Hallucinogen-Related Disorders

5

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Introduction

Hallucinogens comprise a diverse group of substances with differing chemical structures and mechanisms of action, but are classified together for their similar subjective effects, including alterations in perception, mood, and cognition (see Table 5.1). Many names have been proposed for this class of drugs, including *psychotomimetic* (meaning "mimicking psychosis"), *entheogen* ("bringing into being the god within"), and *psychedelic* ("mind- or soul-manifesting"). *Hallucinogen* has been its common designation in the scientific literature. However, the term *psychedelic*, which has prevailed in the lay press for decades, is increasingly the preferred term even in research settings [1, 2]. For the purposes of consistency with DSM-5 nomenclature, we use the term *hallucinogens* to refer to this group of substances in this chapter.

This diverse group of substances includes indoleamines (e.g., psilocybin, N,N-dimethyltryptamine [DMT], and the admixture ayahuasca which contains DMT), ergolines (e.g., lysergic acid diethylamide [LSD] and lysergic acid amide [LSA], which is found in morning glory seeds), phenethylamines (e.g., 3,4-methylenedioxymethamphetamine [MDMA] and mescaline), NMDA antagonists (e.g., phencyclidine [PCP] and ketamine), as well as other ethnobotanical compounds such as *Salvia divinorum* and jimsonweed [3]. Many hallucinogens are ingested orally, either swallowed as tablets, pills, or liquids; consumed raw or dried; or brewed into teas; though some can be inhaled (DMT, PCP, Salvia), snorted (ketamine, PCP), or injected (ketamine, PCP) [4].

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Table 5.1 Signs and symptoms associated with hallucinogen intoxication

Autonomic arousal (e.g., dilated pupils, hypertension, hyperthermia, gastrointestinal distress, tachycardia, tachypnea)
Depersonalization
Derealization
Distortions in one's sense of time
Ego death/dissolution (i.e., reduction in normal self-referential awareness leading to an increased feeling of unity with others and one's surroundings)
Mood changes (both perceived as good and bad and can be quite variable during the course of intoxication)
Impaired judgment
Impaired motor coordination
Mystical-type experiences
Perceptual changes (e.g., intensification of sensations, illusions or visual hallucinations (rarer), synesthesia)
Thought process changes

Table 5.2 Hallucinogen-related disorders (as described in the DSM-5 [3])

Phencyclidine use disorder
Other hallucinogen use disorder
Phencyclidine intoxication
Other hallucinogen intoxication
Hallucinogen persisting perception disorder
Other phencyclidine-induced disorders
Other hallucinogen-induced disorders
Unspecified phencyclidine-related disorder
Unspecified hallucinogen-related disorder

Though a comprehensive discussion of the history of these substances is beyond the scope of this clinical text, there exists a notable history, documented on most continents, of the use of various preparations of hallucinogenic plants as part of religious and spiritual ceremonies. Substances used in this context include, but are not limited to: hallucinogenic mushrooms, used by the Aztecs and other indigenous groups from Central and North America; the DMT-containing brew ayahuasca, used by indigenous tribes in the Amazon; and mescaline-containing peyote cactus, used by indigenous peoples of Mexico and North America [5–7].

Under the category of hallucinogen-related disorders, the DSM-5 describes hallucinogen use disorders, hallucinogen-induced disorders, and acute intoxication (see Table 5.2). Although maladaptive patterns of drug use can be seen in users of PCP and ketamine, hallucinogen use disorders generally are rare, with a lifetime prevalence estimated at around 0.1–0.6% in the United States [3, 8]. Lifetime use, however, is relatively common (9.32%) [8]. Recreational use of classical hallucinogens, a group of serotonergic substances that includes LSD and

psilocybin, has been found to be relatively safe from a physiologic perspective, and their use is associated with lower utilization of emergency medical treatment compared to the use of methamphetamine, cannabis, and alcohol [9–12]. Lifetime use of classical hallucinogens is not associated with the development of mental health disorders, increased rates of panic attacks, or decreased cognitive function [9].

