Hallucinogen Use and Misuse in Older Adults

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KEYWORDS

• Hallucinogen • Psychedelic • LSD • PCP • Ketamine • Older adults

INTRODUCTION

Hallucinogens, also known as psychedelics ("mind manifesting"), are substances that have been used for over a millennium.[1] These drugs produce sensory distortions and have been used by various cultures for several reasons ranging from religious ceremonies to recreational activities. The term hallucinogen is used to describe compounds, such as psilocybin and D-lysergic acid diethylamide (LSD), based on the belief that these drugs elicit hallucinations. It has been argued that, at the doses commonly taken recreationally, rarely will one experience frank hallucinations.[2]

The US federal law placed strict control of these substances in 1970. This greatly halted research efforts on the benefits of these drugs. Subsequently, there are limited comparable data available on hallucinogenic drug abuse in older adults. The evidence suggests that although illegal drug use is relatively rare among older adults compared with younger adults and adolescents, there is a growing problem of misuse and abuse of prescription drugs with abuse potential. At present, these data do not include hallucinogen use.

Recent studies have renewed interest in hallucinogens and their potential therapeutic use.[3–6] Most of the studies do not include a significant number of patients that would be classified as elderly (aged 65 years and greater). Most publications discussing or classifying hallucinogen use refer to older adults aged 50 or greater.

WHAT ARE HALLUCINOGENS?

Psychedelic plants, such mescaline and psilocybin, have been used for religious, healing, and celebratory purposes for more than six thousand years.[7,8]

Hallucinogens, as a drug category, include an enormous range of pharmacologic substances, with mechanisms of action ranging from *N*-methyl-D-aspartate (NMDA) antagonism (ie, phencyclidine [PCP]), muscarinic receptor antagonism (ie, scopolamine), k opioid agonism (ie, salvinorin A), mixed action monoamine release (ie,

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3,4-methylenedioxymethamphetamine [MDMA]), and a common main agonistic action on 5-HT2A receptors (ie, LSD).[9]

On a fundamental level, hallucinogens can be described as substances that predominantly cause changes in thought, perception, and mood with minimal intellectual or memory impairment.[10] They are typically divided into 2 types: classical and dissociative drugs (**Table 1**).

The classical hallucinogens comprise 3 main chemical classes: the plant-derived tryptamines (eg, psilocybin), phenethylamines (eg, mescaline), and the semisynthetic ergolines (eg, LSD).[11]

Psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine) comes from certain types of mushrooms found in tropical and subtropical regions of South America, Mexico, and the United States. Mescaline (Peyote) is a small, spineless cactus used to make synthetic LSD. It was first synthesized in 1938 by a Swiss natural products chemist, Dr Albert Hofmann,[12] who was looking for possible therapeutic uses of ergot derivatives.

In addition, there are synthetic ergolines, which include MDMA (also known as ecstasy), as well as 251-NBOMe, which has similarities to both LSD and MDMA but is much more potent. Also, of note, the drug ecstasy is often classified a hallucinogen because of its ability to cause subjective effects to distort time and induce distortions in visual perceptions as well as enhance enjoyment from tactile experiences. However, it also has some structural and psychoactive properties of stimulants.

N,*N*-Dimethyltryptamine (DMT) is a powerful chemical found naturally in some Amazonian plants. Ayahuasca is a tea made from such plants.[13] It is a brew used in traditional spiritual ceremonies by indigenous people of the Amazon Basin and has been legalized for ritual purposes in Brazil since 1987. It is often prepared with mixture of 2 plants, one containing the psychoactive substance DMT, a serotonin and sigma-1 receptor agonist, and another containing reversible monoamine oxidase inhibitors.[14]

The dissociative drugs include the following:

PCP was developed in the 1950s as a general anesthetic for surgery, but it is no longer used for this purpose because of serious side effects. PCP has various slang names, such as Angel Dust, Hog, Love Boat, and Peace Pill.[13]

