

The rebirth of psychedelic psychiatry

Recent research suggests psychedelic agents might help treat anxiety, depression, other disorders

Brian Holoyda, MD, MPH, MBA

Forensic Psychiatrist
Martinez Detention Facility
Martinez, California

Disclosure

The author reports no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

doi: 10.12788/cp.0079

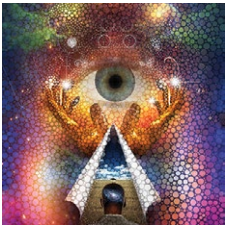
Mr. P, age 65, has a history of major depressive disorder (MDD), generalized anxiety disorder, and social phobia. Mr. P's personality is high in neuroticism and he has often responded to new situations with feelings of impending doom. For him, fear, anxious rumination, helplessness, and catastrophizing are familiar mental processes.

When he was in his 30s, Mr. P had a severe major depressive episode with suicidal ideation and sought care from a psychiatrist. He began a treatment program of psychotherapy and concomitant psychopharmacotherapy with consecutive trials of fluoxetine, sertraline, and amitriptyline, each of an adequate dose and duration. With each medication, Mr. P experienced new adverse effects, including nausea, constipation, tremors, and headache. His psychiatrist transitioned him to bupropion, which helped Mr. P most. For the next several decades, Mr. P continued to experience low-grade depressive symptoms with intermittent exacerbation to mild-to-moderate major depressive episodes, but he remained adherent to his medication and continued psychotherapy.

Shortly after his 65th birthday, Mr. P experiences progressively worsening nausea and abdominal pain. Initially, he assumes the symptoms are secondary to anxiety. Taking his psychiatrist's advice, Mr. P visits his primary care physician. A work-up reveals that Mr. P has advanced pancreatic cancer, and an oncologist estimates Mr. P has 6 months of life remaining.

Following his cancer diagnosis, Mr. P quickly develops symptoms of MDD despite continuing to take bupropion. Within a week he becomes withdrawn and hopeless, and thinks about ending his life "before God does." His psychiatrist urges Mr. P to contact the local academic medical center because it is conducting a trial of a "new" drug, psilocybin, to treat anxiety and depression in patients with terminal illness.

continued



Psychedelic psychiatry

Clinical Point

Increased research and relaxed political concern related to psychedelics might make it possible for the FDA to approve their clinical use



Discuss this article at
www.facebook.com/MDedgePsychiatry

Beginning in the 1940s, a growing body of scientific evidence suggested that psychedelic compounds such as lysergic acid diethylamide (LSD) could benefit individuals with various psychiatric maladies. Research interest in LSD and substances with similar effects persisted until the late 1960s. In response to the growing counterculture movement in the United States and the efforts of Harvard researchers Timothy Leary and Richard Alpert to popularize psychedelic drug use in the general population, in 1970 President Richard M. Nixon signed the Controlled Substances Act (CSA) into law. The CSA categorized LSD as a Schedule I drug, rendering its manufacture and distribution illegal. Research into the potential therapeutic benefits of LSD was effectively halted.¹ In recent decades, however, there has been a quiet but growing renaissance of scientific interest in the effects of psychedelics on a variety of conditions, including terminal illness-related anxiety and depression, treatment-resistant depression, and substance use disorders (SUDs). One example is psilocybin, which is currently undergoing Phase 2 and 3 clinical trials in North America and Europe for treatment-resistant depression.

As researchers have once again picked up the torch in the pursuit of psychedelic therapeutics, jurisdictions in the United States are also relaxing their stance on these drugs. In 2019 and early 2020, Denver, Oakland, and Santa Cruz became the first 3 cities in the United States to decriminalize the possession of various psychedelic substances.²⁻⁴ With the passage of Measure 109 in November 2020, Oregon became the first state to decriminalize the use of psychedelic mushrooms in therapeutic settings.⁵ The combined forces of increased research and relaxed political concern related to psychedelics might make it possible for the FDA to approve their use for psychiatric conditions. Therefore, it is critical for psychiatrists to understand the psychopharmacology, range of effects, and potential risks and benefits of these agents. In this article, I describe what psychedelics are and how they work, summarize a few research findings about psilocybin, and offer a framework for psychedelic psychiatric practice in the years to come.