In light of their physiological safety and their unique psychological effects, the therapeutic potential of hallucinogens has emerged as an area of clinical research [1, 2, 13]. Recent phase 1 and phase 2 clinical studies have investigated the utility of psilocybin for a number of psychiatric disorders including, but not limited to, major depressive disorder [13, 14], end-of-life psychological distress [15], and alcohol use disorder [16]; and the use of MDMA for post-traumatic stress disorder [17]**.** Moreover, research over the last 10 years has established a substantial evidence base for the therapeutic utility of ketamine in the treatment of acute suicidal ideation [18] as well as unipolar and bipolar depression [19]. Although thought to be physically safe for consumption for most adults, hallucinogens cause a temporary disruption to ordinary mind states, which, for some, can cause psychological distress during the experience. Other adverse effects can include physiological toxicity, physiological tolerance, and prolonged psychopathology [20], which we explore in the case examples below.

Clinicians may encounter patients presenting with either acute intoxication or complications related to hallucinogen use. Acute hallucinogen intoxication may present with symptoms that overlap to some extent with endogenous manic, psychotic, or dissociative states. Other conditions that may cause hallucinations, delusions, and cognitive impairment, such as traumatic brain injury, delirium, and acute mania, psychosis, or dissociation, should also be considered. A history of recent consumption of a hallucinogenic substance, as well as what is typically the very transient nature of these presenting symptoms, should help to clarify the diagnosis. In making the diagnosis of hallucinogen intoxication, other conditions that may cause hallucinations, delusions, and cognitive impairment, such as traumatic brain injury, delirium, and acute mania, psychosis, or dissociation, should also be considered. Severe adverse effects and fatalities associated with hallucinogens are usually due to illicit drug impurities and/or coingestion of other drugs or alcohol [21].

The cases outlined in this chapter depict a variety of clinical scenarios related to the use of hallucinogens. They illustrate a comprehensive approach to treatment, including the stabilization of patients in the acute phase of intoxication with supportive psychological interventions. Should such an intervention fail to relieve the acute distress, psychopharmacological interventions can be used. We also discuss how to meet the long-term needs of patients with hallucinogen-related disorders, including the management of potential complications, and counseling patients in ongoing treatment.

Clinical Cases

Case 1

Angel is a 32-year-old man brought to the emergency room (ER) by emergency medical services (EMS) with a police escort after being agitated in public, where he had been yelling at passersby and attempting to fight with police officers when approached. This is his fifth visit in the past six months under similar circumstances. The clinical impression in his prior visits had been acute intoxication of various substances, including PCP, which was occasionally confirmed by urine toxicology when Angel was more agreeable to diagnostic workup. On initial assessment at triage, Angel is oddly related, paranoid, and endorses various delusions. His heart rate and blood pressure are elevated, and he has prominent nystagmus. Shortly into the triage process, while awaiting assessment in the busy ER milieu, Angel becomes increasingly agitated and verbally threatening. Despite the staff's efforts at verbal de-escalation, he begins swinging his fists at them and ultimately requires intramuscular medication and physical restraints to ensure safety.

Discussion

Angel is presenting with signs of altered mental status, paranoid ideation, delusional thoughts, autonomic hyperactivity, nystagmus, and acute aggression. Given his history of similar clinical presentations, many of which objectively confirmed recent PCP use, phencyclidine intoxication is high on the differential diagnosis (see Table 5.3). This diagnosis is made based upon the history and clinical evaluation. However, because a clear history can be difficult to obtain in these circumstances, a

Table 5.3 Phencyclidine intoxication diagnostic criteria (excerpt from the DSM-5 [3])

A. Recent use of phencyclidine (or a pharmacologically similar substance).
B. Clinically significant problematic behavioral changes (e.g., belligerence, assaultiveness, impulsiveness, unpredictability, psychomotor agitation, impaired judgment) that developed during, or shortly after, phencyclidine use.
C. Within 1 hour, two (or more) of the following signs or symptoms: *Note*: When the drug is smoked, "snorted," or used intravenously, the onset may be particularly rapid. 1. Vertical or horizontal nystagmus. 2. Hypertension or tachycardia. 3. Numbness or diminished responsiveness to pain. 4. Ataxia. 5. Dysarthria. 6. Muscle rigidity. 7. Seizures or coma. 8. Hyperacusis.
D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance

working diagnosis must suffice until safety has been established and the altered mental status and impulsive, dangerous behavior have improved.