Ketamine is a noncompetitive NMDA-receptor antagonist and a dissociative anesthetic developed in 1962. Much of the ketamine sold on the streets is stolen from veterinary offices. It is primarily sold as a powder or as pills, but it is also available as an injectable liquid. Ketamine is snorted or sometimes added to drinks as a date-rape drug. Slang names for ketamine include Special K and Cat Valium.[13]

Salvia (*Salvia divinorum*) is a plant common to southern Mexico, Central America, and South America. Salvia is typically ingested by chewing fresh leaves or by drinking

Table 1
Hallucinogens[9–13]

Classical	Dissociative
• Psilocybin known as magic mushrooms	• Phencyclidine (PCP)
• Mescline (Peyote)	• Ketamine: anesthetic
• D-Lysergic acid diethylamide (LSD)	• Dextromethorphan cough suppressant
• Methylenedioxymethamphetamine (MDMA): known as ecstasy	
• 251-NBOMe is a synthetic hallucinogen with similarities to both LSD and MDMA	
• *N*,*N*-dimethyltryptamine (DMT)	
• Ayahuasca tea	

their extracted juices. The dried leaves of salvia can also be smoked or vaporized and inhaled. Popular names for salvia are Diviner's Sage, Maria Pastora, Sally-D, and Magic Mint.[13]

Epidemiology

The Controlled Substances Act of 1970 was a federal act passed by the US Congress that placed comprehensive drug control policy under federal control. This included the laws related to the manufacturing, possession, sale, import, and distribution of certain substances. The initial bill passed by Congress included a list of substances, but the Drug Enforcement Agency and the Food and Drug Administration (FDA) have regulated the ongoing restrictions in partnership.[15]

They classified hallucinogens as schedule 1 drugs, which are defined as having no accepted medical use and potential to cause significant harm and dependence. Even during inception, this ruling was viewed as being unscientific. Despite the lack of scientific evidence to support the initial claims, these drugs have remained schedule 1 drugs as originally ruled.

Therefore, by the late 1960s and early 1970s, the scientific inquiries fell out of favor because classical psychedelics were being used outside of medical research and in association with the emerging recreational use.

The lifetime prevalence rates and 12-month prevalence rates for total drug use disorders for age group 45 to 64 are 9.7% and 2.5%, respectively. For those aged 65 and up, lifetime and past-year prevalence rates reach 2% and 0.8%, respectively.[16]

In 2010, an estimated 32 million people reported a lifetime use of LSD, psilocybin, mescaline, or peyote. The prevalence of psychedelic use was low among people aged 65 and older, being reported as 1.3%.[17] In a follow-up study, it was shown that the lifetime hallucinogen use is prevalent and highly comorbid with other substance use and psychiatric disorders. In a study published in 2019 (data were collected from April 2012 through June 2013), the 12-month prevalence and lifetime hallucinogen use were 0.62% and 9.32%, respectively, for all ages. For the age group 45 to 64 years, lifetime prevalence was 11.32%, with a 12-month prevalence of 0.08%. In those aged 65 years and older, rates were 1.74% for lifetime and 0% for the past-year use.[18]

The overall LSD use in the United States increased to 56.4% from 2015 to 2018. For those aged 50 years or older, there was an increase from 1.83% to 2.66%. There was a significant increase (223.1%) in LSD use in older adults (particularly those aged 35–49) and a 45% increase in individuals greater than 50 years of age.[19]

MECHANISMS OF ACTION

It has been hypothesized that the hallucinogenic effects of these drugs in humans are mediated in whole or in part via 5-HT2 receptors.[20] It is the agonistic action on 5-HT2A receptors that produces the psychedelic effect, independently of dopamine stimulation.[21]

Both PCP and ketamine exert their effects by antagonism of NMDA receptors. This may also play a role in their potential therapeutic benefits.[22]

EFFECTS ON MIND AND BODY

The effects of hallucinogens are heavily dependent on the expectations of the user ("set") and the environment ("setting") in which the use takes place. Indeed, no clinician experienced with these substances would fail to consider set and setting as primary determinants of the experience. Thus, expectations and environments that

would foster religious or spiritual experiences increase the probability of the drug producing such an effect. Conversely, use in a nonstructured, unwise, or recreational way can have unpredictable and even disastrous psychological consequences.[23]

