A Case of Prolonged Mania, Psychosis, and Severe Depression After Psilocybin Use: Implications of Increased Psychedelic Drug Availability

Gregory Barber, M.D., Charles B. Nemeroff, M.D., Ph.D., Steven Siegel, M.D., Ph.D.

A 32-year-old woman presented for continuation of treatment in May 2021 with a chief complaint of "cognitive dysfunction and severe reduced functionality." Eight months before her first appointment with one of the authors, the patient was in her usual state of health. She had a history of mild depression and generalized anxiety disorder, successfully treated with venlafaxine prescribed by her psychiatrist. At this time, her sleep, appetite, concentration, and range of mood were normal. She was employed as a senior associate at a high-level accounting firm and had graduated from a prestigious graduate school, both competitive environments in which she excelled. She enjoyed a rich and fulfilling social life with family and friends. At no point in her history had she needed time off or other accommodations because of mental health issues. She had no history of trauma or substance abuse. She had been on antidepressants and engaged in psychotherapy for over 10 years, and had no history of mania or hypomania. Prior treatment included trials of sertraline and bupropion for low-grade depression in college. A sibling had a history of bipolar disorder, and there was no other family history of major psychiatric illness.

In the fall of 2020, at the urging of friends, the patient decided to ingest psilocybin mushrooms. She was still consistently taking venlafaxine at the time of ingestion. She had a highly pleasurable experience after ingesting the mushrooms and decided to repeat the experience the following day with friends, all of whom consumed the same amount from the same supply and had uncomplicated drug experiences. The precise amount of psilocybin that she consumed over the 2 days is unclear. Within hours of her first ingestion, she began experiencing symptoms of mania. Hours after the second ingestion, she developed paranoid delusions, which persisted for months. In the following weeks, she experienced a marked reduction in sleep, to 3–4 hours per night, despite feeling well-rested. She had intrusive racing thoughts and acted impulsively on the basis of paranoid ideation. Her presentation was consistent with a mixed manic state, as she also experienced concurrent depressive symptoms and dysphoria during this phase. While in this state, she was in regular contact with her psychiatrist, who agreed to slowly discontinue venlafaxine, as well as with her psychologist. After 3 months, during which she changed residences, alienated herself from family and friends, and acted noticeably out of character, these symptoms abated.

As her mania and psychosis resolved, she settled into a severe depression. This next phase of her illness was primarily characterized by a total lack of feeling. She fulfilled diagnostic criteria for major depressive disorder on the basis of symptoms including severely depressed mood, anhedonia, insomnia, decreased concentration and appetite, fatigue, feelings of worthlessness, and suicidal ideation. Nothing in life carried any valence, positive or negative. All emotions—happiness, sadness, passion, disappointment—became foreign. Particularly notable was her total lack of connection with her previously beloved dog, whom she had raised as a puppy. She stopped socializing and was barely able to participate in work. She had no desire to be with friends or family, since she was not able to enjoy interpersonal interactions—another major change from her life prior to taking psilocybin. Routine tasks, like running errands and doing basic self-care, became nearly impossible. Her mood range was "zero," with no variation in how she felt throughout the day. She also complained bitterly of cognitive dysfunction, including a profound inability to concentrate. She indicated that the only reason she had not been terminated from her position in the accounting firm was that these events had transpired during the COVID-19 pandemic.

Over the course of her illness, she underwent a wide range of tests, including basic laboratory tests (complete blood count, comprehensive metabolic panel, thyroid function tests, and vitamins D and B_{12} levels), EEG, brain MRI with and without contrast, paraneoplastic and autoimmune encephalitis panels, various infectious, inflammatory, and autoimmune markers (HIV, syphilis,

