Hallucinogens And Dissociative Drug Use And Addiction

Introduction

Hallucinogens are a diverse group of drugs that cause alterations in perception, thought, or mood. This heterogeneous group has compounds with different chemical structures, different mechanisms of action, and different adverse effects. Despite their description, most hallucinogens do not consistently cause hallucinations. The drugs are more likely to cause changes in mood or in thought than actual hallucinations. Hallucinogenic substances that form naturally have been used worldwide for millennia to induce altered states for religious or spiritual purposes. While these practices still exist, the more common use of hallucinogens today involves the recreational use of synthetic hallucinogens.

Hallucinogen And Dissociative Drug Toxicity

Hallucinogens comprise a collection of compounds that are used to induce hallucinations or alterations of consciousness. Hallucinogens are drugs that cause alteration of visual, auditory, or tactile perceptions; they are also referred to as a class of drugs that cause alteration of thought and emotion. Hallucinogens disrupt a person’s ability to think and communicate effectively. Hallucinations are defined as false sensations that have no basis in reality: The sensory experience is not actually there. The term “hallucinogen” is slightly misleading because hallucinogens do not consistently cause hallucinations.
How hallucinogens cause alterations in a person’s sensory experience is not entirely understood. Hallucinogens work, at least in part, by disrupting communication between neurotransmitter systems throughout the body including those that regulate sleep, hunger, sexual behavior and muscle control. Patients under the influence of hallucinogens may show a wide range of unusual and often sudden, volatile behaviors with the potential to rapidly fluctuate from a relaxed, euphoric state to one of extreme agitation and aggression. Synesthesias is an anomalous blending of the senses, where an affected person may hear colors, feel or see sounds and taste shapes. Synesthesias are often reported by an individual using hallucinogens such as lysergic acid diethylamide (LSD).

**History And Use Of Hallucinogens**

Naturally occurring hallucinogens can be found in plants and mushrooms in certain parts of the world, and they grow in many locations in the United States. Included in these naturally occurring substances are dimethyltryptamine (DMT), psilocybin and psilocin, mescaline, salvinorin A, lysergic acid amide (LSA), and atropine and scopolamine. Because hallucinogenic drugs may alter human consciousness, they have been used throughout history by diverse cultures for religious, medicinal or mystical purposes.

The Hindu holy book, *Rig Veda*, mentions *soma*, a sacred substance used to induce higher levels of consciousness. No definition is given for *levels* of consciousness. Soma is extracted from the juice of the hallucinogenic mushroom *Amanita muscaria*. The Aztecs of pre-Columbian Mexico have talked about the ceremonial use of teotlaqualli, which is a paste made from
a hallucinogenic flower, called ololiuqui. It was rubbed on the skin of Aztec priests and soldiers, because it was thought to eliminate fear and place the user in a “proper” mental state to serve the Aztec gods. The Mexican Indians have a long history of using peyote, which is a mescaline-containing cactus, in religious ceremonies. Hallucinogens have also been proposed as a cause of the "immoral and illicit" behavior of women who were tried in the Salem, Massachusetts witch trials.

The first synthetic hallucinogen, lysergic acid diethylamide (LSD), was discovered unintentionally in 1938 by Sandoz laboratories, a commercial pharmaceutical enterprise, while they were searching for a new ergot-derived analeptic agent. Its discoverer, a Swiss chemist named Albert Hoffman, began to experience hallucinations after an accidental percutaneous exposure to the drug. Sandoz began marketing the new drug in 1947. Delysid, as the drug was called, was used by psychiatrists who believed its use in psychotherapy could help the patient access repressed emotions.

It first appeared in the United States in 1949 when it was used as a model to study schizophrenia due to its potent psychotomimetic effects. The applications of LSD quickly broadened to include numerous other medical and clandestine uses. The United States Central Intelligence Agency conducted human experiments with LSD. They were testing its use as an interrogation tool and as a possible mind-control agent. Unfortunately, many of these studies were conducted without the consent or knowledge of the participant.
Lysergic acid diethylamide use was believed to enhance creativity and promote well-being. In the late 1950s and early 1960s, LSD use increased. In the late 1950s, use of LSD had been proposed as a way to achieve intellectual and spiritual awakening and enlightenment. Initial studies in the early 1960s concluded that the drug was safe; and, popularized by the media and by individuals like Timothy Leary, experimentation with psychedelics reached a peak in the mid-1960s. In 1966, because of mounting public health concerns, the federal government banned LSD; however, illicit manufacture and use of hallucinogens continued.

Hallucinogen use declined in the 1970s and early 1980s. Recent studies showed an increase in use during the 1990s, particularly in high school and college populations. Why interest grew for hallucinogen use was not known.

Lysergic acid diethylamide is presently classified as a schedule I drug, meaning that it is an agent with high potential for use and there are no documented medical indications. However, there is renewed interest in investigating hallucinogens to treat diseases associated with perceptual distortions, such as schizophrenia, obsessive-compulsive disorder, bipolar disorder, post-traumatic stress disorder, dementia, substance use disorders, anxiety, and depression.

**Categorizing And Grouping Hallucinogens**

There is no perfect method to categorize hallucinogenic substances because many overlap in structure, pharmacology, and clinical features. A common
way of categorizing hallucinogens is to put them into two groups: 1) Classic hallucinogens that cause alterations in perception, thought, and mood, such as LSD; and, 2) Dissociative hallucinogens that cause the user to feel more out-of-control than with the classic hallucinogens, such as PCP. A dissociative drug user may feel disconnected from his/her body and/or environment. The dissociative drugs are more likely to cause respiratory depression and to be associated with a withdrawal syndrome.

One system groups hallucinogens into the following families: 20 1) Indole alkaloids (tryptamines), 2) Piperidines/piperazines, 3) Phenylethylamine derivatives, and 4) Miscellaneous psychoactive substances.

Another way to classify hallucinogens is to group them by their chemical structure and the compounds from which they are derived. Substances that are chemically related to each other may exhibit similar effects. Many other agents may be classified as pseudo-hallucinogens because they produce psychotic and delirious effects without the user suffering from the visual disturbances associated with traditional hallucinogens. Hallucinogens grouped by structural criteria include lysergamides, phenylethylamines, piperidines, indolealkylamines, and cannabinoids. These are briefly discussed here.

**Lysergamides**

The lysergamides include lysergic acid diethylamide (LSD), and lysergic acid hydroxyethylamide.
**Lysergic Acid Diethylamide (LSD)**

Lysergic acid diethylamide was initially derived from the ergot alkaloids produced by the fungus *Claviceps purpurea*, which is a contaminant of wheat and rye flour. Lysergic acid diethylamide is the most potent psychoactive drug known, with doses as low as 1-1.5 mcg/kg capable of producing psychedelic effects. Despite its potency, LSD has a very large safety margin; no deaths associated with isolated LSD ingestion, and no other drugs simultaneously consumed, have been reported, despite ingestions of several thousand micrograms. Lysergic acid diethylamide has dozens of street names, many of which are referring to the pattern printed on the blotter paper, including acid, sorcerer's apprentice, paper acid, Lucy in the Sky with Diamonds, Beavis and Buttheads, Bart Simpsons, and Sandoz. Some other street names of LSD include *doses, hits, tabs, sugar cubes, and white*. Typical street doses are 20-80 mcg of LSD per dose. This is much less than the amounts reported during the 1960s and early 1970s. At that time, the doses ranged from 100-200 mcg or higher, per unit.

Overall, hallucinogen use is estimated to have remained fairly constant over the past decade. While LSD is included in national drug trending reports, the accuracy of these reports for actual LSD use is complicated by novel non-lysergamide hallucinogenic compounds being marketed as LSD.

Lysergic acid diethylamide is a tasteless, colorless, odorless liquid, which is most often sold and consumed as liquid-impregnated blotter paper, gelatin squares (also called window panes), or tiny tablets (also called microdots). Although usually ingested in blotter form, LSD can also be taken by various
other routes, intranasal, sublingual, parenteral, inhalational, or even conjunctival (i.e., in eye drops). LSD is active on the serotonin and dopamine receptors in the brain. The neurotransmitter serotonin modulates mood, pain, perception, personality, sexual activity, and other functions. The *hallucinogenic activity* of LSD is thought to be mediated by LSD's effect on serotonin receptors. Lysergic acid diethylamide acts post-synaptically to both inhibit serotonin release and to increase retention of serotonin at serotonin-2 receptors. Its net effect is that of a serotonin agonist.

The user begins to experience the psychological effects at approximately 30-60 minutes after ingestion of LSD. The effects peak at approximately 5 hours after ingestion. The psychological effects on a person ingesting LSD vary based on the individual’s characteristics (the person’s size and his or her mental and emotional states), and the physical environment or the setting in which the user is taking the drug.

Several common elements of the episodes of use, spoken of as "trips," are recognized. Changes in mood and perception are uniform, everyone experiences those effects. Boundaries between users and their environment are blurred, time becomes distorted (speeding up or slowing down). Stationary objects may seem to flow or pulsate, and color perception is exaggerated. Synesthesias (an anomalous blending of the senses) are often reported. A feeling of clarity of consciousness may be reported by the user, during which the importance of reality is diminished. Hallucinations may occur, although they are not as common as the label “hallucinogenic” may imply. Lysergic acid diethylamide users are usually aware that they are hallucinating. Occasionally, a threatening or stressful environment may provoke feelings of severe anxiety and paranoia. This acute panic reaction is
often referred to as a "bad trip" and is the most common reason for users to seek medical attention.

A transient depression may occur after LSD use. Acute psychosis after LSD use has been reported, and an underlying or previously undiagnosed, schizophrenic disorder may become worse. An unusual aspect of the use of LSD and LSD-like substances, is the occurrence of "flashbacks" or Hallucinogen Persisting Perception Disorder (HPPD) experienced by a user. These events may occur months to years after LSD use. They are observed more often in persons who have used LSD more than 10 times.

The terms flashback and HPPD are often used interchangeably but there is a recognized distinction between the two. Flashbacks may be short-term, spontaneous and recurrent experiences. They may be characterized as a benign, reversible condition that is pleasant, not distressing, to the user. On the other hand, flashbacks may occur over a long period of time, even years. The condition may be difficult to reverse or be non-reversible, and they may be distressing to the user and, as such, rise to the level of a hallucinogenic disorder. This disorder is recognized and classified as Hallucinogen Persisting Perception Disorder (HPPD) in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). In this regard, the terms flashback and HPPD are not the same.

During a psychotic episode, danger of suicide and homicide exists.¹ These impulses may also cause a user to seek medical attention. In addition to the psychological effects, LSD also produces sympathomimetic effects. There are
significant increases in heart rate, blood pressure rises, and occasionally, a rise in body temperature may occur. Mydriasis usually occurs and appears to parallel the intensity of the psychologic and somatic trip, with pupils returning to normal when the patient returns to the previous, non-drug-induced mental state. Rarely, LSD can produce life-threatening symptoms. Hyperthermia (particularly when a monoamine oxidase [MAO] antidepressant is being used), severe hypertension, coma, respiratory arrest, and bleeding have been reported. Users, however, remain more at risk from behavior-related trauma than they do from the toxic sympathomimetic effects of the LSD.

Lysergic Acid Hydroxyethylamide

Lysergamides are found naturally in several species of morning glory (Rivea corymbosa), the “Beach Moonflower” (Ipomoea violacea) and Hawaiian baby woodrose (Argyreia nervosa). The seeds of these plants contain lysergic acid hydroxyethylamide. The plants and seeds are legal to purchase and possess in the United States under certain circumstances but extraction of the active lysergamide is illegal, as LSA is a Schedule III controlled substance.

Indolealkylamines

Common indole alkaloids (tryptamines) include dimethyltryptamine (DMT), psilocybin and psilocin. These indole alkaloids are listed below with other less common forms:

- Psilocybin
- Psilocin
- Bufotenin
- Dimethyltryptamine (DMT)
The indolealkylamine group appear to cause their psychogenic effects through activity at the serotonin receptor. Psilocybin is found in the following 3 major genera of mushrooms - *Psilocybin*, *Conocybe*, and *Panaeolus*. These often grow on cow dung, and they are found in most regions of the United States with the exception of desert regions. Ingesting only a few mushroom caps can produce hallucinogenic affects, but in general large numbers of mushrooms are required. Several drug-oriented magazines advertise home cultivation kits that include live mycelia, which can also be purchased over the Internet.

The effects of psilocybin cannot be inactivated by cooking or freezing the mushroom. As a result, the mushrooms may be brewed as a tea or added as an ingredient to foods.

The effects of psilocybin appear within 20 minutes of ingestion and last approximately 4-6 hours. Hallucinations are a common effect. Psilocybin seems to cause fewer adverse reactions than LSD but there are reported cases of hyperthermia, seizures, and coma.

More seriously, mushrooms in the wild or on the street may be easily mislabeled. Only one-third of so-called "magic mushrooms" bought on the
street contain psilocybin so misidentification is common. There is an added
danger that a person may unintentionally ingest a poisonous mushroom
resembling *Psilocybin, Conocybe, or Panaeolus* mushrooms. The user could
suffer poisoning that is potentially fatal.

In some cases, sellers buy mushrooms from the grocery store and add PCP
to them. The mushrooms are sold as psilocybin but the user is unwittingly
taking PCP.

Psilocybin is metabolized into the drug psilocin. Psilocin induces a sense of
euphoria, causes visual hallucinations, and can alter spiritual perception
(entheogen). The drug was widely studied in the 1960s by Timothy Leary
and Richard Alpert in the Harvard Psilocybin Project and has recently gained
a renewed interest in its treatment for many disorders including obsessive-
compulsive disorder, cluster headaches, drug dependence, and anxiety in
advanced-stage cancer.

