild sedative to relieve anxiety, nervous tension and insomnia, although benzodiazepines (see p. 89) are superior.

3. **Absorption and metabolism:** *Phenobarbital* is well absorbed orally. The drug freely penetrates the brain. Approximately 75% of the drug is inactivated by the hepatic microsomal system; the remaining drug is excreted unchanged by the kidney. *Phenobarbital* is a potent inducer of the P-450 system, and when given chronically, it enhances the metabolism of other agents.

4. **Adverse effects:** Sedation, ataxia, nystagmus, vertigo, and acute psychotic reactions may occur with chronic use. Nausea and vomiting are seen as well as a morbilliform rash in sensitive individuals. Agitation and confusion occur at high doses. Rebound seizures can occur on discontinuance of *phenobarbital*.

D. Primidone

Primidone [PRI mi done] is structurally related to *phenobarbital*, and resembles *phenobarbital* in its anticonvulsant activity. *Primidone* is an alternate choice in partial seizures and tonic-clonic seizures. Much of *primidone*'s efficacy comes from its metabolites *phenobarbital* and phenylethylmalonamide (see Figure 15.7), which have longer half-lives than the parent drug. *Phenobarbital* is effective against tonic-clonic and simple partial seizures, and phenylethylmalonamide is effective against complex partial seizures. *Primidone* is often used with *carbamazepine* and *phenytoin*, allowing smaller doses of these agents to be used. It is ineffective in absence seizures (Figure 15.3). *Primidone* is well absorbed orally. It exhibits poor protein binding. This drug has the same adverse effects as those seen with *phenobarbital*.

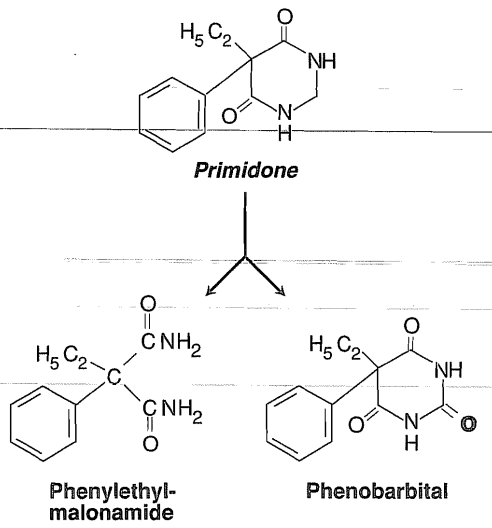

Figure 15.7
Metabolism of *primidone*.

E. Valproic acid

Valproic acid [val PROE ic] reduces the propagation of abnormal electrical discharge in the brain. It may enhance GABA action at inhibitory synapses. *Valproic acid* is the most effective agent avail-

able for treatment of myoclonic seizures. The drug diminishes absence seizures but is a second choice because of its hepatotoxic potential. *Valproic acid* also reduces the incidence and severity of tonic-clonic seizures (see Figure 15.3). The drug is effective orally and is rapidly absorbed. About 90% is bound to plasma proteins. Only 3% is excreted unchanged; the rest is converted to active metabolites by the liver. *Valproic acid* is metabolized by the P-450 system, but it does not induce P-450 enzyme synthesis. The glucuronylated metabolites are excreted in the urine. *Valproic acid* can cause nausea and vomiting; sedation, ataxia, and tremor are common (Figure 15.8). Hepatic toxicity may cause a rise in hepatic enzymes in plasma, which should be monitored frequently. In some individuals, a rash and alopecia may occur. Bleeding times may increase because of both thrombocytopenia and an inhibition of platelet aggregation. *Valproic acid* inhibits *phenobarbital* metabolism, thereby increasing circulating levels of that barbiturate.

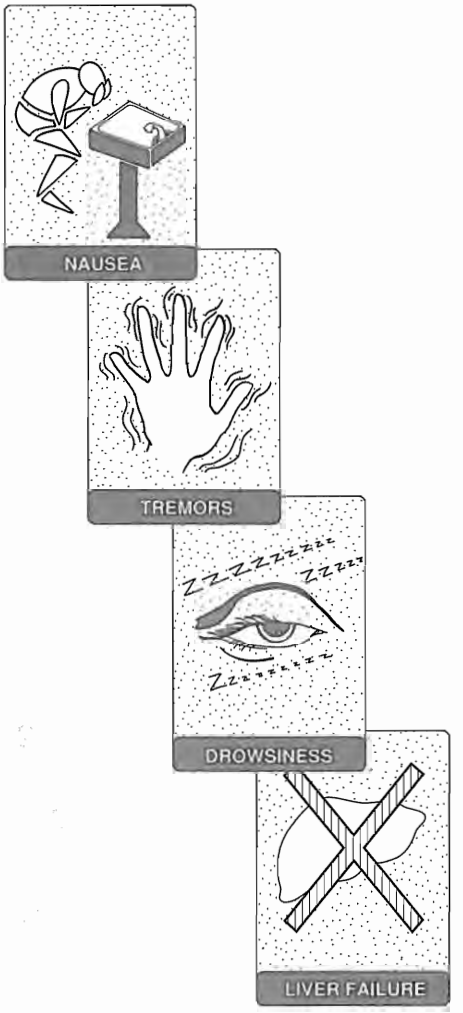

Figure 15.8
Some adverse effects of *valproic acid*.

