Hallucinogens

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- Complete the questions at the end of the course.
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Faculty
Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure
Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Audience
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Course Objective
This course is designed for health and mental health professionals who are involved in the evaluation or treatment of persons who use hallucinogens.

Learning Objectives
Upon completion of this course, you should be able to:

1. Outline the history of hallucinogen use, including research regarding the role of these compounds in clinical treatment.
2. Discuss the epidemiology of hallucinogen use in the United States.
3. Describe the classification of various types of hallucinogens available today.
4. Compare and contrast the pharmacology and clinical effects of hallucinogens and their impact on healthcare utilization.
5. Identify both the short-term and the long-term psychologic effects of hallucinogen use.
6. Outline the effective treatment of hallucinogen toxicity.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

While hallucinogenic compounds have been used for thousands of years in cultures throughout the world, interest in their use in medical as well as social contexts in the United States peaked in the 1950s and 1960s. Though use of these classical hallucinogens has decreased, new compounds (sometimes referred to as "designer drugs") have emerged.

The consumption of hallucinogenic drugs has the potential to result in short-term and long-term negative outcomes, though the effects vary greatly among the available compounds. A negative reaction to hallucinations upon ingestion of these drugs (a "bad trip") can present with similar signs and symptoms of mental illness, particularly psychosis and schizophrenia. Therefore, careful patient history and knowledge of the signs of hallucinogen intoxication can facilitate appropriate diagnosis and treatment.

BACKGROUND

The term "hallucinogen" is derived from the Latin *alucinari*, meaning to wander in mind or talk idly [1]. Hallucinogens are agents that alter perceptions without major autonomic or metabolic changes or agents that cause alterations in perception, cognition, and mood as their primary psychobiologic action in the presence of an otherwise clear sensorium [2]. A typical hallucination induced by a classical hallucinogen (i.e., mescaline, peyote) is more accurately described as a modification of regular perception, with the user usually aware of the illusory and personal nature of their perceptions [1]. In 1956, the psychiatrist Humphrey Osmond coined the term "psychedelic," meaning "mind-manifesting," to describe drugs such as lysergic acid diethylamide (LSD) and mescaline. The term is a reference to the drugs' ability to illuminate normally hidden aspects of the mind or psyche [3]. This term became popularized in the 1960s and is often used interchangeably with the term hallucinogen to describe both the classical hallucinogens and their effects.

Hallucinogenic drugs have been used for thousands of years. The oldest hallucinogen is thought to be the fly agaric mushroom, *Amanita muscaria*, the action of which was discovered in Siberia by observing the behavior of intoxicated reindeer. In many prehistoric and ancient cultures, the use of plant materials discovered to have hallucinogenic properties became incorporated into religious beliefs and practices, with the plants becoming sacraments used ceremonially and medicinally. In this context, they are often referred to as entheogens, used to facilitate healing, divination, communication with spirits, and coming-of-age ceremonies [1; 52]. Some of these sacramental practices continue today and are legally sanctioned.

Historically, the most widely documented hallucinogens have been psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine), N,N-dimethyltryptamine (DMT), and mescaline (3,4,5-trimethoxyphenethylamine) [4]. In the last 75 years, these naturally occurring hallucinogens have been supplemented by a wide range of synthetic compounds, beginning with the discovery of LSD in 1943, followed by N,N-dipropyltryptamine (DPT), 2,4-dimethoxy-4-methylamphetamine (DOM), 3,4-methylenedioxy-N-ethylamphetamine (MDE), 3,4-methylenedioxymethamphetamine (MDMA), and countless other structural analogs [4; 5].

Intense interest in hallucinogens in Western society began with the discovery of LSD. In 1938, in search of a new migraine medicine, Swiss biochemist Albert Hofmann synthesized LSD at the Sandoz Pharmaceutical laboratories. It was not until 1943, when some of the liquid chemical substance spilled onto his hand, that Hofmann experienced the first recorded LSD "trip." He recounted that 45 minutes after absorbing some of the chemical into his skin, he became increasingly dizzy, developed visual disturbances, and had a marked desire to laugh. An hour into the experience, he asked his assistant to call a doctor and accompany him home. In Hofmann's mind, he was not on the familiar street that led him home but instead on a street painted by Salvador Dali, a funhouse roller coaster where the buildings yawned and rippled [3].

The introduction of LSD to Europe and the United States in 1949 ushered in an era in which millions of people had access to these extremely potent drugs for religious or recreational use. The personal use of hallucinogenic drugs markedly differed from their historical use under shamanic guidance, in that processing and integrating the experience was left to the individual user. LSD was regarded as a drug with enormous scientific and therapeutic potential and was used to develop new insights into the mechanisms of nerve cell transmission, visual hallucinations, and the phenomenology of schizophrenia. During the 1950s, more than 500 papers on LSD were published in scientific journals, none of which described the drug in terms of addiction or abuse [3]. Early military research focusing on hallucinogens as incapacitating agents was also conducted during this period. Intelligence agencies tested these drugs, in some cases on unwitting subjects, hoping they would provide an effective means of interrogation and mind control, with little success [6].

In 1962, Harvard psychologist Timothy Leary was fired for his indiscriminate promotion of LSD. Although the story made the national news, the balance of articles on LSD remained positive. Around 1966, the tone of media coverage began to turn negative, with newspaper articles about LSD increasingly warning of the drug's danger. A moral panic over drug use began to unfold that same year, with LSD the focal point. The use of LSD was banned by the governments of the U.S., Canada, the Netherlands, France, and the United Kingdom, despite the insistence by some medical researchers that LSD had important therapeutic benefits [3].

The most widespread, and at the same time most stigmatized, use of psychedelics in the West has been in the search for direct religious experience, enhanced creativity, personal development, and "mind expansion." These drugs were a major element of the 1960s counterculture, where they became associated with various political movements, youthful rebellion, and cross-generational strife in general [7]. Hallucinogens continue to be used recreationally, although at rates below those seen in the 1960s and 1970s.

THERAPEUTIC USE OF HALLUCINOGENS

LSD

The introduction of LSD to medical and behavioral research in the late 1940s was considered timely. During the 1950s and 1960s, thousands of biochemical and behavioral studies were conducted with the intent of finding chemical substances that would facilitate a breakthrough in understanding and treating mental illness. Most of the antidepressants and antipsychotics in use today were developed from the psychopharmacologic research that took place in this period [3].

Research involving LSD was conducted across multiple paradigms. Psychoanalysts were interested in evaluating the drug's ability to release memories or reveal the subconscious. Psychotherapists evaluated the ability of the drug to bring patients to new levels of self-awareness, while psychopharmacologists assessed whether LSD reactions supported the assumption that mental disorders had chemical origins. During this era, medical research investigating LSD proceeded with heightened expectations and few interruptions. LSD appeared to produce a "model psychosis," providing a new method for studying symptoms of mental illness. Conversely, the drug also appeared to have inherent therapeutic qualities that were more difficult to explain, underscored by regular reports by volunteers and patients of new insights, personal enlightenment, or self-reflection that presented individuals with a kind of personal insight or clarity [3].

Perhaps one of the most promising areas of investigation involving LSD was in the treatment of alcoholism. The initial rationale for LSD use in this context was the perceived similarity between the LSD effect and the experience of delirium tremens (DT) as described by patients with alcohol use disorder. It was hypothesized that LSD could safely replicate the DT experience, inducing fear and possibly benefiting patients with alcohol use disorder. Researchers revised their theoretical basis for using LSD for patients with alcohol use disorder when they realized that LSD had the potential to cause a surge of previously repressed material [50].

