05 - 20.5 Hallucinogen Related Disorders

20.5 Hallucinogen-Related Disorders

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covered in Section 20.9. Table 20.5-1 lists some representative hallucinogens. Table 20.5-1 Overview of Representative Hallucinogens

Phencyclidine (PCP; 1-1 [phenylcyclohexyl] piperidine), also known as angel dust, was first developed as a novel anesthetic in the late 1950s. This drug and the closely related compound ketamine were termed dissociative anesthetics, because they produced a condition in which subjects were awake but apparently insensitive to, or dissociated from, the environment. Phencyclidine and ketamine exert their unique behavioral effects by blocking N-methyl-D-aspartate (NMDA)–type receptors for the excitatory neurotransmitter glutamate. Their intoxication can present with a variety of symptoms, from anxiety to psychosis. Phencyclidine and ketamine are classified as Schedule II and Schedule III controlled substances, respectively. Although different in pharmacology and clinical effects, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes PCP and ketamine within the hallucinogen category due to their hallucinogenic effects. EPIDEMIOLOGY The incidence of hallucinogen use has exhibited two notable periods of increase. Between 1965 and 1969, there was a tenfold increase in the estimated annual number of initiates. This increase was driven primarily by the use of LSD. The second period of increase in first-time hallucinogen use occurred from around 1992 until 2000, fueled mainly by increases in use of ecstasy (i.e., MDMA). Decreases in initiation of both LSD

and ecstasy were evident between then and 2013, coinciding with an overall drop in hallucinogen incidence from 1.6 million to 1.1 million. The National Survey on Drug Use and Health (NSDUH) found that approximately 10 percent of persons age 12 years or older reported lifetime use of hallucinogens. Of this group, 9 percent reported lifetime use of LSD, 6 percent reported lifetime use of ecstasy, and 3 percent reported lifetime use of PCP. The highest rates of current use are among 18 to 25 year olds (2 percent) followed by 12 to 17 year olds (0.9 percent) and adults 25 years or older (0.2 percent). Males (9 percent) are more likely than females (11 percent) to use hallucinogens. Approximately 331,000 persons age 12 years or older were dependent on or abused hallucinogens within the past year. Hallucinogen use is most common among young (15 to 35 years of age) white men. The ratio of whites to blacks who have used a hallucinogen is 2:1; the white to Hispanic ratio is about 1.5:1. Men represent 62 percent of those who have used a hallucinogen at some time and 75 percent of those who have used a hallucinogen in the preceding month. Persons 26 to 34 years of age show the highest use of hallucinogens, with 16 percent having used a hallucinogen at least once. Persons 18 to 25 years of age have the highest recent use of a hallucinogen. Cultural factors influence the use of hallucinogens; their use in the western United States is significantly higher than in the southern United States. Hallucinogen use is associated with less morbidity and less mortality than use of some other substances. For example, one study found that only 1 percent of substance-related emergency room visits were related to hallucinogens, compared with 40 percent for cocaine-related problems. Of persons visiting the emergency room for hallucinogen-related reasons, however, more than 50 percent were younger than 20 years of age. Resurgence in the popularity of hallucinogens has been reported. Phencyclidine Phencyclidine and some related substances are relatively easy to synthesize in illegal laboratories and relatively inexpensive to buy on the street. The variable quality of the laboratories, however, results in a range of potency and purity. PCP use varies most markedly with geography. Most users of PCP also use other substances, particularly alcohol, but also opiates, opioids, marijuana, amphetamines, and cocaine. PCP is frequently added to marijuana, with severe untoward effects on users. The actual rate of PCP dependence and abuse is not known, but PCP is

associated with 3 percent of substance abuse deaths and 32 percent of substance-related emergency room visits nationally. In the United States, 2.5 percent of those ages 12 and older acknowledged ever using PCP. The highest lifetime prevalence was in those aged 26 to 34 years (4 percent), whereas the highest proportion using PCP in the prior year (0.7 percent) was in those aged 12 to 17 years. Some areas of some cities have a tenfold higher usage rate of PCP than other areas. The highest PCP use in the United States is in Washington, DC, where PCP accounts for

