CNS Stimulants

10

I. OVERVIEW

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

PSYCHOMOTOR STIMULANTS

Amphetamine ADDERALL
Armodafinil NUVIGIL
Atomoxetine STRATTERA
Caffeine CAFCIT, NO DOZ, VIVARIN
Cocaine
Dexmethylphenidate FOCALIN
Dextroamphetamine DEXEDRINE, DEXTROSTAT
Lisdexamfetamine VYVANSE
Methylphenidate RITALIN, CONCERTA, DAYTRANA
Modafinil PROVIGIL
Nicotine COMMIT, NICODERM CQ, NICORETTE
Theophylline ELIXOPHYLLIN, THEO-24, THEOCHRON, UNIPHYL
Varenicline CHANTIX

HALLUCINOGENS

Dronabinol MARINOL
Lysergic acid diethylamide (LSD)
Phencyclidine (PCP)
Tetrahydrocannabinol (THC)

Figure 10.1
Summary of central nervous system (CNS) stimulants.

II. PSYCHOMOTOR STIMULANTS

A. Methylxanthines

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

1. **Mechanism of action:** Several mechanisms have been proposed for the actions of methylxanthines, including translocation of extracellular calcium, increase in cyclic adenosine monophosphate and cyclic guanosine monophosphate caused by inhibition of phosphodiesterase, and blockade of adenosine receptors. The latter most likely accounts for the actions achieved by the usual consumption of caffeine-containing beverages.

2. **Actions:**

   a. **CNS:** The *caffeine* contained in one to two cups of coffee (100–200 mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain. Consumption of 1.5 g of *caffeine* (12 to 15 cups of coffee) produces anxiety and tremors. The spinal cord is stimulated only by very high doses (2–5 g) of *caffeine*. Tolerance can rapidly develop to the stimulating properties of *caffeine*, and withdrawal consists of feelings of fatigue and sedation.

   b. **Cardiovascular system:** A high dose of *caffeine* has positive inotropic and chronotropic effects on the heart. [Note: Increased contractility can be harmful to patients with angina

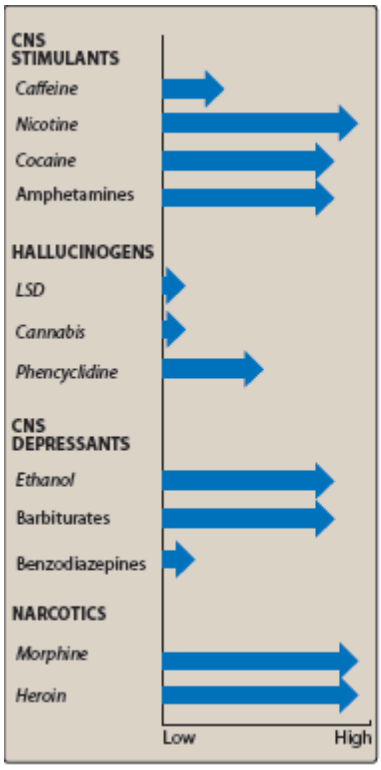

Figure 10.2
Relative potential for physical dependence on commonly abused substances. LSD = lysergic acid diethylamide.

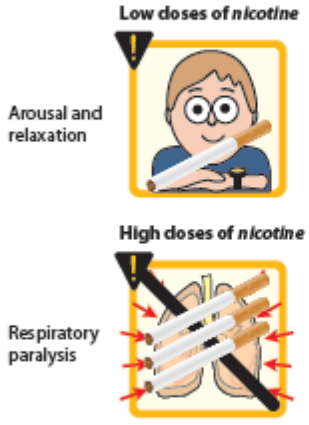

Figure 10.3
Actions of *nicotine* on the central nervous system.

pectoris. In others, an accelerated heart rate can trigger premature ventricular contractions.]

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

d. **Gastric mucosa:** Because all methylxanthines stimulate secretion of hydrochloric acid from the gastric mucosa, individuals with peptic ulcers should avoid foods and beverages containing methylxanthines.

3. **Therapeutic uses:** *Caffeine* and its derivatives relax the smooth muscles of the bronchioles. [Note: Previously the mainstay of asthma therapy, *theophylline* has been largely replaced by other agents, such as β_2 agonists and corticosteroids.]