Earlier results of the LSD trials with patients with alcohol use disorder suggested favorable rates of recovery. However, initial optimism gave way to skepticism, as the results were not obtained in trials that isolated the drug effect from what were viewed as confounding factors. Trials were implemented in which attempts were made to isolate the drug effect from other stimuli. Subjects were given the drug and subsequently blindfolded or restrained, and observers were instructed not to interact with the subjects. These trials found that subjects did show some improvements, but overall, the controlled trial environment demonstrated that LSD did not produce results analogous to those claimed by the previous studies. It was determined that the environment had a significant effect on study outcome [3].

The first controlled trial involving LSD and alcoholism was published in 1962 and compared subjects who received group therapy, individual therapy from a psychiatrist, or LSD at the end of a hospital stay. The two-year study followed patients for 6 to 18 months, and the author reported that 38 of the 58 patients treated with LSD remained abstinent during the follow-up period [3; 44].

During the same year, the first scientific paper warning the medical community of the dangers of LSD was published [45; 49]. Further evaluation of LSD's efficacy became moot by the mid-1960s, when popular news stories exposed unheard-of dangers caused by the drug. By this time, the growing popular association of radicalized youth and psychedelic drugs further reinforced LSD's image as a dangerous recreational drug not worthy of serious scientific investigation. Despite protests from certified psychiatrists, governments throughout the Western world criminalized the drug, profoundly altering the image of hallucinogens in popular and medical circles [3]. In the United States, criminalization occurred in October 1966.

By 1965, more than 2,000 papers had been published describing the positive results of thousands of patients who took hallucinogens, with few side effects and a high level of safety [3]. Despite the large number of studies and human subject participants, most of the research failed to utilize study designs incorporating subject randomization, placebo controls, blinded observations, standardized measurement of outcome, and other elements of contemporary research standards, putting into question any claims of efficacy. A 2012 meta-analysis of six randomized controlled trials (536 patients) published between 1966 and 1970 found that at short-term follow-up, a single dose of LSD had significant benefit; however, abstinence was not maintained at one-year follow-up [61]. In light of the consolidation of modern psychotherapy methods and the development of alternative hallucinogens, cautious re-examination of the therapeutic potential of hallucinogens may be in order [1].

MDMA

Research involving MDMA as a potential tool in psychotherapy began in the 1970s in California following renewed interest and improved synthesis by former Dow chemist Alexander Shulgin, who designed hundreds of psychedelic drugs [74]. MDMA differs from LSD and other classical hallucinogens in that it is classified as an "empathogen" rather than a true hallucinogen. MDMA appears to offer a similar therapeutic potential as LSD for lowering a patient's defenses and aiding the psychotherapeutic process, but without the perceptual changes, emotional unpredictability, and occasional adverse reactions associated with LSD [46; 57]. Friend of Shulgin and pioneering LSD psychotherapist Leo Zeff trained hundreds of therapists in MDMA-assisted psychotherapy before the drug was banned in 1985 [74]. It is estimated that 200,000 clients were treated using MDMA talk therapy in the late 1970s and early 1980s.

While MDMA has been advocated as a psychotherapy adjunct, relatively few studies or clinical trials have been completed. One open-label study of 29 subjects who received 75–350 mg of the drug reported positive changes in attitude and emotion, with 22 reporting enhanced psychotherapeutic insight and 21 patients in couples' treatment reporting increased closeness and communication with their partner [47; 48].

A 2011 randomized, controlled study of MDMA explored the safety and efficacy of the drug as a catalyst during psychotherapy for chronic, treatment-resistant post-traumatic stress disorder (PTSD) [53]. During each of two 8- to 10-hour psychotherapy sessions, participants in the study group were administered one dose of MDMA and alternated between relaxation exercises and active psychotherapy every hour thereafter. Two hours after administration of the first dose, a second half-dose was offered (and taken by more than half the participants in the study groups) to prolong the therapeutic window. The primary outcome measure was a 30% improvement from the baseline Clinician-Administered PTSD Scale score. Clinical response was achieved in 10 out of 12 participants in the MDMA group versus 2 out of 8 in the placebo group; in a crossover arm of the study, 6 participants who failed to improve with placebo achieved clinical response with MDMA. Additionally, all participants who responded to MDMA-assisted psychotherapy no longer met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for PTSD, compared with two from the placebo group. In addition, three participants from the MDMA group returned to work after having previously reported being unable to work due to PTSD symptoms. The authors noted that 15 of the 20 participants had failed to improve after previous medication trials (mean: 4.2 different psychotherapeutics). Furthermore, MDMA appeared to be safe, although participants were carefully prescreened; no medical interventions were required at any time during the study. Adverse effects were mostly mild, the most frequent being fatigue, headache, and insomnia, with rates similar to placebo groups [53].

Another randomized, controlled study of MDMA explored the topic of the safety and efficacy of MDMA-assisted psychotherapy for treatment-resistant PTSD [66]. A total of 12 patients were given weekly doses of either low-dose or regular-dose MDMA for three weeks, and were then assessed using the Clinician-Administered PTSD Scale (CAPS) and the Post-Traumatic Diagnostic Scale (PDS). Patients were assessed at baseline, end of treatment (three weeks), and at two-month and one-year follow-ups. No drug-related adverse events occurred, and treatment was considered safe when administered in a clinical setting. Of the 12 patients, no significant reductions in treatment-resistant PTSD were seen in CAPS scores, but clinically and statistically significant reductions were seen in the self-reported PDS scores [66].

A randomized, double-blind, dose-response phase 2 clinical trial published in 2018 was conducted among 26 veterans and first responders with chronic PTSD. Participants were given 30 mg, 75 mg, or 125 mg of MDMA in conjunction with psychotherapy. At the primary endpoint of the trial, participants receiving the 75-mg and 125-mg doses had significantly decreased CAPS scores, indicating treatment in the controlled setting was effective and well-tolerated in reducing PTSD symptoms in this group [67]. The results of a randomized, double-blind, placebo-controlled phase 3 study clinical trial with 81 participants with severe PTSD (42 in the MDMA group) were published in 2021. The trial, involving three 8-hour therapeutic sessions at four-week intervals, demonstrated significantly decreased CAPS scores in the MDMA group at the study endpoint. The researchers noted positive results even among participants with significant comorbidities (e.g., dissociation, depression, history of alcohol and substance use disorders, childhood trauma) [75].

Despite the small scale of these studies, the results illustrate MDMA's potential as a therapy adjunct for treatment-resistant PTSD. Several researchers are advocating clinical trials for MDMA as a rapid-onset treatment for unipolar depression [62].

KETAMINE

The emergence of ketamine as an anesthetic drug began with the drug phencyclidine (PCP), which was first synthesized in 1956. Phencyclidine was shown to produce safe and reliable anesthetic effects in humans; however, it also induced prolonged emergence delirium that ultimately made it an undesirable choice for human use [69]. To obtain the effectiveness of phencyclidine without the untoward effects, a shorter-acting analog, ketamine, was produced in 1962, with a potency of one-tenth of its parent drug. In 1964, the first human dose of ketamine was administered, and in 1966, the first clinical study of ketamine as an effective anesthetic was published. The study concluded that ketamine produced rapid anesthesia with a unique state of altered consciousness, a limited duration of effect, and minimal side effects and emergence delirium [69].