continued

CRP, ESR, ANA, RF, SSA/SSB antibodies, ANCA), and genetic testing (an analysis of various genes with significant associations with mental disorders). These were all grossly within normal limits or non-illuminating. She was treated with multiple psychopharmacological agents, including lamotrigine, lurasidone, bupropion, venlafaxine, quetiapine, mixed amphetamine salts, lorazepam, zolpidem, eszopiclone, and trazodone, as well as melatonin, magnesium, and oxytocin. She completed several full courses of transcranial magnetic stimulation, using various configurations and multiple machines at a major academic medical center. She also went to holistic doctors and tried various dietary interventions, hypnotherapy, cannabidiol, nicotinamide adenine dinucleotide (NAD+) infusions, dialectical behavioral therapy, acceptance and commitment therapy, trauma-informed therapy, reiki healing, and spiritual guidance. Despite adequate trials of these interventions, none had any significant beneficial effects.

During the depressive phase of her illness, the patient was referred for treatment with one of the authors. At her first evaluation, she indicated that she had spoken to several other professionals, who found her case "unique and intriguing, albeit too complex for them to resolve on their own." On her second contact, she stated that she had almost lost hope after so many consultations, which had "wiped out [her] savings." She reiterated the total failure of several interventions for which many clinicians had described her as "the perfect candidate."

She declared that life would not be worth living if she remained unable to feel emotions or function at work. By this time, she had developed pervasive but passive suicidality related to the meaninglessness that her state of unfeeling induced. She did not require inpatient psychiatric care. Additional medical workups were conducted in collaboration with her gynecologist, all of which were negative for hormonal or anatomic abnormalities. Although some of her previous psychiatrists had recommended ECT as the next treatment option, the patient had performed her own research and was eager to try a dopamine agonist.

Coincident with her lack of progress, preliminary findings from a study being conducted by one of her treatment team members indicated that a subset of patients with recent-onset psychosis had tested positive for anti–D_1 dopamine receptor antibodies. At that point, the patient agreed to be tested using a comprehensive battery of autoimmune neuronal targets. Interestingly, she had borderline elevated titers only for anti–D_1 receptor antibodies on two samples. Based on these findings, she completed a course of methylprednisolone, following a regimen of 24 mg/day for 3 days and decreasing by 4 mg every third day for a total of 18 days. This treatment had no effect, however. At this point, attention turned to nontraditional pharmacologic approaches. In consultation with her treatment team, she elected to initiate a trial of treatment with pramipexole, a dopamine D_2/D_3 agonist, which was chosen for its potential action on her severe anhedonia. She began at a low dosage, 0.25 mg/day, which was slowly increased, by 0.75 mg per week, pausing at times because of mild nausea, which ultimately abated. During this escalation, she began to appear less distressed and paid more attention to her appearance and demeanor.

After 2 months, during which she titrated up to the relatively high dosage of 4.5 mg/day of pramipexole, she reported a significant shift in her functioning. She started to feel emotions again, and began to perform basic errands and self-care. She was eventually able to change residences and participate in basic social functions. She developed motivation to see friends, and went on a date (although she still felt unable to emotionally connect with new people). Her suicidality diminished significantly, becoming only an infrequent disturbance, which she said was far less distressing. She felt more hopeful, more patient, and better able to concentrate. She was ultimately able to return to work, both remotely and in-person. At the time this writing, she remains on 4.5 mg/day of pramipexole and continues to report significant improvement over time. Her ability to appreciate the basic comforts of life—positive relationships, meaningful work—endures today.

Using the experience of the patient presented in this case—a patient who experienced a profound negative reaction after recreational ingestion of psilocybin mushrooms—to understand some of the risks associated with psychedelic use, we discuss several challenging issues that are emerging as psychedelics receive more media attention and become more available. We explore differences between clinical and nonclinical psychedelic use and their attendant risks and benefits. This case suggests that current policy trends, including efforts to render psychedelics widely available for therapeutic use, will place patients at undue risk. Finally, we make recommendations for the future of psychedelic research and clinical applications based on the patient's experience. Details of the case have been modified to protect the patient's identity, and the patient has approved publication of the case for educational purposes.