What are psychedelics?

Psychiatrist Humphry Osmond first coined the term “psychedelic” in 1957 at a meeting of the New York Academy of Sciences, where he was discussing his research on the effect of LSD on patients at the Weyburn Mental Hospital in Saskatchewan, Canada.⁶ Prior to 1957, LSD had been described as a “psychotomimetic” drug because it was believed to induce a state of psychosis similar to that experienced in schizophrenia. But LSD does not generally induce frank auditory hallucinations or clearly defined delusional beliefs. Osmond’s new term—derived from the Greek words *psyche*, meaning “mind,” and *delos*, meaning “to show”—referred to the “mind-manifesting” capacities of LSD and related drugs.⁶ Psychedelic drugs can cause an array of changes to an individual’s conscious experience, from relatively mild changes in visual perception to profound derangements in sense of self and reality.

Classic psychedelics vs other compounds

Before describing the effects of psychedelic drugs and how they may relate to their therapeutic potential, it is useful to define which compounds are considered “classic psychedelics.”

The classic psychedelics are substances that operate primarily through activation of the serotonin 5-hydroxytryptamine receptor 2A receptor (5-HT_{2A}) (*Table 1, page 15*). Many psychedelic drugs are derived from natural sources, including plants, fungi, and animals. For example, *N,N*-dimethyltryptamine (DMT), which is one of the most potent psychedelic compounds, is found in various plant species and can be imbibed in a tea known as ayahuasca, most commonly in the context of spiritual ceremonies.

Other compounds. Some researchers continue to classify other compounds as “psychedelics,” although the mechanisms of action and effects of these compounds may vary greatly from those of the classic psychedelics. These include the dissociative anesthetics ketamine and phencyclidine (PCP), which exert their effects via *N*-methyl-D-aspartate

Table 1

The classic psychedelics and their natural sources

Chemical name	Common name(s)	Natural sources
5-methoxy- <i>N,N</i> -dimethyltryptamine (5-MeO-DMT)	Toad	Yopo tree (<i>Anadenanthera peregrina</i>) seeds Colorado River toad (<i>Bufo alvarius</i>) and Sonoran Desert toad (<i>Incilius alvarius</i>) skin exudate
<i>N,N</i> -dimethyltryptamine (DMT)	Spirit molecule	Chacruna shrub (<i>Psychotria viridis</i> ; a component of the ayahuasca brew) and other plant species
Lysergic acid diethylamide (LSD)	Acid	Derived synthetically from ergot fungus (<i>Claviceps purpurea</i>)
Mescaline (3,4,5-trimethoxyphenethylamine)	Peyote	Cacti species (<i>Lophophora williamsii</i> , <i>Echinopsis pachanoi</i> , <i>Echinopsis peruviana</i>)
Psilocybin, psilocin	Magic mushrooms, shrooms	<i>Psilocybe</i> mushroom species

Source: Reference 7

(NMDA) receptor antagonism, and the empathogen 3,4-methylenedioxymethamphetamine (MDMA), which acts primarily through monoamine reuptake inhibition.

The DSM-5⁸ does not differentiate between classic psychedelics and related compounds. In its chapter on Substance-Related and Addictive Disorders, the section Hallucinogen-Related Disorders provides criteria for the diagnoses of phencyclidine use disorder and other hallucinogen use disorder. Researchers generally have abandoned the term “hallucinogen” because psychedelics typically do not induce frank hallucinations. Furthermore, lumping psychedelics and compounds such as MDMA and ketamine into the category of “other hallucinogen” fails to address important distinctions between them, including diagnostically relevant issues. For example, psychedelics do not cause symptoms of physiologic dependence such as craving or a withdrawal syndrome, whereas MDMA can.⁹ The DSM-5 also contains a diagnosis called hallucinogen persisting perception disorder (HPPD), referring to residual distortions of visual perception that remain following psychedelic intoxication. Although the text notes the estimated prevalence of HPPD in individuals who use psychedelics is 4.2%, the condition is thought to occur infrequently in both therapeutic and recreational users.¹⁰