18 percent of all substance-related deaths and more than 1,000 emergency room visits per year. In Los Angeles, Chicago, and Baltimore, the comparable figure is 6 percent. Overall, most users are between 18 and 25 years of age and they account for 50 percent of cases. Patients are more likely to be male rather than female, especially those who visit emergency rooms. There are twice as many white as blacks users, although blacks account for more visits to hospitals for PCP-related disorders than do whites. PCP use appears to be rising, with some reports showing a 50 percent increase, particularly in urban areas. NEUROPHARMACOLOGY Although most hallucinogenic substances vary in their pharmacological effects, LSD can serve as a hallucinogenic prototype. The pharmacodynamic effect of LSD remains controversial, although it is generally agreed that the drug acts on the serotonergic system, either as an antagonist or as an agonist. Data at this time suggest that LSD acts as a partial agonist at postsynaptic serotonin receptors. Most hallucinogens are well absorbed after oral ingestion, although some are ingested by inhalation, smoking, or intravenous injection. Tolerance for LSD and other hallucinogens develops rapidly and is virtually complete after 3 or 4 days of continuous use. Tolerance also reverses quickly, usually in 4 to 7 days. Neither physical dependence nor withdrawal symptoms occur with hallucinogens, but a user can develop a psychological dependence on the insight-inducing experiences of episodes of hallucinogen use. Phencyclidine Phencyclidine and its related compounds are variously sold as a crystalline powder, paste, liquid, or drug-soaked paper (blotter). PCP is most commonly used as an additive to a cannabis- or parsley-containing cigarette. Experienced users report that the effects of 2 to 3 mg of smoked PCP occur in about 5 minutes and plateau in 30 minutes. The bioavailability of PCP is about 75 percent when taken by intravenous administration and about 30 percent when smoked. The half-life of PCP in humans is about 20 hours, and the half-life of ketamine in humans is about 2 hours. The primary pharmacodynamic effect of PCP and ketamine is as an antagonist at the NMDA subtype of glutamate receptors. PCP binds to a site within the NMDA-associated calcium channel and prevents the influx of calcium ions. PCP also activates the dopaminergic neurons of the ventral tegmental area, which project to the cerebral cortex and the limbic system. Activation of these neurons is usually involved in mediating the reinforcing qualities of PCP. Tolerance for the effects of PCP occurs in humans, although physical dependence generally does not occur. In animals that are administered more PCP per pound for longer times than most humans, PCP does induce physical dependence, however, with marked withdrawal symptoms of lethargy, depression, and craving. Physical symptoms of withdrawal in humans are rare, probably as a function of dose and duration of use.

Although physical dependence on PCP is rare in humans, psychological dependence on both PCP and ketamine are common, and some users become psychologically dependent on the PCP-induced psychological state. That PCP is made in illicit laboratories contributes to the increased likelihood of impurities in the final product. One such contaminant is 1-piperidenocyclohexane carbonitrite, which releases hydrogen cyanide in small quantities when ingested. Another contaminant is piperidine, which can be recognized by its strong, fishy odor. DIAGNOSIS

Hallucinogen Use Disorder Long-term hallucinogen use is not common. Some long-term users of PCP are said to be “crystallized,” a syndrome characterized by dulled thinking, decreased reflexes, loss of memory, loss of impulse control, depression, lethargy, and impaired concentration. Although psychological dependence occurs, it is rare, in part because each LSD experience is different and in part because there is no reliable euphoria. B, a 16-year-old boy from divorced parents, was admitted to the psychiatric unit of a local hospital. He had slashed his wrists with a knife, severing nerves and tendons in his left hand, and drifted in and out of consciousness during the night. He finally contacted the mother of a friend who lived nearby in the morning who immediately brought him to the hospital. B had a history of juvenile delinquency from the age of 13 when he began hanging out with some older boys at his junior high school. He and his friends shoplifted, stole, smoked marijuana, and took LSD. B’s grades dropped and he got in trouble at school on two occasions for getting into fights with other students. On admission, B stated that he did not intend on committing suicide when he slashed his wrist. After some questioning, he revealed that he had been “dropping acid” with some friend and after they left he thought he heard the sirens of police cars approaching his home. He did not wish to get arrested, so he slashed his wrist and then lost consciousness. He denies feeling depressed, although he claims his life is pointless and that he felt it made no difference whether he lived or died. Hallucinogen Intoxication Intoxication with hallucinogens is characterized by maladaptive behavioral and perceptual changes and by certain physiological signs (Table 20.5-2). The differential diagnosis for hallucinogen intoxication includes anticholinergic and amphetamine intoxication and alcohol withdrawal. The preferred treatment for hallucinogen intoxication is talking down the patient; during this process, guides can reassure patients that the symptoms are drug induced, that they are not going crazy, and that the