Dimethyltryptamine (DMT) is a potent psychedelic with a brief duration of
action (15-60 min). This has earned it the nickname "businessman's trip." It
is found naturally in the bark of trees of the genus *Virola*, which grows in the
Amazon basin. DMT is only active when smoked or snorted. It causes the
same effects as LSD but it produces more visual hallucinations and more
sympathetic effects than LSD.
There are several species of toads which produce venom that has psychoactive properties. Members of the genus *Bufo*, particularly *Bufo marinus* and *Bufo alvarius*, contain bufotenine and 5-MeO-DMT. The compound 5-MeO-DMT is firmly established as a hallucinogen, but the role of bufotenine has not yet been established. The toads are either licked or milked for their venom, which may then be ingested or smoked. Their dried skin also may be smoked.

Synthetic 5-MeO-DIPT, (Foxy, Foxy Methoxy, or fake ecstasy) has experienced a recent surge in popularity and is frequently publicized as an erotic enhancer. It has hallucinogenic properties that are like other tryptamine compounds and is known to be mildly euphoric. AMT has also been emerging in the club and rave scenes and is often sold in conjunction with 5-MeO-DIPT.

Ayahuasca, which is also known as “hoasca” or “aya,” and “yage,” contains dimethyltryptamine (DMT) a naturally occurring tryptamine found in over 65 species of plants, primarily in the South American, Amazon region. For centuries, DMT-containing plants have been used for religious purposes, as they rapidly induce brief but powerful hallucinogenic effects. DMT is primarily smoked or insufflated, as it is orally inert due to rapid inactivation by intestinal monoamine oxidase (MAO). This inactivation can be overcome by the addition of a monoamine oxidase inhibitor (MAO-I), as is found in the ritualistic brew from ayahuasca. There is a naturally occurring alkaloid in the vine of the ayahuasca plant that prevents breakdown of DMT in the digestive tract. That feature is behind the practice of humans drinking the urine of people and reindeer which have eaten the plant from which DMT is derived.
Over the past decade, DMT use has gained popularity following the publication of the 2001 book DMT: The Spirit Molecule by Dr. Rick Strassman, MD. Of note, DMT ingestion produces significant gastrointestinal distress and universal emesis shortly after ingestion, the development of which is a desired effect in spiritual purgative ritual use.

**Phenylethylamines**

The phenylethylamine derivatives are the broadest group of hallucinogens and incorporate many substances. While 3,4-methylenedioxy-\(N\)-methylamphetamine (MDMA \([i.e., ecstasy]\)) is likely the most common of the phenylethylamine derivatives, some others include such newer novel synthetics as cathinones ("bath salts"), the 2C family of drugs, as well as their N-o-methoxybenzyl analogs (NBOMe). These and other forms are listed as follows:

- Mescaline
- Methamphetamines
- 3,4-methylenedioxymethamphetamine (MDMA)
- 3,4-methylenedioxymethamphetamine (MDEA)
- 3-methoxy-4,5-methylenedioxymethamphetamine (MMDA)
- 4-methyl-2,5-dimethoxymethamphetamine (DOM)

As mentioned above, phenylethylamine derivatives include mescaline and several hallucinogenic amphetamines. Mescaline is the psychogenic amphetamine found in the peyote cactus, *Lophophora williamsii*. Native Americans and Mexican Indians have used peyote since before recorded
history. Use continues today; members of the Native American Church are still permitted to use the drug in religious ceremonies, although it is a controlled substance with no known medical indications.

In terms of complications and overdoses, the hallucinogenic amphetamines seem more dangerous than other psychedelic drugs. Many of their toxicities are identical to those of amphetamines, with the sympathomimetic effects predominating. Hypertension and tachycardia are quite common. Hyperthermia is a common and occasionally serious complication that seems to be associated especially with the amphetamine-like hallucinogens. The combination of sympathomimetic effects, along with strenuous physical activity, dehydration, and high ambient temperatures found at raves all contribute to severe hyperthermia. This may be accompanied by rhabdomyolysis (a rapid breakdown of skeletal muscles), severe enough to cause myoglobinuric renal failure and, infrequently, disseminated intravascular coagulation (DIC).

Mescaline

Mescaline is a phenylethylamine-derived alkaloid that is found worldwide in a variety of cacti, the best known being the North American peyote cactus. Similar to the mushroom-derived hallucinogens, mescaline in the form of peyote cactus buttons has been used in rituals by many Native Americans for centuries. To achieve the desired effect, 5-10 buttons are chewed and ingested. Mescaline is thought to induce hallucinations by an amphetamine-like action, although the precise mechanism is unknown. After ingestion of 6-12 peyote buttons (the dried bitter fleshy tops of the cactus), the user first begins to feel effects in 30 minutes to 2 hours. Blood pressure may rise, as well as body temperature, heart rate and respiratory rate. Nausea, vomiting,
diaphoresis, and ataxia precede the hallucinogenic effects, which may last 8-12 hours. Mescaline also may be sold as pills containing ground peyote, or as a synthetic congener, but the prohibitively high cost of the raw materials often leads many dealers to simply substitute PCP. This should be kept in mind for treatment purposes; although the user may report that he or she ingested mescaline, it may have been substituted with PCP. Such a possibility must be considered when treating the patient.

**Hallucinogenic Amphetamines**

Some of the hallucinogenic amphetamines are also known as enactogens (literally, enabling the user to "touch within"). These are structural analogs of mescaline and amphetamine. Most were derived from their parent compounds, with some alterations in chemical structure to avoid U.S. Drug Enforcement Agency detection and prosecution. They all have similar psychogenic effects and toxicity. They include MDMA, MDA, MDEA, and MMDA.

**Ecstasy**

Ecstasy, an MDMA, is likely the most well-known of these compounds. While the name "ecstasy" originally referred to MDMA, many drugs are sold as "ecstasy" today. It was first synthesized in 1914. Currently, MDMA is the drug of choice at "raves," (i.e., all-night dance parties which are popular in the United States and the United Kingdom). It appears to affect serotonin neurotransmission at presynaptic and postsynaptic sites, as does LSD.

One study suggests that MDMA use is associated with changes in the cerebral serotonergic transmitter system (presynaptic) and that subcortical,
but not cortical, recovery of serotonin transporter (SERT) binding might take place after several months of MDMA abstinence.²

Although it usually does not cause hallucinations, MDMA is grouped with hallucinogenic drugs. It causes changes in mood and music may be perceived differently. It is reputed to increase interpersonal communication, and is said to enhance feelings of intimacy and empathy. Although these may be positive-sounding attributes, concern is growing that ecstasy use may cause permanent nerve damage to its users, particularly those involved in serotonergic neurotransmission. MDMA produces hallucinogenic effects by causing release of serotonin, norepinephrine, and dopamine. Clinical effects of this drug are similar to those of other phenethylamine drugs. The street terms "E," "X," "Molly," and others may also refer to the drug MDMA.

There is significant degradation of serotonergic neurons following MDMA use.³ This degradation is cumulative and dose-related. This has led some experts to warn of the possibility of permanent mood disorders in individuals who use the drug regularly. Wilcox, et al., studied 2 young men who chronically used MDMA and later developed movement disorders which resembled the pathologic movements of Parkinson’s disease.⁴

Several deaths have been reported with MDMA use. Media coverage of these deaths alluded that dehydration was the cause of the MDMA-associated deaths. This gave rise to the belief that water was an antidote for MDMA use. However, consumption of large amounts of water combined with MDMA often leads to hyponatremia severe enough to occasionally cause seizures.
This results because the combination produces an intrinsic *syndrome of inappropriate antidiuretic hormone secretion* or SIADH-like effects.

Other reported complications of MDMA use are MAOI–induced hypertensive crisis, as may occur with LSD, serotonin syndrome (when excessive serotonin is active at pre- and post-synaptic receptor sites), seizures, hepatotoxicity, and tachydysrhythmias. Frequent users rapidly develop tolerance to the drug, requiring increasingly higher doses for the same effect.

**Other Designer Drugs**

This group of drugs refers to psychoactive drugs initially discovered in pharmaceutical or research labs but sold illegally by clandestine labs. Just like other hallucinogens, these drugs can be classified by effect or chemical structure. Most of these drugs belong structurally to the phenylethylamine derivative group. The newer designer drug category is the most rapidly growing and changing group of drugs among the hallucinogens. While this is ever-changing, some of the common substances include the MDMA congeners (*i.e.*, MDA, MDEA, MDPV), the 2C family of drugs (*i.e.*, NBOMe, 2CB, 2CI, and Bromodragonfly), and the D series of ring-substituted amphetamines (*i.e.*, DOB, DOI, DOM).

The designer drug category is likely the most dangerous group of drugs for many reasons. These drugs are typically made in clandestine labs by amateur chemists, which produce variable results with poor quality control. Oftentimes these clandestine labs may inadvertently produce a drug other
than their intended product, although it may be structurally similar. This unknown agent may have untoward effects above and beyond those of the intended drug. Dosing and potency are also common problems with clandestine labs — especially when chemicals are added to blotter paper or organic material, as is done with NBOMe and synthetic cannabinoids, respectively.

**Synthetic Cathinone**

"Bath salt" is the informal street name given to designer drugs containing substituted or synthetic cathinone chemicals. These substances are sold as innocuous products such as "baths salts" and are marketed under names such as "Bliss," "Ivory Wave," and "Vanilla Sky." "Not for Human Consumption" labels are used in an effort to circumnavigate law enforcement. Synthetic cathinone or "bath salt" use has emerged over the last decade and gained popularity in large part due to these agents' accessibility and ambiguous legal status. In 2011, The DEA designated methylenedioxypyrovalerone (MDPV), methylone, and mephedrone as schedule I substances, to make their sale and possession illegal. However, the clandestine production of these substances remains ahead of legislative action to avoid prohibition.

Cathinones are found in the leaves and stems of *Catha edulis* (khat), a plant native to East Africa and the Arabian Peninsula. Historically, consumption of this naturally occurring cathinone has been through chewing the fresh, unprocessed leaves of the khat plant. Substituted cathinones found in "bath salts" are created in clandestine labs and have effects similar to those of
amphetamines and the phenethylamine class. Currently, substituted cathinones such as MDPV, methylone, or mephedrone are used by insufflation of the crystalline powder.

*N-o-methoxybenzyl analogs (NBOMe)*

This new class of designer research chemicals includes highly potent hallucinogenic serotonin agonists. 25I-NBOMe and 25C-NBOMe are the two most common forms of this drug. "Bomb" or "N-Bomb" is commonly sold on blotter paper and the drug user administers the drug via the buccal or sublingual route, just like LSD. NBOMe is commonly misrepresented as LSD because of their similar routes of administration and effects. While the two drugs are similar, there are numerous reports of fatal overdoses in the U.S. due to NBOMe.

**Piperidines**

The most common piperidines and piperazine are phencyclidine (PCP), benzylpiperazine (BZP), and ketamine. This group also includes cannabinoids (tetrahydrocannabinol, *i.e.*, marijuana, hashish). These hallucinogenic alkaloids have approximately one-tenth the potency of LSD. Phencyclidine (PCP) and ketamine are known as dissociative drugs. Phencyclidine and ketamine are piperidine derivatives with potent anesthetic and illusionogenic properties.

*Phencyclidine (PCP)*
Phencyclidine was developed at Parke-Davis and Company in the late 1950s as a potent and effective dissociative anesthetic. It was initially marketed under the brand name Sernylan. Its use was short-lived, as it produced strong adverse side effects, including emergence reactions with extreme agitation, disorientation, and hallucinations.\textsuperscript{24} Severe dysphoria, extreme agitation, and psychotic behavior were all noted to be quite common. Phencyclidine enjoyed a short use in the veterinary world during the 1960s, during which time it was diverted in pill form throughout the San Francisco region and eventually spread to surrounding states in the form of powder ("angel dust") added to plant substances for smoking.

Phencyclidine “Angel dust,” also dubbed the PeaCe Pill, or PCP for short, had limited appeal because of its dysphoric effects and erratic absorption; however, its popularity eventually increased (or it was simply used more) as dealers misrepresented PCP as delta-9-tetrahydrocannabinol (THC), which is the active, mood-altering chemical in marijuana. Producers promote PCP because it is cheap and easy to synthesize. It was also sold as mescaline, LSD, or other amphetamines.

Phencyclidine is still cheap and easy to produce, so it continues to be marketed in place of other harder-to-obtain drugs. Although it is not known why, it remains popular in some cities, namely in Philadelphia and Washington, D.C. Use peaked in the late 1970s, declined in the 1980s, but seemed to have made a resurgence in the 1990s. Phencyclidine goes by several street names, including killer weed, elephant tranquilizer, rocket fuel, and hog.
The onset of effects occurs in about 2-5 minutes after ingestion or smoking of PCP (often it is sprinkled on marijuana cigarettes). Peak effect occurs by 15 minutes. The duration of action is as long as 16 hours (some users report effects persisting as long as 24-48 hours). The drug antagonizes the action of glutamate at the N-methyl-D-aspartate receptor, which blocks the influx of calcium and thereby inhibits neurotransmitter release. Depending on the dose, PCP may cause either CNS excitation or depression. Sympathomimetic effects are prominent, especially increases in heart rate and blood pressure. During a psychotic episode, the user is in danger of committing suicide and/or homicide.

The clinical manifestations of PCP use are extremely variable and unpredictable. The patient may appear calm or wild, disoriented, violent, sleepy or comatose, depending on the ingested dose and whatever adulterants may be used. Patients will often have a blank stare, which may show no reaction to stimulation by others, such as conversation. Ataxia, grimacing, bruxism, muscle rigidity, and myoclonus are common. Temperature, heart rate, and blood pressure are elevated.

Bizarre and psychotic behaviors are often noted. Phencyclidine is associated with a much higher morbidity and mortality than other classes of hallucinogens. The combination of sympathetic effects, along with severe agitation, and the presence of muscle rigidity, place these patients at very high risk for the complications of severe hyperthermia, rhabdomyolysis, and subsequent myoglobinuric-induced renal failure. Their violent and bizarre
behavior places them at high risk for trauma, and may place those around them in danger of trauma. The dissociative nature of PCP allows users to do tremendous harm to their bodies with little or no perceived pain.