Although ketamine has successfully been used as an anesthetic in both human and veterinary practice for more than 50 years, studies have shown that it may have additional benefits in the treatment of refractory depression and PTSD [69; 70; 72; 73]. A double-blind, placebo-controlled, crossover study examined the effects of ketamine on 33 unmedicated patients with major depressive disorder and 26 healthy controls. Through review of functional magnetic resonance imaging and dot probe, researchers found that a single dose of ketamine produced opposite effects in those with major depressive disorder compared with the control group, but patterns of brain activity following the dose were similar in both groups. Although the mechanism of action is not well-understood, these findings suggest that ketamine may be useful as a rapid antidepressant by normalizing brain function during emotionally valenced attentional processing [72].

A review of literature of the role of ketamine in refractory depression showed similar results, with rapid antidepressant effects and significant clinical improvement in depressive symptoms and suicidal ideation within hours [73]. More research is needed to determine the long-term efficacy and safety of ketamine as a treatment for depression.

EPIDEMIOLOGY

In 2023, an estimated 1,510,000 Americans older than 12 years of age tried a hallucinogen for the first time [54]. An annual national survey of drug use among high school students in the United States found that 7.1% of 12th graders reported lifetime hallucinogen use in 2022 and 4.4% reported hallucinogen use in the past year [8]. When specifically asked about LSD use, 4.4% reported lifetime use and 2.5% reported use in the past year. The percentages among 12th graders represent decreases compared to a peak in the late 1990s/early 2000s.

Although lifetime use of LSD among individuals 26 years of age or older rose slightly between 2002 (10.5%) and 2023 (12.1%), its use has declined significantly among persons 18 to 25 years of age, from 15.9% in 2002 to 8.8% in 2023; however, rates that had been steadily declining since 2002 reached a low in 2012 (5.9%) and have been increasing each year since [54]. Lifetime MDMA use among individuals 26 years of age or older has slightly increased since 2012 (to 8.9%); however, lifetime MDMA use among persons 18 to 25 and 12 to 17 years of age dropped (to 6.3% and 0.5%, respectively), indicating an overall decrease in use among younger generations.

PCP use among high school seniors has also declined. Ever since the Monitoring the Future Study began tracking PCP use in 1979, lifetime prevalence among 12th graders has shown a more or less downward progression. With the exception of a moderate increase between 1992 and 1998, lifetime use has slowly declined from a high of 12.8% in 1979 to the lowest recorded use, 1.3%, in 2014 (the last year the question regarding lifetime use for PCP was asked in the study) [8]. In 2022, 1.2% of high school seniors reported annual use of PCP [8].

During 2023, approximately 3.1 million individuals 12 years of age or older used a hallucinogen on at least one occasion [54]. Among first-time hallucinogen users, an estimated 0.1% to 3% will become hallucinogen dependent [9; 54; 55]. In a study examining the characteristics of persons who become hallucinogen dependent, first use at an early age (10 to 11 years) was associated with increased risk, with the median elapsed time from onset of use to onset of dependence being 12 to 13 months [12]. These data validate previous reports of a very infrequent but tangible dependence syndrome developing soon after the onset of hallucinogen use [12]. The risk of hallucinogen dependence is also believed to be low if the hallucinogen was the first drug used. The risk of hallucinogen dependence is highest for recent-onset users of mescaline, MDMA, and PCP, and lower for psilocybin.

There has been no evidence of gender differences in the risk of development of hallucinogen dependence among recent-onset users; however, hallucinogen use is generally more prevalent among men [12; 54]. According to one study, Hispanic individuals were less likely to develop hallucinogen dependence than non-Hispanic whites [12]. This is not surprising considering lifetime use among whites is 20.8% and the rate among Hispanic or Latino individuals is 12.5% [54]. Mixed race individuals are most likely to have used hallucinogens in their lifetimes (26.9%), and American Indian/Alaska Natives also have high prevalences of lifetime use (22.9%).

CLASSIFICATION

Drugs with hallucinogenic effects can be placed into three categories: the classical hallucinogens, dissociative anesthetics, and deliriants. A fourth category, "designer drugs," refers to drugs with hallucinogenic properties that are slight modifications of a parent compound. Examples of designer drugs with hallucinogenic properties are amphetamine analogs, such as MDMA ("ecstasy"). These drugs have in common the catechol nucleus and are grouped with other

drugs with the same molecular core. Other designer drugs, such as the piperazine-derived hallucinogenic molecules, are structurally unrelated to the classical hallucinogens, dissociative drugs, and deliriants, and thus comprise the separate category.

The classical hallucinogens are divided into two main classes based on molecular structure: indole and catechol. The indole class, also referred to as the tryptamines, consists of alkaloids that act on serotonin. They are thus named because the basic structure of the neurotransmitter serotonin is referred to as an indole nucleus, which comprises the core structure of all of the drugs in this group. Indole hallucinogens include psilocybin, LSD, lysergic acid hydroxyethylamide (LSA), DMT, and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) [1; 5; 13; 58].

The catechol class, or the phenethylamines, constitutes the second group of classical hallucinogens. This group is made up of plant alkaloids, such as mescaline and nutmeg. The amphetamine analogs that are considered designer drugs, such as DOM, 3,4-methylenedioxyamphetamine (MDA), MDMA, 2,5-dimethoxy-4-ethylamphetamine (DOET), and 3,4,5-trimethoxyamphetamine (TMA), may also be categorized in this class. The amphetamine analogs are a large group of drugs, and due to substitution on the ring of the catechol nucleus, their effects more closely resemble mescaline than amphetamine. The catechol nucleus closely resembles the catecholamine neurotransmitters dopamine and norepinephrine, and catechol hallucinogens act on catecholamine neurotransmitter systems [5].

The more psychotomimetic class of hallucinogenic drugs, the N-methyl D-aspartate (NMDA) antagonists, comprises the dissociative anesthetics. Drugs in this group, exemplified by phencyclidine and ketamine, produce a different profile of effects, overlapping to only a limited degree with the effects of the classical hallucinogens. The third group of agents, termed deliriants, consists of drugs with anticholinergic properties that originate from plants in the Datura genus [14].

PHARMACOLOGY AND CLINICAL EFFECTS

CLASSICAL HALLUCINOGENS

Hallucinogenic drugs are pharmacologically heterogeneous and diverse, produce dissimilar effects, and likely work through distinct mechanisms. However, the classical hallucinogens all share a common mechanism: 5-HT2A receptor binding as partial agonists [2; 15; 60]. Of the hundreds of plants known to possess hallucinogenic properties, the active agents of these botanicals fall into surprisingly few chemical classes, with the indole nucleus of serotonin common to the majority of these compounds [1].

There is a direct association between the affinity of both indoleamine and phenethylamine hallucinogens for 5-HT2 receptors and their hallucinogenic potency. Actions at 5-HT2C receptors, associated with the anxiogenic effects of these drugs, could also contribute to the effects of hallucinogens [15]. Antipsychotic drugs are able to reverse the hallucinogen action in the locus coeruleus at doses correlating with their affinity for 5-HT2A receptors [15].