F. Ethosuximide

Ethosuximide [eth oh SUX i mide] reduces propagation of abnormal electrical activity in the brain, and is the first choice in absence seizures (see Figure 15.3). *Ethosuximide* is well absorbed orally. It is not bound to plasma proteins. About 25% of the drug is excreted unchanged in the urine, and 75% is converted to inactive metabolites in the liver by the microsomal P-450 system. *Ethosuximide* does not induce P-450 enzyme synthesis. The drug is irritating to the stomach, and nausea and vomiting may occur on chronic administration. Drowsiness, lethargy, dizziness, restlessness, agitation, anxiety, and the inability to concentrate are often observed. In sensitive individuals, a Stevens-Johnson syndrome or urticaria may occur, as well as leukopenia, aplastic anemia, and thrombocytopenia.

G. Benzodiazepines

Several of the benzodiazepines show antiepileptic activity. *Clonazepam* and *clorazepate* are used for chronic treatment, whereas *diazepam* is the drug of choice in the acute treatment of status epilepticus (see p. 91). *Clonazepam* suppresses seizure spread from the epileptogenic focus, and is effective in absence and myoclonic seizures (see Figure 15.3), but tolerance develops. *Clorazepate* is effective in partial seizures when used in conjunction with other drugs. Of all the antiepileptics, the benzodiazepines are the safest and most free from severe side effects. All benzodiazepines have sedative properties; thus, drowsiness, somnolence, and fatigue can occur with higher dosage as well as ataxia, dizziness and behavior changes. Respiratory depression and cardiac depression may occur when given intravenously in acute situations.

H. Gabapentin and Lamotrigine

For the first time in many years, new classes of antiepileptic drugs are becoming available. *Gabapentin* [gah ah PEN tin] is an analogue of GABA, but its mechanism is not known. *Lamotrigine* [la MO tri geen] inhibits glutamate and aspartate release, blocks sodium channels, and prevents repetitive firing. Both drugs are approved for the treatment of simple or complex partial seizures and generalized

tonic-clonic seizures. *Gabapentin* does not bind to plasma proteins and is excreted unchanged through the kidneys, minimizing the likelihood of drug interactions. *Lamotrigine* is metabolized in the liver. Its $t_{1/2}$ is decreased by enzyme-inducing drugs (*carbamazepine*, *phenytoin*) and is increased by *valproic acid*. Mild CNS effects occur with both drugs, and development of a rash with *lamotrigine*, have been the most noted adverse reactions.

Study Questions

Choose the ONE best answer.

15.1 For which one of the following drugs is the therapeutic indication INCORRECT?

A. Ethosuximide: Absence seizures
B. Phenobarbital: Febrile seizures in children
C. Diazepam: Status epilepticus
D. Phenytoin: Absence seizures
E. Carbamazepine: Tonic-clonic seizures

Correct choice = D. Phenytoin is effective in suppressing tonic-clonic and partial seizures, and in the treatment of status epilepticus caused by recurrent tonic-clonic seizures. It is not effective for absence seizures.

15.2 Which of the following statements concerning phenytoin is INCORRECT?

A. Causes less sedation than phenobarbital.
B. Causes gingival hyperplasia.
C. May cause fetal hydantoin syndrome if given during pregnancy.
D. Is excreted unchanged in the urine.
E. The plasma half-life increases as the dose is increased.

Correct choice = D. Less than 5% of phenytoin is excreted unchanged in the urine; it is metabolized by the hepatic hydroxylation system. Saturation of hepatic metabolizing enzymes at high doses of phenytoin leads to an increase in the half-life of the drug.

15.3 All the following drugs are useful in treating complex partial seizures EXCEPT:

A. Ethosuximide
B. Phenobarbital
C. Carbamazepine
D. Phenytoin
E. Gabapentin

Correct choice = A. Ethosuximide is used in the treatment of absence seizures.

15.4 Which of the following drug/toxicity pairs is INCORRECT?

A. Valproic acid: Nausea and vomiting
B. Ethosuximide: Stevens-Johnson syndrome
C. Carbamazepine: Bone marrow suppression
D. Primidone: Hepatotoxicity
E. Phenobarbital: Sedation

Correct choice = D. Primidone does not cause hepatotoxicity. The adverse effects seen with this drug are the same as those seen with phenobarbital.