The term *hallucinogen* has been used to describe the clinical effect of a variety of xenobiotics; however, most drugs do not produce actual hallucinations. The drugs that are classified as hallucinogens are more likely to cause misperceptions of real objects, which are more accurately termed *illusions*. Some drugs are called psychedelics, a subset that alters cognition and perception. This chapter describes serotonergic agents, sympathomimetic amines (entactogens), dissociative agents, and selected plants and fungi.

**SEROTONIN-LIKE AGENTS**

**Perspective: Background and Epidemiology**

Serotonin-like agents are a broad category of compounds that share chemical similarities with serotonin (5-hydroxytryptamine [5-HT]) or enhance serotonergic tone within the body. These agents include various lysergic acid derivatives and tryptamines. Serotonin-like agents produce changes in thought, mood, perception, and consciousness. Orientation to person, place, and time is usually preserved, but severe intoxication may cause confusion. Patients present to the emergency department because of acute panic reactions, massive ingestions, or accidental ingestions (e.g., children or adults who have ingested the drugs unknowingly). There is no addictive component in psychedelics and no euphoria-dysphoria cycle, as with cocaine. The rapid development of tolerance also limits the effect of repeated doses.1

**LSD**

Lysergic acid diethylamide (LSD), or acid, is the most potent psychoactive drug. Doses of 1 to 1.5 µg/kg produce psychedelic effects. The typical dose taken for an acid “trip” is approximately 25 to 100 µg. LSD is sold in tablets (microdots), liquid, powder, gelatin squares (window panes), and “blotter” acid. Sheets of blotting paper are sprayed with LSD, dried, and perforated into small squares. Graphics are incorporated onto the blotting paper in designs that include cartoon characters (e.g., Felix the Cat) and geometric designs (Fig. 156-1). Each sheet is composed of hundreds of squares that are placed sublingually or eaten whole. Massive ingestions are rare.

In addition to synthetic LSD, several plants contain alkaloids similar in structure and action to LSD. These plants include Hawaiian baby woodrose (*Argyreia nervosa*), Hawaiian woodrose (*Merremia tuberosa*), morning glory (*Ipomoea violacea*), and oliluqui (*Rivea corymbosa*). Intoxication may result after ingestion of the seeds or an extract.2

**Tryptamines**

Substances in the tryptamines category are both naturally occurring and synthesized. For centuries, Native Central and South Americans have used tryptamine-containing beverages, ayahuasca, in their religious ceremonies. This plant-derived drink, which contains dimethyltryptamine (DMT) and 5-methoxydimethyltryptamine (5-MeO-DMT), has gained popularity in Europe and North America. Designer tryptamines can be synthesized and possess the psychotropic effects of the naturally found compounds.

Psilocybin and psilocin are naturally occurring tryptamines found in some species of *Psilocybe* (Fig. 156-2), *Panaeolus*, and *Conocybe* mushrooms.3 Psilocybin remains active even when the mushrooms are dried or cooked. Street psilocybin sold as pills or capsules is usually substituted with phencyclidine (PCP) or LSD. Misidentification of other poisonous species is a danger of consuming mushrooms.

Naturally occurring tryptamines are found not only in plants and fungi but also in the parotid glands of the *Bufo* toad species. The venom of the Sonoran Desert or Colorado River toad (*Bufo alvarius*) contains the hallucinogenic substance 5-MeO-DMT, found in the drink ayahuasca. Smoking of the dried venom results in psychoactive effects similar to those of 5-MeO-DMT.4 In addition to the tryptamines that occur in nature, designer tryptamines have been synthesized and are orally active.5 Included in this group are α-methyltryptamine, diisopropyltryptamine, and diisopropyl-5-methoxytryptamine, which is also known on the streets as “foxy” or “foxy methoxy”.6 The effects of these synthetic derivatives are similar to those of naturally occurring tryptamines.

**Principles of Disease: Pharmacology and Pathophysiology**

Evidence indicates that these drugs act on serotonergic neurons, particularly the 5-HT_{2A} subtype class of serotonin receptors.7 The onset of action of the psychoactive effects of LSD is usually within 30 minutes, with peak effects in 3 or 4 hours. The duration of effects may be approximately 12 hours. During the last half of the 12-hour effect, irritability, increased muscle tension (especially in the face), and paranoia can be present. Psilocybin effects begin within 30 minutes of ingestion, with the psychedelic phase lasting 30 minutes to 2 hours. The effects then wane, with resolution by 4 to 6 hours.
Clinical Features

In Western society, psychoactive agents are taken for internal mental exploration or more commonly for “recreation.” Changes include loss of boundaries between the user and the environment; the sensation that colors and sounds are distorted and intensified; and the perception that usual objects appear novel, fascinating, or awe inspiring. This state differs from the confusional and dissociative state produced by PCP. Users are usually aware that they are under the influence of the drug. A sense of euphoria is typical, but it may alternate with an intense dysphoric experience that is accompanied by suffering (e.g., that of dying or being born).

Acute panic reaction is the most common adverse reaction to psychedelics. Paranoid delusions and fear of impending death may be present. Behavior is either agitated or, occasionally, withdrawn. Symptomimetic effects include dilated, reactive pupils and moderate increases in blood pressure, heart rate, and, rarely, temperature. Mydriasis seems to parallel the intensity of the trip. In contrast to PCP, nystagmus, ataxia, muscle rigidity, and increased secretions are not present.