Other etiologies that might present with similar symptoms include substance withdrawal from alcohol or benzodiazepines, toxidromes, or infections (such as encephalitis, meningitis, or sepsis), particularly given the combination of altered mental status and vital sign abnormalities. Metabolic abnormalities that may cause altered mental status, including hypoglycemia, hyponatremia, or hyperthyroidism, as well as seizure disorders and vascular pathologies, should also be ruled out with the appropriate medical workup. Additionally, given the variable symptoms associated with intoxication, and because both intentional and unintentional coingestion of multiple substances are common, the differential diagnosis should include intoxication with other psychoactive substances, including not only those commonly presenting with agitation and altered mental status (e.g., amphetamines, cocaine), but also novel psychoactive substances, particularly given the growing online market for various synthetic ("designer") drugs, most of which cannot be detected on standard urine drug screens.

As the DSM-5 points out, the combination of nystagmus, elevated heart rate and/or blood pressure, and bizarre and aggressive behavior often helps to distinguish PCP intoxication from intoxication due to other substances, particularly other hallucinogens. Urine toxicology may be useful in the diagnostic workup, especially in a setting that allows for extended observation, where a clinician might have the benefit of longitudinal observation to distinguish between a short-term, substance-induced etiology and a primary psychotic or affective illness that warrants hospital admission. With respect to diagnostic workup, PCP is detectable in the urine, but may be detected up to approximately 8 days after use, so its presence is not necessarily diagnostic. Other common laboratory abnormalities associated with PCP intoxication include an elevated creatine kinase (CK or CPK) and elevated hepatic transaminases [3]. As noted above, if clinical suspicion for a medical etiology is high, then the appropriate laboratory tests should also be performed.

In this particular case example, Angel is presenting as paranoid with delusional content, and so, per the DSM-5, an additional diagnosis of phencyclidine-induced psychotic disorder should be considered in a patient presenting with the symptoms of PCP intoxication with the noted absence of intact reality testing. Moreover, a review of Angel's history, particularly his repeated presentations and continued use of PCP despite consequences within a 12-month period, suggests that phencyclidine use disorder should also be considered.

As noted in the case introduction, Angel's behavior quickly escalated to the point of serious concern for safety to both staff and the patient. In cases of PCP intoxication with agitation, particularly in busy medical settings, a supportive approach to reduce agitation would include efforts to reduce external stimulation, for example, by placing the patient in a darker, quieter space that still allows for adequate monitoring. Offering a patient a benzodiazepine, particularly in a quiet, calm, environment, can be an effective strategy that may eliminate the need for involuntary medication and/or physical restraints. However, if these measures are unavailable or ineffective, and patient or staff safety is at risk, safe and efficient symptom reduction is essential.

Physical restraints may be initially necessary to safely administer sedating medications. Safe and effective physical restraint may require several staff members, given PCP's propensity to cause both significant activation and reduced perception of pain.

Based upon observational reports and clinical experience, antipsychotics and/or benzodiazepines are often the preferred types of sedating agents. Regarding benzodiazepines, general clinical consensus recommends lorazepam 4 mg intravenously (IV) or midazolam 5 mg IV, or by intramuscular (IM) injection if IV access is not available [22]. Regarding antipsychotics, droperidol 2.5 mg or haloperidol 5 mg IM or IV can be used as adjunctive therapy if benzodiazepines do not adequately control symptoms [22]. These doses may be repeated until adequate sedation is achieved to establish safety. In reviewing the literature, there is some anecdotal caution to avoid antipsychotics such as droperidol or haloperidol due to the potential concern of lowering a patient's seizure threshold or that these agents may impair heat dissipation in patients experiencing hyperthermia. However, there do not appear to be any high-quality human studies to support these claims, and significant clinical experience suggests that antipsychotics or the coadministration with benzodiazepines can be safely utilized.