How psychedelics work

Psychedelics can induce a spectrum of effects that are not necessarily dose-dependent. Mild effects of intoxication include altered sensory perception in visual, auditory, proprioceptive, and somatosensory spheres, including synesthesia. Progressively more severe changes include a distorted or eliminated perception or awareness of space, time, body, and self, resulting in derealization and depersonalization. Some of the most extreme alterations of consciousness reported by users include mystical or transcendent experiences of birth, giving birth, death, exchanging bodies with a nonhuman species, and meeting otherworldly beings.¹¹ In terms of neurophysiology, psychedelics cause altered cerebral blood flow and metabolism, increased connectivity between brain regions that do not typically communicate, and a reduction in the activity of a group of cortical structures called the default mode network (DMN).¹²

Researchers hypothesize that the disruption of DMN activity may be a key mechanism accounting for psychedelics' therapeutic effects in mental illness. The DMN is a group of structures that includes the posterior cingulate cortex, the medial prefrontal cortex, the angular gyrus, and other cortical areas that are active when an individual is not engaged in a particular mental task (for example, during mind wandering). It is thought to underlie introspection and to

Clinical Point

Disruption of the default mode network may account for psychedelics' therapeutic effects



Psychedelic psychiatry

Clinical Point

Psychedelics might help patients develop greater emotional and cognitive flexibility

Table 2
Practical considerations for psychiatrists who prescribe psychedelics

Consideration	Relevant factors
Screening for patients likely to have a challenging or adverse experience (“bad trip”)	In clinical trials, researchers have largely screened out participants with a personal or family history of psychotic or bipolar disorders. ²² It remains unclear if psychedelic sessions can cause de novo psychotic disorders or trigger psychotic episodes in vulnerable patients.
Managing acute medical and psychiatric complications	There have been case reports of patients experiencing limb ischemia and rhabdomyolysis with subsequent renal failure from the use of LSD and psilocybin, respectively. ¹¹ Although less likely, patients may become agitated and violent during a challenging experience, and may require a sedative or physical restraint to maintain safety.
Informed consent	Patients should understand the potential serious risks of undergoing psychedelic treatment. Patients will likely lose capacity to make medical decisions once a psychedelic session begins. Patients’ wishes regarding certain scenarios should be known prior to initiating treatment (for example, whether they allow supportive touch during a session).
The use of guides	Due to time constraints, psychiatrists are not likely to be present during a patient’s psychedelic session, but supportive staff or “guides” should be present. Guides should be trained and up-to-date on published recommendations from leading organizations involved in community psychedelic practice. ^{23,24}

LSD: lysergic acid diethylamide
Source: Adapted from Reference 21

serve as an “orchestrator” of global brain function.¹³ Theoretically, then, by temporarily disrupting the neural circuits responsible for maintaining ingrained, negative thought and behavioral patterns, as observed in patients with depression or SUDs, psychedelics can help patients develop greater emotional and cognitive flexibility and identify new ways to view the world and to solve problems.

Evaluating psychedelics as therapeutic agents

The renaissance of research into psychedelics as therapeutic agents during the last 2 decades has produced some promising preliminary findings. In 2020, the American Psychiatric Association’s Work Group on Biomarkers and Novel Treatments published a review of the best evidence on the topic.¹⁴ Psilocybin is the most studied drug because compared with LSD, it carries less of a stigma and has a shorter duration of action. Psilocybin has been studied as a potential

treatment for several psychiatric disorders, including terminal illness–related depression and anxiety, and SUDs.