The effects of hallucinogens on complex processes such as cognition, perception, and mood suggest cerebral cortex involvement. In the cerebral cortex, enhancement of the prolonged, late, asynchronous component of glutamatergic transmission by hallucinogens may underlie some of the cognitive and perceptual distortions produced by these drugs [15]. Dopamine systems are unaffected by the classical hallucinogens, which explains why reality testing is generally unaffected by these drugs [16].

LSD

LSD is primarily a non-selective 5-HT agonist. It produces its hallucinogenic effects via 5-HT2A partial agonism and through mimicking 5-HT at 5-HT1A receptors to substantially slow the firing rate of serotonergic neurons. LSD is also a potent sympathetic pathway stimulator, which accounts for the initial excitatory response [11]. LSD readily passes through the blood-brain barrier and exerts its psychologic effects at a concentration of 0.5 ng/gm of brain tissue [17]. LSD has a plasma half-life of 2.5 to 4 hours, with psychophysiologic effects lasting 6 to 12 hours. Metabolites of LSD include N-desmethyl-LSD, hydroxy-LSD, 2-oxo-LSD, and 2-oxo-3-hydroxy-LSD, all of which are inactive [18].

As with most (but not all) hallucinogens, frequent and compulsive use of LSD is unusual. Tolerance to the behavioral effects will develop after three to four daily doses, but no withdrawal syndrome has been documented from cessation of regular use [16].

LSD is usually orally ingested and is often supplied absorbed on small squares of paper, termed "blotter acid" or "acid" (frequently printed with designs); in sugar cubes or aspirin tablets; or dissolved in water or alcohol [17]. Low doses (25–50 mcg) of LSD produce effects of relatively brief duration, affective lability, and visual illusions in the absence of hallucinations. Perception tends to be intensified rather than distorted. At this dose, meaning may be heightened, with the experience taking on a mystical, epiphanic quality and old memories being re-experienced with a photographic intensity [1].

At higher doses, the initial effect consists of sympathetic arousal 20 to 30 minutes following ingestion, manifested as dizziness, anxiety, increased pulse and blood pressure, dilated pupils, piloerection, hyperreflexia, and mild pyrexia. Following this, there is a period of increasingly intense perceptual distortion; hallucinations can occur in any sensory modality, the most common being visual and the least common auditory [17]. The perception of time passage is often distorted. Synesthesia, whereby two or more senses are blended, and delusions are unusual.

Mental functions are differentially affected by LSD. Memory is unaffected, although perception, orientation, concentration, and other measures of cognition may be impaired in a dose-dependent manner. Cross-tolerance has been demonstrated in humans between LSD, psilocybin, and mescaline but not between LSD and amphetamines or cannabis. There have been no documented toxic fatalities from LSD ingestion [1].

Affective changes can be profound and often take the form of an exaggeration of pre-existing mood. There is wide response variability to LSD between persons and in the same person at different times, influenced in part by the environment, the mindset, and the personality of the user [1].

The most common adverse effect of LSD is a "bad trip," which is essentially an extremely dysphoric or panic reaction to the drug experience. Users describe these bad trips as nightmarish in their intensity, and panic/dysphoric reactions can lead the user, often accompanied by friends, to present to the emergency department. The adverse psychologic effects of LSD are best managed by placing the user in a quiet room, offering reassurance, and administering benzodiazepines [17].

Lysergic Acid Hydroxyethylamide

Lysergamide is a class of hallucinogens that includes LSD and LSA. LSD is a manmade synthetic, but LSA, an analogue one-tenth the potency of LSD, exists in nature [14].

LSA is a tryptamine found in the seeds of *Ipomoea violacea* (morning glory) and Argyreia nervosa (Hawaiian baby woodrose). When ingested, the drug is psychoactive through 5-HT2A receptor agonism.

Morning glory seeds were used in Aztec rituals in ancient Mexico, and their popularity increased in the 1960s, when the seeds were used as a substitute for LSD. Morning glory seeds are consumed orally, either pulverized or as an extract of the psychoactive alkaloids. Threshold effects are noted with the ingestion of 3–6 g, with dosages of 200 to 500 seeds producing intense hallucinations as well as intense nausea, vomiting, and abdominal pain. Morning glory seeds and plants are sold in most nurseries and botanic supply stores. However, commercial morning glory seed producers coat the seeds with emetic agents in an attempt to discourage recreational ingestion [14; 19].

Hawaiian baby woodrose is a perennial vine native to India. Its name stems from its prolific growth in Hawaii, where it has traditionally been used as a hallucinogen. Recreational use in the West began around 1965, when the seeds became available for purchase in specialty shops. LSA is present in the large seeds, which are surrounded by pods. For ingestion, the seeds are crushed, eaten whole, germinated then consumed, or consumed as an extract. Ingesting 5 to 10 seeds produces psychedelic effects similar to morning glory seeds, with effects beginning within 60 minutes and lasting five to eight hours. Hallucinogenic effects occur with doses of 2–5 mg of LSA. Adverse effects can include sympathomimetic effects such as tachycardia, hypertension, and mydriasis. As with LSD, benzodiazepines are recommended to blunt agitation and sympathomimetic effects in patients experiencing toxicity [14; 19].

Psilocybin

Although pure psilocybin was manufactured for experimental and clinical use in the 1960s, until recently little has been known about the pharmacologic properties of psilocybin [20]. The hallucinogenic molecule psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) is the N,N-dimethyl derivative of 4-hydroxytryptamine. Along with psilocin, 4-hydroxy-N,N-dimethyltryptamine is found in many species of mushrooms worldwide. Psilocybin was first isolated from Central American mushrooms in 1957 and was produced synthetically for the first time in 1958 [19; 20].

Psilocybin primarily interacts with serotonin 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C receptor subtypes, with highest affinity to 5-HT2A and lower affinity to 5-HT1A. Psilocybin and its active metabolite psilocin have no affinity for dopamine D2 receptors. However, pretreatment with the D2 receptor antagonist haloperidol reduces psilocybin-induced psychotomimesis, which is explained by the functional interactions between central dopaminergic and serotonergic systems [20; 59].

Oral administration results in the absorption of 50% of psilocybin, distributed uniformly throughout the body. Significant levels of psilocybin are detectable in the plasma within 20 to 40 minutes, and the compound has a mean elimination half-life of 50 minutes. The full effect occurs within 70 to 90 minutes and lasts three to six hours following oral ingestion of 8–25 mg. Although significant tolerance does occur with repeated use of psilocybin, physical dependence does not develop [19; 20].

A dosage of 12–20 mg of psilocybin produces an altered state of consciousness characterized by stimulation of affect; enhanced ability for introspection; altered psychologic functioning; perceptual changes, including illusions, synesthesia, and affective activation; and alterations of thought and time sense. As with any hallucinogen, the potential exists for a panic or severely dysphoric reaction in the user, although less so than with LSD [20; 51].

DMT

DMT (N,N-dimethyltryptamine) shares its chemical structure with 5-MeO-DMT, bufotenine, psilocybin, and other indole hallucinogens. DMT naturally occurs in many botanic sources in South and North America, including Acacia spp., yopo tree, and reed canary grass. It is most commonly used in ayahuasca tea. Some plant preparations, such as ayahuasca, also contain reversible beta-carboline alkaloids that inhibit monoamine oxidase enzymes in the gastrointestinal tract and liver. Inhibition of monoamine oxidase allows the oral absorption of DMT. Although synthetic DMT became popular in the 1960s, DMT consumed now is more likely to be in its natural form. DMT is a serotonin 5-HT1A, 5-HT1C, and 5-HT2A receptor agonist and also has cholinergic properties. The peak effects occur within three minutes if smoked or injected but are delayed with oral ingestion. The subjective effects are described as overpoweringly intense, with vivid hallucinations, dissociation, and shifts in mood and perception [13; 14; 19].