Phencyclidine use has declined nationally over the past three decades, but remains common in certain cities including Philadelphia and Washington, D.C. Phencyclidine is most commonly sold as a liquid solvent in which a user will dip a cigarette or marijuana joint (a so-called wet, dip, dipper, or sherm) and the product is smoked, producing rapid clinical effects. Because of PCP’s strong volatile solvent smell, it has often been referred to as "embalming fluid" or "formaldehyde." This had led to some users to erroneously believe that the clinical effects from using formaldehyde are similar. Currently, illicit PCP is not diverted from healthcare sources, but rather produced illegally in clandestine labs due to ease of synthesis and readily available precursors.

*Ketamine*

Ketamine, structurally similar to PCP, is currently a widely used dissociative anesthetic. Ketamine was synthesized in 1962 as a replacement for PCP, and it remains a widely used anesthetic with increasing non-operative usage, including emergency departments and the pre-hospital setting. Ketamine is used recreationally primarily as an insufflated powder. Its effects are dose-dependent and wide-ranging, from mild alteration of sensorium to complete dissociation of consciousness with powerful and sometimes disturbing hallucinogenic experiences known as the "K hole." Used since the 1970s, ketamine is currently undergoing a resurgence in popularity.
Ketamine is known for being more psychologically addictive than most psychedelics. Called "Special K," it is a popular drug at raves and it is commonly used at large concerts and clubs.²⁸

**Cannabinoids and Synthetic Cannabinoids**

Marijuana is the leaf or flower of the plant *Cannabis sativa* and is commonly known as pot, grass, weed, or Mary Jane. It is used recreationally and medicinally for many conditions. The *Cannabis sativa* plant contains high levels of a psychoactive substance, tetrahydrocannabinol (THC), as well as other psychoactive cannabinoids. Although THC is the principal psychoactive component of cannabis, this plant is chemically complex and contains many other cannabinoids, including cannabidiols, cannabinol, and tetrahydrocannabinivarin (THCV). The psychoactive effects seen with cannabis use include relaxation, euphoria, and heightened mood.

Although it is usually grouped with other hallucinogens, it is very rare that marijuana causes hallucinations. Hallucinations may be more prominent if the marijuana has been adulterated with some other compound or compounds. The acute effects from smoking marijuana include an alteration in perception or mood, laughing, increased appetite, conjunctival injection, tachycardia, and mild CNS depression.

Synthetic marijuana is a designer class of drugs created to act as a cannabinoid receptor augmenter. These synthetic cannabinoids are added to
herbal mixtures to facilitate smoking to produce what many term a "legal high" or "herbal high." These products, much like the bath salts, are sold as "herbal incense" and are commonly referred to as "spice." Synthetic marijuana is commonly packaged and marketed under such names as K2, Spice, Bombay Blue, and Black Mamba. The label "Not For Human Consumption" is used to avoid regulation. In 2011, five synthetic cannabinoids [JWH-018, JWH-073, CP-47,497, JWH-200, and cannabicyclohexanol (CCH)] were designated Schedule I by the Controlled Substances Act which made it illegal to manufacture, import, possess, distribute, or use these substances.

Synthetic cannabinoid users typically use these substances in order to avoid illicit drug detection on standardized blood and urine drug testing. While THC from marijuana use is easily detected on a standard urine drug test, most synthetic cannabinoids are not similar enough in structure to THC and therefore do not trigger positive results on typical urine drug screens. This has led to its popularity in populations with obligatory drug testing (i.e., the penal system, psychiatric setting, military, department of transportation, professional athletics).

**Other Hallucinogens**

Other hallucinogens are listed here and some will be discussed in more depth below.

- Muscimol from the mushrooms *Amanita muscaria* and *Amanita panthentia*
• Antimuscarinic Xenobiotics
• Dextromethorphan
• *Salvinorin A*
• Nutmeg
• Anticholinergics (including atropine and scopolamine)
• GABA receptor agonists
• ibotenic acids

*Muscimol*

Muscimol is the principle psychoactive component found in mushrooms. There are several mushrooms of the genus *Amanita* which produce hallucinogenic effects. These include *Amanita muscaria, Amanita pantherina,* and *Amanita cothurnata.* These should not be confused with the deadly *Amanita phalloides* group. Despite its name, *A. Muscaria* contains just a small amount of muscarine. It does not cause cholinergic toxicity.5

*A. Muscaria*

*A. muscaria,* or fly agaric, has been used as a psychotropic agent by Siberians for centuries. The most-active substances in the mushrooms, which are muscimol and ibotenic acid, are thought to act primarily on GABA receptor sites. Effects begin about 20 minutes after ingestion, and last for about 6-12 hours. There may be visual hallucinations, and manic states may alternate with periods of deep sleep. The drug is excreted unchanged in the urine, which has led to the Siberian practice of drinking the urine of persons or reindeer that have eaten the mushroom.
Treatment with atropine is contraindicated, especially given that anticholinergic substances can also be hallucinogens. In particular, the plant family *S. olanaceae* (nightshade) contains atropine and scopolamine, which cause hallucinations, often unpleasant and dissociative in nature.

**Antimuscarinic Xenobiotics**

Atropine and scopolamine act as antimuscarinics and are found in a variety of plants, and large doses can induce hallucinations as well as a number of more serious effects. Both are found in *Datura stramonium* (Jimson weed), *Atropa belladonna* (deadly nightshade), and *Mandragora officinarum* (mandrake). Scopolamine alone occurs in *Hyoscyamus niger* (henbane).

**Dextromethorphan**

Dextromethorphan (DXM) is the antitussive agent found in many over-the-counter cough and cold medicines. DXM’s clinical effects at doses higher than recommended include a euphoric-like effect, changes of perception, and visual hallucinations. When recreationally used in high doses, DXM acts like ketamine or PCP, blocking NMDA receptors and causing an altered level of consciousness commonly described as a dissociative state. Clinical effects vary by dose and time; users commonly refer to these stages as "plateaus." The over-the-counter remedies that contain DXM also typically contain other ingredients, such as decongestants, antihistamines, analgesics, and expectorants. Consequently, drug users can unwittingly consume toxic amounts of those other ingredients when using DXM.
Nutmeg

Nutmeg (seed of the *Myristica fragrans* tree) is widely available for culinary use. Historically, nutmeg has been used as an abortifacient and to induce menses, albeit ineffectively. In large quantities, nutmeg can produce anticholinergic effects, including visual hallucinations due to activity of the compound myristicin. While often ingested intentionally for hallucinogenic effects, case reports exist where therapeutic misadventures for naturalistic purposes have induced hallucinations.\(^{23}\)

Salvinorin A

Salvinorin A is a naturally occurring hallucinogen that is found in a variety of plants but is named from *Salvia divinorum*, or diviner's sage, a member of the mint family. Salvinorin A is unique in that, unlike other known hallucinogenic substances that interact with serotonin (5-HT2 receptors) metabolism, it is the first known naturally occurring kappa-opioid receptor agonist.\(^{29}\) This substance has been used by the Mazatec Indians in Mexico for ceremonial purposes.

While *Salvia divinorum* and salvinorin A are not classified under the Controlled Substances Act, several states have placed regulatory controls on either or both.\(^{30}\)

### Epidemiology Of Hallucinogen Use

According to the 2013 National Household Survey on Drug Abuse (NHSDA), an estimated 1.3 million persons aged 12 or older (0.5 percent) used
hallucinogens in the past month. In 2013, the rate of use of hallucinogens among 18 to 25 year olds was 1.8 percent. Hallucinogens continue to be among the most frequently abused class of drugs among high school students, after alcohol and marijuana.7

First-time users aged 12 or older numbered 1.1 million persons.6 The incidence of first-time hallucinogen use has exhibited 2 prominent peaks of increase: 1) from 1965-1969 there was a marked increase predominately from LSD use, and 2) from 1992-2000 there was a marked increase predominately from use of MDMA.

Although hallucinogen use is found in almost all cultures, several other hallucinogens bear special mention.

• *Khat*, the leaves and stems of the *Catha edulis* shrub, is an amphetamine-like compound used by millions of people in the Middle East and Africa. The leaves are chewed to produce a euphoriant effect and as a mood-altering agent.

• *Methylenedioxymethamphetamine* (MDMA), a derivative of the active agent in khat, has been used in Russia since the 1970s and is responsible for several deaths. Reports indicate that it is the most popular drug of use in the former Soviet Union.

• MDMA is one of the most popular drugs in the club scene in Taiwan. Between January 2001 and December 2008, 59 deaths tested positive for MDMA.
All of these, although less-commonly used, can be found in regions of the United States.\textsuperscript{8}

**Demographics**

The National Survey on Drug Use and Health (NSDUH) provides statistics on drug use in the United States. According to the 2014 NSDUH survey, rates of illicit drug use in the past year among different ethnic groups were as follows:

- American Indians or Alaska Natives: 24.0%
- Native Hawaiians or other Pacific Islanders: 21.3%
- Blacks: 19.5%
- Whites: 16.9%
- Hispanics: 15.6%
- Asians: 8.0%
- Two or more races: 23.3%

Further, according to the 2014 NSDUH, the rate of illicit drug use was higher in males, at 19.8%, than in females, at 13.7%. Males were more likely than females to be users of hallucinogens (2.1% vs. 1.1%). An estimated 0.3 percent of this population was current users of hallucinogens in 2014, which represents 535,000 individuals. Estimates of current hallucinogen use ranged between 0.1 and 0.3 percent from 2002 to 2014, with the 2014 estimate being slightly higher than the estimates in 2003, 2004, 2006, 2008, 2010, and 2011.
Results from the 2013 survey by the NSDUH showed that in 2012, 1.2 million persons aged 12 or older had used hallucinogens within the past year; 229,000 were current users, and 33,000 reported current use of PCP. The age group with the highest incidence of hallucinogen use in 2014 was adults that were 26 years old and older. The percentage of adolescents (aged 12 to 17) in 2014 who were current hallucinogen users was similar to the percentages in 2012 and 2013, but it was lower than the percentages in most years from 2002 through 2011.\textsuperscript{34}

In a 2014 survey of hallucinogen use, ecstasy appeared to be the most frequently used drug with 609,000 users. The percentage of users over 12 years old was mostly similar when compared to the years 2002 through 2013. However, among adolescents, current ecstasy usage was lower when compared to that same period, 2002 to 2013.\textsuperscript{34} Among high school seniors, the herb salvia was significantly more popular than LSD or PCP. Past year use was reported to be 5.9 percent for salvia, 2.7 percent for LSD, and 1.3 percent for PCP. Fortunately, rates for salvia use have dropped significantly, to 1.8 percent in 2014. LSD and PCP use dropped slightly as well.

Although regular use of hallucinogenic and dissociative drugs in general has remained relatively low in recent years, one study reported that the United States ranks first among 36 nations in the proportion of high school students who have used LSD or other hallucinogens at some time. By comparison, the proportion of U.S. high school students who have used LSD or other hallucinogens at some time is 6 percent, whereas the rate in Europe is 2 percent.
International Estimates of Drug Use

Australia reported that in 2014, ecstasy was second only to cannabis as the most commonly used illicit drug with 2.1 million (10.9%) people aged 14 or older having used the drug during their lifetime and 500,000 having done so in the past 12 months, representing 2.5% of the population. In Europe, an estimated 1.8 million young adults (15–34) used ecstasy in 2014 (1.4% of this age group), with national estimates ranging from under 0.1% to 3.1%.

Globally, use of ecstasy has been declining, according to many reports. However, the United Nations World Drug Report shows that use of ecstasy in Europe is still increasing. The regions with highest prevalence of ecstasy use are Australia and Oceania (2.9%), North America (0.9%) and Europe (0.7%).

The drink ayahuasca has become popular among American and European tourists to the Amazon. Although DMT is a schedule I drug in the United States, plants containing DMT are not scheduled. There is uncertainty about the legal status of ayahuasca in the U.S. Some churches in the U.S., which follow the practices of their founding church in Brazil, have obtained permission from the federal government to import and use these plants in their religious ceremonies.

Morbidity and Mortality
Deaths from drug overdose are currently the leading cause of injury death in the United States and have been rising steadily over the past two decades. While data on mortality directly attributable to hallucinogen use is not readily available, many estimate that hallucinogenic drugs are among the drugs with highest mortality, including prescription painkillers, heroin, and cocaine.

The Drug Abuse Warning Network (DAWN), a public health surveillance system that monitors drug-related morbidity and mortality, estimates that 49% of all emergency departments’ visits are due to drug use or misuse.

**Hallucinogen Use And Clinical Presentation**

Most people who take hallucinogens never seek medical attention. Most who do seek attention do so because of a massive overdose, an acute panic reaction, or an accidental ingestion. A history of recent hallucinogen use can often be obtained from the patient or the patient's friends and family. All available resources should be used during the history taking.

Organic causes for altered mental state, acute psychosis, and agitation should be sought aggressively. Even when the clinician has obtained a positive history of hallucinogen use, other drugs may be involved, and patients often do not honestly disclose the history. Other concerns may be present. Identifying the agent does not mean that only hallucinogen use is the only problem responsible for the presentation. The clinician should also consider ingestion of drugs that have the potential to cause hyperthermia if
patients are in different stages of undress. These drugs include PCP, mescaline, MDMA, and Jimson weed (not discussed in this article). Users of PCP seem to be fond of swimming, probably as a result of this hyperthermia, and drownings have been reported.

Persons who present following LSD ingestions most often do so because of a bad trip, characterized by disturbing visual hallucinations, anxiety, and paranoid delusions. An acute panic reaction is frequently observed. Behavior is usually agitated. Restraint is sometimes necessary, to protect both the patient and the staff.

Patients who ingest peyote often have pronounced gastrointestinal effects (nausea and vomiting), diaphoresis, and ataxia before the onset of hallucinations.