Griffiths et al.¹⁵ In a double-blind randomized crossover study at Johns Hopkins School of Medicine, Griffiths et al¹⁵ administered a high dose (22 or 30 mg/70 kg) and a very low, placebo-like dose (1 or 3 mg/70 kg) of psilocybin at 2 separate sessions to 51 patients with terminal cancer and associated depressive and anxiety disorders. After 5 weeks, the participants assigned to one condition crossed over to the other condition. High-dose psilocybin had a significant effect on depression and anxiety symptoms within 5 weeks that persisted over 6 months of follow-up. At 6 months, 78% of participants experienced a response in depressive symptoms ($\geq 50\%$ decrease in GRID-Hamilton Depression Rating Scale [HAM-D-17] baseline scores) and 65% remitted (GRID-HAM-D-17 score ≤ 7). At 6 months, 83% of participants had a response in anxiety symptoms ($\geq 50\%$ decrease in Hamilton Rating Scale for

continued on page 18



Psychedelic psychiatry

Clinical Point

Some initial evidence suggests psilocybin may be useful for treating terminal illness–related anxiety and depression

Table 3

Typical elements of ‘set’ and ‘setting’ during psychedelic sessions

Set elements	Setting elements
Presence and severity of distressing psychiatric symptoms	Physical location of the session
Relevant personality traits (eg, neuroticism, openness, etc.)	Perceptual stimuli present during the session (eg, use of music, visual imagery, tactile cues)
Goals, expectations, and fears regarding the psychedelic session	Presence of a trained guide to support and assist
Knowledge of psychedelics and prior experience using them	
Religious and spiritual beliefs	

Source: Reference 7

Anxiety [HAM-A] baseline scores) and 57% remitted (HAM-A \leq 7).

Johnson et al.^{16,17} In an open-label pilot study¹⁶ and \geq 12-month follow-up study,¹⁷ Johnson et al administered a moderate (20 mg/70 kg) and high (30 mg/70 kg) dose of psilocybin to 15 participants enrolled in a 15-week smoking session program. The psilocybin sessions were scheduled at Weeks 5 and 7, with an optional psilocybin session at Week 13. The sessions included nondirective support from program staff, but not smoking cessation content. Relying on laboratory-verified exhaled carbon monoxide and urine cotinine measures, researchers found an 80% abstinence rate at 6 months, a 67% abstinence rate at 12 months, and a 75% abstinence rate at 2.5 years.^{16,17}

Bogenschutz et al¹⁸ conducted a study of 10 patients who met DSM-IV criteria for alcohol dependence and had at least 2 heavy drinking days in the previous 30 days. They found that a 14-session treatment program that included 2 psilocybin-assisted psychotherapy sessions with dosages of 0.4 mg/kg resulted in a significant increase in self-reported alcohol abstinence at 4 weeks that persisted for 36 weeks.¹⁸

Although these studies were small, open-label, and had other methodologic flaws, their pilot work has led to larger-scale projects assessing psilocybin’s therapeutic potential. Psilocybin has also been studied for treatment-resistant depression and obsessive-compulsive disorder. Other clinical trials underway are investigating psilocybin for the treatment of cocaine and opioid use

disorder, anorexia nervosa, and depression in Alzheimer’s disease.¹⁴ Although psilocybin is currently the best-studied psychedelic, there is some research demonstrating that LSD can also induce a persistent reduction in anxiety symptoms associated with terminal illness¹⁹ and that ayahuasca causes a rapid reduction in depressive symptoms that persists over 21 days.²⁰

The future of psychedelic psychiatry

If psychedelic compounds become approved for the treatment of psychiatric conditions, psychiatrists will likely be responsible for prescribing them and managing patients who receive them.²¹ **Table 2**^{11,21-24} (**page 16**) summarizes practical considerations for psychiatrists who may someday be prescribing psychedelic drugs. Areas of psychedelic treatment in which psychiatric expertise is necessary include:

- screening for patients at increased risk for a challenging or adverse experience or “bad trip”
- conducting a thorough informed consent process in which the risks are discussed and the patient’s wishes regarding potential situations are elicited
- managing acute medical and psychiatric complications, including agitation and violent behavior
- ensuring the use of trained guides during sessions.