4. **Pharmacokinetics:** The methylxanthines are well absorbed orally. *Caffeine* distributes throughout the body, including the brain. These drugs cross the placenta to the fetus and are secreted into the mother's milk. All the methylxanthines are metabolized in the liver, generally by the CYP1A2 pathway, and the metabolites are then excreted in the urine.

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

B. Nicotine

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

1. **Mechanism of action:** In low doses, *nicotine* causes ganglionic stimulation by depolarization. At high doses, *nicotine* causes ganglionic blockade. *Nicotine* receptors exist at a number of sites in the CNS, which participate in the stimulant attributes of the drug.

2. **Actions:**

a. **CNS:** *Nicotine* is highly lipid soluble and readily crosses the blood-brain barrier. Cigarette smoking or administration of low doses of *nicotine* produces some degree of euphoria and arousal as well as relaxation. It improves attention, learning, problem solving, and reaction time. High doses of *nicotine* result in central respiratory paralysis and severe hypotension caused by medullary paralysis (Figure 10.3). *Nicotine* is also an appetite suppressant.

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

. Pharmacokinetics: Because *nicotine* is highly lipid soluble, absorption readily occurs via the oral mucosa, lungs, GI mucosa, and skin. *Nicotine* crosses the placental membrane and is secreted in the milk of lactating women. By inhaling tobacco smoke, the average smoker takes in 1 to 2 mg of *nicotine* per cigarette (most cigarettes contain 6 to 8 mg of *nicotine*). The acute lethal dose is 60 mg. More than 90 percent of the *nicotine* inhaled in smoke is absorbed. Clearance of *nicotine* involves metabolism in the lung and the liver and urinary excretion. Tolerance to the toxic effects of *nicotine* develops rapidly, often within days after beginning usage.

. Adverse effects: The CNS effects of *nicotine* include irritability and tremors. *Nicotine* may also cause intestinal cramps, diarrhea, and increased heart rate and blood pressure. In addition, cigarette smoking increases the rate of metabolism for a number of drugs.

. Withdrawal syndrome: As with the other drugs in this class, *nicotine* is an addictive substance, and physical dependence develops rapidly and can be severe (Figure 10.4). Withdrawal is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia. Appetite is affected, and GI pain often occurs. [Note: Smoking cessation programs that combine pharmacologic and behavioral therapy are the most successful in helping individuals to stop smoking.] The transdermal patch and chewing gum containing *nicotine* have been shown to reduce *nicotine* withdrawal symptoms and to help smokers stop smoking. For example, the blood concentration of *nicotine* obtained from *nicotine* chewing gum is typically about one-half the peak level observed with smoking (Figure 10.5). *Bupropion*, an antidepressant (see p. 155), can reduce the craving for cigarettes.

arenicline

arenicline [ver-EN-ih-kleen] is a partial agonist at neuronal nicotinic cetylcholine receptors in the CNS. Because *varenicline* is only a partial gonist at these receptors, it produces less euphoric effects than those roduced by *nicotine* itself (*nicotine* is a full agonist at these receptors). hus, it is useful as an adjunct in the management of smoking cessation n patients with *nicotine* withdrawal symptoms. Additionally, *varenicline* ends to attenuate the rewarding effects of *nicotine* if a person relapses nd uses tobacco. Patients should be monitored for suicidal thoughts, ivid nightmares, and mood changes.

Figure 10.4
Nicotine has potential for addiction.

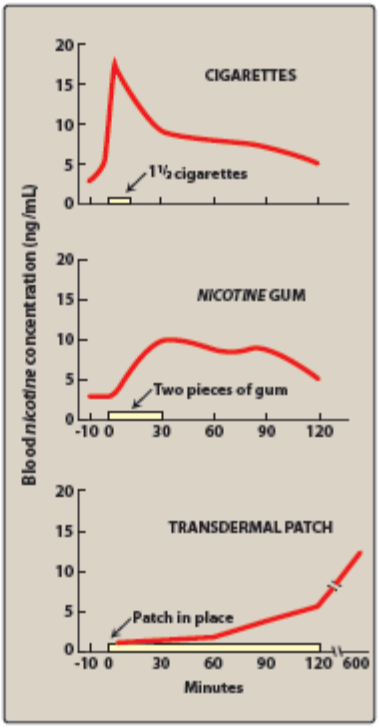

Figure 10.5
Blood concentrations of *nicotine* in individuals who smoked cigarettes, chewed *nicotine* gum, or received *nicotine* by transdermal patch.