symptoms will resolve shortly. In the most severe cases, dopaminergic antagonists—for example, haloperidol (Haldol)—or benzodiazepines—for example, diazepam (Valium)— can be used for a limited time. Hallucinogen intoxication usually lacks a withdrawal syndrome. Table 20.5-2 Physiological Changes from Hallucinogens Short-term PCP intoxication can have potentially severe complications and must often be considered a psychiatric emergency. Some patients may be brought to psychiatric attention within hours of ingesting PCP, but often 2 to 3 days elapse before psychiatric help is sought. Persons who lose consciousness are brought for help earlier than those who remain conscious. Most patients recover completely within a day or two, but some remain psychotic for as long as 2 weeks. Patients who are first seen in a coma often exhibit disorientation, hallucinations, confusion, and difficulty communicating on regaining consciousness. These symptoms may also be seen in noncomatose patients, but their symptoms appear to be less severe than those of comatose patients. Behavioral disturbances sometimes are severe; they can include public masturbation, stripping off clothes, violence, urinary incontinence, crying, and inappropriate laughing. Patients frequently have amnesia for the entire period of the psychosis. A 17-year-old male patient was brought to the emergency room by the police, having been found disoriented on the street. As the police attempted to question him, he became increasingly agitated; when they attempted to restrain him, he became assaultive. Attempts to question or to examine him in the emergency department evoked increased agitation. Initially, it was impossible to determine vital signs or to draw blood. Based on the observation of horizontal, vertical, and rotator nystagmus, a diagnosis of PCP intoxication was entertained. Within a few minutes of being placed in a darkened examination room, his agitation markedly decreased. Blood pressure was 170/100; other vital signs were within normal limits. Blood was drawn for toxicological examination. The patient agreed to take 20 mg of diazepam (Valium) orally. Thirty minutes later, he was less agitated and could be

interviewed, although he responded to questions in a fragmented fashion and was slightly dysarthic. He stated that he must have inadvertently taken a larger-than-usual dose of “dust,” which he reported having used once or twice a week for several years. He denied use of any other substance and any history of mental disorder. He was disoriented to time and place. The qualitative toxicology screen revealed PCP and no other drugs. Results of

neurological examination were within normal limits, but brisk deep tendon reflexes were noted. Some 90 minutes after arrival, his temperature, initially normal, was elevated to 38°C, his blood pressure had increased to 182/110, and he was poorly responsive to stimulation. He was admitted to a medical bed. His blood pressure and level of consciousness continued to fluctuate over the ensuing 18 hours. Results of hematological and biochemical analyses of blood, as well as urinalyses, remained within normal limits. A history obtained from his family revealed that the patient had had multiple emergency room visits for complications from PCP use during the previous several years. He had completed a 30-day residential treatment program and had participated in several outpatient programs but had consistently relapsed. The patient was discharged after vital signs and level of consciousness had been within normal limits for 8 hours. At discharge, nystagmus and dysarthria were no longer present. A referral to an outpatient treatment program was made. (Courtesy of Daniel C. Javitt, M.D., Ph.D., and Stephen R. Zukin, M.D.) Hallucinogen Persisting Perception Disorder Long after ingesting a hallucinogen, a person can experience a flashback of hallucinogenic symptoms. This syndrome is diagnosed as hallucinogen persisting perception disorder in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). According to studies, from 15 to 80 percent of users of hallucinogens report having experienced flashbacks. The differential diagnosis for flashbacks includes migraine, seizures, visual system abnormalities, and posttraumatic stress disorder. The following can trigger a flashback: emotional stress; sensory deprivation, such as monotonous driving; or use of another psychoactive substance, such as alcohol or marijuana. Flashbacks are spontaneous, transitory recurrences of the substance-induced experience. Most flashbacks are episodes of visual distortion, geometric hallucinations, hallucinations of sounds or voices, false perceptions of movement in peripheral fields, flashes of color, trails of images from moving objects, positive afterimages and halos, macropsia, micropsia, time expansion, physical symptoms, or relived intense emotion. The episodes usually last a few seconds to a few minutes, but sometimes last longer. Most often, even in the presence of distinct perceptual disturbances, the person has insight into the pathological nature of the disturbance. Suicidal behavior, major depressive disorder, and panic disorders are potential complications. A 20-year-old undergraduate presented with a chief complaint of seeing the air. The visual disturbance consisted of perception of white pinpoint specks too numerous to count in both the central and peripheral visual fields. They were constantly present and were accompanied by the perception of trails of moving objects left behind as they passed through the patient’s visual field. Attending a hockey game was difficult, as the brightly dressed players left streaks of their own images against the white of

the ice for seconds at a time. The patient also described the false perception of movement in stable objects, usually in his peripheral visual fields; halos around objects; and positive and negative afterimages. Other symptoms included mild depression, daily bitemporal headache, and a loss of concentration in the last year. The visual syndrome had gradually emerged over the last 3 months following experimentation with the hallucinogenic drug LCD-25 on three separate occasions. He feared he had sustained some kind of “brain damage” from the drug experience. He