Clinicians should be aware of multiple serious complications that can occur with PCP intoxication and the attendant behaviors, particularly with ingestion of large quantities of PCP. These include rhabdomyolysis, seizures, hypoglycemia, trauma, and coma. Any patient with such significant complications should be triaged to an appropriate medical setting and likely requires admission to an intensive care setting for monitoring and treatment.

Given the variable presentation of PCP toxicity and the potentially problematic behavioral issues associated with intoxication, most patients presenting in the emergency setting benefit from observation. The intoxication period from PCP usually lasts for several hours, so a patient presenting early following ingestion could quickly escalate in terms of problematic behaviors and safety concerns, and so should be retained in an appropriate setting where they can be safely monitored while metabolizing any ingested substances. Of note, in individuals with a co-occurring mental illness, other substance use disorders, genetic loading for mental illness, or other psychiatric or behavioral vulnerabilities, the hallucinogenic effects of PCP may last beyond the typical time period and may precipitate a persistent psychotic episode resembling schizophrenia spectrum illness.

PCP use disorder is defined by the same criteria as other substance use disorders in the DSM-5. The use of motivational interviewing can be helpful in assisting patients to become aware of and resolving ambivalence of decreasing or stopping PCP use [23]. One large study found the incidence of PCP intoxication-related injuries to be 13%, with self-inflicted injuries representing 22% of those [24]. As such, when counseling active PCP users, a harm-reduction approach that emphasizes the maintenance of physical safety is important. Although pharmacological treatments for any co-occurring substance use or psychiatric disorders may be helpful in this patient population, there are no FDA-approved treatments for PCP use disorder. However, enrollment in outpatient counseling or inpatient rehabilitation

centers may be helpful in patients who are motivated for treatment. Additionally, 12-step support programs are a widely available and free community resource that may assist in supporting abstinence.

Case 2

Phil is a 22-year-old man that comes into the ER accompanied by his friend, who informs staff that the patient had ingested some "shrooms" a couple hours earlier with a group of friends. The friend notes that shortly thereafter, Phil became acutely anxious and paranoid. He reported visions of frightening figures on the wall and began repeatedly announcing that the "world is corrupt." Given his level of distress, he asked his friend to take him to the ER. During the assessment, Phil is able to provide a narrative of the day's events and his mushroom ingestion, but he appears anxious and guarded and states that he is afraid that these experiences and feelings will never go away. His heart rate and blood pressure are elevated, and his pupils appear dilated. He responds to verbal reassurance and is taken to a quiet room, where he is offered medications, which appear to calm him. Some hours later, after a subjective report of improvement in symptoms and apparent return to his physical, cognitive, and psychological baseline, he is discharged from the ER.

One month later, Phil presents to his primary care doctor complaining of visual abnormalities, including visual trailing, spontaneous flashes of color, and illusory palinopsia (a persistence of a visual image after the stimulus has been removed). He reports that he has not used any substances since his ER visit.

Discussion

At his initial visit, Phil is presenting with the acute onset of significant psychological changes (e.g., marked anxiety, fear of losing control, and paranoia), alterations in sensory perception, and abnormal vital signs following ingestion of presumed psilocybin-containing mushrooms. His signs and symptoms meet the DSM-5 diagnostic criteria for other hallucinogen intoxication.