Results suggest that even in today's context of "recreational" drug use, psychedelics, such as LSD and psilocybin, when taken at higher doses, continue to induce mystical experiences in many users.[24]

There was a study in which low doses of LSD were given to older healthy volunteers to measure the safety risks. A total of 48 subjects were divided into 1 of 4 dose groups: 5 μg, 10 μg, or 20 μg LSD, or placebo. They received their assigned study dose on 6 separate occasions over 21 days within a 96-hour interval. Overall, results suggest that administration of low-dose LSD carried no safety risk and was well tolerated during the limited 21-day period studied. Evaluation of cognitive and behavioral outcomes indicates a favorable safety profile overall, further supporting the feasibility of periodic LSD administration up to 20 μg.[25]

Healthy patients (with the oldest being aged 51) were given 200 μg of LSD, and they experienced pronounced alteration in waking consciousness, including visual perceptual alterations, audiovisual synesthesia, and positively experienced derealization and depersonalization. LSD did not induce pronounced anxiety and overall produced high ratings of good drug effects and low ratings of bad drug effects.[26]

ACUTE EFFECTS

Clinical effects of hallucinogens range from somatic symptoms, such as dizziness, to major psychological symptoms, including visual hallucinations[27] (**Table 2**).

Although hallucinogens are relatively safe physiologically and are not considered drugs of dependence, their use involves unique psychological risks. The most likely risk is overwhelming distress during drug action ("bad trip"), which could lead to potentially dangerous behavior.[28]

Of note, the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) makes distinction between PCP use disorders and other hallucinogen use disorders. There is also a notable difference with intoxication symptoms because of PCP versus other hallucinogens (shown in **Table 3**). One main difference is that the other hallucinogens, such as LSD, exert their physical effects via stimulation of the sympathetic nervous system. This can lead to dilated pupils, tachycardia, increased cardiovascular risk, insomnia, and increased blood pressure.[29]

These adverse effects may be amplified in older patients, who may also have multiple medical comorbidities. For example, dizziness may put them at increased risk of falls, or increased blood pressure may increase their risk of stroke or cardiovascular events.

Table 2
Effects from hallucinogens[27–29]

Mind and Body	Short- and Long-Term Effects
• Mystical experience • Ego dissolution • Positively experienced derealization and depersonalization • Dizziness and weakness	• Blurred vision and paresthesia • Difficulty focusing but improving hearing • Mood swings • Visual hallucinations • Flashback/hallucinogen persisting perception disorder (HPPD)

Table 3
Intoxication[50]

Phencyclidine (PCP)	Other Hallucinogens
• Behavioral changes, such as belligerence, aggressivity, and agitation • Nystagmus • Hypertension or tachycardia • Numbness • Ataxia • Dysarthria • Muscle rigidity • Seizures or coma • Hyperacusis	• Behavioral changes, such as anxiety, depression, "losing one's mind," or paranoia • Depersonalization or derealization • Hallucinations or illusions • Pupillary dilation • Tachycardia • Sweating and palpitations • Blurring vision • Tremor • Incoordination

POTENTIAL BENEFITS

Over the past several years, a phenomenon known as "microdosing" has become popular, leading to several observational studies demonstrating benefits and challenges related to the use of these substances.[30]

"Microdosing" is associated with enhanced mood and work performance, via increased energy, concentration, and creativity. Also, most individuals who engage in microdosing had at some point in their life used psychedelics as the regular recreational dose.[31] This could lead one to hypothesize that older people who engaged in recreational use of hallucinogens when younger might engage in using microdoses of hallucinogens to help improve mood and cognition in late life.

More recently, several human studies have been conducted that are driving further research into the possible therapeutic benefits of hallucinogens in the management of psychiatric disorders. Some of these are mentioned in later discussion.