NEGATIVE PSYCHOLOGICAL CONSEQUENCES OF PSYCHEDELIC USE

The case presented here demonstrates a portion of the vast range of psychological experiences potentially induced by psychedelics. While our patient's experience began positively, it ultimately resulted in profoundly deleterious

consequences for her mental health and personal life, both acutely and long-term. As this case demonstrates, people can experience highly dysphoric states of mind under the influence and in the aftermath of psychedelics. While outcomes from clinical trials on psilocybin have been generally positive, one large trial for major depressive disorder confirms the possibility of negative experiences during the acute psychedelic experience (1). In that study, psilocybin had a beneficial effect on reducing symptoms of major depressive disorder. However, a majority of patients experienced challenging psychological states, from "sadness" and "grief" to "emotional suffering" and "despair" during the dosing session. Thirty-one percent of patients were "afraid that the state I was in would last forever." A survey among recreational psilocybin users (2) similarly revealed that 39% of respondents rated psychedelic use "among the top five most challenging experiences of his/her lifetime," and 11% had put themselves or others at risk of physical harm while on psilocybin. On the other hand, the survey also suggests that our patient's case of an extremely prolonged negative reaction to psilocybin is rare. Nevertheless, these results suggest that patients are likely to experience some degree of highly challenging reactions while under the influence of psychedelics.

SAFETY AND PSYCHEDELICS

In clinical trials, strong measures are taken to prevent psychedelic experiences from becoming dangerous (3). Patients with a personal or family history of psychotic or manic illness are excluded, to minimize the risk of inducing such episodes (4). The setting of psychedelic sessions is carefully controlled, and patients receive psychotherapeutic support over several weeks, before, during, and after the dosing (5). Psychedelic research protocols are designed with safety at the forefront, creating a holding environment for patients as they go through what may be a difficult psychological experience. Moreover, the patients selected for clinical trials are carefully screened and selected, meaning that they are less likely to experience negative outcomes than the general population. These experiences are overseen by experienced psychiatrists and therapists who can manage any potentially dangerous situations that may arise. These interventions are crucial for maintaining positive mindset and setting—often referred to as "set and setting"—and are considered essential for ensuring the positive outcomes that have been seen so far in clinical trials (although even with a thoughtful approach to set and setting, there remains the reality that some patients will inevitably be vulnerable to idiosyncratic reactions to psychedelics).

However, in nonclinical settings, where psychedelics are increasingly popular—a trend driven in part by increasing optimism about their potential as mental health treatments (6)—these safety measures are not always in place. Recreational psychedelic users may not be aware of personal risk factors, and recreational settings do not always have thoughtful safety and support systems built in. People taking psychedelics in non-research settings could experience just as much anxiety as patients in clinical trials, but lack the resources to manage those experiences safely. These risks are more pronounced if the substances consumed are adulterated with other compounds, a risk that is more likely in recreational settings.

EFFECTS OF PSYCHEDELIC LEGALIZATION EFFORTS

Despite these risks, certain jurisdictions, including Denver, Colorado (7); Oakland, California (8); and Washington, D.C. (9), have in recent years passed legislation to decriminalize psilocybin for recreational use. Oregon, which we discuss in more detail below, became the first state to legalize psilocybin for therapeutic purposes, in 2019 (10). Various states, including California, are likely to follow suit. In the summer of 2021, the California state attorney general approved a signature-gathering campaign to place psilocybin legalization on the ballot as early as 2022 (11).

As psilocybin becomes increasingly available, psychiatrists will have to contend with increasing rates of negative outcomes from recreational use, as in the case presented here. Fortunately, data suggest that psilocybin users may require lower rates of emergency medical care compared with users of other recreational drugs (12). Moreover, long-term severe consequences seem rare (2). Research has previously suggested that psilocybin, LSD, and MDMA may be less harmful than alcohol (13). Nevertheless, severe idiosyncratic reactions—such as in our patient's case—are possible, and the mental health consequences for these patients can be serious (14). The increasing popularity of psychedelics will require psychiatrists to become familiar with strategies for managing patients who need help after a difficult psychedelic experience.