Psychiatrists who are interested in providing psychedelic-assisted therapy should

understand the concept of “set and setting,” which was defined by Timothy Leary in the 1960s and is thought to play an important role in determining the types of experiences that arise during a psychedelic session.²⁵ “Set” refers to an individual’s mindset going into a session, and “setting” refers to the environment in which the session occurs. Typical elements of each are summarized in *Table 3*⁷ (page 18). Psychiatrists will play a critical role in assessing and preparing the “set” by screening patients appropriately, assessing patient goals, and providing a thorough informed consent procedure. Psychiatrists should also be mindful of the “setting,” providing a comfortable, safe, familiar environment and access to appropriate music and eyeshades, if desired. Due to time restraints, psychiatrists are not likely to be responsible for guiding patients through sessions, and should educate themselves about ethical practices of psychedelic guides, if they are in the position to hire guides.^{23,24}

Psychiatrists may also play a role in providing psychotherapy to patients receiving treatment with psychedelics. These substances can induce both transcendent and terrifying experiences. Patients therefore require “integration” therapy sessions to assist with processing the content of their psychedelic treatment and incorporating the experiences into day-to-day life. In an online survey of nearly 2,000 individuals who used psilocybin recreationally, 7.6% reported that they had to seek treatment for enduring psychological symptoms that they attributed to their psilocybin use, including persistent anxiety, fear, paranoia, and depression.²⁶ Integrative psychotherapy sessions may help reduce the risk of persistent negative effects from therapeutic

Related Resources

- Nutt D. Psychedelic drugs—a new era in psychiatry? *Dialogues Clin Neurosci*. 2019;21(2):139-147.
- Garcia-Romeu A, Kersgaard B, Addy PH. Clinical applications of hallucinogens: a review. *Exp Clin Psychopharmacol*. 2016; 24(4):229-268.

Drug Brand Names

Amitriptyline • Amitril, Elavil	Fluoxetine • Prozac
Bupropion • Wellbutrin	Sertraline • Zoloft

psychedelics, as well as enhance their beneficial effects.

CASE CONTINUED

Mr. P is enrolled in the academic medical center study assessing the effect of psilocybin on terminal illness-related anxiety and depression. During a 5-hour, 30-mg psilocybin session, he initially experiences distorted visual cues, with vivid, colorful geometric patterns collapsing into each other. He then loses the concepts and experience of time, space, and his body, as his visual distortions convert to darkness. After what seems like a decade within the darkness, he sees himself lying in a hospital bed with loved ones surrounding him. He watches himself take his last breaths and his family members weep as he dies. As he regains his senses, Mr. P feels that he is being reborn.

In the therapy sessions that follow the psychedelic session, Mr. P reports feeling “finally freed” from the fear, sadness, and anger that he has felt throughout his life. He comes to accept his impending death with gratitude and peace. In his final days, he no longer experiences depression or anxiety. Mr. P’s friends and family members comment that he seems to be the best version of himself in the months that lead up to his death.

continued on page 44

Clinical Point

‘Set’ and ‘setting’ are thought to play an important role in determining the types of experiences that arise during a psychedelic session

Bottom Line

Psychedelics are a class of consciousness-altering agents that have become a potentially promising source of new treatments for psychiatric illness. Although more evidence is needed, compounds such as psilocybin may one day become FDA-approved for conditions such as terminal illness-related depression and anxiety, and substance use disorders. When this occurs, psychiatrists should be responsible for prescribing psychedelics and managing patients who receive treatment.



Psychedelic psychiatry

Clinical Point

Patients require 'integration' therapy sessions to assist with processing the content of their psychedelic treatment