The individual’s altered perceptions may result in lack of awareness of dangers in the environment, resulting in injury. Psychosis after LSD trips is reported, and schizophrenia (overt and borderline) may worsen. Transient depression sometimes occurs after LSD use. Flashbacks, or post-hallucinogen perceptual disorder, are transient episodes of altered consciousness that occur months or years after an LSD trip. However, LSD use and these episodes have not been shown convincingly to have a cause-and-effect relationship.

Massive ingestions may result in a person’s becoming comatose and unresponsive to pain. The person may also be hyperactive with marked auditory and visual hallucinations. Fixed and dilated pupils, diaphoresis, vomiting, bleeding complications, and seizures may result.8

Euphoria and a distortion of reality usually occur after ingestion of one to five Psilocybe cubensis mushrooms. In contrast to peyote, vomiting is unusual. Larger doses (5-20 P. cubensis mushrooms) produce visual hallucinations. Few adverse reactions occur, and the incidence of “bad trips” or panic reactions is lower than with LSD. There are reports of seizures, coma, and hyperthermia after psilocybin use.

Diagnostic Strategies

Because most patients are either in a panic or brought in by a worried companion, the drug is usually known. Although mass spectrometry can identify psychedelics in serum, urine, or gastric contents, it is not available in the clinical setting, so diagnosis and treatment are based on clinical grounds. Even when tests are available, however, the results are delayed and useful only to confirm or to document the event.

Differential Considerations

Other drugs and mixed ingestion are a possible source of the patient’s symptoms, especially with coma or marked physiologic changes. Cocaine, PCP, anticholinergic drugs, and amphetamines should be considered because their effects may require specific treatment. Acute psychosis may appear similar to psychedelic ingestion at first, but detailed evaluation of the patient will clearly differentiate the two conditions.

Management

The basic principle of out-of-hospital care is reassurance and supportive care. If the patient is a danger to himself or herself or others, the patient may need to be sedated or restrained temporarily to permit sedation. There is no specific antagonist to the effects of serotoninergic agents. Empathic reassurance in a calm, quiet environment is an effective therapeutic modality. The drug effect lasts for hours, but when it wears off, the patient feels normal again.

Benzodiazepines, such as lorazepam (1 or 2 mg intravenously, then titrated to effect), can be given to decrease agitation. Phenothiazines should be avoided in case the symptoms are actually caused by an anticholinergic drug and not a psychedelic. Butyrophenones, such as haloperidol and droperidol, are quickly effective and may be given by intramuscular or intravenous injection in doses titrated to clinical response if the patient is violent and must be sedated. Monitoring for QT prolongation is recommended, if possible, when a butyrophenone is used.

Disposition

Patients with anxiety or panic reactions can be talked down and sent home with responsible family or friends. Patients who persist with confused or paranoid behavior should be admitted. If the diagnosis is in question, the patient should be observed for several hours for significant changes in the condition. Follow-up evaluation should be recommended with a psychiatrist, primary care
physician, or drug counseling facility. Patients with massive ingestions or having incurred injuries or medical complications (rhabdomyolysis) may need admission to a monitored setting for serial reassessments.

**ENTACTOGENS**

**Perspective: Background and Epidemiology**

Hallucinogenic stimulants, also called entactogens, are structural analogues of amphetamine, mescaline, and N-substituted piperazines. These agents share effects in varying degrees of true stimulants and the serotonin-like hallucinogens.

**Designer Amphetamines and Cathinones (Bath Salts)**

New designer amphetamines appear in drug communities each year. This class of chemicals usually has a structural base of a phenylalkylamine with addition or substitution of side chains or rings. Agents include 3,4-methylenedioxymethamphetamine (MDMA, ecstasy, XTC, or Adam), 3,4-methylenedioxymphetamine (MDA), 3,4-methylenedioxyethamphetamine (Eve), paramethoxyamphetamine (PMA or death), 4-methyl-2,5-dimethoxyamphetamine (serenity, tranquility, and peace [STP]), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamine (DOB), and others.9

MDMA is the best known of these agents. It was first synthesized in 1914 as an appetite suppressant. Recreational and psychotherapeutic use began in the late 1970s and has remained ubiquitous. MDMA and MDA have been called love drugs because of claims from users that sexual pleasure and feelings are heightened, but the sympathomimetic effects of these drugs may produce erectile dysfunction. MDMA can produce euphoria and increase emotional awareness, and it has been reported to improve interpersonal communications. The psychedelic and stimulant effects of MDMA are preferred to MDA by most users. Overt hallucinations of the type experienced with LSD are rare; however, sensory enhancement and distortion and illusions can occur. Because of these effects, these drugs are called entactogens (i.e., enabling the user to “touch within”). MDMA was classified as a Schedule I drug by the Drug Enforcement Agency (DEA) in 1985.

Entactogens are predominantly used in three main settings: (1) as “psychotherapeutic adjuncts,” (2) recreationally in small groups or by couples, and (3) at dance clubs or “rave” parties. Herbal ecstasy, known as ma huang or ephedra, is sometimes substituted for MDMA at these gatherings when MDMA is scarce. Although this herb contains ephedrine, its effects are not as psychodelic as those of MDMA. Ecstasy tablets may also contain other chemicals, such as amphetamine, methamphetamine, caffeine, and ketamine. MDMA is widely available and is sold in clubs, on the street, and at raves (usually 30–150 mg/pill), with a typical dose of 1 or 2 mg/kg.10 The continuous muscle activity required during these parties in combination with the psychostimulants may produce rhabdomyolysis and hyperthermia. Nine deaths in Canada associated with paramethoxyamphetamine (PMA) were originally reported in 1974, but clusters of multiple deaths in association with PMA exposure have occurred in Europe and Australia.11,12 Signs and symptoms of adrenergic excess occur before death, but whether PMA is more toxic in equipotent dosages than other amphetamines is not known.