Users of hallucinogenic amphetamines, such as ecstasy, often have a history of attending raves. Preoccupation with light is common. Bruxism is also a common finding; many users carry something to put in their mouth, and this might be an 18-year-old person with a pacifier. Some experts are concerned about long-term mood disorders and potential suicidal behavior in long-term users. Also, legal issues may become part of the patient’s health history. PCP users are more likely than other users to present in the custody of law enforcement officials. They often have a blank stare, may be extremely agitated or violent, and may show no regard for pain. PCP users are at risk for both suicidal and homicidal behavior. Use of PCP may occasionally be difficult to distinguish from cocaine toxicity.
A history of mushroom ingestion, particularly in novices, should prompt a thorough attempt to identify the ingested mushroom and to differentiate it from more toxic varieties.

**Physical Examination**

A complete set of vital signs should be obtained during the physical examination. Hallucinogen use may manifest with tachycardia, hypertension, and hyperthermia. Hypotension, hypoxia, and marked tachycardia or bradycardia are strong clues that imply serious disease, other than just drug use, but does not rule out drug use.

Sympathomimetic effects are common and often precede the hallucinogenic effects. Findings may include mydriasis, tachycardia, sweating, hyperthermia, hypertension, ataxia, and vomiting. Note pupil responses where appropriate.

A complete mental status examination should be performed on all patients. Affect, speech, appearance, presence of auditory/visual hallucinations, delusional thinking, and suicidal/homicidal ideation should be carefully assessed. The mental status exam should be repeated as the presentation changes. Most persons experiencing the effects of a hallucinogen are awake, alert, and oriented. Obtunded patients or those with a focal neurologic examination should prompt an aggressive search for an organic etiology. Although nystagmus in any direction can occur with PCP use, rotatory nystagmus is a classic sign.
Trauma is common, resulting from drug-induced behavior. Conjunctival injection is commonly observed with marijuana use, rarely with other drugs. Toad licking may cause profound drooling, seizures, and cyanosis. Severe hyperthermia may be observed with PCP or MDMA use.

The subjective experience of using a hallucination can vary tremendously, not only person to person, but also between ingestions. This makes the violence potential difficult to predict. Nevertheless, PCP is generally considered to have the most potential for violence and suicidal or homicidal behavior.¹⁰

**Laboratory Studies**

In general, laboratory studies to identify the drug used do not play a large role in the diagnosis and treatment of hallucinogen poisoning.

- Only a few hallucinogenic agents show up on standard toxicological screens. These include MDMA (positive for amphetamines), PCP, and marijuana.
- Treatment of hallucinogen poisoning is rarely affected by drug screen results.
- Dextromethorphan (as in Robitussin DM) may cause a false-positive result for the presence of PCP. This is especially common in younger users.
Metabolic abnormalities should be sought and aggressively treated.

- MDMA may cause hyponatremia (via a water retaining effect) or the popular belief that consuming a lot of water prevents adverse reaction.
- PCP and MDMA may cause rhabdomyolysis and subsequent myoglobinuric renal failure. The creatinine kinase level should be checked.
- Hypoglycemia should always be excluded as a cause of altered mental status.

**Medical Care Of Patients Using Hallucinogens**

As with any toxic ingestion, proper attention first should be directed to the assessment and stabilization of the patient's airway, breathing, and circulation. For any person presenting with hallucinations or psychosis, even if a hallucinogen is strongly suggested as the inciting agent, the basic approach to a patient with altered mental status should be followed. This includes administration of dextrose (or demonstration of a normal blood glucose level), thiamine, and naloxone. Other etiologies for the patient's symptoms should not be discounted. Even in the presence of hallucinogens, there may be more than one disease process responsible for altered mental status.

Prehospital care providers should attempt to ascertain the type and amount of hallucinogen ingested and the presence of any other co-ingested drugs or psychoactive substances. The care of persons who have ingested hallucinogens usually begins with calm reassurance. Patients presenting with an acute panic reaction should be placed in a quiet nonthreatening
environment with minimal stimuli. Patients should be reassured that the anxiety and other nervous system mental and emotional effects, as well as somatic effects are caused by the drug or drugs, and that the effect will wear off in several hours.

Patients that are medically stable but remain anxious or agitated, have continued hallucinations, and remain a danger to themselves or others will not be able to care for themselves after several hours of observation. Placement in a calm, relaxed environment may help. Security personnel, physical restraints, and chemical sedating agents should be prepared and readily available if agitation suddenly develops, or if a patient is a danger to himself or others.

Physical restraints should be used as briefly as possible, as a bridge to chemical restraint, to protect the patient, staff and the surroundings. Benzodiazepines are the first-line agents, and should be administered liberally.

All patients should be evaluated for the presence of emergent medical conditions, including traumatic injuries and cardiac arrhythmias. Special attention should be paid to the patient’s temperature, as many hallucinogenic agents can induce life-threatening hyperthermia. However, it is important to watch the duration of physical restraints. Avoid prolonged or excessive physical restraint because this can contribute to hyperthermia, rhabdomyolysis, and acidosis, and it can also substantially exacerbate the patient's paranoia. Aggressive cooling measures may be necessary, such as
a cooling blanket, if significant hyperthermia is noted. In severe cases, paralyzation and endotracheal intubation should be undertaken. Rhabdomyolysis, if diagnosed, should be treated with fluid repletion and alkanilization of the urine.

Benzodiazepines are the cornerstone of treatment for anxious or agitated patients. They reduce anxiety and the sympathomimetic effects of hallucinogens. Phenothiazines should not be used, because they may reduce the seizure threshold, and their anticholinergic effects may cause worsening of the patient's hyperthermia and tachycardia. The role of butyrophenones, particularly droperidol and haloperidol, is less clear. Condemned by some physicians as lowering the seizure threshold and inducing an epileptogenic reaction, they are still in wide use to chemically restrain violent and psychotic patients.

Severe hypertension and tachycardia may need treatment with nifedipine or nitroprusside, although the hypertension and tachycardia associated with hallucinogens rarely require any treatment beyond a benzodiazepine. Avoid beta-blockers because many of these drugs have both alpha- and beta-adrenergic effects. Isolated beta-blockade leads to unopposed alpha-adrenergic activity, worsening the hypertension and increasing mortality.

Consultations

Consulting a toxicologist or the local poison control center should strongly be considered in the following situations:
• Ingestion of multiple or unknown substances has occurred
• Any ingestion causing severe and/or potentially life-threatening adverse effects
• Ingestion of a drug or plant not readily familiar to the treating physician; an unknown mushroom ingestion should prompt a call to not only the poison control center but also perhaps to a trained mycologist.

A consultation or transfer to a mental health professional should be considered in the following circumstances:

• Any ingestion associated with a suicide attempt or a suicide gesture
• Any individual demonstrating psychotic symptoms after organic causes have been eliminated or after the psychoactive effects of the hallucinogen should have worn off

All individuals demonstrating signs and symptoms of substance use should be referred to the appropriate rehabilitation facility.

**Pharmacotherapy**

The goals of pharmacotherapy are to neutralize the effects of the toxic agent, to reduce morbidity, and to prevent complications.
Benzodiazepines

Lorazepam and diazepam, in particular, are the benzodiazepines of choice for hallucinogen ingestion. Anxiolytic and sedating properties calm agitated patients and help blunt coexisting hypertension and tachycardia.

Lorazepam (Ativan)

Lorazepam is a sedative-hypnotic with short onset of effects and relatively long half-life. By increasing the action of GABA, which is a major inhibitory neurotransmitter in the brain, it may depress all levels of the CNS, including limbic and reticular formation. When patients need to be sedated for longer than a 24-h period, this medication is excellent.

Diazepam (Valium)

Diazepam expresses all levels of the CNS (i.e., limbic and reticular formation), possibly by increasing activity of GABA.

Neuroleptics

These may be useful for severe agitation and/or psychosis. They may decrease the seizure threshold.
**Haloperidol (Haldol)**

Butyrophenone noted for high potency and low potential for causing orthostasis. Downside is high potential for extrapyramidal symptoms (EPS) or dystonia.

**Antidotes for Drug Reversal**

Dextrose, thiamine, and naloxone are quickly administered to an unconscious patient.

**Complications Of Acute And Outpatient Care**

Patients who are discharged should receive follow-up care from their primary care physician, their psychiatrist, or a drug counseling facility.

Patients with anxiety or panic reactions who present following an uncomplicated hallucinogen ingestion can often be sent home with responsible family members. Stable patients in the emergency department can be observed if any doubt exists as to the diagnosis or its severity. Any patient who persists with confused or psychotic behavior should be admitted for more thorough workup.
Patients whose ingestion is complicated by seizures, hyperthermia, or rhabdomyolysis should be admitted for monitoring. Those who present following massive overdose or those who demonstrate severe hyperthermia or any hemodynamic instability should be admitted to an intensive care unit. Stable patients with a persistent psychosis that does not wane as the hallucinogenic effect of the drug abates should be transferred to a mental health facility for evaluation and treatment. Those who present with suicidal ideation, homicidal ideation, or command hallucinations should also be admitted to a mental health facility when they are medically stable.

Complications

Long-term effects of LSD use may include prolonged psychotic reactions, severe depression, and flashbacks (i.e., HPPD). Flashbacks are the recurrence of LSD-like effects several months to years after cessation of use. They may be triggered by stress or illness and may cause significant distress. Patients using LSD are more at risk for injuries and death from behavior-related trauma than from the toxicological effects of LSD. Rarely, massive overdoses of LSD may result in hyperthermia, hypertension, coma, or respiratory arrest.

Patient Education

Patient education should encourage changes in the patient's life-style. Clinicians should emphasize the importance of avoiding people, places, and things related to hallucinogen use. Referrals should be offered to available psychiatric and community resources for follow-up. Users may benefit from referral to Narcotics Anonymous. Local chapters can be found in the white
pages of the phone book. Educating family members regarding the signs and symptoms of drug use is recommended to help in patient recovery. Enlist family help as a support system for the patient. Websites of value to the patient and family include: 1) The National Institute on Drug Abuse: https://www.drugabuse.gov/, 2) NIDA, Hallucinogens and Dissociative Drugs, and 3) NIDA for Teens, Mind Over Matter: Hallucinogens

**Summary part 1**

Hallucinogens comprise a collection of compounds that are used to induce hallucinations or alterations of consciousness. They are drugs that cause alteration of visual, auditory, or tactile perceptions, and are also referred to as a class of drugs that cause alteration of thought and emotion. Hallucinogens disrupt a person’s ability to think and communicate effectively, and are defined as *false sensations* that have no basis in reality.

How hallucinogens cause alterations in a person’s sensory experience is not entirely understood. Hallucinogens work, at least in part, by disrupting communication between neurotransmitter systems throughout the body including those that regulate sleep, hunger, sexual behavior and muscle control. Patients under the influence of hallucinogens may show a wide range of unusual and often sudden, volatile behaviors with the potential to rapidly fluctuate from a relaxed, euphoric state to one of extreme agitation and aggression.

There is no perfect method to categorize hallucinogenic substances because many overlap in structure, pharmacology, and clinical features. A common
way of categorizing hallucinogens is to put them into two groups: 1) Classic hallucinogens that cause alterations in perception, thought, and mood, such as LSD; and, 2) Dissociative hallucinogens that cause the user to feel more out-of-control than with the classic hallucinogens, such as PCP. A dissociative drug user may feel disconnected from his/her body and/or environment. The dissociative drugs are more likely to cause respiratory depression and to be associated with a withdrawal syndrome.

Currently, drug control scheduling classifications and popular misconceptions about the relative risks and harms of psychedelic drugs make research involving humans difficult. However, continued medical research and scientific inquiry into psychedelic drugs may offer new ways to treat mental illness and addiction in patients who do not benefit from currently available treatments. More is said about this important direction in the course The Hallucinogenic Brain: Diagnosis And Treatment included in the Hallucinogen Drug Use and Addiction series. The re-emerging paradigm of psychedelic medicine may open clinical and therapeutic doors long closed. Preliminary findings show some successful results for these treatments, with significant clinical improvements and as well as risks that include the potential for serious adverse effects. The emerging results may have implications for future medical and neuroscientific research, medical education and training, and public policy.
Part 2  The Hallucinogenic Brain: Diagnosis And Treatment

The Hallucinogenic Experience

Hallucinogenic substances work by stimulating secretion of a neurotransmitter, inhibiting reuptake, or delaying enzymatic breakdown of a neurotransmitter. All of these mechanisms may increase the synaptic concentration of major neurotransmitters. Minor differences in these mechanisms, or minor differences in the way a substance may act on the process of neurotransmission, partially explains why hallucinogenic experiences differ. For example, tryptamines (such as, LSD, psilocybin, dimethyltryptamine (DMT)) impact receptor sites that stimulate serotonin release. MDMA (ecstasy) enhances presynaptic release and reuptake of serotonin and norepinephrine.31 Synthetic cannabinoids, such as K2 and Spice, influence a secondary effect on the balance of circulating catecholamines.32 These differences not only help explain the varied hallucinogenic experiences, they also may predict the many negative effects associated with ingesting a hallucinogen.

Serotonin syndrome (serotonin toxicity) can occur with any agent that increases concentrations of serotonin, including lysergic acid diethylamide (LSD), psilocybin, and mescaline.33 The neurotransmitter dopamine is associated with the reward system of the brain. Substances that stimulate release or inhibit reuptake of dopamine typically exhibit a strong addictiveness, as seen with cathinones (bath salts) and methamphetamines.
Subtle differences in potency of hallucinogens may lead to different, sometimes adverse or unfavorable effects; this may occur even if the structure and mechanism of action of hallucinogens are similar. These varied effects may be seen by comparing “spice” with organic tetrahydrocannabinol. Spice is a highly potent, synthetic cannabinoid receptor agonist. It is more potent than its organic counterpart marijuana (tetrahydrocannabinol). In addition to its higher potency, spice, like other synthetic cannabinoids, has a longer half-live than marijuana. This may lead to negative effects with spice, such as psychosis, which is not routinely associated with low-potency organic tetrahydrocannabinol.