Within psychiatry, there will be risks if therapeutic psychedelic use eventually expands beyond carefully designed research settings. The current literature suggests that psychedelic-assisted psychotherapy in research settings is largely safe and well tolerated (1, 15). There have been no reports of completed suicide or long-term psychosis among patients participating in clinical trials. As psychedelics become available for therapeutic use in the community, however, screening and safety protocols may become more lax. Currently, researchers must adhere to strict protocols for the sake of both research integrity and regulatory adherence. These obligations ensure that clinical trials maintain high standards of safety and therapeutic support, and they are part of what has made psychedelic trials so successful thus far. Community psychedelic clinics of the future may not be motivated by such demands and could be incentivized to reduce investment in costly psychotherapeutic support in ways that make psychedelic treatments less safe and effective. The field has witnessed this phenomenon with the large increase in the number of ketamine clinics in this country, with some predicable negative outcomes (16). Regulators may need to consider a requirement that certain minimum safety and psychotherapy protocols be implemented to ensure that quality does not deteriorate. Unfortunately, the current trend

is moving in the opposite direction, potentially creating dangerous situations for patients.

CURRENT TRENDS IN PSYCHEDELICS

In 2019, Oregon voters passed Measure 109, a statewide ballot initiative, to create a mental health commission tasked with developing a psilocybin-assisted psychotherapy program (17). Under Oregon's proposed psychedelic treatment system, treatment can be provided by people who may be unequipped to manage the complexities of psychedelic experiences and psychopharmacology. Measure 109 does not require that psilocybin-assisted psychotherapy be administered or overseen by psychiatrists with the training to understand potential psilocybin side effects or drug interactions. While the initiative will require some training, psilocybin facilitators do not need to have a formal background in clinical psychiatry or psychology.

Oregon's psilocybin program is specifically designed to meet the demands posed by the high burden of mental illness in society. Despite this therapeutic intent, however, Oregon's law ignores the fact that mental illnesses are medical conditions for which pharmacological treatment historically has been and should continue to be provided by medical professionals. Psilocybin and other psychedelics are at least as psychopharmacologically complex as other psychiatric medications, and perhaps more so (18). The push in Oregon is to have these treatments offered by people with no experience in psychiatry, psychopharmacology, psychotherapy, or risk assessment. This is a highly dubious ethical position, imperiling the ability of patients to make informed clinical decisions and putting them at unnecessary risk for bad outcomes. Moreover, the nature of psychedelic experiences—in particular the strong emotions and vulnerable positions they can elicit in users—demands careful attunement to boundaries by psychedelic therapists. Oversight of psilocybin administration by highly trained psychiatrists, working within clear ethical guidelines, is essential to ensuring that such boundaries are upheld. We recognize the promise of psilocybin, which has performed well in clinical trials so far, to help meet the demand for improved psychiatric treatments. Still, when people have negative experiences on psilocybin—the unfortunate reality of any medical treatment—it will have been a preventable tragedy that they were not receiving care from trained professionals who can safely manage the situation.

PSYCHEDELICS AND THE NEED FOR BETTER PSYCHIATRIC TREATMENTS

One argument made in favor of the minimal requirements to become a psilocybin facilitator is that psychedelic treatments should be highly accessible to people from socioeconomic and racial backgrounds who have historically been excluded from high-quality psychiatric care (19, 20). By creating a wider pool of possible psychedelic facilitators, it will be possible to provide psychedelic therapy more equitably. Moreover, the ever-worsening public mental health crisis demands urgent and creative solutions, and some may argue that widespread psychedelic clinics could make a difference as more and more people experience psychological suffering.