Designer cathinones may be advertised and distributed as “bath salts” or “plant food” in packaging that suggests the actual intent of the product even though it might be labeled “not for human consumption.” These synthetic cathinones sold unregulated over the Internet initially contained methylone, butylone, pyrovalerone, methylenedioxypyrovalerone (MDPV), methcathinone, ethcathinone, and numerous others. These products may be ingested, inhaled, or injected and result in severe agitation, sympathomimetic effects, or even death.13 Detection of these cathinones is more difficult as their structures are dissimilar enough to classic amphetamines and methamphetamines that routine urine drug testing is not able to detect them.

**Mescaline**

Mescaline is usually consumed in the form of peyote buttons, which are derived from the small blue-green cacti *Lophophora williamsii* and *Lophophora diffusa* (Fig. 156-3). The cacti grow in the deserts of the southwestern United States and Mexico. Peyote buttons are the round fleshy tops, which are removed and dried. Mescaline is the active hallucinogenic alkaloid found in the buttons of the cactus.

Peyote has been used in religious ceremonies for 8000 years. Mescaline is also contained in the San Pedro cactus (*Trichocereus pachanoi*) of South America and is used ritualistically by Andean Native Americans.1 These cacti contain many other alkaloids, some of which are also psychoactive. The use of peyote is legal for members of the Native American Church in some states. Adverse reactions (e.g., panic) to peyote are rare in this structured religious use. Mescaline has an onset of action of 45 to 60 minutes with a duration of 4 to 8 hours. The central nervous system (CNS) and physiologic effects of mescaline use are similar to those of LSD, but more vivid hallucinations can occur. Nausea and vomiting are pronounced and almost always precede the hallucinogenic effects.

**Piperazines**

*N*-Substituted piperazine compounds such as 1-benzylpiperazine (BZP or A2), 1-(trifluoromethylphenyl)piperazine (TFMPP or Molly), and 1-(chlorophenyl)piperazine (CPP) have emerged as drugs of abuse and have been sold as safe, legal alternatives to MDMA; they are referred to as Legal E or Legal X on Internet websites.14,15 Although BZP was originally synthesized as a potential anthelmintic agent, there are currently no therapeutic applications for BZP or its congeners. Both in vitro and animal studies demonstrated that these piperazine compounds stimulate release of serotonin and other monoamines but are less potent in comparison to MDMA.15 In 2002, both BZP and TFMPP were classified as Schedule I drugs because of their potential for abuse and
Nutmeg

Nutmeg is a spice derived from the seed of the nutmeg tree, Myristica fragrans. Use of nutmeg as a natural and legal psychotropic agent was popularized in the 1960s. Despite lack of any in vivo human studies, myristicin and elemicin have been suggested as the agents responsible for intoxication because their chemical structures resemble that of mescaline. Reports of intoxication are uncommon. Ingestion of 5 to 30 g (1-4 tablespoons) of the spice is said to induce euphoria and hallucinations but is more likely to cause gastroenteritis.

Principles of Disease: Pathophysiology

The psychoactive effects of MDMA and other entactogens are thought to result from alterations in catecholamine neurotransmission at postsynaptic and presynaptic sites, particularly affecting 5-HT. These agents cause a release of serotonin, dopamine, and norepinephrine from nerve terminals as well as inhibit catecholamine reuptake. Release of epinephrine and norepinephrine may produce the cardiovascular effects. MDMA and possibly other entactogens are serotonergic neurotoxins. When MDMA is administered to nonhuman primates and laboratory animals, serotonin is released initially from serotonergic neurons followed by degradation of 5-HT projections. Magnetic resonance imaging shows significant neurodegeneration. These effects may persist for weeks or longer after a single dose. The significance of this neurotoxic effect for humans at the doses taken is unknown.

Psychostimulant-associated hyperthermia is well described in humans. Animal models exposed to entactogens develop hyperthermia in the absence of physical exertion but are less capable of regulating core body temperature in response to environmental hyperthermia. In addition, increasing body temperature in the presence of MDMA or other entactogens seems to enhance serotonergic neurotoxicity. Hyperthermia resulting in seizures, stupor, and death is another complication of MDMA use not described as commonly with other amphetamines. Two hypotheses suggested for the hyponatremia are (1) excessive intake of free water because users of MDMA are advised to keep well hydrated by drinking lots of water and (2) MDMA-mediated release of antidiuretic hormone.

Clinical Features

MDMA effects last 3 to 5 hours. Blood pressure increases during the first hour and gradually returns to baseline within 6 hours. CNS effects of MDMA may persist for 6 to 12 hours. Larger doses or greater frequency of MDMA may lead to more frequent unpleasant side effects, such as agitation and confusion. Recreational users rarely report dysphoria.

Clinical effects expected from the entactogens would be similar to clinical effects of other amphetamine derivatives (see Chapter 154). Use of recreational doses of MDMA at rave parties may result in seizures, hyperthermia, and death. MDMA may precipitate a hypertensive crisis in patients taking monoamine oxidase inhibitors, and it may precipitate serotonin syndrome in combination with other serotonergic agents (see Chapter 151). MDMA and its analogues also have contributed to fatal overdoses.

Diagnostic Strategies

Urine screening with immunoassay techniques can detect entactogens that are similar in structure to the phenylalkylamine struc-
pharmacologic effect and cause dissociation of the patient from the environment. They have analgesic and amnestic activity but do not cause respiratory or cardiovascular depression.