Although most patients who present to an emergency department (ED) with hallucinogen intoxication have a history of recent ingestion, not all are diagnosed easily. Some patients may provide a history of consuming a specific drug, but may in fact have used a different one, as surreptitious substitution of one drug for another by the manufacturer is common. The product in question may not even have contained an active hallucinogenic agent at all.

Altering drug composition or dose can have profound consequences on presentation. In addition, these products are often adulterated with drugs such as acetaminophen, caffeine, barbiturates, antipsychotics, or other pharmaceuticals. While a broad differential should be maintained in cases of altered mental status or psychotic behavior, often key historical details may be elicited from family members or bystanders. Experienced users often have contingencies for a “bad trip” and may be accompanied by a designated companion who can provide information. Without this
information, reliance on pre-hospital personnel to provide a history of empty bottles, containers, or drug paraphernalia is key.

The duration of effect may also provide helpful clues for the agent ingested. Dimethyltryptamine (DMT) has the shortest duration of action, peaking in seconds and lasting less than 60 minutes. Methyleneoxymethamphetamine (MDMA) may produce effects for 4-8 hours, whereas LSD can be active for well beyond 12 hours. Novel phenylethylamine derivatives (substituted phenylethylamine compounds) have widely variable durations of action, ranging from 90 minutes to 20 hours or more.

**Emergency Evaluation And Differential Diagnosis**

Patients under the influence of a hallucinogenic agent may present with a wide range of physical findings, depending on the agent. In cases where the hallucinogenic effect is uncomplicated, a health clinician may expect to see altered sensorium, tachycardia, tachypnea and possibly mild to moderate blood pressure elevations. Hyperthermia is not a usual effect of uncomplicated, hallucinogen use of a single-agent with a standard dose. If hyperthermia is present, a clinician should consider whether the patient used multiple agents that may have interacted. These interactions may indicate serotonin syndrome or ingestion of an anticholinergic agent such as dextromethorphan (DXM) or the poisonous plant, *Datura*.

During examination of a patient who has ingested a hallucinogen, the physical findings may include marked mydriasis (pupil dilation), especially in
the setting of tryptamine (*i.e.*, dimethyltryptamine (DMT), or lysergamide use, which includes lysergic acid diethylamide (LSD) and lysergic acid hydroxyethylamide. Findings on a focused neurologic examination are often normal except in the setting of phencyclidine or ketamine use, which can produce marked horizontal and vertical nystagmus (involuntary eye movement).

Muscle tremors and fasciculation may be found with the use of phenylethylamines. Frank muscular rigidity, hyper-reflexia of the lower extremities or clonus should prompt the consideration of serotonin syndrome, which may be triggered by DMT/Ayahuasca or dextromethorphan in patients already on a serotonergic antipsychotic. Finally, gastrointestinal distress is common with mescaline, DMT, or Ayahuasca use and is viewed to be a desirable occurrence when used for spiritual purposes.

Nausea and vomiting may be associated with the recent use of hallucinogens. A patient may present with *delayed* gastrointestinal effects of nausea and vomiting after ingestion of hallucinogenic mushrooms. This could be due to mushroom poisoning. If this condition appears more than 6 hours after ingestion, the patient will require special attention. Mushroom poisoning may be the result of a user misidentifying a mushroom type. Mushrooms that contain psilocybin are recognizable and these are ingested recreationally for their hallucinogenic effect. However, other hallucinogenic mushrooms such as *Amanita muscaria*, which is also used for its hallucinogenic effect, may be mistaken for the *Amanita phalloides* mushroom. While both types are listed as poisonous, the *Amanita phalloides* is a deadly poisonous mushroom that is extremely hepatotoxic.
Finally, a careful physical exam should be performed to evaluate for traumatic injury, which is not infrequently associated with hallucinogen use. As with all types of illicit substances, patients under the influence of hallucinogens may have abnormal sensory perceptions and abnormal behaviors, resulting in unrecognized injury.

Physical examination findings that are inconsistent with hallucinogen use should prompt appropriate general medical evaluation. Other co-occurring conditions that should be considered include:

- Acute hypoglycemia
- Alcohol toxicity
- Amphetamine toxicity
- Anticholinergic toxicity
- Antidepressant toxicity
- Antihistamine toxicity
- Brain abscess
- Carbamazepine toxicity
- Carbon Monoxide toxicity
- Clonidine toxicity
- Cocaine toxicity
- Delirium tremens (DTs)
- Dementia, amnesia
- Encephalitis
- Epidural and subdural infections
- Ethylene glycol toxicity
- Gamma-hydroxybutyrate toxicity
• Hallucinogenic mushroom toxicity
• Herb poisoning
• Herpes simplex encephalitis
• Hyponatremia in emergency medicine
• Meningitis
• Methemoglobinemia
• Organochlorine pesticide toxicity
• Pediatrics, meningitis and encephalitis
• Phencyclidine toxicity

Immediate testing directed at confirming exposure to a hallucinogenic substance is rarely useful. Treatment is symptom guided and results of confirmatory testing are not rapidly available.

**Urine Drug Screen**

The urine drug screen (UDS) may be misleading when used to diagnose the cause of presenting clinical features. The UDS is limited and often does not contain a screen for common hallucinogens. In addition, false-positive and false-negative results are common with the typical UDS immunoassay (diphenhydramine, dextromethorphan, and venlafaxine have been reported to cause a false-positive phencyclidine screen).\(^{41,42}\) Finally, even a true-positive UDS result does not always identify the cause of a patient's current presentation; for example, the UDS could be positive for phencyclidine because the patient used it 3 days ago.

**Laboratory Testing And Imaging Procedures**
Laboratory tests such as basic metabolic profiles, blood gases, hormonal concentrations (thyroid-stimulating hormone, cortisol), and creatinine kinase can be used to identify complications from hallucinogen use and exclude alternative causes of altered mental status (acid-base disturbances, metabolic and endocrine pathology, electrolyte abnormalities, rhabdomyolysis, renal failure, or stroke). When exposure confirmation is necessary (forensic cases, research purposes) expanded drug testing can be performed using specialized immunoassays, liquid chromatography and mass spectrometry, or a variety of other methods which are available through specialized reference laboratories.

Imaging is rarely useful in evaluating the effects of hallucinogen exposure. However, advanced imaging, including computed tomography or magnetic resonance imaging of the brain, can be useful in identifying complications and clinical disorders often associated with recreational hallucinogen use, including trauma, infection, hyperthermia, and hypertensive crisis.

**Treatment And Management Of Hallucinogen Use**

Patients under the influence of hallucinogens may exhibit a wide range of behaviors with the potential to rapidly fluctuate from a relaxed, euphoric state to one of extreme agitation and aggression. Calm, reassuring, and nonthreatening behavior can be useful in "talking down" patients to allow care and interventions to proceed. Often times, transporting a severely agitated patient requires numerous responders. In the pre-hospital setting, clinicians should focus on preventing harm and transporting patients to an appropriate facility for further evaluation.
In the situation of significant agitation, the primary goal for transport is to ensure both patient and clinician safety through chemical and physical restraint. Whenever possible, adequate chemical restraint should be the primary objective in behavioral control. Cases of arrest-related deaths (ARD) are not infrequent in the setting of physical restraint.

Various mechanisms have been proposed for sudden cardiac death related to restraint use including the combination of marked lactic acidosis due to struggling against restraint combined with impaired chest wall motion. Patients pinned down by law enforcement may also have marked compression of the inferior vena cava. If physical restraint must be used, it should be performed with the patient in the supine position when possible; the “hogtied” approach should be avoided at all costs due to an increased association with sudden death. Physical restraints should be used as a bridge to allow for appropriate chemical restraint.

The choice of agent for pharmacologic restraint may be dictated by local pre-hospital protocols. Whenever possible, however, benzodiazepines should be the first-line agent, as they are effective both intravenously and intramuscularly, have rapid onset of activity, and do not have the potential for cardiac conduction delays or decreased seizure threshold associated with antipsychotics such as haloperidol or droperidol. Intramuscular diazepam (Valium) or midazolam (Versed) have rapid onset of action and should be used in preference to lorazepam (Ativan) if safe intravenous access is not obtainable.
Intramuscular ketamine (4-5 mg/kg IM) may be a promising approach for the pre-hospital management of agitated delirium.\textsuperscript{45,46} When used intramuscularly, ketamine has a rapid onset of action, resulting in complete dissociative sedation within 2-5 minutes, and duration of action of 30-40 minutes, all while preserving respiratory drive. Ketamine is not contraindicated in the setting of head trauma and may, in some instances, be neuroprotective.\textsuperscript{47-50}

Comparison of prehospital ketamine versus haloperidol in agitated delirium has demonstrated more rapid onset of action and less need for re-dosing with ketamine. Adverse effects were more common with ketamine, mostly related to development of emergence reactions. The need for intubation in the pre-hospital or ED setting with ketamine use is rarely reported and appears to be related to underlying medical pathology (intracranial hemorrhage, severe acidosis), higher doses (6 mg/kg IM) or repeated doses.\textsuperscript{45} To date, no cases of death have been reported with pre-hospital or ED use of ketamine for chemical restraint.

**Emergency Medical Care**

The general approach to hallucinogen-induced behavioral changes in the emergency department (ED) mirrors the recommendations for the pre-hospital setting, as described above. As the ED is a potentially more controlled setting, fostering a calm and relaxed environment may obviate physical and chemical restraint. When possible, non-agitated patients should be placed in a quiet room with a one-to-one observer if available. Security
personnel, physical restraints, and chemical sedating agents should be prepared and readily available if agitation suddenly develops.

All patients should be evaluated for the presence of emergent medical conditions, including traumatic injuries, at the time of arrival. All patients should be placed on cardiac monitoring and they should have intravenous (IV) access established. Special attention should be paid to the patient’s temperature, as many hallucinogenic agents can induce hyperthermia, which may be life-threatening if not recognized early. An electrocardiogram should be considered as well, especially in the setting of abnormal vital signs, with attention to the QT interval.

Agitated behavior should be met with liberal doses of benzodiazepines. Haloperidol or droperidol may be useful adjuncts to benzodiazepines, but may be associated with QT prolongation and torsade de pointes, decreased seizure threshold, or temperature dysregulation. The use of atypical antipsychotics should be avoided, as these agents could potentiate a serotonin syndrome. The use of ketamine in the ED has been shown to be extremely effective for behavioral control, especially to facilitate appropriate medical screening and trauma evaluations in agitated patients.51

Hyperthermia in patients with agitated delirium from a hallucinogen or other xenobiotic is an ominous and life-threatening emergency and should be managed aggressively. Phencyclidine, dextromethorphan, and the novel hallucinogenic agents have various degrees of amphetamine-like qualities, which may produce marked hyperthermia due to temperature dysregulation.
and diffuse muscle fasciculation. Rapid initiation of cooling measures is mandatory and may require complete paralysis. Patients with extreme agitation should be given adequate hydration and watched closely for the development of rhabdomyolysis. This approach may be applied to any type of excited delirium and is not exclusive to hallucinogen-induced behavioral changes.

Management of simple hallucinogen intoxication that resolves without intervention does not require specialty consultation. Patients may benefit from education information regarding drug addiction and local support groups at the time of discharge.

Patients that present with marked agitation, vital sign abnormalities or instability should be managed through a multi-disciplinary approach between critical care specialists, medical toxicologists, and the regional poison control center (1-800-222-1222). While the exact agent causing the symptoms may not be known, clinical features and identification of specific toxidromes may help guide specific management.

**Goals Of Pharmacotherapy**

The goals of pharmacotherapy are to reduce morbidity and to prevent complications. Agents that may prove helpful include benzodiazepines and traditional antipsychotics. The goal of sedation is to decrease agitation or combative behavior when patients are at risk of harming themselves or others.
**Lorazepam**

Lorazepam is a benzodiazepine sedative-hypnotic with short onset of effects and relatively long half-life. Increasing the action of gamma-aminobutyric acid (GABA), which is a major inhibitory neurotransmitter in the brain, may depress all levels of the central nervous system (CNS), including limbic and reticular formation.

**Diazepam**

Diazepam is a benzodiazepine which depresses all levels of the CNS, possibly by increasing activity of gamma-aminobutyric acid (GABA). Individualized dosage and increasing this drug cautiously helps to avoid adverse effects.

**Midazolam**

Midazolam is a benzodiazepine sedative-hypnotic with short onset of action and a relatively long half-life. Increasing the action of GABA, which is a major inhibitory neurotransmitter in the brain, may depress all levels of CNS, including limbic and reticular formation. Because it is water soluble, it takes approximately 3 times longer than diazepam to peak electroencephalogram (EEG) effects. Thus, the clinician must wait 2-3 minutes to fully evaluate sedative effects before initiating the procedure or repeating a dose. Midazolam has twice the affinity for benzodiazepine receptors than diazepam. It may be administered intramuscularly if unable to obtain vascular access.
**Haloperidol**

Haloperidol is an antipsychotic drug that blocks postsynaptic dopamine receptors. Haloperidol is the drug of choice for patients with acute psychosis so long as there are no contraindications such as a very rapid heartbeat or Torsades de Pointes. Haloperidol is highly potent but it does not usually cause orthostatic hypotension (low blood pressure that happens when a person stands up from sitting or lying down). A downside of haloperidol is the high potential for extrapyramidal symptoms (EPS), which are drug-induced movements. Parenteral dosage form may be admixed in syringe with 2-mg lorazepam for better anxiolytic effects.

**Inpatient And Outpatient Care**

Patients with only minor agitation and adverse sympathomimetic effects can be treated and observed in an emergency department until symptoms have resolved. Patients with hyperthermia, uncontrolled hypertension, seizures, or any evidence of cardiovascular instability should be admitted to a monitored patient care area. Consultation with a toxicologist or regional poison control center should be considered.