The overall effect of any psychoactive drug is a complex interaction of many elements beyond direct pharmacological mechanisms, including physiological, psychological, cultural, and environmental factors [20]. Although we assess for the influence of these factors with any patient, they may have an especially important role in the experience of a person who has ingested a hallucinogenic compound. A group of influences in this context has been collectively termed "set and setting." "Set" refers to individual factors such as one's mindset, personality structure, and expectations; "setting" includes environmental factors, such as the physical location, the situation, and the cultural context in which the hallucinogen use occurs. These elements are thought to underlie the differences in emotional valence, level of anxiety, and overall experience of different users at different times despite ingesting the same substance. Colloquially, the subjective experience of acute intoxication is

referred to as a "trip," and a "bad trip" refers to those experiences predominantly marked by anxiety, dysphoria, fear, or agitation. Neuropsychiatric effects occur in response to administration of any hallucinogen, and although the various substances (e.g., LSD versus MDMA) differ in their onset, duration, and intensity of effects, their acute psychological and behavioral symptoms can be quite similar (see Table 5.1).

As in both Angel's and Phil's cases, many hallucinogens produce sympathomimetic effects such as dilated pupils, elevations in blood pressure and heart rate, and, on rare occasions, hyperthermia. The DSM-5 requires at least two physiologic signs, in addition to psychological and perceptual changes, to meet diagnostic criteria for other hallucinogen intoxication (in this case, with psilocybin). Though mild vital sign fluctuations can occur with psilocybin intoxication, significant vital sign abnormalities are uncommon and should prompt consideration of another intoxicant (e.g., PCP, amphetamines, or cocaine) or other medical etiologies. Hyperthermia rarely occurs with isolated hallucinogen intoxication, and this is a sign of severe toxicity. It can also be a sign of serotonin toxicity ("serotonin syndrome"), a condition characterized by the presence of altered mental status, neuromuscular abnormalities, and autonomic hyperactivity that typically occurs in the setting of coingestion of serotonergic hallucinogens (e.g., LSD, MDMA, or psilocybin) and other serotonergic medications such as antidepressants (e.g., SSRIs or MAOIs), analgesics (e.g., meperidine), antiemetics (e.g., ondansetron), or herbal supplements (e.g., St. John's wort). A patient presenting with signs and symptoms concerning for serotonin syndrome, especially with hyperthermia, should be promptly triaged to an appropriate medical setting and likely requires admission to an intensive care setting for monitoring and treatment.

Of note, most patients presenting with hallucinogen intoxication are awake and oriented, are able to provide a coherent history of preceding events including hallucinogen use, and have good insight that their symptoms are substance-induced. These patients, in the absence of severe symptoms, typically do not require, nor benefit, from routine laboratory tests, especially given the fact that most hallucinogens are not detectable on routine urine toxicology screens. However, the presence of altered mental status, overt psychosis (especially with auditory hallucinations), severe agitation, or bizarre behavior should prompt further medical workup to rule out other medical etiologies [25].

In most cases of intoxication, supportive care is all that is needed to manage a patient's distress. The general clinical consensus suggests embracing a nondirective and nonconfrontational approach while allowing the patient to relax in a calming environment until the substance's effects subside. In Phil's case, he was offered medications in the ER, which is often done. Psychopharmacological interventions, such as benzodiazepines and/or antipsychotics, are generally only necessary if there is concern for the safety of the patient or others. Some clinicians who have had significant experience in working with patients having difficult psychological experiences while intoxicated from hallucinogens have cautioned that pharmacologically terminating a "bad trip" can potentially have a negative

psychological impact on a patient [25, 26], although this has not been explored in clinical trials.

Most cases of other hallucinogen intoxication are time-limited and resolve over the course of several hours, ultimately resulting in a patient returning to their neuropsychiatric baseline and being able to leave the ER without residual symptoms or complications. However, in the case of Phil, he began to experience some distressing symptoms some weeks later, consistent with the unique disorder of hallucinogen persisting perception disorder (HPPD).