Phencyclidine

PCP was initially marketed for use as a general anesthetic; however, severe emergence reactions rapidly led to its recall. In the 1960s, PCP was sold as the “PeaCe Pill,” which was consumed orally, but the effects were often unpredictable and unpleasant. In the mid-1970s, PCP was the most common cause of recreational drug–related emergencies. Its popularity decreased because of unpredictable effects, long clinical course, dysphoria, and association with violence. In 1978, PCP was classified as a Schedule I drug.

Ketamine

Ketamine is known as “vitamin K,” “special K,” “kit kat,” and “cat valium”; however, preparations available on the street are often adulterated with various stimulants. The most common use of street ketamine is insufflation, but subcutaneous and intramuscular injection and even rectal infusion are done to achieve a level of intoxication or “high” known as the K-hole.

Dextromethorphan

Dextromethorphan is not truly a dissociative agent but does share a similarity in structure to PCP and its binding to the PCP site of the N-methyl-D-aspartate (NMDA) receptor. With the availability of concentrated pill formulations, abusers of dextromethorphan are able to ingest large doses without having to drink large volumes of the less palatable cough syrup formulation. Particularly popular in the adolescent community, dextromethorphan is known as “DXM,” “robo,” “skittles,” triple C, and “red hots.”

Principles of Disease: Pharmacology and Pathophysiology

Despite being simple molecules, PCP and ketamine have a complex pharmacology, including the NMDA receptor, dopamine-norepinephrine-serotonin reuptake pump, sigma opioid receptor, and cholinergic receptors. PCP is well absorbed from any oral, nasal, or rectal mucous membrane and can be insufflated or smoked. It can be injected intramuscularly, subcutaneously, or intravenously. Ingested PCP is well absorbed with onset between 15 and 60 minutes. When it is smoked, PCP produces symptoms within 5 minutes, with peak activity in 15 minutes. Intoxication with PCP usually lasts 8 to 16 hours, but it can be prolonged in chronic users. Although enterohepatic recirculation has been proposed, a more likely cause is either gastrointestinal concretion or delayed release from lipid stores.

Ketamine is only approximately one tenth as potent as PCP. With ketamine, the intensity of intoxication is less pronounced, although in larger doses the effects may parallel those of PCP. Duration of action of ketamine is typically shorter, with symptoms lasting approximately 1 hour after insufflation but up to 4 to 8 hours after an oral dose. PCP and ketamine are highly lipid-soluble agents that undergo extensive metabolism in the liver and are eventually excreted in the urine.

Although dextromethorphan is typically classified as an opioid, it has a complex pharmacology. Dextromethorphan is the dextro-rotary isomer of the synthetic opioid levorphanol. At high dosages, dextromethorphan is an agonist at the sigma opiate receptor, and naltrexone has been reported to reverse intoxication. Dextromethorphan antagonizes the NMDA receptor, which results in its dissociative effects. It also inhibits the uptake of serotonin, and drug interactions with selective serotonin reuptake inhibitors and monoamine oxidase inhibitors are reported.

Clinical Features

Patients with PCP intoxication have a wide spectrum of findings, with autonomic signs and symptoms similar to those with other sympathomimetic agents. Behavior may be bizarre, lethargic, agitated, confused, or violent. A blank or catatonic stare is common. Vertical, horizontal, and rotary nystagmus is often present. Moderate hypertension and tachycardia may be present. Pupils usually are midsized and reactive, although there may be miosis or mydriasis. Bizarre posturing, grimacing, and writhing may be seen.

Other variable findings include ataxia, muscle rigidity, increased deep tendon reflexes, increased secretions, bronchospasm, hyperthermia, and seizures. The percentage of violent patients ranges from 10 to 40% for PCP, and control of these patients may be the most challenging problem in the emergency department. “Superhuman” strength is possible because of the dissociative action of PCP. Although mild hypertension in PCP intoxication is common, hypertension requiring antihypertensive treatment is rare. Severe hypertension with PCP overdose has caused intracerebral hemorrhage but less often than with cocaine or amphetamine.

Hyperthermia can range from mild to life-threatening. Core temperatures of PCP victims can exceed 40°C and often go undetected for prolonged periods in the emergency department. Severe hyperthermia with temperatures above 42°C resembles heatstroke and is often associated with multiple organ damage. High-output congestive heart failure has been reported. Rhabdomyolysis and acute myoglobinuric renal failure are the most common serious medical complications. The presumed mechanism is muscle damage from seizures, extreme muscle activity such as struggling against restraints, or prolonged immobility. Renal function returns after several weeks in most cases. Among the most lethal complications of PCP are respiratory depression, apnea, and cardiac arrest.

Although dextromethorphan has activity at opioid receptors, the typical triad of opioid intoxication (miosis, respiratory depression, and mental status depression) is not generally encountered. Similar to meperidine, dextromethorphan may result in mydriasis through paralysis of the ciliary body with intoxication. More typical clinical findings are lethargy, agitation, slurred speech, ataxia, diaphoresis, hypertension, and nystagmus. With larger doses, nausea and vomiting are common, and intoxication resembles that of LSD with euphoria and hallucinations.

Diagnostic Strategies

Most hospital laboratories use radioimmunoasays that can detect urinary PCP with a detection limit of 5 ng/mL. Urine may be positive for PCP for 2 to 4 days after use, but it can be positive for more than 1 week after chronic exposure. Serum screening for PCP is of little clinical benefit because levels correlate poorly with symptoms. Several substances, including dextromethorphan, may cross-react with urine screens for PCP because of their structural similarities. Chlorpromazine, methadone, mesoridazine, ketamine, diphenhydramine, venlafaxine, meperidine, and tramadol may also cross-react with some assays. Because dextromethorphan is typically formulated as a hydrobromide salt, chronic use may result in spurious hyperchloremia with a low or negative anion gap due to interference of chloride analysis by the bromide ion in the laboratory autoanalyzer.