Depression

Hallucinogens have been a subject of curiosity in the treatment of depression for many decades. Psilocybin has been of particular interest in this regard in recent years. Therapeutically, psilocybin has made subjects more vividly aware of memories and promotes an overall feeling of well-being as well as reverses negative cognitive biases or distortions. Therefore, in clinical trials, psilocybin is often used to target anxiety-related disorders and depression.[32] Acutely, treatment with psilocybin has been shown to decrease amygdala reactivity during emotion processing and that this was associated with an increase of positive mood in healthy volunteers. These findings may be relevant to the normalization of amygdala hyperactivity and negative mood states in patients with major depression.[33] Larger double-blind, randomized, placebo-controlled, crossover trials have shown acute and sustained decrease in anxiety and depression symptoms after therapeutic administration of psilocybin in patients with cancer.[34]

Although LSD was an area of interest in the mid-twentieth century, statistically significant efficacy in the treatment of depression was not found. A recent study examined the effects of low-dose LSD versus placebo via functional MRI scans. Remarkably, the findings revealed extensive changes in brain connectivity and a subjective change in mood positivity.[35]

Other smaller studies have revealed a reduction in impulsive behavior, psychological distress, and suicidal ideation in patients with hallucinogen use. In comparison, other illicit drug use has been associated with an increase in such behavior.[36]

NMDA receptor-modulating drugs, such as ketamine, have been used in the treatment of depression. Safety and tolerability profiles with ketamine at low single dose are generally good in depressed patients. However, there is a lack of data concerning ketamine with repeated administration at higher doses.[6]

In a recent double-blind, controlled, multiple-crossover study, ascending doses of ketamine were given to older adults with treatment-resistant depression. There were a total of 16 participants 60 years or older. They were given single dose of 0.1, 0.2, 0.3, 0.4, or 0.5 mg/kg in separate treatment sessions at least a week apart. A single dose of midazolam 0.01 mg/kg was used as an active control treatment and was randomly inserted within the first 3 treatment sessions. Seven of 14 randomized controlled trial (RCT)-phase completers remitted with ketamine treatment. In addition, 2 of the 7, who did not remit after a single treatment (in the RCT phase), did attain remission after multiple treatments in the open-label phase. The investigators suggest that some who do not remit after 1 treatment may yet attain a meaningful remission after repeated treatments given at the same dose level at this treatment frequency. Ketamine was well tolerated, with the most common side effects being transient dizziness, fatigue, and blurred vision.[37]

In a small study, intravenous ketamine was given to older adults with treatment-resistant depression to evaluate its safety and efficacy. Six patients, aged 65 to 82, were given subanesthetic ketamine at a dose of 0.5 mg/kg delivered intravenously over 40 minutes. Five patients showed a robust response, after the acute phase, but they all lost the response over time. However, none returned to their baseline level of depression.[38]

The clinical use of ketamine has been increasing. Intranasal (S)-ketamine has recently been approved for depression by the FDA. It could be a promising treatment in depressed patients with suicidal ideation.[39]

Thus far, there have been limited results with the use of esketamine in older patients. In a double-blind randomized study, patients aged 65 and older with treatment-resistant depression were given either esketamine nasal spray combined with oral antidepressant (esketamine/antidepressant) or oral antidepressant and placebo nasal spray (antidepressant/placebo). There was no statistically significant change in the Montgomery-Åsberg Depression Rating Scale from baseline to day 28, as the primary endpoint. Further studies are thus needed to better evaluate the efficacy of esketamine in the elderly.[40]

In addition, there is some evidence supporting the safety and therapeutic value of single-dose ayahuasca, to help treat depression.[41]

Anxiety and Posttraumatic Stress Disorders

As mentioned above, psilocybin has been shown to also reduce symptoms of anxiety in patients with cancer.[41] A small modified double-blind study revealed a marked decrease in symptoms of obsessive-compulsive disorder in 9 patients when treated with psilocybin in a controlled environment.[42] MDMA has also shown promise in the treatment of anxiety disorders when used with adjunctive psychotherapy. MDMA-assisted psychotherapy with close follow-up, monitoring, and support has been shown to be effective in the treatment of chronic, treatment-resistant posttraumatic stress disorder.[43]