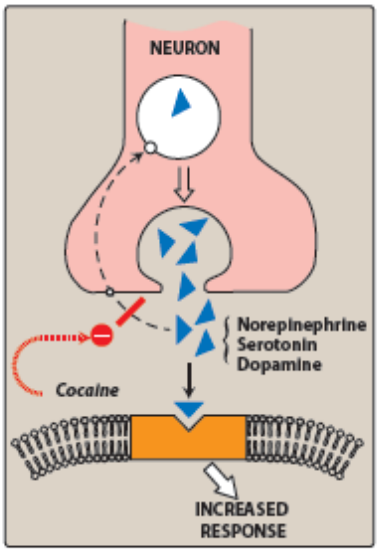

Figure 10.6
Mechanism of action of *cocaine*.

Figure 10.7
Cocaine and *amphetamine* have potential for addiction.

D. Cocaine

Cocaine [KOE-kane] is a widely available and highly addictive drug that is currently abused daily by more than 3 million people in the United States. Because of its abuse potential, *cocaine* is classified as a Schedule II drug by the U.S. Drug Enforcement Agency.

1. **Mechanism of action:** The primary mechanism of action underlying the central and peripheral effects of *cocaine* is blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals from which these neurotransmitters are released (Figure 10.6). This blockade is caused by *cocaine* binding to the monoaminergic reuptake transporters, and, thus, potentiates and prolongs the CNS and peripheral actions of these monoamines. In particular, the prolongation of dopaminergic effects in the brain's pleasure system (limbic system) produces the intense euphoria that *cocaine* initially causes. Chronic intake of *cocaine* depletes dopamine. This depletion triggers the vicious cycle of craving for *cocaine* that temporarily relieves severe depression (Figure 10.7).

2. **Actions:**

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

   b. **Sympathetic nervous system:** Peripherally, *cocaine* potentiates the action of norepinephrine, and it produces the "fight-or-flight" syndrome characteristic of adrenergic stimulation. This is associated with tachycardia, hypertension, pupillary dilation, and peripheral vasoconstriction. Recent evidence suggests that the ability of baroreceptor reflexes to buffer the hypertensive effect may be impaired.

   c. **Hyperthermia:** *Cocaine* is unique among illicit drugs in that death can result not only as a function of dose, but also from the drug's propensity to cause hyperthermia. [Note: Mortality rates for *cocaine* overdose rise in hot weather.] Even a small dose of intranasal *cocaine* impairs sweating and cutaneous vasodilation. Perception of thermal discomfort is also decreased.

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

4. **Pharmacokinetics:** *Cocaine* is often self-administered by chewing, intranasal snorting, smoking, or intravenous (IV) injection. The peak effect occurs 15 to 20 minutes after intranasal intake of *cocaine* powder, and the "high" disappears in 1 to 1.5 hours. Rapid but short-lived effects are achieved following IV injection of *cocaine* or by smoking the freebase form of the drug ("crack"). Because the onset of action is most rapid, the potential for overdosage and dependence is greatest with IV injection and crack smoking. *Cocaine* is rapidly de-esterified and demethylated to benzoylecgonine, which is excreted in the urine. Detection of this substance in the urine identifies a user.

5. **Adverse effects:**

   a. **Anxiety:** The toxic response to acute *cocaine* ingestion can precipitate an anxiety reaction that includes hypertension, tachycardia, sweating, and paranoia. [Note: Little tolerance to the toxic CNS effects of *cocaine* (for example, convulsions) occurs with prolonged use.] Because of the irritability, many users take *cocaine* with alcohol. A product of *cocaine* metabolites and *ethanol* is cocaethylene, which is also psychoactive and believed to contribute to cardiotoxicity.

   b. **Depression:** As with all stimulant drugs, *cocaine* stimulation of the CNS is followed by a period of mental depression. Addicts withdrawing from *cocaine* exhibit physical and emotional depression as well as agitation. The latter symptom can be treated with benzodiazepines or phenothiazines.

   c. **Toxic effects:** *Cocaine* can induce seizures as well as fatal cardiac arrhythmias (Figure 10.8). Use of IV *diazepam* may be required to control *cocaine*-induced seizures. The incidence of myocardial infarction in *cocaine* users is unrelated to dose, to duration of use, or to route of administration. There is no marker to identify those individuals who may have life-threatening cardiac effects after taking *cocaine*.