Differential Considerations

PCP, ketamine, and dextromethorphan intoxications can mimic such diverse entities as head trauma, meningitis, catatonia, and other variable conditions.
heatstroke. Sympathetically mediated vital sign changes can be found with numerous other agents, including cocaine, amphetamine, and LSD. Antimuscarinic (anticholinergic) compounds, such as diphenhydramine, benztoprine, and tricyclic antidepressants, can also simulate the tachycardia and altered mental status found with PCP or ketamine. Salicylate poisoning, thyrotoxicosis, and sepsis should be considered. Meningitis, intracerebral hemorrhage, and viral encephalitis can be manifested with altered mental status of unclear etiology. Even with a urine screen positive for PCP, the diagnosis is not certain unless a definite history of recent PCP, ketamine, or dextromethorphan use is obtained and other conditions have been eliminated.

**Management**

**Out-of-Hospital Care**

Life-threatening complications, such as apnea and seizures, should be stabilized before transport. The threat of violence to nonhospital care providers from patients with PCP intoxication makes it dangerous for only two or three nonhospital care providers to restrain these patients until additional help arrives. Oxygen and glucose testing should be deferred until the patient is controlled. Violent patients under the influence of PCP may have traumatic injuries.

**Emergency Department**

Patients with PCP toxicity can have unpredictable, violent behavior. Sudden complications, such as cardiac arrest and seizures, may occur but are not common. Violent behavior, although possible, is less common with ketamine. Most patients with minor intoxication are alert, oriented, and neurologically normal after 4 to 6 hours. All patients with signs of trauma or struggle should be evaluated for injuries. Reliable assessments of these individuals are difficult, and sedation and restraint are often necessary before diagnostic tests or examinations can be performed.

Chemical sedation or restraint is preferred to physical restraint in cases of PCP or ketamine intoxication, although temporary physical restraint may be necessary to ensure the patient's safety, to establish intravenous access, and to administer benzodiazepines intravenously (IV). Butyrophenones can be given intramuscularly to establish intravenous access, and to administer benzodiazepines in cases of PCP or ketamine intoxication, although temporary diagnostic tests or examinations can be performed. Reliable assessments of these individuals are difficult, and sedation and restraint are often necessary before diagnostic tests or examinations can be performed.

Chemical sedation or restraint is preferred to physical restraint in cases of PCP or ketamine intoxication, although temporary physical restraint may be necessary to ensure the patient’s safety, to establish intravenous access, and to administer benzodiazepines intravenously (IV). Butyrophenones can be given intramuscularly (IM) with a rapid response, avoiding the danger of intravenous establishment. Haloperidol, 5 to 20 mg IM or IV, or droperidol, 2.5 to 10 mg IM or IV (noting the Food and Drug Administration black box warning), is usually effective but can be titrated at 10- to 15-minute intervals until the patient is calm. These agents may antagonize CNS receptor sites that are responsible for much of the violent behavior in these individuals. Benzodiazepines, such as lorazepam, 2 to 4 mg IV or IM, or diazepam, 5 to 10 mg IV, may be used to calm patients with all types of sympathomimetic poisonings. A well-coordinated team may be needed to apply hard restraints simultaneously to all four extremities and the body. Assessment of mental status may not be as reliable after chemical sedation, but the benefits of protecting the staff and patient far outweigh the disadvantages.

Comatose patients or patients with a questionable airway should be intubated to ensure adequate ventilation. Although PCP intoxication can cause mild hypotension, profound hypotension is unusual and represents blood loss from trauma, a mixed-drug ingestion, or another underlying medical problem, and the patient should be resuscitated with fluids as evaluation ensues. Seizures should be treated with intravenous benzodiazepines (see Chapter 102). Tachycardia does not require additional treatment except for sedation.

Hyperthermia (temperature of 40°C) is common in severe cases of PCP poisoning. All patients with significant symptoms, psychosis, or history of violent behavior should have core temperatures measured. Individuals with hyperthermia should be treated with active, evaporative cooling measures (see Chapter 141).

Renal status and creatine kinase level should be monitored to detect rhabdomyolysis and myoglobinuric renal failure. Urinary acidification had been used in the past to trap PCP in urine and to aid in elimination, but its use has been abandoned because of the insignificant renal clearance of the drug (10%) and the potential adverse impact of acid urine on myoglobin in renal tubules that is often present after PCP intoxication. Activated charcoal is of no value in acute intoxication. If patients have never been hyperthermic and have no signs of trauma, laboratory or other diagnostic tests are not needed.

Dextromethorphan poisoning can be managed with supportive care and measures to prevent injury to the patient. Sedation with a benzodiazepine may be used for agitation. Respiratory depression may respond to intravenous administration of naloxone; however, the dissociative effects do not typically respond to naloxone. The patient should improve during 4 to 6 hours. Many dextromethorphan cough and cold preparations also contain acetaminophen, so acetaminophen levels should be measured.

**Disposition**

For nonviolent patients with PCP intoxication, a quiet holding room is ideal for 4 to 6 hours of observation. Patients with violent behavior or obtundation often require admission to the hospital, where close observation and treatment of potential life-threatening complications can be accomplished. Serial chemistry evaluations, including serum creatinine and creatine kinase, should be monitored. Most of these patients can be medically cleared the next day.