Substance Use Disorders

Psilocybin has been shown to be effective and safe in the treatment of alcohol dependence. It helped to decrease cravings and increase in length of abstinence from

alcohol use.[44] Positive results were also seen when psilocybin was used for smoking cessation.[45]

Treatment with LSD has been studied and has shown benefit in the management of alcohol use disorder. A meta-analysis of RCT to evaluate the clinical efficacy of LSD in the treatment of alcohol use disorder revealed that a single dose of LSD, in conjunction with various alcoholism treatment programs, is associated with a decrease in alcohol misuse.[5]

Neurocognitive Disorders

Some preliminary findings indicate that psychedelic drugs have effects on several cognitive/affective processes that are altered in older adulthood. These findings also propose that hallucinogen use increases neuroplasticity, neurogenesis, connectedness, and mystical experiences, which have been reasoned to underlie cognitive/affective changes.[46] In addition, functional MRI studies have shown increased connectivity between regions with high 5HT2A receptor density following LSD administration, suggesting that reorganizing of dysfunctional neural circuitry is an important component of the neuroplastic effects of 5HT2A receptor agonists.[47] Furthermore, hallucinogens have been shown to have strong anti-inflammatory properties, which may represent an opportunity in the prevention of Alzheimer disease, which has largely been thought to result from inflammatory processes.[48]

Recently, a study has been proposed to evaluate the effects of repeated low doses of psilocybin and LSD on cognitive and emotional dysfunctions in Parkinson disease.[49]

DIAGNOSTIC CRITERIA FOR PHENCYCLIDINE AND OTHER HALLUCINOGEN USE DISORDER

Its main features include a problematic pattern of use that leads to clinically significant impairment or distress.[50] One can have tolerance without having dependence (**Box 1**).

LONG-TERM EFFECTS

It was initially thought that the lifetime use of psychedelics would not cause any undesirable long-term effects. In fact, early evidence showed there was no association with any past year negative mental health outcomes, which included serious psychological distress, mental health treatment (inpatient, outpatient, medication, felt a need but did not receive), or symptoms of major mental health disorders.[51] In a review involving contemporary studies (1994 to present), the long-term effects that were associated with use of classical hallucinogen were generally positive ones. These effects include sustained changes in personality/attitudes, depression, spirituality, affect/mood, anxiety, well-being, substance use, meditative practices, and mindfulness.[52]

Evidence supports the association of LSD use with panic reactions, prolonged schizoaffective psychoses, and posthallucinogen perceptual disorder, the latter being present continuously for up to 5 years.[53] MDMA use has been associated with depression, anxiety, elevated impulsiveness, and memory deficits. The symptoms may persist for up to 2 years after cessation.[54]

The terms flashback and hallucinogen persisting perception disorder (HPPD) are often used interchangeably in professional literature. This unique condition is described as the recurrence of some of the symptoms that appeared during the intoxication after the immediate effect of the hallucinogen has worn off. This recurring syndrome, mainly visual, has not been clearly understood, appreciated, or distinguished from other clinical entities by clinicians. Flashback is usually a short-term,

Box 1
Diagnostic criteria for phencyclidine and other hallucinogen use disorder[50]

A problematic pattern of phencyclidine (or other hallucinogen) use leading to clinically significant impairment or distress, as manifested by at least 2 of the following, occurring within a 12-month period:

1. Phencyclidine (or other hallucinogen) is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control phencyclidine (or other hallucinogen) use.
3. A great deal of time is spent in activities necessary to obtain phencyclidine (or other hallucinogen), use phencyclidine, or recover from its effects.
4. Craving, or a strong desire or urge to use phencyclidine (or other hallucinogen).
5. Recurrent phencyclidine (or other hallucinogen) use resulting in a failure to fulfill major role obligations at work, school, or home (eg, repeated absences from work or poor performance related to phencyclidine use; phencyclidine-related absences, suspensions, or expulsions from school; or neglect of children or household).
6. Continued phencyclidine (or other hallucinogen) use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of phencyclidine (eg, arguments with a spouse about consequences of intoxication or physical fights).
7. Important social, occupational, or recreational activities are given up or reduced because of phencyclidine (or other hallucinogen) use.
8. Recurrent phencyclidine (or other hallucinogen) use in situations in which it is physically hazardous (eg, driving an automobile or operating a machine when impaired by a phencyclidine).
9. Phencyclidine (or other hallucinogen) use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by phencyclidine.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of phencyclidine to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of phencyclidine.

Withdrawal symptoms and signs are not established for phencyclidines and other hallucinogens, so this criterion does not apply.

nondistressing, spontaneous, recurrent, reversible, and benign condition accompanied by a pleasant affect. In contrast, HPPD is a generally long-term, distressing, spontaneous, recurrent, pervasive, either slowly reversible or irreversible, nonbenign condition accompanied by an unpleasant dysphoric affect.[55] In most cases, most HPPD cases have been induced by LSD or PCP.[56]

Additional long-term effects were associated with thinning of the posterior cingulate cortex, thickening of the anterior cingulate cortex, and decreased neocortical 5-HT2A receptor binding. These results suggest that hallucinogens increase introspection and positive mood by modulating brain activity in the fronto-temporo-parieto-occipital cortex.[57]

At very high doses, patients have experienced severe behavioral disorders, paranoid ideations, and amnesia for the entire period of the in-hospital stay. In addition, shallow respiratory excursions and periods of apnea and cyanosis coincided with generalized extensor spasm and spasm of neck muscles. In drug-abusing patients,

PCP toxic psychosis should be considered if patients present with schizophrenia-like symptoms, psychosis, or other bizarre behavior, whether they admit to taking PCP or not.[58]

It is estimated that 10.2% of the current US population has taken LSD. That averages to approximately 31 million people that have ever used LSD. Thus far, there has not been a single documented death owing to LSD at recreational doses. When fatalities occur after LSD use, they have been attributed to risky and dangerous activities, such as walking across a busy highway, attempting to swim, or rock climbing. In the only 2 documented cases when LSD presumably directly led to fatality, postmortem analysis indicated that the decedents had ingested massive doses of LSD.[59]

TREATMENT OPTIONS

For hallucinogen use disorder and substance-induced psychosis, no controlled trials for treatment have been performed. No established pharmacologic treatments to decrease use of hallucinogens currently exist. Medication options are often used to control the behavioral symptoms.

SUMMARY

Even though hallucinogens have been around for a millennium, there are limited data showing their impact in older adults. However, it is known that when these substances are used, they can induce a variety of effects, including hallucinations, depersonalization, and derealization as well as changes in one's mood and behaviors. The effects may last for a short period or even cause long-term issues. Hallucinogens are not usually associated with dependency and uncontrollable drug-seeking behaviors. Therefore, there has been a renewed interest in possible therapeutic benefits, notably at small doses. More time and in-depth studies are needed in humans across all ages before we can truly gain more insight into the actual benefits versus long-term consequences of these powerful, mind-altering agents, notably in the geriatric population.

CLINICS CARE POINTS

- Hallucinogens are a diverse group of drugs that alter perception, thoughts, and feelings. They cause hallucinations or sensations and images that seem real, but they are not.
- Hallucinogens are split into 2 categories: classical hallucinogens and dissociative drugs.
- They produce their psychedelic effect via their agonistic action on 5-HT2A receptors, independently from dopamine stimulation.
- These substances are not usually viewed as drugs of abuse because of a lack of dependency or dopamine reward.
- Some long-term consequences associated with their use include flashbacks and hallucinogen persisting perception disorder.
- Hallucinogens may have potential therapeutic benefits to enhance mood, decrease anxiety, and decrease posttraumatic stress disorder, help with alcohol use disorder, and promote neuroplasticity.

DISCLOSURE

The authors have nothing to disclose.

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