Hallucinogen Persisting Perception Disorder (HPPD)

HPPD is a relatively rare and poorly understood phenomenon, with anecdotal reports associating this diagnosis primarily, though not exclusively, with LSD use [3]. HPPD is described in the DSM-5 as the reexperiencing of one or more perceptual symptoms after cessation of hallucinogen use. Of note, these perceptual disturbances may not have been experienced during the acute intoxication experience, a period typically not lasting more than several hours maximum [27]. Visual symptoms can include geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes or intensification of colors, trailing images of moving objects, positive afterimages, halos around objects, and misperceptions of relative size (macropsia, micropsia). HPPD may co-occur with dissociative phenomena. The symptoms can emerge after one-time use or at any point after more frequent use and may be experienced episodically or persistently [28]. The symptoms can begin after a latent period of days to months or even years, and they may last for months to years. Interestingly, without treatment, both spontaneous improvement and persistent symptoms have been reported [29, 30].

HPPD is a diagnosis of exclusion. Patients need to be carefully evaluated for other causes of perceptual disturbances, such as anatomical brain lesions and central nervous system infections, seizure disorders, migraines, head trauma, hypnopompic/hypnagogic hallucinations, delirium, major neurocognitive disorders, primary psychotic disorders, substance intoxication, and substance-induced psychotic disorders. Given the relatively low incidence of HPPD, a neurological evaluation that includes an EEG and brain MRI may be warranted to rule out neurological causes. In addition to ruling out psychiatric disorders that may better explain the visual symptoms, screening for concurrent psychiatric comorbidities such as depression, anxiety, panic disorder, and psychotic disorders is critical, as HPPD can cause significant distress and clinical impairment. As with any psychiatric presentation, the patient should also be assessed for suicidality [31].

Counseling provided to patients with HPPD should include recommendations to avoid further use of hallucinogens and to limit the use of other substances. Assessment of the triggers for visual symptoms may prevent further exacerbation. The use of motivational interviewing may be helpful in those who, despite persisting symptoms of HPPD, appear unmotivated or ambivalent around the recommendation to limit their use of hallucinogenic substances [23]. Educating patients on the

possible outcomes of HPPD, which include spontaneous remission or persistent symptoms with unpredictable frequency and intensity, can be helpful in managing expectations. To this end, psychotherapeutic interventions, including the use of mindfulness- and acceptance-based psychotherapies, may also be helpful. Cognitive-behavioral approaches can also be used to target any distorted cognitions, depression, and/or anxiety that might occur secondary to HPPD symptoms.

Lastly, judicious use of psychotropic medications may be of some utility in patients whose symptoms cause persistent and clinically significant distress despite non-pharmacologic therapies. However, given the paucity of data regarding efficacy of psychotropic medications in HPPD and the possibility of spontaneous remission, a thorough discussion of the risks and benefits of pharmacologic treatment is particularly important in these cases. Open-label studies and case reports suggest possible benefit from treatment with benzodiazepines, anticonvulsants, and alpha-2-agonists, while results from studies of selective serotonin reuptake inhibitors (SSRIs) and antipsychotics are mixed. Among the latter, risperidone appears to worsen symptoms [32, 33]. However, given the low prevalence of HPPD, a meaningful interpretation of these findings is limited by a very small sample size. Given the potential side effects of medications, a shorter course of treatment should be considered; however, the risk of rebound symptoms after withdrawing such treatment has not been studied.

Integration

It is worth emphasizing that, although hallucinogen intoxication is generally an acute, time-limited experience that does not result in chronic adverse effects and hallucinogen use disorders are rare, these experiences can be very challenging and cause significant psychological distress that can leave a person feeling unsettled for some time after the acute intoxication has resolved. Additionally, even the visions and insights one may experience during a so-called "good trip" can be challenging to understand, and it can be difficult to incorporate these experiences into one's daily life. In response to this perceived need, there is a growing number of licensed mental health clinicians that offer ongoing psychotherapeutic services, often referred to as "Psychedelic Integration Therapy," focused on providing psychoeducation, and to help individuals process and integrate their experiences with hallucinogens.