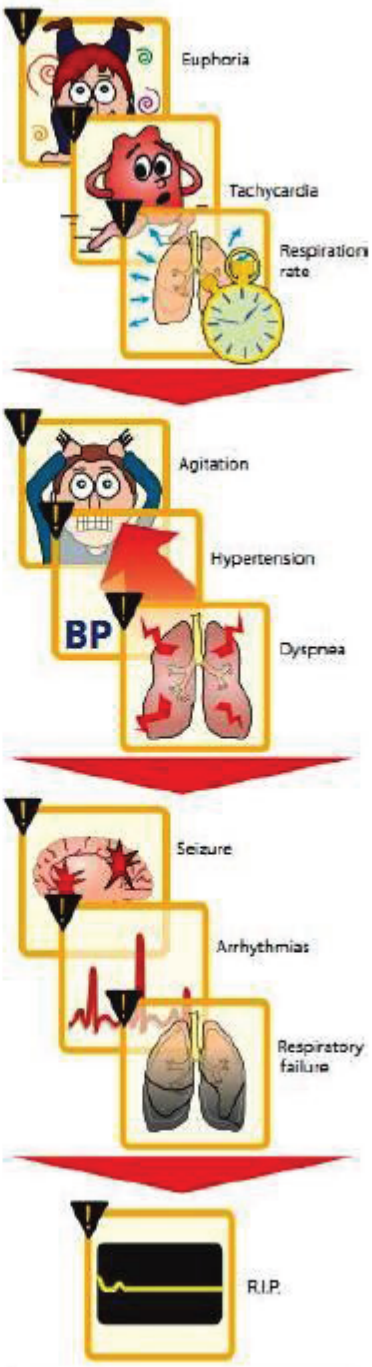

Figure 10.8
Major effects of *cocaine* use.

E. Amphetamine

Amphetamine [am-FET-a-meen] is a sympathetic amine that shows neurologic and clinical effects quite similar to those of *cocaine*. *Dextroamphetamine* [dex-troe-am-FET-a-meen] is the major member of this class of compounds. *Methamphetamine* [meth-am-FET-a-mine] (also known as "speed") is a derivative of *amphetamine* available for prescription use. It can also be smoked and is preferred by many abusers. *3,4-Methylenedioxymethamphetamine* (also known as MDMA, or Ecstasy), a synthetic derivative of *methamphetamine* with both stimulant and hallucinogenic properties, is discussed on p. 537

1. **Mechanism of action:** As with *cocaine*, the effects of *amphetamine* on the CNS and peripheral nervous system are indirect. That is, both depend upon an elevation of the level of catecholamine neurotransmitters in synaptic spaces. *Amphetamine*, however, achieves this effect by releasing intracellular stores of catecholamines (Figure 10.9). Because *amphetamine* also inhibits monoamine oxidase (MAO), high levels of catecholamines are readily released into synaptic spaces. Despite different mechanisms of action, the behavioral