References

1. Smith DE, Raswyck GE, Davidson LD. From Hofmann to the Haight Ashbury, and into the future: the past and potential of lysergic acid diethylamide. *J Psychoactive Drugs*. 2014; 46(1):3-10.
2. Siegel M. Threading Denver's magic mushrooms needle: promising as medicine, risky as recreation. *USA Today*. Published May 13, 2019. Accessed December 4, 2020. <https://www.usatoday.com/story/opinion/2019/05/13/denver-magic-mushrooms-promising-medicine-reckless-recreation-column/1182543001>
3. Epstein, K. Oakland decriminalizes 'magic mushrooms' and other natural psychedelics. *The Washington Post*. Published June 5, 2019. Accessed December 4, 2020. <https://www.washingtonpost.com/nation/2019/06/05/oakland-decriminalizes-magic-mushrooms-other-natural-psychedelics>
4. York JA. Santa Cruz decriminalizes natural psychedelics. *Santa Cruz Sentinel*. Published January 30, 2020. Accessed December 4, 2020. <https://www.santacruzsentinel.com/2020/01/29/santa-cruz-decriminalizes-natural-psychedelics>
5. Acker L. Oregon becomes first state to legalize psychedelic mushrooms. *The Oregonian/Oregon Live*. Published November 4, 2020. Accessed December 4, 2020. <https://www.oregonlive.com/politics/2020/11/oregon-becomes-first-state-to-legalize-psychedelic-mushrooms.html>
6. Dyck E. Flashback: psychiatric experimentation with LSD in historical perspective. *Can J Psychiatry*. 2005;50(7):381-388.
7. Holoyda BJ. The psychedelic renaissance and its forensic implications. *J Am Acad Psychiatry Law*. 2020;48(1):87-97.
8. Diagnostic and statistical manual of mental disorders, 5th ed. American Psychiatric Association; 2013.
9. Davis AK, Rosenberg H. The prevalence, intensity, and assessment of craving for MDMA/ecstasy in recreational users. *J Psychoactive Drugs*. 2014;46(2):154-151.
10. Halpern JH, Lerner AG, Passie T. A review of hallucinogen persisting perception disorder (HPPD) and an exploratory study of subjects claiming symptoms of HPPD. *Curr Top Behav Neurosci*. 2018;36:333-360.
11. Nichols DE. Psychedelics. *Pharmacol Rev*. 2016;68(2): 264-355.
12. Nichols DE. Hallucinogens. *Pharmacol Ther*. 2004;101(2): 131-181.
13. Carhart-Harris RL, Leech R, Hellyer PJ, et al. The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. *Front Hum Neurosci*. 2014;8:20.
14. Reiff CM, Richman EE, Nemeroff CB, et al. Psychedelics and psychedelic-assisted psychotherapy. *Am J Psychiatry*. 2020;177(5):391-410.
15. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. *J Psychopharmacol*. 2016;30(12):1181-1197.
16. Johnson MW, Garcia-Romeu A, Cosimano MP, et al. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *J Psychopharmacol*. 2014;28(11):983-992.
17. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. *Am J Drug Alcohol Abuse*. 2017;43(1):55-60.
18. Bogenschutz MP, Forcehimes AA, Pommy JA, et al. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *J Psychopharmacol*. 2015;29(3): 1182-1190.
19. Gasser P, Holstein D, Michel Y, et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *J Nerv Ment Dis*. 2014;202(7):531-520.
20. Osório F de L, Sanches RF, Macedo LR, et al. Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. *Braz J Psychiatry*. 2015;37(1):13-20.
21. Holoyda B. Psychedelic psychiatry: preparing for novel treatments involving altered states of consciousness. *Psych Serv*. 2020;71(12):1297-1299.
22. Johnson MW, Richards W, Griffiths RR. Human hallucinogen research: guidelines for safety. *J Psychopharmacol*. 2008; 22(6):603-620.
23. Council on Spiritual Practices. Code of ethics for spiritual Guides. Published August 10, 2001. Accessed November 25, 2020. <https://csp.org/docs/code-of-ethics-for-spiritual-guides>
24. Multidisciplinary Association for Psychedelic Studies. Zendo psychedelic harm reduction training manual. Published 2017. Accessed November 25, 2020. <https://zendoproject.org/wp-content/uploads/2017/06/Zendo-Manual-2017.pdf>
25. Zinberg NE. *Drug, set, and setting: the basis for controlled intoxicant use*. Yale University Press; 1984.
26. Carbonaro TM, Bradstreet MP, Barrett FS, et al. Survey study of challenging experiences after ingesting psilocybin mushrooms: acute and enduring positive and negative consequences. *J Psychopharmacol*. 2016;30(12):1268-1278.