A psychiatric evaluation should be obtained for patients with signs of persistent or severe psychotic behavior. Patients should be completely detoxified. Patients should be transferred for inpatient psychiatric care if psychiatric symptoms persist. Titration of benzodiazepines may be indicated to control agitation; phenothiazines should only be administered when indicated by severe psychotic reaction. Phenothiazines should not be administered to patients with signs of sympathomimetic overstimulation.
Patients may be discharged from a hospital safely with minimal or resolving symptoms. No outpatient medications should be required. These patients should be advised to avoid similar exposures and they should be referred to a behavioral health specialist for substance use evaluation.

**Transfer of Patients**

Patients with significant psychotic manifestations that are unresponsive to therapy should be transferred to an inpatient setting if appropriate behavioral health specialists are not available for evaluation. Caution should be exercised when transferring patients who demonstrate signs of continued intoxication.

**Psychedelic Medication and Illness**

In clinical research settings everywhere, there is renewed interest in using psychedelic drugs (hereafter referred to as psychedelics) for treating illnesses such as depression, anxiety, and posttraumatic stress disorder (PTSD). Investigations are in progress on their use. There was a period of vigorous research from the 1950s to the early 1970s, but no medical value could be established, therefore research was terminated. Since that time, psychedelic substances have been classified as "drugs of abuse". Recently, controlled clinical studies have been conducted to assess the basic psychopharmacological properties and therapeutic efficacy of these drugs as additions to existing psychotherapeutic methodologies. This revival acknowledges the importance of expectations, the physical environment, and
the clinician–patient relationship as critical elements for healing experiences with positive outcomes.\textsuperscript{52,53}

The public often knows the potential harms of psychedelic drugs, but much of this knowledge is from cases involving patients who used illicit substances in unsupervised, nonmedical contexts. The emerging research for therapeutic purposes considers both the possible benefits and the potential harms of using psychedelic agents.

**Types of Psychedelic Drugs**

Psychedelic drugs include a diverse group of substances with varying pharmacological properties that have significant effects on conscious experiences. Psychedelics may be divided into two classes: classic psychedelics and “entactogens”.\textsuperscript{54-69}

The classic psychedelics are agonists which work on serotonin receptors (\textit{i.e.}, lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT) and mescaline).\textsuperscript{70} Many of these substances, or close analogues, are found in plants or fungi used for millennia in spiritual or folk healing rituals, such as the ergot fungus (\textit{Claviceps purpurea}) from Eurasia, morning glory (\textit{Turbina corymbosa}) and peyote cactus (\textit{Lophophora williamsii}) from Central and North America, and the ayahuasca brew (\textit{Banisteriopsis caapi} and \textit{Psychotria viridis}) from the Amazon.\textsuperscript{71}

The second class of psychedelic substances, which are called the
entactogens, includes methylenedioxymethamphetamine (MDMA, ecstasy), which is a serotonin-releasing agent and has effects that overlap with classic psychedelics; however, some of the effects of entactogens are also substantially distinct from classic psychedelics. Other drugs that are sometimes classified as psychedelic may include ketamine (a dissociative anesthetic), scopolamine (an anticholinergic) or ibogaine (a substance with complex neuropharmacology).

Some of the mental disorders for which psychedelic-assisted treatments are currently being researched include anxiety, addiction and PTSD. The findings are preliminary; most are results from pilot studies with few participants. Further study is warranted before any declarative statement about clinical utility may be confirmed. Current investigations are attempting to overcome the methodological weaknesses of earlier research.

**Anxiety**

In 2014, a randomized, controlled trial of 12 participants with life-threatening illnesses was conducted in Switzerland. It was suggested that LSD-assisted psychotherapy had the potential to reduce the anxiety associated with terminal illnesses. The trial used the State-Trait Anxiety Inventory (STAI) to measure the level of trait and state anxiety. The State-Trait Anxiety Inventory is a self-reporting evaluation that is used in clinical settings to diagnose anxiety and to distinguish it from depressive disorders. In a series of psychotherapy treatments, drug-free and LSD-supplemented sessions alternated, two to three weeks apart. At two months’ follow-up, the STAI showed insignificant reductions in trait anxiety but significant reductions in state anxiety. Follow-up, one year after treatment,
with nine participants, showed a sustained therapeutic benefit with no acute or chronic drug-related severe adverse events. There were no adverse effects lasting more than one day after an LSD-assisted session.\textsuperscript{55}

Psilocybin is also showing promise as a treatment for anxiety in patients with terminal illness.\textsuperscript{59} A study on relieving end-of-life anxiety focused on 12 participants with end-stage carcinomas.\textsuperscript{59} After several non-drug-assisted therapy sessions, participants underwent a within-subject crossover study in which they received the experimental medication (0.2 mg/kg psilocybin) and the active placebo (250 mg of niacin) across two sessions a few weeks apart. Findings showed that psilocybin-assisted psychotherapy lowered anxiety and improved mood, without clinically significant adverse effects.\textsuperscript{59} MDMA-assisted therapy is also being studied as a treatment for social anxiety in adults with autism, although findings have yet to be published.\textsuperscript{73}

**Addiction**

Researchers in the 1950s and 1960s studied the use of psychedelic-assisted therapy for the treatment of addictions such as with alcohol use;\textsuperscript{74} some key findings of which were recently reviewed in a meta-analysis that suggested a significant beneficial effect.\textsuperscript{54} In renewed clinical research on treating alcohol use with psilocybin-assisted therapy, a New Mexico team recruited 10 participants with a diagnosis of active alcohol use (and no concurrent mental illness or other substance use disorder).\textsuperscript{57} Participants received pre- and post-psychosocial support (motivational enhancement therapy) over 12 weeks, with one or two intervening open-label sessions at weeks four (0.3 mg/kg psilocybin) and eight (0.4 mg/kg psilocybin or 0.3 mg/kg psilocybin).
Among the participants who completed the study, the self-reported mean percent drinking days and percent heavy drinking days were reduced by more than half of what had been reported at baseline.\textsuperscript{57} Acute adverse effects such as nausea and mild headaches were reported by some participants, but no clinically significant or lasting harms resulted from the administration of psilocybin.

Other recent research on psilocybin-assisted psychotherapy for addiction included a pilot study of the treatment for tobacco use. This investigation was an open-label design involving 15 participants who smoked at least 10 cigarettes per day and had multiple previous unsuccessful cessation attempts.\textsuperscript{58} Participants received cognitive behavioral therapy before and after treatment with psilocybin. Treatment included two or three psilocybin-assisted psychotherapy sessions (doses of either 20 mg/70 kg or 30 mg/70 kg); with the first session occurring on the target quit date. At six months’ follow-up, 12 of the 15 participants were abstinent (biologically verified by exhaled carbon monoxide and urinary cotinine levels).\textsuperscript{58}

Smoking cessation outcomes were significantly correlated with a measure of mystical experience on session days, as well as retrospective ratings of personal meaning and spiritual significance of psilocybin sessions.\textsuperscript{75} A follow-up randomized controlled study to compare a similar psilocybin intervention with nicotine-replacement therapy has been currently underway.

The Amazonian folk medicine ayahuasca is a plant-based preparation with the psychoactive constituents of Dimethyltryptamine (DMT), which is
chemically related to psilocybin, and harmala alkaloids, which are reversible monoamine oxidase inhibitors (MAOs). An observational study of an ayahuasca-assisted intervention in a Coast Salish First Nations community in British Columbia for people seeking treatment for addictions to substances such as alcohol and cocaine showed statistically significant improvements in measures of mental health and reductions in self-reported use of these substances after six months, with no lasting adverse physical or psychological effects.\textsuperscript{60}

Observational research involving members of Brazilian religious groups who regularly drink ayahuasca sacramentally has shown that, compared with a matched control group, long-term regular drinkers of ayahuasca tend to have a lower prevalence of substance use,\textsuperscript{61} structural brain changes that do not suggest evident pathology\textsuperscript{62} and better neuropsychological performance and psychosocial adaptation.\textsuperscript{63} Other studies involving similar populations of long-term drinkers of ayahuasca have shown lower rates of psychoactive substance use and psychopathology.\textsuperscript{64,65} Canadian researchers are currently coordinating an international research study to investigate ayahuasca’s potential as a treatment for addiction, with clinical sites in Brazil, Peru and Mexico.\textsuperscript{76}

Ayahuasca differs from the other substances covered in this review, inasmuch as it is a plant-based preparation of variable composition and strength, and typically used in ceremonial contexts, which makes it more difficult for researchers to isolate the factors that may contribute to therapeutic efficacy.\textsuperscript{76,77}
Posttraumatic Stress Disorder

In a pilot randomized controlled trial investigating MDMA-assisted psychotherapy to treat chronic treatment-resistant PTSD in the U.S., outcomes from 20 participants with a mean illness duration of 19 years showed that the experimental treatment may improve upon the best currently available pharmacotherapies and psychotherapies. The clinical protocol involved several weeks of preparatory and follow-up non-drug-assisted psychotherapy, during which the members of the experimental group received two MDMA-assisted sessions. No serious adverse effects were reported. Outcomes included a significant and sustained reduction in PTSD symptoms as measured by the Clinician-Administered PTSD Scale (CAPS), with 83% of participants in the experimental group (versus 25% in the placebo group) showing a reduction in symptom severity of more than 30%. Furthermore, some members of the experimental group no longer met criteria for PTSD as stated in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV). A long-term follow-up study involving the same participants showed that, although two patients relapsed, 74% (14/19) of patients still showed meaningful, sustained reductions in their CAPS scores three and a half years later.

An additional small randomized controlled trial investigating MDMA-assisted psychotherapy for PTSD was recently completed in Switzerland. This study compared three full-dose MDMA-assisted sessions per patient (with non-drug-assisted therapy before and after) with low-dose active placebo in a crossover design. Participants had no serious drug-related adverse events, and although reductions in CAPS scores were not statistically significant,
self-assessment of PTSD symptoms as measured by the Posttraumatic Diagnostic Scale questionnaire was significantly reduced.

In 2015, researchers in Vancouver began a similar pilot study of MDMA-assisted psychotherapy for patients with PTSD, the first clinical study involving psychedelic drugs in Canada in more than 40 years.

**Previous Research**

Experience from previous research — both positive and negative — has provided important lessons for current methodological designs, ethical strictures and clinical protocols and for renewed research on psychedelics involving human participants. In the 1950s and 1960s, methodological challenges confounded the advancement of psychedelic medicine, with researchers disagreeing about the suitability of randomized controlled trials and the possibility of double-blinding.28

More infamously, egregious violations of ethical protocols, such as lack of informed consent (in some cases through military or intelligence agency-supported research) resulted in substantial and long-lasting harms to some patients.74 Furthermore, unsupported claims about purported benefits of psychedelics, and sometimes explicit encouragement for non-clinical use, by some members of the research community, may have contributed to unsupervised and uncontrolled recreational use of psychedelic substances. Consequently, by the mid-1970s, clinical access to and professional interest in psychedelic drugs waned, leading to a quiescence in research for several decades.
Although methodological and political challenges remain to some degree, recent clinical studies have shown that studies on psychedelics as therapeutic agents can conform to the rigorous scientific, ethical and safety standards expected of contemporary medical research. For example, patients undergo careful screening, fully informed consent is obtained and protocols are approved by ethics review boards. In addition, contemporary investigators are mindful of the checkered history of psychedelic research, and are thus cautiously reserved in reporting their findings, doing so with appropriate caveats and limitations.

**Potential Risks and Benefits**

Most psychedelic drugs are classified and legally scheduled as having no or very limited medical purpose, a high potential for use and addiction, and a lack of accepted safety for use under medical supervision. Potential health risks of these substances include the precipitation of psychotic breaks in patients with psychotic disorders or a predisposition to these disorders. Thus, participation in contemporary psychedelic research typically excludes people with a personal or family history of psychosis or bipolar disorder.

A further risk associated with psychedelic drugs is Hallucinogen Persisting Perception Disorder (HPPD), sometimes known as “flashbacks,” although HPPD is more uncommon and more clinically severe than the flashbacks or visual distortions sometimes described in the days following illicit use of psychedelics. However, the incidence of adverse effects such as psychosis or HPPD in the general population is believed to be relatively low,
and these effects are generally associated with the use of illicitly procured psychedelic substances, which often involves multiple use of substances in uncontrolled settings without supervision. In light of these concerns, it is worth noting that lifetime use of classic psychedelics at the population level is associated with decreased psychological distress; thus, potential individual instances of harm may be overshadowed by instances in which people experience benefit or no harm.

The most common adverse effects from the administration of psychedelics under clinical supervision are limited to the time of drug action, such as acute increases in anxiety, fear, heart rate and blood pressure. Without careful supervision, fearful responses could lead to dangerous behavior (i.e., fleeing the study site). In addition, delayed-onset headache is sometimes caused by psilocybin use and possibly by other classic psychedelics. Although adverse effects of MDMA overlap somewhat with those of classic psychedelics, cardiovascular effects (i.e., tachycardia) are generally greater with MDMA, whereas adverse psychological reactions are more likely with classic psychedelics. It is important to note that acute adverse effects are readily managed, and that, as described previously, none of the new clinical research studies have reported long-term harms.

The clinical protocols for contemporary psychedelic studies draw on lessons learned from the earlier era of psychedelic research, and incorporate some common elements to minimize risks and maximize potential therapeutic benefit. After obtaining fully informed consent from the patient, clinical sessions take place in healthcare facilities, in quiet treatment rooms with pleasant and comfortable decor. Headphones deliver music, hospital and
laboratory equipment are minimal and discreetly placed, and a two-person therapy team is in attendance throughout the drug’s action. During a session, interaction between patient and therapists is kept to a minimum, with the patient encouraged to spend much of the time engaging in self-reflection while listening to carefully selected music.