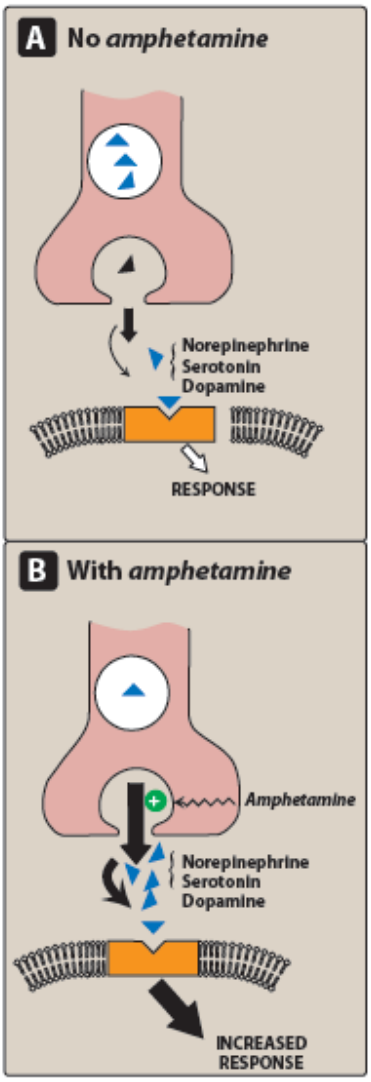

Figure 10.9
Mechanism of action of *amphetamine*.

effects of *amphetamine* and its derivatives are similar to those of *cocaine*.

2. **Actions:**

   a. **CNS:** The major behavioral effects of *amphetamine* result from a combination of its dopamine and norepinephrine release-enhancing properties. *Amphetamine* stimulates the entire cerebrospinal axis, cortex, brainstem, and medulla. This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia. These CNS stimulant effects of *amphetamine* and its derivatives have led to their use in therapy for hyperactivity in children, for narcolepsy, and for appetite control. At high doses, psychosis and convulsions can ensue.

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

3. **Therapeutic uses:** Factors that limit the therapeutic usefulness of *amphetamine* include psychological and physiological dependence similar to those with *cocaine* and, with chronic use, the development of tolerance to the euphoric and anorectic effects.

   a. **Attention deficit hyperactivity disorder (ADHD):** Some young children are hyperkinetic and lack the ability to be involved in any one activity for longer than a few minutes. *Dextroamphetamine* and the *amphetamine* derivative *methylphenidate* [meth-ill-FEN-ih-date] can help improve attention spans and alleviate many of the behavioral problems associated with this syndrome, in addition to reducing the hyperkinesia that such children demonstrate. *Lisdexamfetamine* [lis-dex-am-FET-a-meen] is a prodrug that is converted to the active component *dextroamphetamine* after GI absorption and metabolism. *Lisdexamfetamine* prolongs the patient's span of attention, allowing better function in a school atmosphere. *Atomoxetine* [AT-oh-MOX-ih-teen] is a nonstimulant drug approved for ADHD in children and adults. [Note: This drug should not be taken by individuals on MAO inhibitors and by patients with narrow-angle glaucoma.] Unlike *methylphenidate,* which blocks dopamine reuptake, *atomoxetine* is a norepinephrine-reuptake inhibitor. Therefore, it is not habit forming and is not a controlled substance.

   b. **Narcolepsy:** Narcolepsy is a relatively rare sleep disorder that is characterized by uncontrollable bouts of sleepiness during the day. It is sometimes accompanied by catalepsy, a loss in muscle control, and even paralysis brought on by strong emotions such as laughter. However, it is the sleepiness for which the patient is usually treated with drugs, such as *amphetamine* or *methylphenidate*. Recently, a newer drug, *modafinil* [moe-DA-fi-nil], and its R-enantiomer derivative, *armodafinil* [ahr-moe-DA-fi-nil], have become available to treat narcolepsy. *Modafinil* produces fewer psychoactive and euphoric effects as well as fewer alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. It does promote wakefulness. The mechanism of action remains unclear, but may involve the adrenergic and

dopaminergic systems, although it has been shown to differ from that of *amphetamine*. *Modafinil* is effective orally. It is well distributed throughout the body and undergoes extensive hepatic metabolism. The metabolites are excreted in urine. Headaches, nausea, and rhinitis are the primary adverse effects. There is some evidence to indicate the potential for abuse and physical dependence with *modafinil*.

4. **Pharmacokinetics:** *Amphetamine* is completely absorbed from the GI tract, metabolized by the liver, and excreted in the urine. [Note: Administration of urinary alkalinizing agents will increase the nonionized species of the drug and decrease its excretion.] *Amphetamine* abusers often administer the drugs by IV injection and/or by smoking. The euphoria caused by *amphetamine* lasts 4 to 6 hours, or four- to eightfold longer than the effects of *cocaine*.