denied use of any other agents, including amphetamines, phencyclidine, narcotics, or alcohol, to excess. He had smoked marijuana twice a week for a period of 7 months at age 17. The patient had consulted two ophthalmologists, both of whom confirmed that the white pinpoint specks were not vitreous floaters (diagnostically insignificant particulate matter floating in the vitreous humor of the eye that can cause the perception of “specks”). A neurologist’s examination also proved negative. A therapeutic trial of an anticonvulsant medication resulted in a 50 percent improvement in the patient’s visual symptoms and remission of his depression. Hallucinogen Intoxication Delirium Hallucinogen intoxication delirium is a relatively rare disorder beginning during intoxication in those who have ingested pure hallucinogens. An estimated 25 percent of all PCP-related emergency room patients may meet the criteria for hallucinogen intoxication delirium. Hallucinogens are often mixed with other substances, however, and the other components or their interactions with the hallucinogens can produce clinical delirium. Hallucinogen-Induced Psychotic Disorders If psychotic symptoms are present in the absence of retained reality testing, a diagnosis of hallucinogen-induced psychotic disorder may be warranted. The most common adverse effect of LSD and related substances is a “bad trip,” an experience resembling the acute panic reaction to cannabis but sometimes more severe; a bad trip can occasionally produce true psychotic symptoms. The bad trip generally ends when the immediate effects of the hallucinogen wear off, but its course is variable. Occasionally, a protracted psychotic episode is difficult to distinguish from a nonorganic psychotic disorder. Whether a chronic psychosis after drug ingestion is the result of the drug ingestion, is unrelated to the drug ingestion, or is a combination of both the drug ingestion and predisposing factors is currently unanswerable. Occasionally, the psychotic disorder is prolonged, a reaction thought to be most common in persons with preexisting schizoid personality disorder and prepsychotic personalities, an unstable ego balance, or much anxiety. Such persons cannot cope with the perceptual changes, body-image distortions, and symbolic unconscious material stimulated by the hallucinogen. The rate of previous mental instability in persons

hospitalized for LSD reactions is high. Adverse reactions occurred in the late 1960s when LSD was being promoted as a self-prescribed psychotherapy for emotional crises in the lives of seriously disturbed persons. Now that this practice is less frequent, prolonged adverse reactions are less common. A 22-year-old female photography student presented to the hospital with inappropriate mood and bizarre thinking. She had no prior psychiatric history. Nine days before admission, she ingested one or two psilocybin mushrooms. Following the immediate ingestion, the patient began to giggle. She then described euphoria, which progressed to auditory hallucinations and belief in the ability to broadcast her thoughts on the media. Two days later she repeated the ingestion, and continued to exhibit psychotic symptoms to the day of admission. When examined she heard voices telling her she could be president, and reported the sounds of “lambs crying.” She continued to giggle inappropriately, bizarrely turning her head from side to side ritualistically. She continued to describe euphoria, but with an intermittent sense of hopelessness in a context of thought blocking. Her self-description was “feeling lucky.” She was given haloperidol, 10 mg twice a day, along with benztropine (Cogentin) 1 mg three times a day and lithium carbonate (Eskalith) 300 mg twice a day. On this regimen her psychosis abated after 5 days. Hallucinogen-Induced Mood Disorder Unlike cocaine-induced mood disorder and amphetamine-induced mood disorder, in which the symptoms are somewhat predictable, mood disorder symptoms accompanying hallucinogen abuse can vary. Abusers may experience manic-like symptoms with grandiose delusions or depression-like feelings and ideas or mixed symptoms. As with the hallucinogen-induced psychotic

disorder symptoms, the symptoms of hallucinogeninduced mood disorder usually resolve once the drug has been eliminated from the person’s body. Hallucinogen-Induced Anxiety Disorder Hallucinogen-induced anxiety disorder also varies in its symptom pattern, but few data about symptom patterns are available. Anecdotally, emergency room physicians who treat patients with hallucinogen-related disorders frequently report panic disorder with agoraphobia. Anxiety is probably the most common symptom causing a PCP-intoxicated person to seek help in an emergency room. Unspecified Hallucinogen-Related Disorder When a patient with a hallucinogen-related disorder does not meet the diagnostic criteria for any of the standard hallucinogen-related disorders, the patient may be classified as having unspecified hallucinogen-related disorder. DSM-5 does not have a