We fully agree that equity and accessibility are essential social justice missions that should feature prominently in the discussion of psychedelic therapies. But psychiatry should not compromise on its standards of care, nor its confidence in its treatments, to rush into a new treatment modality; we should not put the cart before the horse. If psychedelic therapies do demonstrate themselves to be safe and effective, strong measures should be implemented to ensure that people from all backgrounds can access treatment. High-quality psychedelic therapist training programs should expand to meet the needs of patients once clinical trials and the regulatory process are complete. All efforts should be made to ensure that therapists of color are included in the evolution of this burgeoning field. Licensed mental health professionals should receive specialized training in this challenging psychotherapeutic domain, and should be supervised by a psychiatrist with expertise in both psychopharmacology and psychotherapy. If clinical trials demonstrate efficacy and safety, insurance companies should cover psychedelic treatments, another vital aspect of ensuring access.

CONCLUSIONS

Psychiatrists have an ethical obligation to maintain clinical equipoise with regard to new treatments while they are still in the investigational stage. At this point, psychedelics are on track to becoming an evidence-based psychiatric intervention, with positive clinical trials thus far. Optimism about these positive results is warranted, but psychiatrists should be aware that only a few hundred patients have actually received psilocybin in clinical research settings—which suggests a field that is still in its infancy—and, in contrast to other randomized placebo-controlled clinical trials, blinding is simply not possible with psilocybin. Psychiatrists should remain open to any outcome of clinical research while the safety and efficacy of psychedelics are still being determined.

Right now, a promising psychiatric treatment risks getting swept up in a broader cultural moment—a dynamic that could lead to compromises in quality and reduce the efficacy of psychedelic therapies. Similar cultural forces led to the demise of psychedelic therapies a half century ago. Today we find ourselves in the unprecedented position where the safety and efficacy of medical treatments are being decided by popular opinion—and at the expense of the scientific process. The field of psychiatry should stand for the integrity of the scientific process, and encourage the development and administration of new treatments, including psychedelic therapies, in ways that maximize their safety and efficacy.

AUTHOR AND ARTICLE INFORMATION

Department of Psychiatry, University of Maryland School of Medicine, Baltimore (Barber); Department of Psychiatry and Behavioral Sciences,

Dell Medical School, University of Texas at Austin (Nemeroff); Department of Psychiatry and Behavioral Sciences, University of Southern California, Los Angeles (Siegel).

Send correspondence to Dr. Nemeroff (cnemeroff@austin.utexas.edu).

Dr. Barber holds stock in AbbVie, Bristol-Myers Squibb, Danaher Corporation, Eli Lilly, Johnson & Johnson, and UnitedHealth Group. Dr. Nemeroff has served as a consultant for Acadia Pharmaceuticals, Alfasigma, ANeuroTech (division of Anima BV), BioXcel Therapeutics, Clexio, Corcept Therapeutics, EcoR1, EMA Wellness, Engrail Therapeutics, GoodCap Pharmaceuticals, Intra-Cellular Therapies, Magstim, Navitor Pharmaceuticals, Neuritek, Pasithea Therapeutics, Sage, Senseye, Signant Health, Silo Pharma, SK Life Science, and XW Pharma; he has served on scientific advisory boards for the Anxiety and Depression Association of America (ADAA), ANeuroTech, the Brain and Behavior Research Foundation, Heading Health, the Laureate Institute for Brain Research, Magnolia CNS, Pasithea Therapeutics, Sage, Signant Health, Skyland Trail, and TRUUST Neuroimaging, and on the boards of directors of ADAA, Gratitude America, Lucy Scientific Discovery, and Xhale Smart; he holds stock in Antares, BI Gen Holdings, Corcept Therapeutics, EMA Wellness, Naki Health, Seattle Genetics, TRUUST Neuroimaging, and Xhale; and he is named on U.S. patents 6,375,990B1 and 7,148,027B2. Dr. Siegel has received research grants from Astellas and NIH; he has served as a consultant for Zynerba and as an advisory board member for Skyland Trail; and he is named on Australian patents 2005206143, 2006269927, and 2006269927; European patents 2010184 and 2633853; Israeli patent 194506; Korean patents 10-1197540 and 10-1283946; Japanese patent 5306599; Canadian patents 2553254 and 2,614,601; and U.S. patents 7,666,445, 8,221,778, 8,329,203, 8,475,830, 8,475,829, 8,741,327, 8,802,127, 8,758,795, 10-736,965 B2, and 2019/0105396 A1.