5. **Adverse effects:** The *amphetamines* may cause addiction, leading to dependence, tolerance, and drug-seeking behavior. In addition, they have the following undesirable effects.

   a. **CNS effects:** Undesirable side effects of *amphetamine* usage include insomnia, irritability, weakness, dizziness, tremor, and hyperactive reflexes (Figure 10.10). *Amphetamine* can also cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients. Chronic *amphetamine* use produces a state of "*amphetamine* psychosis" that resembles the psychotic episodes associated with schizophrenia. Whereas long-term *amphetamine* use is associated with psychic and physical dependence, tolerance to its effects may occur within a few weeks. Overdoses of *amphetamine* are treated with *chlorpromazine* or *haloperidol*, which relieve the CNS symptoms as well as the hypertension because of their α-blocking effects. The anorectic effect of *amphetamine* is due to its action in the lateral hypothalamic feeding center.

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

   c. **GI system effects:** *Amphetamine* acts on the GI system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea. Administration of *sodium bicarbonate* will increase the reabsorption of *dextroamphetamine* from the renal tubules into the bloodstream.

   d. **Contraindications:** Neither patients with hypertension, cardiovascular disease, hyperthyroidism, or glaucoma should be treated with this drug, nor should patients with a history of drug abuse, nor anyone taking MAO inhibitors.

F. Methylphenidate

Methylphenidate has CNS-stimulant properties similar to those of *amphetamine* and may also lead to abuse, although its addictive poten-

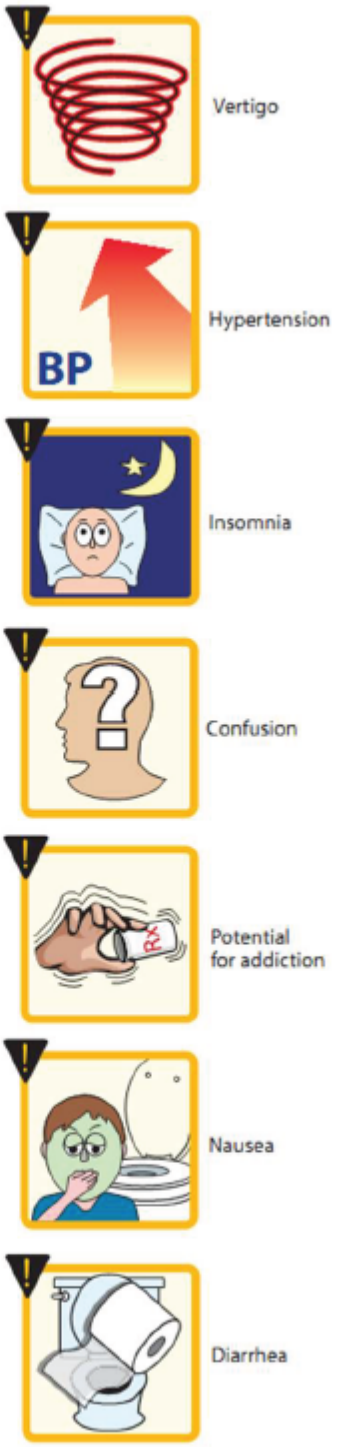

Figure 10.10
Adverse effects of amphetamines.

tial is controversial. It is a Schedule II drug. It is presently one of the most prescribed medications in children. It is estimated that 4 to 6 million children in the United State take *methylphenidate* daily for ADHD. The pharmacologically active isomer, *dexmethylphenidate*, has also been approved in the United States for the treatment of ADHD.

1. **Mechanism of action:** Children with ADHD may produce weak dopamine signals, which suggests that once-interesting activities provide fewer rewards to these children. *Methylphenidate* is a dopamine transport inhibitor and may act by increasing dopamine in the synaptic space. [Note: *Methylphenidate* may have less potential for abuse than *cocaine*, because it enters the brain much more slowly than *cocaine* and, thus, does not increase dopamine levels as rapidly.]

2. **Therapeutic uses:** *Methylphenidate* has been used for several decades in the treatment of ADHD in children ages 6 to 16 years. It is also effective in the treatment of narcolepsy. Unlike *methylphenidate*, *dexmethylphenidate* is not indicated in the treatment of narcolepsy.