5-MeO-DMT

5-MeO-DMT, a naturally occurring hallucinogen, is closely related to DMT. One source of 5-MeO-DMT is the Sonoran Desert toad, *Bufo alvarius*, which secretes large amounts of the hallucinogen from its parotid glands. Although the venom of *B. alvarius* is known to be toxic when consumed orally, it can be safely smoked. To extract the venom, the toad is held against a flat surface while the parotid gland is massaged. The liquid venom is then collected, dried, and smoked. Based on reported experiences, a single deep inhalation of the vaporized venom is powerfully psychoactive within 15 seconds. Consistent with the known effects of 5-MeO-DMT, the drug effect has been described as intense and short-lived, characterized by auditory and visual hallucinations. The strongest effects dissipate after five minutes, but residual changes in perception persist longer than one hour. No toxic effects have been reported. A single *B. alvarius* toad yields 0.25–0.5 g of dried venom. As concentrations of 5-MeO-DMT in the venom may be as high as 15%, one toad can yield as much as 75 mg of the hallucinogen that, when smoked, is effective in humans at doses of 3–5 mg. Thus, a single toad can produce more than 15 doses of one of the most potent psychoactive drugs found in nature [21].

Other Tryptamine Hallucinogens

Several other hallucinogens have very similar structures and properties to those of DMT. Diethyltryptamine (DET) is a DMT analog with comparable but less intense pharmacologic effects. Alpha-ethyltryptamine (AET) is another tryptamine hallucinogen, illegal in the United States since 1994. Bufotenine (5-hydroxy-N-N-dimethyltryptamine) is a substance found in certain mushrooms, seeds, and the glands of certain species of Bufo toads. In general, most bufotenine preparations from natural sources are highly toxic [13; 15].

Mescaline

Peyote (*Lophophora williamsii*) is a spineless cactus native to the southwestern United States and northern Mexico. Archeologic evidence suggests that peyote has been used by Native Americans for thousands of years as a religious sacrament. Mescaline (3, 4, 5-trimethoxyphenethylamine), the primary psychoactive alkaloid in peyote, is a central 5-HT and dopaminergic agonist responsible for the psychoactive and sympathomimetic effects of the plant [14]. Other mescaline-containing cacti include Trichocereus pachanoi (San Pedro) and Trichocereus peruvianus (Peruvian torch), both of which contain less mescaline by weight than peyote and are not indigenous to the United States [14].

The 1- to 4-inch diameter top portion of the cactus, referred to as the peyote button, is the section of the plant with the highest mescaline concentration. The peyote button can be eaten fresh or dried, steeped, or ground into a powder. A typical dose is 6 to 12 buttons, with each button containing 45 mg of mescaline. Mescaline is well absorbed in the gastrointestinal tract and within one hour of ingestion induces nausea, vomiting, abdominal cramps, dizziness, sweating, restlessness, and palpitations. The second phase of the drug effect begins within one to 3 hours of ingestion and is characterized by visual imagery, altered perceptions, and psychologic insight. The psychoactive effects typically last 6 to 12 hours [14]. Peyote use is legal for the 300,000 members of the Native American Church for ceremonial or religious purposes or to promote physical and mental well-being. Only licensed representatives of the Native American Church may legally harvest peyote cactus [19].

Nutmeg

Nutmeg is the kernel inside the fruit of the evergreen tree *Myristica fragrans*, indigenous to the Maluku Islands in Indonesia. Historically, nutmeg has been used medicinally for various afflictions, including gastrointestinal disorders, musculoskeletal problems, and psychiatric conditions, and has a long history of recreational use. Although nutmeg use often results in unpleasant side effects, it is preferred by some users in search of a legal and easily obtainable euphoric drug with hallucinogenic effects. The hallucinogenic properties of nutmeg are caused by alkyl benzene derivatives (myristicin, elemicin, and safrole) and terpenes. Although the exact psychoactive mechanism is unclear, myristicin and elemicin are believed to be metabolized to amphetamine-like compounds similar to 3-methoxy-4,5-methylenedioxyamphetamine (MMDA) and TMA. Ground nutmeg is ingested in 5–20 g doses, or approximately 2 tablespoons of powder. Most users develop nausea and vomiting within an hour, followed by central nervous system (CNS) intoxication and hallucinations for three to eight hours. Undesirable effects include blurred vision, dizziness, drowsiness, xerostomia, flushing, palpitations, paresthesias, numbness, hypotension, and tachycardia [14; 22].

OTHER HALLUCINOGENS

Salvia divinorum

Salvia divinorum is a hallucinogenic plant in the mint family used by the Mazatecs of Oaxaca, Mexico, in traditional spiritual practices for its psychoactive properties. The plant gained popularity in the mid-1990s as a recreational hallucinogen, advertised and sold by various internet-based botanic companies as a legal high. Through smoking the concentrated extract, users describe an intense, 15- to 40-minute period of modified perception of external reality. Oral absorption following ingestion of the leaves or seeds of the plant produces a longer but less intense effect [14; 19]. The active ingredient is the neoclerodane diterpene salvinorin-A, which does not have 5-HT2A serotonergic activity but instead produces its psychoactive effects through kappa-opioid receptor agonist activity. As with pharmaceutical kappa opioid agonists, many people find the drug effect to be aversive [23].

Amanita Mushrooms

Amanita are psychoactive mushrooms, and there is extensive cross-cultural and historical documentation of *Amanita* use as a sacrament and intoxicant. Evidence of *Amanita* use dates back to the Aryan invaders of India roughly 3,500 years ago and was referred to as "soma" by ancient civilizations. *Amanita* use is also associated with several Native American tribes. Tribes in Siberia continue to use *Amanita* today as an intoxicant. The psychoactive agents in *Amanita* are excreted in the urine unchanged and are thus "reusable" when the urine is consumed [24; 25; 26].

Psychoactive mushrooms in this family include *Amanita muscaria* and *A. pantherina*, which contain the psychoactive chemicals muscimol, ibotenic acid, muscazone, and muscarine. Muscimol is considered the principle psychoactive, with oral dosages of pure muscimol active at 10–15 mg. Muscimol's primary action is at gamma-aminobutyric acid (GABA) receptor sites as a potent GABA-A agonist. It is active in several brain regions, including the cerebral cortex, hippocampus, and cerebellum [27; 28]. Ibotenic acid is also active orally, but at doses five to eight times higher than those of muscimol [28].

A. muscaria is usually dried and consumed orally. The drying/heating process decarboxylates the ibotenic acid into muscimol, thus reducing toxicity and increasing the psychoactive effect. All parts of the mushroom are psychoactive, although the portion just under the skin may be most potent. An average dose is 5–10 g, and 10–30 g of dried mushroom is considered a high dose. The drug effect peaks 1 to 2 hours after ingestion, with a duration of 5 to 10 hours [28].