**MARIJUANA AND MISCELLANEOUS PLANTS AND FUNGI**

**Marijuana and Synthetic Cannabinoids**

**Perspective: Background and Epidemiology**

Marijuana is the most common illegal drug in the United States. It was used medicinally in ancient times for conditions such as colic and asthma and has been illegal since 1937, but 16 states have legalized medical marijuana and 7 states allow dispensaries to distribute the drug in 2011. Recreational use of marijuana continues to be common.

*Cannabis sativa* and *Cannabis indica* plants are some of the earliest plants grown by humans. Bioactive substances derived from these plants are collectively called cannabinoids. The seedless flowering tops of the female plant are referred to as sinsemilla and are the commonly grown form of marijuana in the United States. The resin from the flowers is made into hashish. Marijuana is smoked or eaten blended into foods, such as brownies.

**Principles of Disease: Pharmacology and Pathophysiology**

$\Delta^8$-Tetrahydrocannabinol (THC) is the main active agent of the more than 61 cannabinoïd compounds and approximately 300 other substances present in the cannabis plant. Marijuana smoke also contains carbon monoxide, cyanide, acetone, and phenol but not nicotine. The most efficient route of THC delivery is by inhalation. Fifty percent of smoked THC is absorbed compared with 6% by ingestion. Experienced users may be able to absorb larger doses with breath-holding techniques. Peak blood levels occur within 8 minutes of inhalation, with rapid distribution into
tissues, especially tissues with high lipid content. The duration of perceived effects is usually 2 to 4 hours when it is smoked and 6 to 12 hours when it is ingested.

Since the turn of the 21st century, various products containing synthetic “designer” cannabinoids have been gradually emerging and are collectively known as spice. These products are marketed as novelty herbal incense and labeled “not for human consumption.” They typically come in 1- to 3-g resealable foil packages and contain various plant leaves sprayed with a solvent mixture of one to several synthetic cannabinoid compounds. Examples of products include Spice (Diamond, Gold, Silver), K2 Summit, Banana Cream Nuke, Yucatan Fire, Genie, and many others. Because these products are also marketed with an emphasis on being “legal highs,” the DEA issued an order in March 2011 to list five synthetic cannabinoids (JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol) into Schedule I of the Controlled Substances Act (CSA) to avoid an imminent hazard to the public safety. Previously, only one synthetic cannabinoid (HU-210), a structural analogue of THC, was listed as such. Because numerous synthetic cannabinoids are available, producers of spice products can simply replace a scheduled cannabinoid with others that remain “legal,” which minimizes the impact of scheduling by the DEA on long-term availability because the demand for the spice products remains high.

Until the first cannabinoid receptor (CB1R) was isolated and cloned in the late 1980s, the effects of cannabis were not thought to be receptor mediated. Subsequently, a second cannabinoid receptor (CB2R) was identified in the early 1990s. Interestingly, CB2Rs are located in the brain stem, which governs basic physiologic functions, the toxicity of THC and synthetic cannabinoids seems to be relatively low with typical recreational use. 

The duration of cannabinoid effects is usually 2 to 4 hours when it is smoked and 6 to 12 hours when it is ingested. Discovery of these cannabinoid receptors has renewed interest in non-physiologic functions. The most common effects from smoking of marijuana include alteration of mood and usually relaxation and euphoria. The only reliable physiologic effects are a mild increase in heart rate and conjunctival injection. Pupillary changes usually do not occur. Other acute peripheral changes include urinary retention, decreased testosterone levels, and decreased intraocular pressure. Short-term memory is impaired, and the ability to perform complex tasks may be adversely affected. Many users report excessive appetite after marijuana use.

Even when “high-potency” marijuana is smoked continuously for hours, adverse effects are rarely seen. Users become more sedated as they continue to smoke but do not become unarousable. No deaths have been solely attributed to marijuana. Pediatric exposures to marijuana may lead to hypothermia, ataxia, nystagmus, tremor, tachycardia, injected conjunctiva, and labile affect. Oral ingestion of potent marijuana in children can produce rapid onset of drowsiness, hypotonia, and lethargy, which can lead to coma and airway obstruction. 

Whereas intoxications with marijuana and spice compounds may be similar in some respects, significant differences have been described. The most common adverse reactions include anxiety, panic, paranoia, and acute psychosis, particularly with novice users or individuals with preexisting psychiatric disease. These episodes are unusual and transient with marijuana but may be more common and pronounced with the synthetic cannabinoids. Nausea and vomiting, which are not typical with marijuana, have been reported with a synthetic JWH-018-containing product.

Clinical Features: Acute Signs and Symptoms

Smoking of marijuana leads to rapid and predictable signs and symptoms. Ingestion can cause delayed and sometimes unpredictable effects. The most common effects from smoking of marijuana include alteration of mood and usually relaxation and euphoria. The only reliable physiologic effects are a mild increase in heart rate and conjunctival injection. Pupillary changes usually do not occur. Other acute peripheral changes include urinary retention, decreased testosterone levels, and decreased intraocular pressure. 

Short-term memory is impaired, and the ability to perform complex tasks may be adversely affected. Many users report excessive appetite after marijuana use.

Even when “high-potency” marijuana is smoked continuously for hours, adverse effects are rarely seen. Users become more sedated as they continue to smoke but do not become unarousable. No deaths have been solely attributed to marijuana. Pediatric exposures to marijuana may lead to hypothermia, ataxia, nystagmus, tremor, tachycardia, injected conjunctiva, and labile affect. Oral ingestion of potent marijuana in children can produce rapid onset of drowsiness, hypotonia, and lethargy, which can lead to coma and airway obstruction.