The resurgence of scientific research focused on hallucinogen-assisted psychotherapy has generated significant positive media coverage in the recent years. As a result, it is possible that there may be an increase in the number of individuals that decide to experiment with hallucinogens. Future studies will likely focus on how to optimize experiences with hallucinogens, and, in particular, explore if, how, and to what extent integration work factors into the overall positive results observed in recent hallucinogen-assisted psychotherapy studies. Given the increased awareness of these substances and the potential for growing prevalence and incidence of use, it will be important for clinicians to be able to provide accurate psychoeducation

about these substances and for there to be resources that can offer appropriate psychotherapeutic support for patients in need.

Case 3

Sasha is a 21-year-old woman who was brought to the emergency department by EMS after being found unconscious at a dance club. She is accompanied by a friend who reported that Sasha had used "Molly" and ketamine during the course of the evening. On physical exam, the patient appears lethargic. Vital signs are notable for mild hypertension and tachycardia. Neurologic exam showed no signs of myoclonus, hyperreflexia, nystagmus, or tremor. Laboratory results show a mild hyponatremia but are otherwise within normal limits. Sasha was admitted to the inpatient medicine service for monitoring and supportive treatment with IV fluids, which corrected her hyponatremia, and her vital signs and mental status normalized. Now returned to baseline, she is discharged home shortly thereafter.

Discussion

MDMA ("Molly" or "Ecstasy") and ketamine are commonly used in the recreational setting, where they are often referred to as "club drugs." MDMA has both hallucinogenic and stimulant-like properties and is used to achieve these and other effects, including a sense of tranquility, euphoria, and increased emotional openness and empathy. Ketamine, which has FDA approval for use as an anesthetic agent, is also used recreationally, as subanesthetic doses induce prominent dissociative and hallucinogenic effects. Like PCP, MDMA and ketamine may have higher abuse potential compared to other hallucinogens [34, 35].

Acute treatment of MDMA and/or ketamine intoxication begins with medical assessment and stabilization, given the potential complications of unmonitored use. Adverse effects of acute MDMA intoxication are well established. MDMA intoxication may cause acute hypertension, tachycardia, and/or hyperthermia. Cardiac complications of MDMA intoxication can include hypertensive emergencies, arrhythmias, heart failure, and myocardial infarction [36]. Hyperthermia may be caused by direct drug effects on the central nervous system, as well as from physical exertion or environmental conditions, and can be lethal. As such, these patients may require rapid cooling to stabilize their temperature and to mitigate downstream adverse effects, including rhabdomyolysis, myoglobinuria, renal failure, and disseminated intravascular coagulopathy, among others [37, 38].

In a patient with autonomic instability, altered cognition, and symptoms of myoclonus, hyperreflexia, or tremor, there should be a high suspicion for serotonin syndrome (see Case 2 above for details regarding serotonin toxicity). In addition to serotonin syndrome, hyponatremia may occur in intoxicated patients (as it did in Sasha's case). This is largely the result of increased fluid intake due to the polydipsia that is commonly caused by MDMA, though syndrome of inappropriate antidiuretic

hormone (SIADH) may also contribute. Significant hyponatremia can lead to nausea, malaise, encephalopathy, seizures, and death [39]. Hepatotoxicity is another possible adverse effect, and laboratory values should be closely monitored [40]. Patients who present to the emergency room with complications of acute MDMA intoxication may require admission to the hospital for appropriate monitoring and treatment.

Various authors have proposed that environmental or behavioral factors surrounding MDMA use likely play more of a contributory role in the development of reported adverse events, such as vigorous dancing or physical activity, inadvertent disregard of physical cues, and excessive or reduced hydration resulting in hyperthermia or hyponatremia [41]. There has also been much concern raised through the years in the lay press, as well as by some researchers, about the potential neurotoxic effects of MDMA in humans [42, 43]; however subsequent reviews of these initial reports with follow-up analyses have countered that the concerning claims are based on animal studies that included unrealistically high doses of MDMA and on human studies comparing repeated use of MDMA, often concurrently with other substances [41, 44, 45]. This debate is ongoing, but from growing studies including MDMA-assisted psychotherapy, it does not appear that cognitive function is negatively impacted [41, 44, 45].