Amanita mushrooms are known for the unpredictability of their effects. Depending on the type, setting, and amount ingested per body weight, effects can range from nausea and twitching to drowsiness, cholinergic effects (low blood pressure, sweating, and salivation), auditory and visual distortions, mood changes, euphoria, relaxation, and loss of equilibrium. Retrograde amnesia frequently results following recovery [28]. Users describe three stages of effects: gastrointestinal and physiologic effects, then a sedated and dreamy state, followed by a predominately psychedelic third stage. The dream state during the sedative stage can be highly detailed and colorful and has been described as lucid dreaming or an out-of-body experience [28].

Perceptual effects often include dramatic shifts in body perception and motor skills, such as perceived changes in the size of body parts, increased strength, dizziness, clumsiness, and changes in proprioception. Some people experience a strong sense of an internal discussion. Others report a feeling of peacefulness and internal quiet. Synesthesia is common, as is difficulty concentrating on external tasks and stimuli [28].

Death from A. muscaria ingestion is extremely rare but has been documented. Serious toxicity and death typically occur when A. phalloides (death cap) and A. ocreata (destroying angel) are mistaken for A. muscaria and A. pantherina [29; 30].

DISSOCIATIVES

Phencyclidine (PCP)

PCP was developed in 1956 as an injectable drug to induce surgical anesthesia and analgesia in the presence of normal reflexes. However, it was soon discovered that some patients exposed to the drug became agitated and confused, with some developing psychotic episodes lasting up to 10 days. As a result, medicinal use of PCP was abandoned and research involving human subjects was halted in the 1960s because of its potential hazards. In the United States, PCP reappeared in 1965 as a street drug, and in the ensuing decades, its use has fluctuated, with an increase in the mid-1990s and early 2000s [31].

PCP is an NMDA antagonist that binds inside the glutamatergic NMDA receptor ion channel to decrease the release of glutamate [31]. PCP is well-absorbed following all routes of administration, although approximately 50% of smoked PCP is converted to an inactive thermal degradation product. PCP is highly lipid soluble and is stored in fat and brain tissue. The plasma binding of PCP is 65%, and its half-life ranges from 7 to 46 hours. PCP is extensively converted into inactive metabolites by a variety of metabolic pathways [32]. PCP's effects may last four to six hours [31]. Smoking speeds the onset of the drug effect and makes the amount ingested easier to control, thus reducing overdosing.

PCP is highly variable in appearance and is sold in liquid, powder, and tablet form. PCP is often mixed with LSD, cocaine, or cannabis, potentially resulting in inadvertent ingestion in a user who did not anticipate taking a drug with such potentially serious side effects [34].

More than 30 chemically similar analogs of PCP have been synthesized, some with effects similar to PCP. These analogs include cyclohexamine (PCE), phenylcyclohexylpyrrolidine (PHP), phenylcyclopentylpiperidine (PCPP), and thienylcyclohexylpiperidine (TCP) [31]. Illicit PCP is often diverted from veterinary sources. Due to difficulty of synthesis, street preparations have highly variable concentrations. PCC, the PCP precursor, is occasionally found in illicit samples and is more toxic than PCP because it releases cyanide [33].

PCP has stimulant, depressant, hallucinogenic, anesthetic, and analgesic properties [31]. A typical dose is 5–10 mg, and doses greater than 10 mg are considered high. At a dose sufficient to induce an anesthetized state, the patient remains conscious with a staring gaze and rigid muscles [31; 35]. The psychologic effects of PCP are usually dose dependent. Psychologic and physiologic signs and symptoms of PCP ingestion include [31; 35]:

- Euphoria
- Calmness
- Feelings of strength and invulnerability
- Disorientation
- Distinct changes in body awareness
- Distorted sensory perceptions
- Impaired concentration
- Disordered thinking
- Illusions and hallucinations
- Combativeness or violence
- Memory loss
- Sedation
- Increased blood pressure and heart rate
- Flushing
- Profuse sweating
- Generalized numbness of extremities
- Blurred vision
- Grimacing facial expression
- Speech difficulties
- Ataxia
- Marked analgesia
- Nystagmus

Side effects of PCP can include excessive salivation, nausea, vomiting, amnesia, combativeness, severe anxiety, paranoia, flashbacks, seizures, coma, and death. Chronic use may lead to long-term effects, including memory loss, difficulties with speech and thinking, depression, weight loss, liver function abnormalities, and rhabdomyolysis [31; 35]. A single dose of PCP can induce transient symptoms of schizophrenia. Repeated use can lead to a long-lasting psychotic syndrome virtually indistinguishable from schizophrenia for several days to several weeks, despite abstinence from PCP. PCP-induced psychosis is characterized by both positive and negative schizophrenic symptoms and may include the formal thought disorder and neuropsychologic deficits associated with schizophrenia [31].

"Fry"

"Fry" is the term used to describe PCP-laced cannabis cigarettes that are soaked in embalming fluid, with embalming fluid consisting of formaldehyde, methanol, and ethanol. In some cases, tobacco cigarettes are used. The primary effect of smoking these cigarettes is toxic psychosis, with other effects including hallucinations, delusions, panic, paranoia, increased sexual arousal, and loss of consciousness. Side effects associated with the inhalation of embalming fluid include disorganized thoughts, decreased attention span, psychomotor agitation, and sympathetic nervous system up-regulation.

Patients who have smoked this drug typically manifest severe dysphoric effects upon emergency room admission. Exposure to embalming fluid can result in bronchitis, body tissue destruction, impaired coordination, inflammation, brain and lung damage, and sores in the throat, nose, and esophagus [36].

Ketamine

As noted, the first use of ketamine in humans was in 1964, and the drug has since been used as an anesthetic drug in clinical and veterinary settings and battlefield injuries. Ketamine is an NMDA receptor antagonist and is an analog of PCP. Ketamine is often used recreationally as a "club drug," going by the street name "Special K" or "Kit Kat" [70; 71].

Use of ketamine produces a detachment from one's environment and distorted perceptions of sight and sound. Low doses of ketamine result in diminished attention span, learning ability, and memory. In higher doses, impaired motor function, high blood pressure, respiratory issues, delirium, amnesia, and a hallucinatory dream-like state can occur. While evidence is lacking as to the addictive properties of ketamine, some studies show binge-use and symptoms of tolerance and craving. Treatment for ketamine-induced toxicity includes supportive therapies for acute symptoms and a focus on maintaining normal cardiac and respiratory functions [71].

DELIRIANTS

Among all psychoactive drugs, only alcohol has been used longer and by more diverse populations throughout human history than deliriants. For thousands of years, deliriants (also referred to as belladonna alkaloids) have been ingested by shamans and sorcerers for the sensations of leaving their bodies, soaring through the air, or changing into an animal form [14]. The term "deliriant" is applied because the drugs exhibit a high-dose effect of incoherent speech, disorientation, delusions, and hallucinations, often followed by depression and amnesia [37]. Compounds in this class are also categorized as anticholinergics, because they block the action of acetylcholine through antagonism of acetylcholine receptors of the muscarinic subtype without an affinity to the nicotinic-subtype acetylcholine receptor.

The classical anticholinergic deliriants are atropine, scopolamine, and hyoscyamine. Scopolamine is the most powerfully psychoactive of the tropane derivatives, possibly due to enhanced blood-brain barrier penetration, and is found in differing concentrations in various plants, including deadly nightshade (*Atropa belladonna*), henbane (*Hyoscyamus niger*), mandrake (*Mandragora officinarum*), jimsonweed (*Datura stramonium*), and more than twenty other species. In the case of jimsonweed, the seeds contain the highest concentration of atropine, with 100 seeds yielding up to 6 mg of the compound. Users most commonly use jimsonweed recreationally for its anticholinergic properties by ingesting, smoking, or brewing a tea from the seeds [37].