Follow-up sessions that are non-drug assisted provide opportunities to integrate the insights gleaned from the experimental sessions. As research on psychedelic medicine advances, further refinements in screening, safety and therapeutic protocols will be possible.

**Future Research**

Numerous scientific and empirical questions remain in the field of psychedelic medicine. With respect to basic neuroscience research, progress in understanding the human brain and its functional relationship to mind and consciousness would be substantially advanced by further determining how psychedelic drugs work neuropharmacologically. This kind of knowledge would in turn be useful in applied fields such as psychology, psychiatry and addiction medicine, both to help explain mechanisms for the therapeutic results that renewed psychedelic studies are yielding and to advance understanding about optimal therapeutic protocols for these forms of treatment. With respect to clinical applications, different psychedelic medications may be indicated for different specific illnesses. Further research should elucidate not only respective efficacy, but also optimal pharmacotherapeutic and ancillary psychotherapeutic choices.
Beyond basic research on neuropharmacological mechanisms and clinical outcomes are potential economic arguments for psychedelic therapies. Substance use and mental disorders, such as depression and anxiety, are substantial and growing sources of illness and health system costs worldwide. Given these trends, investment of resources into researching novel treatments for mental and substance use disorders is warranted. Because preliminary evidence suggests psychedelic therapies require relatively time-limited interventions (i.e., they do not involve long-term ongoing courses of pharmacotherapeutic intervention), they may prove to be economically viable in comparison with currently available treatments.

**Designer Drugs**

Designer drugs are synthetic analogs of controlled substances, manufactured and distributed to circumvent drug laws and evade interdiction. These substances are also referred to as "legal highs." Designer drugs have psychotropic effects and are intended for recreation; they have no medical or therapeutic uses. They are continuously refined to avoid both legal regulation and detection on routine drug testing. Non-chemists can easily manufacture the drugs with readily available raw materials, or purchase the compounds already synthesized. The designer drug packaging often makes false claims about the content, which can vary widely in chemical composition and concentration. Often, the labels are printed with the phrase, “not for human consumption,” a ploy to avoid legal risk. Young adults are the most-frequent users of designer drugs, but the trend is shifting to other groups. One of the populations experiencing the most rapid growth in number of users is members of the military.
Acute toxicity is common. It often manifests as a mixture of psychiatric and medical effects, which may be severe, such as agitation, anxiety, tachycardia and psychosis. There have been deaths attributed to each of the designer drugs. Health professionals need to keep designer drugs in mind when they are evaluating substance abuse in young adults, or in anyone presenting with acute neuropsychiatric signs or symptoms. Management is complicated by a lack of information to guide treatment.

The incidence of designer drug use has been growing rapidly during the preceding decade, as indicated by an increasing number of calls to poison control centers.\textsuperscript{96} The incidence in emergency rooms, hospitals, and other medical centers is unknown. Most users of designer drugs will never interact with healthcare systems, even though the consequences can be severe and call for medical attention. Familiarity with designer drugs and their effects can help a clinician recognize reactions and consequences, and to treat accordingly.

**Epidemiology**

The prevalence of designer drug use is greatest among young adults, especially males in their twenties; the age range is teens to forty years. Users tend to have less education and income, and are usually single. The use of synthetic cathinone (SC) products may be higher in some subpopulations, such as regular cannabis users, and college students.\textsuperscript{97} The annual prevalence of SC consumption in high school seniors was 11 percent in 2011 and 2012; it dropped to 8 percent in 2013. It remains more prevalent, however, than any illicit drug except cannabis.\textsuperscript{98} Bath salts are used considerably less often than SC; just one percent among the same
sample. Use of synthetic hallucinogens is very low in the United States, making its epidemiology obscure.

Novelty, marketing, and availability influence the growth rate of designer drug use. The packaging is colorful and attractive, with catchy names for the products, attracting younger individuals. There is no age restriction on purchasing, which also makes them attractive to younger users. Buying via the Internet contributes to increasing use. Marketing designer drug products as “legal high” alternatives promotes greater consumption. It creates the perception of greater safety or purity, compared to traditional illicit drugs. Risk factors for adolescent designer-drug experimentation include:

- parents with substance use disorders (SUDs)
- poor family relationships
- poor discipline
- high family conflict
- involvement with foster care
- involvement in the criminal justice system.

A series of state and federal initiatives, in response to rising designer drug use, have been established during the past several years. They prohibit the manufacture, sale, and possession of many designer compounds. Designer drug use persists, however, despite attempts at regulation. There may be a national trend toward reduced consumption, although use appears to be growing in some subpopulations – including the U.S., military, possibly to evade detection by urine drug screening. Abuse of other substances, with designer drugs, is common.
Bath Salts

Designer stimulants are usually modifications of cathinone, the most active alkaloid in *Catha edulis*, a natural herbal stimulant. The three most common derivatives of cathinones, sold as bath salts, include: mephedrone, methylenedioxypyrovalerone (MDPV), and methylene. The designer modified cathinones are classified with a larger group of stimulants which includes amphetamine, methamphetamine, and methylenedioxymethamphetamine (MDMA, or “ecstasy”).

Derivatives of cathinones increase extracellular levels of several monoamine neurotransmitters: dopamine, norepinephrine, and serotonin. The neurochemical structures of the modified compounds are responsible for the sympathomimetic, subjective, and rewarding effects of the substituted cathinones. The pharmacologic properties and effects, such as tachycardia, enhanced alertness, and the potential for psychosis, are similar to other stimulants like amphetamines and cocaine.

**Acute Clinical Effects**

Most designer stimulants are administered intranasally, but can also be ingested orally, or by intravenous or intramuscular injection. They are not suitable for smoking. The user starts to experience the effects about 10-20 minutes after dosing, with peak effectiveness at 45-90 minutes after administration, and a duration of 2-3 hours. As with cocaine, amphetamine, and MDMA, users report:

- increased energy and alertness
• enhanced concentration
• sexual stimulation
• empathy
• talkativeness
• mood enhancement with euphoria
• decreased appetite

The effects subside over 6-12 hours, although some users prolong the psychotropic effects by repeating doses during an episode of drugging.

Adverse Psychiatric Effects

Most users report that adverse effects occur with some, but not all, episodes of drugging. Acute toxicity may be associated with drug binging and/or exposure to multiple substances. Toxicity should be suspected if the user experiences acute agitation. Patients often experience paranoia, visual hallucinations, delusions, and other signs and symptoms of psychosis. Such effects may be pronounced.

It is probable that recurrent episodes of dosing modified cathinones lead to tolerance, indicated indirectly by the association between frequency of use and greater amount consumed. Binges have been reported with significant successive dosing of mephedrone. Withdrawal effects reported among chronic users include:
• fatigue
• insomnia
• difficulty concentrating
• irritability
• depression
• nasal congestion

Some users experience a dependence syndrome, with cravings and compulsive use.\textsuperscript{106} The liability is great for development of a severe, diagnosable SUD from chronic use of modified cathinones.

\textit{Adverse Physiologic Effects}

Bath salts were primarily responsible for doubling the number of annual stimulant and sympathomimetic toxicology cases reported, from 6 percent in 2010 to 12 percent in 2011. Users commonly report diaphoresis, palpitations, muscle tension or spasms, and bruxism (jaw clenching). Autonomic hyperactivity with tachycardia and hypertension are common. Users who sniff or snort the drug nasally exclude epistaxis and irritation of the nasal patches, mouth, and throat.

Toxicity is indicated by both neurological and cardiovascular clinical features. Bath salts have been associated with cardiac arrhythmias and myocarditis. Hyponatremia has been reported with mephedrone use (similar to that seen with MDMA), probably due to a combination of sweating, electrolyte loss, and antidiuretic hormone secretion. Serious renal impairment with acidosis and acute renal failure may be associated with rhabdomyolysis.
The cathinone component of bath salts is responsible for the signs and symptoms of acute toxicity, but contaminants may also contribute to adverse effects. Product analysis has revealed adulteration with:

- benzocaine
- lidocaine
- procaine
- caffeine
- cocaine
- amphetamine
- ketamine
- piperazine compounds

Adulterants with stimulant properties could potentiate the effects of bath salts and increase the risk of toxicity by intensifying the sympathetic effects and lowering the threshold for cardiac arrhythmias.\(^\text{107}\)

Empirical and prospective data are limited regarding both acute and long-term adverse physiological effects of commercially synthesized cathinones. Neurotoxicity (i.e., monoamine depletion, neuronal degradation) develops, along with physiological dependence, among regular users. The dependence manifests as tolerance, with a withdrawal syndrome.

**Synthetic Cannabinoids**
The most active cannabinoid in cannabis is delta-9-tetrahydrocannabinol (THC), a partial agonist which is active at CB1 receptors located throughout the body, with the greatest concentration in the central nervous system. Synthetic cannabinoids (SCs) used recreationally may be full or partial CB1 receptor agonists that were originally synthesized for research purposes in different university laboratories. Frequently, the SC-containing products used recreationally include individual or mixtures of different SC compounds sprayed on inert pulverized plant matter of virtually unknown content, which resembles potpourri or incense.\textsuperscript{108}

The term \textit{spice} is now generally applied to all products containing SC, regardless of branding. Compared to THC, SCs have substantially greater variability in product composition and concentration, are often more potent CB1 agonists, which may have a longer half-life, and potentially greater cannabinomimetic toxicity.\textsuperscript{109}

\textit{Acute Clinical Effects}

Synthetic cannabinoids are primarily smoked, via a joint, bowl, or water pipe, although they can be consumed orally or intranasally.\textsuperscript{109} Acute effects are similar to those of cannabis, including alteration in mood, conjunctival injection, and tachycardia.\textsuperscript{110} Effects start within 10 minutes after inhalation, waning over 2-6 hours after use.\textsuperscript{111}

\textit{Adverse Psychiatric Effects}
Adverse psychological effects are common with the use of SC products and may include anxiety, confusion, agitation, paranoia, and delusions.\textsuperscript{112} There are reports of SC provoking acute psychosis, which appears more likely in users with underlying biologic vulnerability due to a family history of psychosis. It may worsen pre-existing chronic psychotic disorders. Psychotic symptoms have been reported to persist from 1 week to 5 months.\textsuperscript{113,114}

Some regular users of cannabis may use SC as a substitute to relieve cannabis withdrawal symptoms, probably an indication of cross-tolerance between SC and THC. Case reports have documented withdrawal symptoms after SC use, as well as a dependence syndrome, similar to those seen with cannabis.\textsuperscript{115}

\textit{Adverse Physiologic Effects}

Commonly reported side effects of SC use include dry mouth, lightheadedness, and headache.\textsuperscript{116} Other unwanted negative physiological effects include diaphoresis, tremors, dystonia, and dyspnea. Tachycardia is common with SC use (similar in cannabis users), and may be due to reduced peripheral vascular resistance, with an increased heart rate to maintain cardiac output, rather than due to a direct sympathetic effect. The tachycardia may be severe, and associated with hypertension and chest pain. One case report of significant bradycardia with chest pain has been reported.\textsuperscript{117}

Several SC compounds (specifically JWH-018, JWH-073, and AM-2201) have been implicated as a cause of cannabinoid hyperemesis syndrome, a chronic disorder characterized by cyclic episodes of vomiting and abdominal pain,
relieved by bathing or showering with hot water.\textsuperscript{118} Cannabis-related hyperemesis syndrome is quite rare.

Severe SC-related toxicity requiring emergency treatment has included seizures, acute renal failure, and myocardial infarction.\textsuperscript{121-124} Deaths have been reported with SC, due to a cardiac ischemic event, and extreme anxiety resulting in suicide.\textsuperscript{125}

The long-term effects of SC are unknown. Smoking SC products results in the inhalation of burned, unidentified plant material, which may have adverse effects on the pulmonary system. Some sources recommend vaporization, rather than smoking as a cannabinoid delivery method.\textsuperscript{126} Additionally, JWH-018 may be a carcinogen.\textsuperscript{127}

**Synthetic Hallucinogens**

Synthetic designer hallucinogens gained popularity after the 1991 publication of Alexander Shulgin’s book, *PIHKAL, A Chemical Love Story*. PIHKAL, an acronym for “Phenethylamines I Have Known and Loved,” details the synthesis of more than 200 psychotropic compounds.\textsuperscript{128} The “2C” series of hallucinogenic phenethylamines, first described by Shulgin, has a chemical structure like MDMA, and also produces serotonergically stimulated hallucinations.

*Acute Clinical Effects*
Liquid and powder forms of 25I-NBOMe have multiple potential routes of administration, including inhalation of vapor, nasal insufflation, oral ingestion, sublingual or buccal administration, and intravenous injection. With the oral/oral mucosal route, 25I-NBOMe is ingested as a pill or as a powder imbedded blotter paper. Use of the drug usually occurs as a single administration of about 0.1 gram. Clinical effects occur rapidly after nasal use, peaking in 20 minutes, and a highly variable duration-of-action. A range of 3-13 hours has been reported. In cases of clinical toxicity, agitation can persist for several days.

The effects of 25I-NBOMe are similar to the effects of lysergic acid diethylamide (LSD) and psilocybin – both of which are prototypical serotonergic hallucinogens. Users report variable degrees of stimulation and alertness. Depersonalization has been reported as well.