3. **Pharmacokinetics:** Both *methylphenidate* and *dexmethylphenidate* are readily absorbed upon oral administration. *Methylphenidate* is available in extended release capsules and as a transdermal patch. The de-esterified product, ritalinic acid, is excreted in urine.

4. **Adverse reactions:** GI effects are the most common and include abdominal pain and nausea. Other reactions include anorexia, insomnia, nervousness, and fever. In seizure patients, *methylphenidate* seems to increase the seizure frequency, especially if the patient is taking antidepressants. *Methylphenidate* is contraindicated in patients with glaucoma.

5. **Drug interactions:** Studies have shown that *methylphenidate* can interfere in the metabolism of *warfarin*, *phenytoin*, *phenobarbital*, *primidone*, and the tricyclic antidepressants.

III. HALLUCINOGENS

A few drugs have, as their primary action, the ability to induce altered perceptual states reminiscent of dreams. Many of these altered states are accompanied by visions of bright, colorful changes in the environment and by a plasticity of constantly changing shapes and color. The individual under the influence of these drugs is incapable of normal decision-making because the drug interferes with rational thought. These compounds are known as hallucinogens or psychotomimetic drugs.

A. Lysergic acid diethylamide

Multiple sites in the CNS are affected by *lysergic acid diethylamide* (*LSD*). The drug shows serotonin (5-HT) agonist activity at presynaptic 5-HT_1 receptors in the midbrain, and it stimulates 5-HT_2 receptors. Activation of the sympathetic nervous system occurs, which causes pupillary dilation, increased blood pressure, piloerection, and increased body temperature. Taken orally, low doses of *LSD* can induce hallucinations with brilliant colors. Mood alteration also occurs. Tolerance and physical dependence have occurred, but true dependence is rare. Adverse effects include hyperreflexia, nausea, and muscular weakness. High doses may produce long-lasting psychotic changes in susceptible indi-

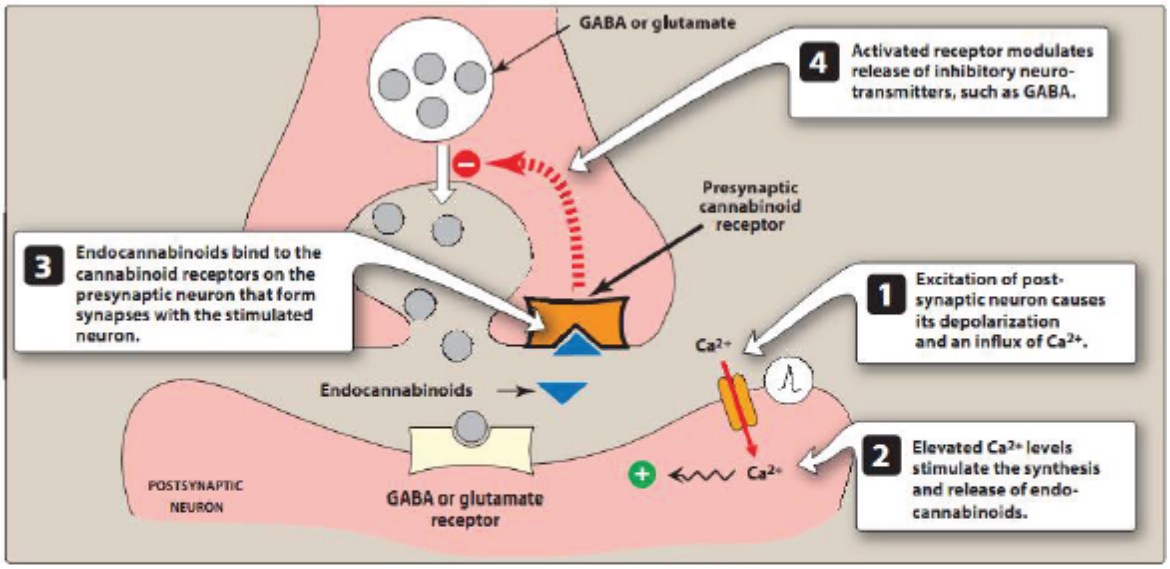

Figure 10.11
Cannabinoid receptor. GABA = γ-aminobutyric aid.

viduals. *Haloperidol* and other neuroleptics can block the hallucinatory action of *LSD* and quickly abort the syndrome.