Received January 25, 2022; revisions received March 14, April 25, and May 11, 2022; accepted May 26, 2022.

Am J Psychiatry 2022; 179:892–896; doi: 10.1176/appi.ajp.22010073

REFERENCES

1. Davis AK, Barrett FS, May DG, et al: Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. JAMA Psychiatry 2021; 78:481–489
2. 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; 30:1268–1278
3. Johnson MW, Richards WA, Griffiths RR: Human hallucinogen research: guidelines for safety. J Psychopharmacol 2008; 22: 603–620
4. Dos Santos RG, Bouso JC, Hallak JEC: Ayahuasca, dimethyltryptamine, and psychosis: a systematic review of human studies. Ther Adv Psychopharmacol 2017; 7:141–157
5. Hartogsohn I: Constructing drug effects: a history of set and setting. Drug Sci Policy Law 2017; 3:1–17
6. Yockey RA, Vidourek RA, King KA: Trends in LSD use among US adults: 2015–2018. Drug Alcohol Depend 2020; 212:108071
7. Hernandez E: Denver may ease magic mushrooms laws further two years after decriminalization. Denver Post, October 8, 2021. https://www.denverpost.com/2021/10/08/magic-mushroom-denver-decriminalization-psilocybin-report/
8. Kennedy M: Oakland City Council effectively decriminalizes psychedelic mushrooms. NPR.org, June 5, 2019. https://www.npr.org/2019/06/05/730061916/oakland-city-council-effectively-decriminalizes-psychedelic-mushrooms
9. Beaujon A: Magic mushrooms are decriminalized in DC as of today. Washington, DC, Washingtonian.com, March 15, 2021. https://www.washingtonian.com/2021/03/15/magic-mushrooms-are-decriminalized-in-dc-as-of-today/
10. Acker L: Oregon becomes first state to legalize psychedelic mushrooms. OregonLive.com, November 3, 2020. https://www.oregonlive.com/politics/2020/11/oregon-becomes-first-state-to-legalize-psychedelic-mushrooms.html
11. The California Psilocybin Initiative 2022. https://oag.ca.gov/system/files/initiatives/pdfs/21-0005%20%28Psilocybin%29.pdf
12. Winstock A, Barratt M, Ferris J, et al: Global Drug Survey 2017: global overview and highlights. https://www.globaldrugsurvey.com/wp-content/themes/globaldrugsurvey/results/GDS2017_key-findings-report_final.pdf
13. Nutt D, King LA, Saulsbury W, et al: Development of a rational scale to assess the harm of drugs of potential misuse. Lancet 2007; 369: 1047–1053
14. Hendin HM, Penn AD: An episode of mania following self-reported ingestion of psilocybin mushrooms in a woman previously not diagnosed with bipolar disorder: a case report. Bipolar Disord 2021; 23: 733–735
15. Mitchell JM, Bogenschutz M, Lilienstein A, et al: MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med 2021; 27:1025–1033
16. Schak KM, Vande Voort JL, Johnson EK, et al: Potential risks of poorly monitored ketamine use in depression treatment. Am J Psychiatry 2016; 173:215–218
17. Oregon Health Authority: Oregon Psilocybin Services. https://www.oregon.gov/oha/ph/preventionwellness/pages/oregon-psilocybin-services.aspx
18. Reiff CM, Richman EE, Nemeroff CB, et al: Psychedelics and psychedelic-assisted psychotherapy. Am J Psychiatry 2020; 177:391–410
19. Williams MT, Labate BC: Diversity, equity, and access in psychedelic medicine. J Psychedelic Stud 2019; 4:1–3
20. Joiner W: Who will benefit from psychedelic medicine? Washington Post Magazine. https://www.washingtonpost.com/magazine/2020/09/21/psychedelic-medicine-will-it-be-accessible-to-all/