Although these plants are abused for their hallucinogenic and euphoric effects, anticholinergic intoxication also results in classic antimuscarinic symptoms due to competitive blockade of acetylcholine at the central and peripheral muscarinic receptor sites. The effects of deliriants typically develop within one to four hours of ingestion. Initially, the peripheral anticholinergic effects are experienced and can include blurred vision, xerostomia, vasoconstriction, dry skin, mild hyperthermia, flushing, tachycardia, decreased exocrine secretion, increased intraocular pressure, and pupil dilation. The CNS effects of the drug then manifest, including restlessness, disorientation, confusion, hallucinations, delusions, and other changes in mental status. The user is likely to be convinced the hallucinations/delusions represent objective reality and may attempt to interact with them. There is often a severe distortion of sense of position or kinetic sense, leading to the perception of free-falling or flying. The duration of clinical effect is dose dependent and can last from a few hours to

several days [14; 37]. One dangerous aspect of tropane use is the strong peripheral effects in relation to their psychoactive effects. The lethal dose/effective dose ratio is dangerously low, and the extracts may contain neurotoxic alkaloids in addition to the tropane alkaloids. The effects of ingestion of these substances are often described as unpleasant and thus possess little abuse liability [11].

DESIGNER DRUGS

Designer drugs or controlled substance analogs are structurally modified derivatives of known drugs of abuse. These drugs are created when the molecular structure of a known drug is altered to produce an analog with the same or similar actions as the parent drug. There are hundreds of such drugs; from 2009 to 2020, more than 1,000 different new psychoactive substances were reported, with more than 100 new novel psychoactive substances identified in 2015 alone [64; 68].

In some instances, it is possible to predict the actions and potencies of designer drugs on the basis of established structure-activity relationships. However, the actions of designer drugs are not always predictable, a prototypical example being MDMA, the N-monomethyl derivative of MDA [63]. Although the established structure-activity relationships predict an absence of significant hallucinogenic activity and significant central stimulant activity, MDMA produces, in addition to a stimulant effect, an effect that is uniquely distinct from that of hallucinogens and central stimulants. This effect is termed "empathogenic" and manifests as increased sociability and heightened empathy. MDMB, the alpha-ethyl homolog of MDMA, retains the latter action but lacks amphetaminergic character [2].

Hallucinogenic designer drugs fall into two categories: amphetamine analogs and new benzylpiperazine or phenylpiperazine analogs [38].

Amphetamine Analogs

Modification of the phenethylamine and amphetamine molecule has produced numerous analogues. These modifications have produced substances with pure CNS stimulant activity, such as methcathinone; pure hallucinogenic activity, such as 4-bromo-2,5-dimethoxyphenethylamine (2C-B); or a combination of both, such as MDA. Changes to the phenyl ring may lead to substances with hallucinogenic activity, while changes to the ethylamine chain usually result in varying levels of stimulant activity [39; 40]. A primary motivation for the introduction of new recreational analog drugs has been to elude legislative control [39].

The amphetamine analogs can be classified in the following three categories, according to the structural alteration of the amphetamine molecule [41]:

- Non-ring substituted amphetamine derivatives, which do not possess significant hallucinogenic properties (e.g., amphetamine, methamphetamine)
- Methylenedioxy amphetamines (e.g., MDA, MDMA)
- Ring and side-chain substituted amphetamines (e.g., PMA [4-MA], DMA [2,5-DMA])

The amphetamine analogs can also be classified according to the parent molecule as MDAs, p-methoxyamphetamines (PMAs), and others.

The methylenedioxy amphetamines represent a new drug class, entactogens, which enhance understanding, communicativeness, and empathy with minimal hallucinogenic effects. Drugs in this class include MDA, MDMA, 3,4-methylenedioxyethylamphetamine (MDEA), and N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB). MDMA is the most popular recreational drug in this class [42].

PMA has a hallucinogenic property approximately five times more potent than mescaline, although the physiologic effects of PMA and PMMA are markedly different. PMMA has MDMA-like effects, while PMA more closely resembles amphetamine and is dissimilar in effect to MDMA. PMA is often sold as "ecstasy;" however, it lacks the MDMA effect and is more toxic, leading to a higher risk of overdose in pursuit of the desired effect [42].

The 2,5-dimethoxyphenalkylamines (2C-series drugs), which include 4-bromo-2,5-dimethoxyphenethylamine (2C-B), 2,5-dimethoxy-4-ethylthiophenethylamine (2C-T-2), and 2,5-dimethoxy-4-(n)-propylthiophenethylamine (2C-T-7), constitute another group of drugs sharing the same molecular core. Sold as "nexus," "venus," or "bromo," 2C-B is known for being psychoactive at a much lower dose (4–30 mg) than MDMA. Higher doses have the potential to cause frightening hallucinations, seizures, and unexpectedly intense "trips" [10; 56; 64]. Following the identification and ban of 2C-B, the 2,5 dimethoxyphenalkylamine drugs, 2C-T-2 and 2C-T-7, were subsequently introduced on the black market as substitute hallucinogenic drugs for 2C-B in Japan, Europe, and the United States [39; 42]. Many more 2C series drugs (2C-B to 2C-Y) have been synthesized.

Newer phenethylamine-based 2C-series N-2-methoxybenzyl analogues, the 25X-NBOMe series, have been sold both legally and illicitly as designer drugs since roughly 2010 [64; 65]. These drugs, including 25B-N(BOMe)2, 25B-NBOMe, 25C-NBOMe, 25D-NBOMe, 25E-NBOMe, 25G-NBOMe, 25H-NBOMe, 25I-NBOMe, 25N-NBOMe and 25iP-NBOMe, are sold as Smiles, 25I, and N-Bomb. The NBOMe series are reported to have higher rates of adverse effects than the 2C series drugs, including agitation, seizures, and renal damage [65].

Piperazine-Derived Drugs

So-called "piperazines" are further divided into two classes: the benzylpiperazines and the phenylpiperazines [38]. In the case of the benzylpiperazines, the parent compound N-benzylpiperazine (BZP) produces amphetamine-like effects through central serotonin uptake inhibition and 5-HT1 receptor agonist effects. Weak inhibition of serotonin uptake by other benzylpiperazines has been described. Chlorophenylpiperazine, a phenylpiperazine, interacts with serotonergic, noradrenergic, and dopaminergic receptor systems to produce stimulant and hallucinogenic effects comparable to those of MDMA. Serotonin syndrome may occur after ingestion of phenylpiperazines [38].

EFFECTS OF HALLUCINOGEN USE

PSYCHOTIC REACTIONS

The earliest suggestions of long-term psychiatric disorders associated with hallucinogen use were made in the decade following the discovery of LSD. However, the apparently low rates of psychoses following LSD use during the period of early human experimentation led researchers to consider LSD a reasonably safe drug. Rates of psychoses following experimentally administered LSD range from 0.08% to 4.6%, with higher rates among psychiatric patients and lower rates among volunteers. Psychosis following LSD more closely resembles a schizoaffective disorder, often with the addition of visual disturbances. Among the most common symptoms of hallucinogen-induced psychosis are mood swings, visual hallucinations, mania, and grandiosity [1].