Like MDMA, ketamine can be used in the recreational setting, either alone or in combination with other drugs. At higher doses (like those used in anesthesia), it can suppress consciousness or induce coma. However, in smaller doses, it can cause reduced alertness, altered sensory perception, ataxia, cognitive impairment, and mild increases in heart rate and blood pressure [34]. Nystagmus can be seen but is less common than that seen in PCP intoxication. Chronic use can lead to urologic injury including ketamine-induced ulcerative cystitis, with symptoms of increased frequency and urgency of urination, dysuria, urge incontinence, and hematuria, and which may be irreversible even after cessation of use [46]. Frequent ketamine use can also be rarely associated with hydronephrosis or papillary necrosis [46]. Abdominal pain is a common complaint among chronic, heavy users of ketamine and may be associated with liver injury [46, 47]. Like with MDMA, chronic use of ketamine may also lead to cognitive deficits [48].

As with other substance use disorders, enrolling in an outpatient treatment program or inpatient rehabilitation center may be helpful for patients who want to decrease or stop use. Psychotherapeutic interventions including motivational interviewing can help patients understand the role that substance use plays in their lives [23]. Psychoeducation on adverse consequences may help patients recognize and seek help for any medical complications of their use; it is especially important for patients to be able to recognize life-threatening conditions such as malignant hyperthermia and serotonin syndrome. Pharmacologically, there are no FDA-approved treatments for hallucinogen use disorders. Pharmacological treatments for co-occurring substance use disorders, as well as treatment of any psychiatric comorbidities, may likely be helpful in these patients. And, as discussed above in Angel's case, 12-step support programs are a widely available and free community resource that may assist in supporting one's desire for abstinence.

Conclusion

In this chapter, we discussed scenarios clinicians may encounter with patients presenting with hallucinogen-related disorders. In acute intoxication of most hallucinogens (not including PCP), supportive care is often all that is needed to manage a patient's time-limited distress while waiting for the substance to metabolize over the typical course of several hours. Patients typically return to their neuropsychiatric and physical baseline without any residual symptoms or complications. However, acute PCP intoxication can present with altered mental status and bizarre and aggressive behavior that puts the patient and others at serious risk of harm, and so this condition often requires pharmacological intervention and continued observation. Additionally, it is imperative for patients presenting with altered mental status or severe vital sign abnormalities to be assessed for medical complications and to be triaged to the appropriate medical setting including an intensive care unit if appropriate. In the outpatient setting, being able to provide psychoeducation and harm reduction strategies for patients may also be useful, including education on the complications of chronic use of hallucinogens. In general, pharmacological treatments are limited for hallucinogen use disorders, but assessment and treatment of co-occurring substance use disorders and other psychiatric disorders are important. Outpatient substance use settings, community-based 12-step support groups, and inpatient rehabilitation programs may be helpful for patients who are struggling, but motivated, to decrease or abstain from use of hallucinogens.

Key Points

- Hallucinogens comprise a diverse group of substances with differing chemical structures and mechanisms of action but are classified together for producing similar subjective alterations in perception, mood, and cognition and for producing altered states of consciousness.
- Maladaptive patterns of drug use can be seen with PCP and ketamine, but hallucinogen use disorders, in general, are rare.
- PCP intoxication can produce significant medical complications and unpredictable neuropsychiatric symptoms that place both the patient and others at risk of harm and may warrant proper medical workup and observation with appropriate treatment to minimize serious complications and safety risks.
- "Set" (individual factors) and "setting" (environmental factors) can greatly impact one's overall experience with hallucinogens.
- Distress associated with other hallucinogen intoxication is often time-limited and can be generally managed with supportive care.
- There is a resurgence of scientific research focused on hallucinogens and hallucinogen-assisted psychotherapy, with numerous positive preliminary reports including safety and tolerability in targeting various psychiatric conditions, but there is much still to be learned about this class of substances.

- There are growing numbers of licensed mental health clinicians and facilities that offer psychotherapeutic services for individuals seeking assistance in processing and integrating difficult experiences with hallucinogens.

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