diagnostic category of hallucinogen withdrawal, but some clinicians anecdotally report a syndrome with depression and anxiety after cessation of frequent hallucinogen use. Such a syndrome may best fit the diagnosis of unspecified hallucinogen-related disorder. CLINICAL FEATURES Lsysergic Acid Diethylamide A large class of hallucinogenic compounds with well-studied structure–activity relationships is represented by the prototype LSD. LSD is a synthetic base derived from the lysergic acid nucleus from the ergot alkaloids. That family of compounds was discovered in rye fungus and was responsible for lethal outbreaks of St. Anthony’s fire in the Middle Ages. The compounds are also present in morning glory seeds in low concentrations. Many homologs and analogs of LSD have been studied. None of them has potency exceeding that of LSD. Physiological symptoms from LSD are typically few and relatively mild. Dilated pupils, increased deep tendon motor reflexes and muscle tension, and mild motor incoordination and ataxia are common. Increased heart rate, respiration, and blood pressure are modest in degree and variable, as are nausea, decreased appetite, and salivation. The usual sequence of changes follows a pattern of somatic symptoms appearing first, then mood and perceptual changes, and, finally, psychological changes, although effects overlap and, depending on the particular hallucinogen, the time of onset and offset varies. The intensity of LSD effects in a nontolerant user generally is proportional to dose, with 25 µg as an approximate threshold dose. The syndrome produced by LSD resembles that produced by mescaline, psilocybin, and some of the amphetamine analogs. The major difference among LSD, psilocybin, and mescaline is potency. A 1.5 µg/kg dose of LSD is roughly equivalent to 225 µg/kg of psilocybin, which is equivalent to 5 mg/kg of mescaline. With mescaline, onset of symptoms is slower and more nausea and vomiting occurs but in general, the perceptual effects are more similar than different. Tolerance, particularly to the sensory and other psychological effects, is evident as soon as the second or third day of successive LSD use. Four to 6 days free of LSD are necessary to lose significant tolerance. Tolerance is associated with frequent use of any of the hallucinogens. Cross-tolerance among mescaline, psilocybin, and LSD occurs, but not between amphetamine and LSD, despite the chemical similarity of amphetamine and mescaline. Previously distributed as tablets, liquid, powder, and gelatin squares, in recent years, LSD has been commonly distributed as “blotter acid.” Sheets of paper are soaked with LSD, and dried and perforated into small squares. Popular designs are stamped on the paper. Each sheet contains as many as a few hundred squares; one square containing 30 to 75 µg of LSD is one chewed dose, more or less. Planned massive ingestion is uncommon but massive ingestion happens by accident. The onset of action of LSD occurs within an hour, peaks in 2 to 4 hours, and lasts 8 to

12 hours. The sympathomimetic effects of LSD include tremors, tachycardia, hypertension, hyperthermia, sweating, blurring of vision, and mydriasis. Death caused by cardiac or

cerebrovascular pathology related to hypertension or hyperthermia can occur with hallucinogenic use. A syndrome similar to neuroleptic malignant syndrome has reportedly been associated with LSD. Death can also be caused by a physical injury when LSD use impairs judgment about traffic or a person’s ability to fly, for example. The psychological effects are usually well tolerated, but when persons cannot recall experiences or appreciate that the experiences are substance induced, they may fear the onset of insanity. With hallucinogen use, perceptions become unusually brilliant and intense. Colors and textures seem to be richer, contours sharpened, music more emotionally profound, and smells and tastes heightened. Synesthesia is common; colors may be heard or sounds seen. Changes in body image and alterations of time and space perception also occur. Hallucinations are usually visual, often of geometric forms and figures, but auditory and tactile hallucinations are sometimes experienced. Emotions become unusually intense and may change abruptly and often; two seemingly incompatible feelings may be experienced at the same time. Suggestibility is greatly heightened, and sensitivity or detachment from other persons may arise. Other common features are a seeming awareness of internal organs, the recovery of lost early memories, the release of unconscious material in symbolic form, and regression and the apparent reliving of past events, including birth. Introspective reflection and feelings of religious and philosophical insight are common. The sense of self is greatly changed, sometimes to the point of depersonalization, merging with the external world, separation of self from body, or total dissolution of the ego in mystical ecstasy. There is no clear evidence of a drastic personality change or chronic psychosis produced by long-term LSD use by moderate users not otherwise predisposed to these conditions. Some heavy users of hallucinogens, however, may experience chronic anxiety or depression and may benefit from a psychological or pharmacological approach that addresses the underlying problem. Many persons maintain that a single experience with LSD has given them increased creative capacity, new psychological insight, relief from neurotic or psychosomatic symptoms, or a desirable change in personality. In the 1950s and 1960s, psychiatrists showed great interest in LSD and related substances, both as potential models for functional psychosis and as possible pharmacotherapeutic agents. The availability of these compounds to researchers in the basic neurosciences has led to many scientific advances. Phenethylamines Phenethylamines are compounds with chemical structures similar to those of the neurotransmitters dopamine and norepinephrine. Mescaline (3,4,5trimethoxyphenethylamine), a classic hallucinogen in every sense of the term, was the first hallucinogen isolated from the peyote cactus that grows in the southwestern United States and northern Mexico. Mescaline human pharmacology was characterized in 1896 and its structure verified by synthesis 23 years later. Although many psychoactive plants have been recognized dating to before recorded history, mescaline was the only structurally identified hallucinogen until LSD was described in 1943. Mescaline