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Diagnostic Strategies

Marijuana screening is not helpful in the emergency department. Urinary metabolites of THC are detectable within 1 hour after smoking of marijuana, but a positive urine test result does not correlate with acute intoxication. A single marijuana cigarette can be detected for 72 hours when a cutoff level of 100 ng/mL is used, and positive urine levels may persist for 3 months after chronic marijuana use. Inadvertent or passive exposure to marijuana may produce positive urine test results, depending on cutoff levels used. False-positive urine screen results may be produced by efavirenz, ibuprofen, and naproxen.

Of the synthetic cannabinoids, only HU-210 is expected to trigger a positive THC immunoassay screen as a result of structural homology. Many other synthetic cannabinoids are structurally distinct from THC and do not result in positive THC.

immunoassay screens. Some reference laboratories are beginning to offer confirmatory testing for several synthetic cannabinoids, but the results are not available to the emergency physicians to guide clinical decision-making.

Differential Considerations

The presentation that most closely resembles marijuana and spice intoxication is acute psychosis. Some individuals with underlying and preexisting psychiatric disorders may progress to overt psychosis after heavy or first-time marijuana use. Because marijuana is so readily available, it is commonly a coinhibitant used with ethanol and other psychotropic agents. Rarely, marijuana can be adulterated with other substances, such as lead.

Management and Disposition

Care of patients intoxicated from marijuana and spice consists of prevention of injury and reassurance of those who have panic reactions. An extremely agitated patient can be sedated with oral or parenteral administration of benzodiazepines. Antiemetics may be used to treat nausea and vomiting associated with the synthetic cannabinoids. Children who are significantly symptomatic may require admission.

Salvia

Salvia divinorum, a perennial herb cultivated well outdoors in mild climates, is a member of the mint (Lamiaceae) family. Common names for S. divinorum are diviner’s sage, mystic sage, magic mint, sage of the seers, Sally-D, and ska Maria Pastora. Although the plant has been used for divination and shamanism by the Mazatec Indians of Oaxaca, Mexico, S. divinorum has become popular in the past decade for recreational purposes because of its recognized hallucinogenic properties; it continues to be sold legally by online vendors and “smoke” or “head” shops. In 2004, the DEA listed S. divinorum as a “drug of concern,” but to date, it remains unscheduled under the CSA. Several states, however, have instituted or are considering legislation making possession, cultivation, and use of S. divinorum or its extracts illegal. Internationally, regulatory controls have been implemented in Australia and a number of European countries; however, S. divinorum and salvinorin A are not currently controlled under the CSA in the United States. Although many states have decided to independently enact legislation with varying degrees of restriction, Salvia remains readily available.

The active ingredient in S. divinorum is salvinorin A (also known as divinorin A), a neoclerodane diterpene with selective agonist activity for kappa opioid receptors, but it does not bind to delta or mu opioid receptors. Salvinorin A is the first naturally occurring non-nitrogenous kappa opioid receptor agonist with psychotropic properties and is the most potent plant hallucinogen discovered to date. The threshold dose of salvinorin A to produce hallucinations is comparable to that of synthetic LSD and 4-bromo-2,5-dimethoxyphenylisopropylamine. Stimulation of kappa opioid receptors in the brain and spinal cord produces psychomimetic and analgesic effects, respectively. However, salvinorin A is distinct from more traditional hallucinogens because it does not bind to the 5-HT1A serotonin receptors, as is the case with LSD.

Salvia is usually chewed and either spit out or swallowed, and it seems to be absorbed better from the oral mucosa than from the rest of the gastrointestinal tract. Effects produced as a result of oral mucosal absorption may persist for 1 hour. Dried leaves also can be smoked. Inhalation of smoke can produce symptoms within 1 minute that subside during 20 to 30 minutes. Sensations experienced are variable but include distortions of color and vision as well as auditory, visual, gustatory, and olfactory synesthesias that are confusions of the senses, such as seeing sounds, hearing touches, or smelling visions. S. divinorum is often used in conjunction with other agents, such as marijuana and MDMA.

Salvinorin A is not detected and is not known to cause interference with routine drug screens used in the clinical setting. Management of intoxication from S. divinorum is mainly supportive with emphasis on injury prevention. Use of naloxone, a nonspecific opioid-receptor antagonist, may theoretically be helpful in reversal of psychotropic manifestations.

Kratom

Mitragyna speciosa Korth., or kratom, is a tree indigenous to Thailand but is also found in tropical and subtropical regions of Asia and Africa. Its extracts have been used in Thailand and Malaysia for their euphoric effect as a substitute for opium or to moderate opium use by addicts. The popularity of kratom has grown because of reports of its successful use to attenuate symptoms of opioid withdrawal. Because kratom remains easily obtainable from Internet sources, individuals are able to self-administer the perceived remedy, obviating the need for physician supervision.

The safety of such practice is unknown.

Although kratom extract contains more than 25 alkaloids, mitragynine is the most abundantly found in the plant. Mitragynine is an indole alkaloid with structural analogy to yohimbine and has agonist activity at mu and delta opioid receptors, producing euphoric, analgesic, and respiratory depressant effects. Despite its structural similarity to yohimbine, a selective antagonist of presynaptic alpha2-adrenergic receptors, animal studies suggest that mitragynine is also an agonist at postsynaptic alpha2-adrenergic receptors and blocks 5-HT1A receptors.