Adverse Psychiatric Effects

Many users experience disturbing psychiatric symptoms, in addition to the expected visual and auditory hallucinations. The psychiatric consequences can require emergency medical services. Some of these consequences include:

- delirium
- agitation
- aggression
- violence
- paranoia
- dysphoria
• severe confusion
• self-harm

A serotonergic or sympathetic toxidrome has been reported in some patients. It presents as an “excited delirium” with extreme agitation, aggression, and violence. There has been one case reported in which a 19-year-old man, a first-time user of 251-NBOMe, developed paranoia, bizarre behavior, and fell multiple stories to his death. Another case was reported in which a 21-year-old male driver who ingested 25I-NBOMe developed sudden rage, stopped his car, started destroying the inside of the vehicle, and suffered sudden death. The cause of death was not reported.\textsuperscript{137}

\textit{Adverse Physiologic Effects}

In the few clinical reports available about 251-NBOMe use, tachycardia, hypertension, and mydriasis are frequently described. Hyperreflexia and clonus have also been reported. Seizures that required medical attention occurred in many of the cases. Hyperthermia, pulmonary edema, and death from trauma have been described with severe toxicity. There is one report of a fatal exposure in a 15-year-old girl. She became unresponsive after ingesting 25I-NBOMe at a party; on arrival at a local hospital she was in asystole with a rectal temperature of 39.9°C. Long-term physiologic effects are not known.
**Drug Testing**

Urine or serum toxicology screens cannot detect all the designer drugs that have been synthesized, making diagnosis and monitoring challenge for clinicians. Although the number of available laboratories which test for designer drugs is growing, testing for the drugs is not yet available in most practice settings and laboratories. The analytical challenge is compounded by the similarities in reactions to designer drugs. The drug product contents, concentration, and chemical constituents, vary between and within products.

Illicit drug manufacturers have remarkable skills for altering the components of designer drugs, to evade regulation and detection. Drug designers modify functional groups, make substitutions, and alter moieties of substances to evade legal restriction. This practice also poses significant challenges for detection of compounds or metabolites through urine drug screening.

The lack of detection on standard urine drug screening tests is a reason given by many users for designer drug use. Populations under criminal justice supervision use designer drugs to evade detection by probation officers. Most of the U.S., soldiers referred for addiction treatment are identified by urine drug screening. Synthetics are consumed by people seeking cannabis-like mood-altering effects, but with less risk of detection.

Even though most emerging designer drugs cannot be detected in a healthcare setting, collection of urine is still valuable clinically, to check for
unreported, co-occurring substance use. A general laboratory screening battery of urine or serum should be tested for common drugs of abuse. The clinician needs to be aware of potential toxicity due to drug interactions, or to the need for closer or prolonged monitoring due to the presence of other, non-designer substances. When comprehensive designer drug testing is unavailable or pending, familiarity with the most common designer drugs allows for recognition of intoxication and prompt management of serious complications.

**Screening and Assessment**

Young adults are the most common seekers of emergency medical services related to designer drug use. Clinicians should directly inquire about designer drug use, particularly among young adults presenting for acute medical care with signs or symptoms that could indicate substance-related toxicity. Since designer drugs are not detected by routine drug screens, health-care providers relying solely on laboratory testing may be misled to believe that illicit drugs have not been used.

The presence of routinely detectable illicit substances does not rule out the presence of designer drugs, since polysubstance use is typical in the population using designer drugs. Clinicians should note inconsistencies between an observed and an expected type of intoxication syndrome from self-reported or detected class of drugs. Such discrepancies could indicate recent designer drug use.
Clinical clues based on patient presentation can help identify designer drug use. Conjunctival injection is an indicator of SC intoxication, as well as other cannabis products. Some patients presenting for emergency treatment may still have the package that contained the designer drug. This can be examined for possible identification of common brand names for a specific class of designer drug and, potentially, any remaining content can be sent to a laboratory for analysis. Internet sites may help identification of specific substances ingested due to their rapidly changing appearance. However, the lack of research-based information on the adverse effects of designer drugs has led to the emergence of a range of websites that may or may not provide accurate information.

Paraphernalia such as a pipe for smoking could indicate designer or other drugs which can be smoked. A strong smell of perfume or cologne may be an attempt to mask the smell of smoking.

Indicators of designer drug use are outlined below according to body system symptoms.

**General**
- hyperthermia may occur with acute intoxication, especially with synthetic hallucinogens and bath salts

**Head and Neck**
- conjunctival injection may indicate recent use of synthetic cannabinoids
- smoky, chemical smell on breath indicates any designer drug which can be smoked
- epistaxis is associated with bath salts and hallucinogens
• nasal septum perforation may be caused by bath salts
• poor dentition, jaw clenching, teeth grinding (bruxism) are associated with bath salts

Cardiac
• tachycardia may occur with recent use of any designer drug
• hypertension may occur with recent use of any designer drug
• chest pain may occur with cardiac ischemia or myocarditis, with bath salts or synthetic cannabinoids

Renal
• may indicate acute kidney injury associated with recent use of synthetic cannabinoids

Gastrointestinal
• nausea, vomiting may be associated with recent use or withdrawal syndrome with synthetic cannabinoids
• enlarged and/or tender liver may indicate acute hepatitis associated with injection of any designer drug

Musculoskeletal
• muscle spasms may indicate intoxication with bath salts
• limb swelling and pain may indicate rhabdomyolysis with bath salts or synthetic hallucinogens

Skin
• diaphoresis may indicate recent use of bath salts
• ecchymosis may indicate recent use or intoxication with synthetic hallucinogens
• fresh needle marks or track marks are associated with drug injections

**Neurologic**
• clonus may indicate recent use of synthetic hallucinogens
• seizures may be associated with intoxication with bath salts, synthetic hallucinogens, or synthetic cannabinoids

**Psychiatric**
• agitation may occur with recent use of any designer drug
• hallucinations may indicate recent use of any designer drug
• psychosis may indicate intoxication with any designer drug

Inquiry about designer drug use should be routine, particularly among patients with a prior substance use disorder, users subject to mandatory urine testing (i.e., law enforcement), and among those who have a history of designer drug use of a different chemical class. Different classes of designer drugs may be used simultaneously, increasing the risk of adverse effects and toxicity. Clinicians should ask about specific products by name, or about “synthetics” in general, to obtain more, and more accurate, information.

Patients may not be aware of names by classes used by medical personnel. Different street names for similar products add confusion. For each drug which the patient admits to using, questions should be asked about frequency and patterns of use, as well as subjective effects. Reported subjective effects may provide insight into the designer drug class used. The inquiry should also include specific questions about factors associated with select designer drugs and their potential consequences.
Medical, interpersonal, financial, and legal difficulties should be identified. Chronic designer drug use often leads to physiologic dependence, with the patient needing more of the drug to reach the intensity of the effects experienced with earlier uses. Abstinence-related withdrawal also indicates physiologic dependence. Thorough questioning regarding the patient’s designer drug use can yield an initial determination of the class of drug used. The clinician can then prepare for the potential severity of effects, and determine early treatment needs.

The assessment of acute medical complications of designer drug use, routine laboratory testing should include a complete blood count and metabolic panel, in addition to standardized urine and serum drug testing. Cardiac enzymes should be done if a cardiac origin of distress is suspected. Creatinine phosphokinase is helpful if rhabdomyolysis is suspected, based on severe muscle spasms, swelling or pain in the extremities, or seizures. Additional diagnostic studies may be necessary, as indicate by the clinical presentation.

**Management of Acute Intoxication**

No specific antidotes are available for designer drug toxicity. Activated charcoal is useless, unless there has been significant oral ingestion. Most nonpsychiatric symptoms are usually self-limited, and resolve within one to several days. Psychological effects of acute intoxication, such as anxiety, agitation, or paranoia are managed with supportive treatment. Placing the distraught user in a quiet environment and maintaining subdued contact are useful, and is often sufficient until acute effects subside.\(^{145}\)
Psychoses due to synthetic cannabinoids (SC) and 25I-NBOMe intoxication are managed with monitored observation. Benzodiazepines have been used to treat anxiety, agitation, and seizures. Antipsychotics are second-line agents for agitation, due to the lowered seizure threshold with use of cathinone and phenethylamine designer drugs. If the patient is markedly agitated and at risk for harm to self or health-care staff, sedation may be required. Psychiatric consultation is indicated in cases of persistent designer-drug associated psychosis. It can require long-term in-patient hospitalization.

Discontinuation of stimulants or hallucinogens is abrupt; it has no dangerous physiologic sequelae, so they are not tapered off or There is no need for replacement with a cross-tolerant drug during medically supervised withdrawal. Discontinuation of SC can result in withdrawal symptoms similar to those with cannabis cessation, such as nausea and irritability. There is no However, there is no indication for pharmacologic replacement (i.e., dronabinol), since SC withdrawal is not life-threatening. Patients can be treated with supportive care by intravenous fluids and antiemetics if necessary. If psychiatric symptoms persist longer than one week after discontinuation, the patient should be evaluated for a co-occurring primary psychiatric disorder. Treatment of prolonged anxiety, depression, or psychosis is the same as when these conditions are not associated with recent designer drug use.

For a significant number of patients, admission to critical care is required. Intoxicated patients should be placed initially on continuous cardiac monitoring with pulse oximetry and frequent neurological assessments.
Intravenous fluids are encouraged to assure good urine output, as these patients often are dehydrated. In the presence of rhabdomyolysis, fluids administration can help prevent acute renal failure. Intensive monitoring allows for early detection and intervention for serious consequences, such as myocardial infarction.\textsuperscript{146}

Patients often present with concurrent ingestion of drugs with opposing pharmacological profiles, including both stimulant and depressant drugs. An unexpected response to a therapeutic intervention or to a change in the clinical presentation as one type of designer drug wears off and ongoing intoxication with another class of designer drug is revealed. Adjustments in treatment may be required. This may require some flexibility in treatment due to changes in mental or cardiovascular status.

**Treatment**

Hospitalization is an excellent opportunity (teachable moment) for counseling patients about substance use and to engage them in treatment. Health-care provider awareness and patient education are cornerstones of public health initiatives to confront challenges presented by designer drugs. Simple admonitions to stop in most cases are insufficient. Many patients who use designer drugs may reject changing behavior. Empathy without confrontation shows respect for the patient’s autonomy. Providing appropriate, accurate information can help patients make the best informed decision about changing behavior. Accurate information about the relative risks and unknown harms of these products helps a patient make an informed choice about continuing to use particular products, to make a quit attempt, or to seek more specific addiction treatment.\textsuperscript{146}
Although prospective treatment data are limited, once a designer drug use disorder diagnosis is made, acute and long-term treatment is likely necessary. Recovery from a substance use disorder in general is possible, and those who are treated have less disability than those who remain untreated. Long-term treatment of designer drug use disorders likely involves similar components to that of other types of addiction treatment, including behavioral components, such as individual and group counseling with cognitive-behavioral therapy, motivational enhancement therapy, and 12-Step self-help group facilitation. Family members should be considered as part of the treatment program, in particular when treating adolescents or young adults. Unfortunately, pharmacologic treatment data to guide management of those with designer drug use disorders are unavailable.

Patients identified with a substance use disorder should be provided with information for local community addiction treatment resources. In the United States, physicians certified in the treatment of addictive disorders can be found through the American Society of Addiction Medicine (www.asam.org) or the American Academy of Addiction Psychiatry (www(aaap.org).

A non-physician counselor can be found through the National Association for Alcohol and Drug Abuse Counselors’ website (www.naadac.org). Substance use treatment services in the United States can be located via the Substance Abuse and Mental Health Services Administration Behavioral Health Services Treatment Locator (http://findtreatment.samhsa.gov).

Treatment of designer drug substance use disorder is challenging for several reasons. There are several different classes of substances, which vary in
their psychological and physiological effects, and the possibility of polysubstance abuse can complicate management. Treatment is often difficult due to the young age of most users. The pattern of use is usually intermittent in social settings, so it may be perceived as less of a problem. Clinicians should be knowledgeable of and prepared to provide treatment for very different combinations, such as what occurs with club drug use. A treatment environment with a supportive structure can be helpful. Addiction treatment is cost-effective, and even multiple episodes of treatment are worthwhile. It can be very rewarding for a health clinician to assist a patient who was impaired by addiction return to normal function. in society.

Bath salts, SC, and 25I-NBOMe, are designer drugs which are popular, especially among young adults. Though chemically different, they are similar in that adverse reactions are common, especially clinically significant psychotic reactions. Detection of these drugs with urine tests is variable, so clinicians should consider designer drug use in young adults with agitation and psychosis, in the presence of a negative urine drug screen. Treatment is primarily supportive. Benzodiazepines may be beneficial. When those who use designer drugs come into contact with the health-care system, it is important for clinicians to facilitate connection to additional, specific treatment for the substance use disorder.146

**Summary part 2**

Patients under the influence of a hallucinogenic agent may present with altered sensorium and wide range of physical findings, depending on the agent. During physical examination of a patient suspected to have ingested a hallucinogen the evaluation findings may be consistent with hallucinogen
use, or inconsistent which should prompt an appropriate general medical evaluation.

The goals of prompt testing and treatment, including pharmacotherapy, are to reduce morbidity and to prevent complications. Agents that may prove helpful include benzodiazepines and traditional antipsychotics. The goal of sedation is to decrease agitation or combative behavior when patients are at risk of harming themselves or others.

Specifically, there is a renewed scientific interest in psychedelic medication, which is generating new knowledge about a class of pharmacologic substances that humans have long used for ceremonial, therapeutic and cultural purposes. As this field of research evolves, healthcare education may need to be updated to include the latest knowledge about psychedelic drugs. This would encompass scientific evidence about relative risks and harmful outcomes of hallucinogenic and psychedelic drug use. Knowledge about the potential therapeutic uses of these agents is needed because patients may ask their medical clinicians about new research findings. If further scientific evidence accumulates on the therapeutic value of psychedelic medication, specialized clinical training for physicians, nurses, psychologists, social workers and other health professionals will be required to meet an increased demand for such treatments.

Policy-makers and health clinicians need to be aware of and open to new approaches to hallucinogenic drug use. This is particularly important for those health professionals concerned about the growing prevalence of
mental illness and drug use and addiction, as well as its associated human, social and economic costs. Advances and innovations translated from clinical research into options for healthcare improvement have been generally raised here, however more research and clinical observations are needed to ensure improved evidence-based options for treating clinicians and patients.
Reference Section

The reference section of in-text citations includes published works intended as helpful material for further reading. [References are for a multi-part series on hallucinogenic drugs].


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