Mescaline is usually consumed as peyote “buttons,” picked from the small blue-green cacti Lophophora williamsii and Lophophora diffusa. The buttons are the dried, round, fleshy cacti tops. Mescaline is the active hallucinogenic alkaloid in the buttons. Use of peyote is legal for the Native American Church members in some states. Adverse reactions to peyote are rare during structured religious use. Peyote usually is not consumed casually because of its bitter taste and sometimes severe nausea and vomiting that precede the hallucinogenic effects. Many structural variations of mescaline have been investigated and structural activity relationships fairly well characterized. One analog, 2,5-dimethoxy-4methylamphetamine (DOM), also known as STP, an unusually potent amphetamine with hallucinogen properties, had a relatively brief period of illicit popularity and

notoriety in the 1960s, but it appears to have disappeared from the illicit market. Another series of phenethylamine analogs with hallucinogenic properties is the 3,4methylenedioxyamphetamine (MDA)–related amphetamines. The currently most popular and, to society, most troublesome member of this large family of drugs is MDMA, or ecstasy, more a relatively mild stimulant than hallucinogen. MDMA produces an altered state of consciousness with sensory changes and, most important for some users, a feeling of enhanced personal interactions. Many plants contain N,N-dimethyltryptamine (DMT), which is also found normally in human biofluids at very low concentrations. When DMT is taken parenterally or by sniffing, a brief, intense hallucinogenic episode can result. As with mescaline in the phenethylamine group, DMT is one of the oldest, best documented, but least potent of the tryptamine hallucinogens. Synthesized homologs of DMT have been evaluated in humans and structure activity relationships have been reasonably well described. Psilocybin Analogs An unusual collection of tryptamines has its origin in the world of fungi. The natural prototype is psilocybin itself. That and related homologs have been found in as many as 100 species of mushroom, largely of the Psilocybe genus. Psilocybin is usually ingested as mushrooms. Many species of psilocybin-containing mushrooms are found worldwide. In the United States, large Psilocybe cubensis (gold caps) grow in Florida and Texas and are easily grown with cultivation kits advertised in drug-oriented magazines and on the Internet. The tiny Psilocybe semilanceata (liberty cap) grows in lawns and pastures in the Pacific Northwest. Psilocybin remains active when the mushrooms are dried or cooked into omelets or other foods. Psilocybin mushrooms are used in religious activities by Mexican Indians. They are valued in Western society by users who prefer to ingest a mushroom rather than a synthetic chemical. Of course, one danger of eating wild mushrooms is misidentification and ingestion of a poisonous variety. At a large American university, 24 percent of students reported using psychedelic mushrooms or mescaline, compared with 17 percent who reported LSD use. Psilocybin sold as pills or capsules usually contains phencyclidine (PCP) or LSD instead.

Studies are underway in several medical centers in the United States (including New York University) to examine the use of psilocybin in terminally ill patients. Preliminary reports indicate that the psilocybin is helpful in reducing morbid anxiety about death and dying. It may play an important role in palliative care medicine in the future. Phencyclidine The amount of PCP varies greatly from PCP-laced cigarette to cigarette; 1 g may be used to make as few as four or as many as several dozen cigarettes. Less than 5 mg of PCP is considered a low dose, and doses above 10 mg are considered high. Dose variability makes it difficult to predict the effect, although smoking PCP is the easiest and most reliable way for users to titrate the dose. Persons who have just taken PCP are frequently uncommunicative, appear to be oblivious, and report active fantasy production. They experience speedy feelings, euphoria, bodily warmth, tingling, peaceful floating sensations, and, occasionally, feelings of depersonalization, isolation, and estrangement. Sometimes, they have auditory and visual hallucinations. They often have striking alterations of body image, distortions of space and time perception, and delusions. They may experience intensified dependence feelings, confusion, and disorganization of thought. Users may be sympathetic, sociable, and talkative at one moment but hostile and negative at another. Anxiety is sometimes reported; it is often the most prominent presenting symptom during an adverse reaction. Nystagmus, hypertension, and hyperthermia are common effects of PCP. Head-rolling movements, stroking, grimacing, muscle rigidity on stimulation, repeated episodes of vomiting, and repetitive chanting speech are sometimes observed. The short-term effects last 3 to 6 hours and sometimes give way to a mild depression in which the user becomes irritable, somewhat paranoid, and

occasionally belligerent, irrationally assaultive, suicidal, or homicidal. The effects can last for several days. Users sometimes find that it takes 1 to 2 days to recover completely; laboratory tests show that PCP can remain in the patient’s blood and urine for more than a week. Ketamine Ketamine is a dissociative anesthetic agent, originally derived from PCP, which is available for use in human and veterinary medicine. It has become a drug of abuse, with sources exclusively from stolen supplies. It is available as a powder or in solution for intranasal, oral, inhalational, or (rarely) intravenous use. Ketamine functions by working at the NMDA receptor and, as with PCP, can cause hallucinations and a dissociated state in which the patient has an altered sense of the body and reality and little concern for the environment. Ketamine causes cardiovascular stimulation and no respiratory depression. On physical examination, the patient may be hypertensive and tachycardic, have increased salivation and bidirectional or rotary nystagmus, or both. The onset of action is within