Typically, kratom leaves are chewed, smoked, or brewed into a tea. Psychotomimetic effects occur within 5 to 10 minutes of use and may persist for 1 hour, with stimulatory effects at lower doses and opioid effects at higher doses. Opioid properties include analgesic, antitussive, anti diarrheal, and emetogenic effects. Reports in the medical literature include intrahepatic cholestasis after abuse for 2 weeks.

Currently, there are no diagnostic tests available to detect the presence of kratom alkaloids. Treatment of intoxication is supportive. Although opioid activity has been demonstrated with kratom, the effectiveness of opioid antagonists in reversing effects is inconsistent. A withdrawal syndrome characterized by anxiety, restlessness, and nausea treated with an opioid agonist and lofexidine (an alpha2-agonist related to clonidine) has also been reported.

Iboga

Ibogaine is a naturally occurring indole alkaloid found in the roots of the African rain forest shrub Tabernanthus iboga. For many centuries, iboga has been ingested by indigenous peoples of western Africa as a remedy for fatigue, hunger, and thirst and as a psychopharmacologic sacrament in religious ceremonies, and it is believed to enable contact with deceased ancestors. As with many plant-derived agents, ibogaine’s physiologic effects are highly complex and may involve opioid, dopaminergic, serotonergic, glutaminergic, GABAergic, glutamatergic, adrenergic, and cellular ion channel signaling systems.

Although iboga in Western culture is used to ease opioid withdrawal and to diminish craving of other abused drugs, the potential for abuse is high because the hallucinogenic effect is extremely vivid. The intensity of visual hallucinations from ingestion of iboga, in contrast to other hallucinogens, is described to be pronounced with closed eyes. There are no clinical tests, and diagnosis is dependent on a history of exposure because clinical
findings are largely nonspecific and management is principally supportive. Since the first report in 1990, there have been 11 reported fatalities within 72 hours of ibogaine use with a hypothesized cardiac etiology. 63

**Absinthe**

Absinthe is a bitter, emerald green liqueur derived from an extract of the wormwood tree, *Artemisia absinthium*. The liqueur was popular in the 19th century, particularly among artists, poets, and playwrights, but has been illegal in most countries since the early 20th century. The legal sale of absinthe has resumed in several European countries and Japan, and with the Internet, there has been resurgence in its use and popularity.

In addition to ethanol, the active ingredient of absinthe is thought to be thujone, an aromatic terpenoid related to camphor and turpentine. Although the mechanism is not clear, thujone is thought to antagonize the inhibitory GABA\(_A\) receptor, which may explain the clinical effects observed with absinthe. 64 The acute clinical effects of absinthe are reported to be beyond those of ethanol alone and include confusion, delirium, euphoria, and hallucinations (auditory and visual). However, some doubt the plausibility of consuming a dose of thujone adequate to achieve the aforementioned neurotoxic effects given the low concentrations of the toxin present in spirits. 65 Nonetheless, thujone is a known proconvulsant in animals and may cause generalized clonic followed by tonic seizure activity. Ingestion of an essential oil of wormwood has been reported to cause seizures complicated with renal failure secondary to rhabdomyolysis. 66 Treatment is supportive.

**Isoxazole Mushrooms**

Isoxazole-containing mushrooms include *Amanita muscaria*, *Amanita pantherina*, *Amanita gemmata*, and *Amanita cothurnata*. *A. muscaria* has a red or yellow cap with white warty structures on its surface and grows in forests of aspen, birch, fir, or pine trees (Fig. 156-5). It has been used by Siberians for centuries and is often described in folklore and fairy tales. Pharmacological evidence indicates that several modern religions began as *A. muscaria* cults.

The active ingredients are the isoxazole derivatives ibotenic acid and its decarboxylation product, muscimol, which are structural analogues of the endogenous neurotransmitters glutamic acid (excitatory) and GABA (inhibitory) and thought to act at these respective receptor sites. 67 The excitatory effects characterized by elation, giddiness, hyperactivity, muscle tremors, and distortion of space-time begin approximately 30 minutes to 2 hours after ingestion and are likely to be mediated by ibotenic acid. Following is a phase of tiredness and deep “sleep,” in which it may be difficult to arouse the patient. During this phase, vivid hallucinations and manic excitement may oscillate with periods of deep sleep. The duration of effect is up to 12 hours. Management of the excitatory phase is similar to that of other hallucinogens previously described in this chapter. Prolonged sleep with *A. muscaria* ingestion requires only observation or supportive care. Tonic-clonic seizures are reported, but occurrences are rare. 68

Because elements of isoxazole poisoning resemble manifestations of anticholinergic toxicity, these mushrooms have also been referred to as anticholinergic mushrooms; however, belladonna alkaloids are not present. Paradoxically, there has been a high incidence of mistreatment of *A. muscaria* ingestion with atropine because the name implies that it contains muscarine, a cholinergic toxin. However, the amount of muscarine is miniscule. Many textbooks recommend the use of atropine, but atropine may exacerbate the anticholinergic effects associated with isoxazole mushrooms. It is important to differentiate isoxazole-containing *Amanita* mushrooms from the deadly hepatotoxic cyclopeptide-containing *Amanita* mushrooms, of which *Amanita phalloides* is a member.

**KEY CONCEPTS**

- Hallucinogens include many types of drugs and chemicals with different associated effects.
- Diagnosis and management are based primarily on the history and physical examination.
- Screening tests for drugs of abuse are of limited utility in acute management of intoxicated patients.
- Overreliance on drug of abuse screening may cause the clinician to mistakenly attribute another acute medical condition to drug intoxication.
- Aggressive sedation is necessary in agitated and violent patients.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.