NEUROPSYCHOLOGIC EFFECTS OF LONG-TERM USE

Several reports tentatively document neuropsychologic impairment in users of the classical hallucinogens. Impairment has primarily been based on changes in evoked potentials, compromised visuospatial integrity, deficits on trail-making tests, and memory deficits. However, there is conflicting evidence, and all positive studies have contained serious methodologic flaws, such as failure to control for premorbid functioning, inclusion of users with a history of psychiatric disorders, failure to control for the use of other illicit drugs and alcohol, and wide variation in the abstinence period. On the other hand, the small sample sizes in many of the negative studies may have led to an inability to detect subtle toxic effects. If residual neuropsychiatric impairment does occur from chronic use, the severity is likely to be mild [4].

Hallucinogen Persisting Perception Disorder

Hallucinogen persisting perception disorder (HPPD), or "flashbacks," are characterized by persistent perceptual abnormalities that mimic the effects of acute hallucinogen intoxication. These abnormalities are not attributable to another medical or psychiatric condition and persist for weeks or months after the last hallucinogen exposure [43]. In order for a diagnosis to be established, the perceptual symptoms must cause clinically significant distress.

The first description of LSD-like recurrences following therapeutic use of the drug occurred in 1954. In 1969, the term "flashback" was introduced to describe perceptual distortions, spontaneous imagery, and recurrent images associated with the original drug experience [1].

Persons administered LSD in therapeutic or research settings are far less likely to develop HPPD than individuals using LSD illicitly, partially attributable to careful selection, supervision, follow-up, and controlled dosages of pharmaceutical quality drug.

A mysterious aspect of HPPD is the absence of a correlation between the number of episodes of hallucinogen exposure and the presence of flashbacks. An example of this comes from a study screening for residual neuropsychologic effects from peyote among the Navajo in the Native American Church. Of the approximately 500 Native American Church members screened, all of whom had taken peyote on at least 100 occasions over years or decades, none described symptoms consistent with HPPD [43].

HPPD may be the result of excitotoxic destruction of inhibitory interneurons that are serotonergic at the soma and GABAergic at the terminals. Support for this comes from the efficacy of benzodiazepines in symptom amelioration. Alternatively, vulnerability may be mediated through protein kinase C blockade [1].

An accurate diagnosis of HPPD may be difficult for the typical patient, who may consult multiple specialists, usually an ophthalmologist, neurologist, psychiatrist, and psychologist, before a correct diagnosis is made. This can be avoided if a complete patient history is obtained, including non-recent drug use, and a multidisciplinary approach is taken. Differential diagnosis involves ruling out organic forms of hallucinosis, including other sources of toxicity, stroke, CNS tumors, infections, and the sequelae of trauma [4].

HPPD often resolves within weeks or months of cessation of use without intervention, but it may persist much longer, with one report of symptoms lasting 26 years. Selective serotonin reuptake inhibitors (SSRIs) attenuate or block the effects of hallucinogens that bind with 5HT2 receptors, such as LSD, suggesting that hallucinogens may cause a reversible neurotoxic impingement upon central serotonergic systems [4]. Benzodiazepines ameliorate but do not eradicate the symptoms of HPPD [1]. Worsening of HPPD has been reported in subjects receiving phenothiazines, the atypical antipsychotic risperidone, and SSRIs [43].

LSD-INDUCED CHROMOSOME DAMAGE

Reports in the early 1970s linking LSD use with chromosome damage resulted in considerable concern. However, consensus was reached that the in vitro-derived data was not supported by evidence derived in vivo. Although hallucinogen use may result in negative pregnancy outcomes, there is no evidence that hallucinogens are teratogenic or oncogenic in humans [17].

TREATMENT OF HALLUCINOGEN TOXICITY

CLASSICAL HALLUCINOGENS

Although all classical hallucinogens have the potential to induce an extremely frightening experience, LSD probably accounts for most of the "bad trips" that come to the attention of medical providers due to the intensity of its effects and its prevalence relative to the other hallucinogens. Acute LSD toxicity commonly presents to the emergency department as a severely dysphoric or panic reaction superimposed on the drug effect. Effective management begins with a careful history and an accurate description of the ingested substance. Adulteration is surprisingly uncommon; mistaken attribution is more common. LSD toxicity historically has been managed with neuroleptics. However, it is now recognized that the neuroleptics may intensify the experience. Benzodiazepines (e.g., diazepam 20 mg orally or alprazolam 1–2 mg intramuscularly) are widely regarded as rapid and effective treatment, with resolution of symptoms often occurring within 30 minutes [1]. Toxic reactions to the other classical hallucinogens should be managed in the same manner [14; 16].

The Michigan Quality Improvement Consortium recommends that patients should be screened by history for substance use at every health maintenance exam or initial pregnancy visit (repeated as indicated), using a validated screening tool.

(https://www.mahp.org/wp-content/uploads/2024/02/mqicscreeningdiagnosisandreferralforsubstanceusedisordersFINAL2024.pdf. Last accessed September 30, 2024.)

Level of Evidence: D (Opinion of expert panel)

Although no medication exists that can reverse the effects of classical hallucinogens, reduction of environmental stimuli by placing the patient in a quiet, dark room is often helpful. Reasoning with patients who have ingested LSD to help them become calm may be attempted, but this approach is ineffective for patients who have taken PCP. For patients who have ingested PCP, benzodiazepines or haloperidol may be used to treat conditions associated with intoxication, including severe agitation, psychosis, hypertension, and tachycardia. Additionally, PCP elimination in the urine may be increased through acidification [11; 16].

DELIRIANTS

Hospitalization is usually required for persons experiencing the prolonged effects of an anticholinergic hallucinogen, such as jimsonweed. Gastric lavage should be attempted even when initial intervention is delayed. Sedating these patients is very important because of the changes in mental status. Benzodiazepines are the treatment of choice; physostigmine 1–2 mg IV or IM may be considered in cases of severe overdose [11; 16].

DISSOCIATIVES

Long-term dissociative use suppresses the production of dopamine and norepinephrine, which can persist into abstinence, possibly leading to depression. Antidepressants with noradrenergic and dopaminergic specificity can counteract this suppressant effect. Patients with post-dissociate depression should be maintained on antidepressant therapy for at least three to nine months [16].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Because specific details about the patient's history are crucial to diagnosing and treating hallucinogen toxicity, effective communication is required. Communicating effectively is more challenging when the patient's primary language differs from that of the practitioner. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter.

HALLUCINOGEN DEPENDENCE

A withdrawal syndrome associated with cessation of classical hallucinogen use has not been clearly defined and may not occur [16]. To date, no treatment modalities specific to hallucinogen abuse or dependence have been published in peer-reviewed literature. Persons with a desire to stop using hallucinogens should be referred to a 12-step program, such as Narcotics Anonymous. Information on Narcotics Anonymous may be obtained at https://www.na.org.

CONCLUSION

Every year, approximately 1.5 million individuals in the United States use a hallucinogen for the first time. Because hallucinogens elicit different responses and are highly variable, even among the same user at different times, predicting the effects of these drugs is difficult. However, some individuals will experience "bad trips" and other adverse effects as a result of ingestion of a hallucinogen. It is imperative that these patients are appropriately diagnosed and treated to avoid adverse mental health outcomes.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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