seconds when used intravenously, and analgesia lasting 40 minutes and dissociative effects lasting for hours have been described. Cardiovascular status should be monitored and supportive care administered. A dystonic reaction has been described, as have flashbacks, but a more common complication is related to a lack of concern for the environment or personal safety. Ketamine has a briefer duration of effect than PCP. Peak ketamine levels occur approximately 20 minutes after intramuscular injection. After intranasal administration, the duration of effect is approximately 1 hour. Ketamine is N-demethylated by liver microsomal cytochrome P450 (CYP), especially CYP3A, into norketamine. Ketamine, norketamine, and dehydronorketamine can be detected in urine, with half-lives of 3, 4, and 7 hours, respectively. Urinary ketamine and norketamine levels vary widely from individual to individual and can range from 10 to 7,000 ng/mL after intoxication. As of yet, the relationship between serum ketamine levels and clinical symptoms has not been formally studied. Ketamine is often used in combination with other drugs of abuse, especially cocaine. Ketamine does not appear to interfere with, and may enhance, cocaine metabolism. Ketamine is being studied for use in the treatment of depression. ADDITIONAL HALLUCINOGENS Canthinones Canthinones are alkaloids similar to amphetamines naturally found in the khat plant and synthetically made and known as “bath salts.” They are CNS stimulants that cause a massive release of dopamine, and a single dose can last up to 8 hours. They produce profound toxic effects that can lead to seizures, strokes, and/or death. Hallucinations and delusions are common. They are swallowed, injected, or “snorted” to produce the desired euphoric effect. Ibogaine Ibogaine is a complex alkaloid found in the African shrub Tabernanthe iboga. Ibogaine is a hallucinogen at the 400 mg dose range. The plant originates in Africa and traditionally is used in sacramental initiation ceremonies. Although it has not been a popular hallucinogen because of its unpleasant somatic effects when taken at hallucinogenic doses, patients exposed to ibogaine may be encountered by a psychiatrist because of the therapeutic claims. Ayahuasca Ayahuasca, much discussed on Internet hallucinogen websites, originally referred to a decoction from one or more South American plants. The substance contains the alkaloids harmaline and harmine. Both of those β-carboline alkaloids have hallucinogenic properties, but the resulting visual sensory alterations are accompanied by considerable nausea. Amazon native tribes discovered that adding leaves from plants containing substantial amounts of DMT markedly enhanced the visual and sacramental impact of ayahuasca. Thus, neither component in the ayahuasca plant mixture works well alone but when taken in combination an extremely effective hallucinogenic agent results. In recent years, the term ayahuasca has evolved to a less specific term to refer to any mixture of two things that are hallucinogenic when taken in combination. For example, harmine and harmaline are available as

fine chemicals and when taken along with many botanicals containing DMT result in a mixture with hallucinogen properties, initially intense but

usually of brief duration. Salvia Divinorum American Indians in northern Oaxaca, Mexico, have used Salvia divinorum as a medicine and as a sacred sacrament, which is now widely discussed, advertised, and sold on the Internet. When the plant is chewed or dried leaves smoked, it produces hallucinogen effects. Salvinorin-A, an active component in the plant, is parenterally potent, active at 250-µg doses when smoked, and of scientific and potential medical interest because it binds to the opioid κ-receptor. TREATMENT Hallucinogen Intoxication A basic principle in treatment is providing reassurance and supportive care. Patients experiencing intense and unpleasant hallucinogen intoxication can be helped by a quiet environment, verbal reassurance, and the passage of time. More rapid relief of intense anxiety is likely after oral administration of 20 mg of diazepam (Valium) or, if oral administration presents problems, an equivalent parenteral dose of a benzodiazepine. Anxiety and other symptoms generally diminish within 20 minutes of medication administration, compared to hours with only psychological and environmental support; however, perceptual symptoms may persist. Patients may need gentle restraint if they are in danger to themselves or others, but restraints should be avoided if possible. Neuroleptic medications, particularly if given at excessive doses, may worsen symptoms and are best avoided unless the diagnosis remains unclear and behavior cannot otherwise be managed. The marketing of lower doses of LSD and a more sophisticated approach to treatment of casualties by drug users themselves have combined to reduce the appearance of this once-common disorder in psychiatric treatment facilities. Hallucinogen Persisting Disorder Treatment for hallucinogen persisting perception disorder is palliative. The first step in the process is correct identification of the disorder; it is not uncommon for the patient to consult a number of specialists before the diagnosis is made. Pharmacological approaches include long-lasting benzodiazepines, such as clonazepam (Klonopin) and, to a lesser extent, anticonvulsants including valproic acid (Depakene) and carbamazepine (Tegretol). Currently, no drug is completely effective in ablating symptoms. Antipsychotic agents should be used only in the treatment of hallucinogeninduced psychoses, because they may have a paradoxical effect and exacerbate symptoms. A second dimension of treatment is behavioral. The patient must be instructed to avoid gratuitous stimulation in the form of over-the-counter drugs, caffeine, and alcohol, and avoidable physical and emotional stressors. Marijuana smoke is a particularly strong intensifier of the disorder, even when passively inhaled. Finally, three comorbid conditions are associated with hallucinogen persisting perception disorder: panic disorder, major depression, and alcohol dependence. All these conditions