B. Tetrahydrocannabinol

The main psychoactive alkaloid contained in marijuana is Δ^9-*tetrahydrocannabinol* [tet-ra-HY-dro-can-NAB-i-nol] (*THC*), which is available as *dronabinol* [droe-NAB-i-nol]. This product is prescribed to treat emesis and to stimulate the appetite. Depending on the social situation, *THC* can produce euphoria, followed by drowsiness and relaxation. In addition to adversely affecting short-term memory and mental activity, *THC* decreases muscle strength and impairs highly skilled motor activity such as that required to drive a car. Its wide range of effects includes appetite stimulation, xerostomia, visual hallucinations, delusions, and enhancement of sensory activity. *THC* receptors, designated CB1 receptors, have been found on inhibitory presynaptic nerve terminals that interact synaptically with pyramidal neurons. CB1 is coupled to a G protein. Interestingly, like the endogenous ligands of the opioid system, endocannabinoids have been identified in the CNS. These compounds, which bind to the CB1 receptors, are membrane derived and synthesized on demand, and they may act as local neuromodulators (Figure 10.11). The action of *THC* is believed to be mediated through the CB1 receptors, but this is still under investigation. The effects of *THC* appear immediately after the drug is smoked, but maximum effects take about 20 minutes. By 3 hours, the effects largely disappear. *Dronabinol* is administered orally and has a peak effect in 2 to 4 hours. Its psychoactive effects can last up to 6 hours, but its appetite-stimulant effects may persist for 24 hours. It is highly lipid soluble and has a large volume of distribution. *THC* itself is extensively metabolized by the mixed-function oxidases. Elimination is largely through the biliary route. Adverse effects include increased heart rate, decreased blood pressure, and reddening of the conjunctiva. At high doses, a toxic psychosis develops

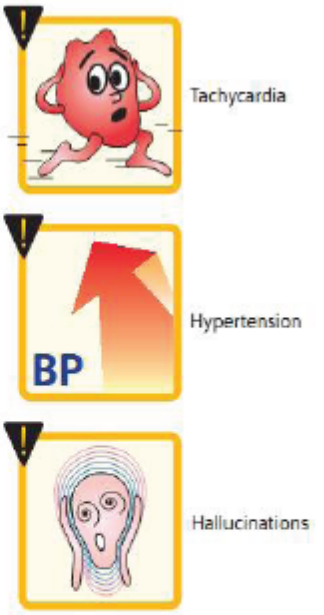

Figure 10.12
Adverse effects of *tetrahydrocannabinol*.

(Figure 10.12). Tolerance and mild physical dependence occur with continued, frequent use of the drug. *Dronabinol* is indicated as an appetite stimulant for patients with acquired immunodeficiency syndrome who are losing weight. It is also sometimes given for the severe emesis caused by some cancer chemotherapeutic agents. The CB1-receptor antagonist, *rimonabant* [ri-MOH-nah-bant], is effective in the treatment of obesity and has been found to decrease appetite and body weight in humans. *Rimonabant* is not currently available in the United States because, during clinical trials, it was found to induce psychiatric disturbances, such as anxiety and depression, which may limit its use.

C. Phencyclidine

Phencyclidine [fen-SYE-kli-deen] (also known as PCP, or "angel dust") inhibits the reuptake of dopamine, 5-HT, and norepinephrine. *Phencyclidine* has anticholinergic activity but, surprisingly, produces hypersalivation. *Phencyclidine*, an analog of *ketamine*, causes dissociative anesthesia (insensitivity to pain without loss of consciousness) and analgesia. In this state, it produces numbness of extremities, staggered gait, slurred speech, and muscular rigidity. Sometimes, hostile and bizarre behavior is seen. At increased dosages, anesthesia, stupor, and coma may result but, strangely, the eyes may remain open. Increased sensitivity to external stimuli results, and the CNS actions may persist for a week. Tolerance often develops with continued use. *Phencyclidine* has no therapeutic applications, and manufacture of the drug in the United States is illegal.