require primary prevention and early intervention. Hallucinogen-Induced Psychosis Treatment of hallucinogen-induced psychosis does not differ from conventional treatment for other psychoses. In addition to antipsychotic medications, a number of agents are reportedly effective, including lithium carbonate, carbamazepine, and electroconvulsive therapy. Antidepressant drugs, benzodiazepines, and anticonvulsant agents may each have a role in treatment as well. One hallmark of this disorder is that, as opposed to schizophrenia, in which negative symptoms and poor interpersonal relatedness may commonly be found, patients with hallucinogen-induced psychosis exhibit the positive symptoms of hallucinations and delusions while retaining the ability to relate to the psychiatrist. Medical therapies are best applied in a context of supportive, educational, and family therapies. The goals of treatment are the control of symptoms, a minimal use of hospitals, daily work, the development and preservation of social relationships, and the

management of comorbid illnesses such as alcohol dependence. Phencyclidine Treatment of PCP intoxication aims to reduce systemic PCP levels and to address significant medical, behavioral, and psychiatric issues. For intoxication and PCP-induced psychotic disorder, although resolution of current symptoms and signs is paramount, the long-term goal of treatment is to prevent relapse to PCP use. PCP levels can fluctuate over many hours or even days, especially after oral administration. A prolonged period of clinical observation is therefore mandatory before concluding that no serious or lifethreatening complications will ensue. Trapping of ionized PCP in the stomach has led to the suggestion of continuous nasogastric suction as a treatment for PCP intoxication. This strategy, however, can be needlessly intrusive and can induce electrolyte imbalances. Administration of activated charcoal is safer, and it binds PCP and diminishes toxic effects of PCP in animals.

Trapping of ionized PCP in urine has led to the suggestion of urinary acidification as an aid to drug elimination. This strategy, however, may be ineffective and is potentially dangerous. Only a small portion of PCP is excreted in urine, metabolic acidosis itself carries significant risks, and acidic urine can increase the risk of renal failure secondary to rhabdomyolysis. Because of the extremely large volume of distribution of PCP, neither hemodialysis nor hemoperfusion can significantly promote drug clearance. No drug is known to function as a direct PCP antagonist. Any compound binding to the PCP receptor, which is located within the ion channel of the NMDA receptor, would block NMDA receptor–mediated ion fluxes as does PCP itself. NMDA-receptor mechanisms predict that pharmacological strategies promoting NMDA receptor activation (e.g., administration of a glycine site agonist drug) would promote rapid dissociation of PCP from its binding sites. No clinical trials of NMDA agonists for PCP or ketamine intoxication in humans have been carried out to date. Treatment must therefore be supportive and directed at specific symptoms and signs of toxicity. Classic measures should be used for medical crises, including seizures, hypothermia, and hypertensive crisis. Because PCP disrupts sensory input, environmental stimuli can cause unpredictable, exaggerated, distorted, or violent reactions. A cornerstone of treatment, therefore, is minimization of sensory inputs to PCP-intoxicated patients. Patients should be evaluated and treated in an environment that is as quiet and isolated as possible. Precautionary physical restraint is recommended by some authorities, with the risk of rhabdomyolysis from struggle against the restraints balanced by the avoidance of violent or disruptive behavior. Pharmacological sedation can be accomplished with oral or intramuscular (IM) antipsychotics or benzodiazepines; no convincing evidence indicates that either class of compounds is clinically superior. Because of the anticholinergic actions of PCP at high doses, neuroleptics with potent intrinsic anticholinergic properties should be avoided. REFERENCES Bokor G, Anderson PD. Ketamine: An Update on Its Abuse. J Pharm Pract. 2014 Mar. [Epub ahead of print] Catts VS, Catts SV. Psychotomimetic effects of PCP, LSD, and ecstasy: Pharmacological models of schizophrenia? In: Sachdev PS, Keshavan MS, eds. Secondary Schizophrenia. New York: Cambridge University Press; 2010:141. Crane CA, Easton CJ, Devine S. The association between phencyclidine use and partner violence: An initial examination. J Addictive Disord. 2013;32:150. Fantegrossi WE, Murnane KS, Reissig CJ. The behavioral pharmacology of hallucinogens. Biochem Pharmacol. 2008;75:17. Fontanilla D, Johannessen D, Hajipour AR, Cozzi NV, Jackson MB, Ruoho AE. The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. Science. 2009;323:934. Geraci MJ, Peele J, McCoy SL, Elias B. Phencyclidine false positive induced by lamotrigine (Lamictal) on a rapid urine toxicology screen. Int J Emerg Med. 2010;3(4):327. Javitt DC, Zukin SR. Phencyclidine (or phencyclidine-like)-related disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams

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