Legal and Ethics Concerns of Psilocybin as Medicine

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Preliminary research shows the psychedelic psilocybin to be a promising potential treatment for psychiatric illnesses. Recent U.S. government legislation and policy indicate that access to psilocybin, which remains illegal on the federal level despite increasing efforts to decriminalize it at the state and local levels, will be expanded to enable further research into its treatment potential. It remains unclear how psilocybin will be regulated and who will have access to this new treatment, raising important legal and ethics questions psychiatrists must consider. This article reviews the current legal regulation of psilocybin and matters related to standard of care, right to effective treatment, and the respectable minority doctrine. It concludes with a discussion of the ethics matters surrounding the use of psilocybin as medicine, including provider bias, the interpersonal dynamic between providers and patients, informed consent, and equity and access.

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Hallucinogens are naturally occurring or synthetically produced substances used to alter thought, perception, and mood. Psychedelics, a class of hallucinogens that cause alterations or expansions of consciousness, have been an evolving fixture in United States history in legal and pop culture domains. Although research into psychedelics' effectiveness for mental health began to emerge in the 1960s, the drug's association with counterculture eventually led to its criminalization, with research essentially being stopped altogether.[1] The psychedelic psilocybin is now reemerging as a potential treatment for medical and psychiatric illnesses in the United States.

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Psilocybin is a psychoactive alkaloid that occurs naturally in many species of fungi, specifically the *Psilocybe* genus of mushrooms. Once broken down into its active form, psilocin, by dephosphorylation, it acts as a nonselective agonist at serotonin 5-HT2A receptors, eliciting downstream effects on the dopaminergic and glutamatergic systems.[2] In healthy adults, it has been shown to disrupt connectivity across cortical and subcortical structures, including in the anterior hippocampus, which is thought to create one's sense of self.[3] Psilocybin's pharmacodynamic mechanisms have led to increasing interest in its psychiatric effects and treatment potential. Although studies to date are limited to small numbers of participants and possibly nonrepresentative samples, those published, along with supporting case reports, have shown promising results in the treatment of a spectrum of psychiatric disorders in the United States, including major depressive disorder (MDD),[4–6] anxiety,[7–9] obsessive compulsive disorder (OCD),[10–13] posttraumatic stress disorder (PTSD),[14] personality disorders,[15,16] and alcohol[17] and tobacco use disorders.[18] More recently, feasibility studies examining the safety and tolerability of psilocybin as a treatment have been conducted in patients with anorexia nervosa, highlighting the expansion of interest in how the substance can be used to potentially treat other

psychiatric disorders.[19] Because of its short half-life and absence of needed daily dosing, psilocybin may benefit those with severe postpartum depression, a major public health concern with great morbidity and often life-threatening consequences for mother and child.[20] Current specific treatments for postpartum depression, such as brexanolone and zuranolone, are unaffordable for many who may need it. Psilocybin has also shown promise for the treatment of chronic pain and debilitating conditions, such as cluster headaches.[21–23]

Psychedelics exhibit clear potential as a tool for difficult to treat mental health conditions. The implementation of treatment remains muddied by various social, ethics, economic, regulatory, and legal questions. Although state medical boards typically provide oversight for prescribing medical treatments, it is currently unclear which governing bodies would be in charge of regulating psilocybin, as many nonphysicians utilize the drug in therapy sessions. At present, access to psilocybin-assisted therapy is limited to clinical trials in most of the country, and underground, i.e., extralegal, routes are utilized.[24,25] A further complicating matter is the identification of the substance in products legally sold over the counter.[26] It is not clear how jurisdiction will affect availability of psilocybin as medicine, as some states have already decriminalized use of the drug, despite an ongoing federal ban. If studies continue to show a benefit of psilocybin for mental health conditions that are otherwise treatment resistant, patients may encounter difficulty accessing the effective treatment if physicians are unable, or unwilling, to offer psilocybin, given the legislative restrictions. In this article, we review current legal regulation of psilocybin and the ethics matters related to standard of care, right to treatment, and the relevance of the respectable minority doctrine to the developing clinical and legal landscape of psilocybin as medicine.

Current Legal Regulation

At the federal level, psilocybin remains illegal. Since 1971, psilocybin has been deemed a Schedule I substance by federal law, defined by statute as a substance having a high potential for abuse, having no currently accepted medical use in treatment, and lacking accepted safety for use under medical supervision.[27,28] Other Schedule I substances include heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy), and peyote.[29] This is in contrast with Schedule II substances, such as cocaine and methamphetamine (B), which are still considered to have high potential for abuse but with potential for medical use.[30] Notably, the physical and psychological dependence potential of psilocybin has been evaluated to be low despite this classification.[31] Psilocybin's classification as a Schedule I substance has had significant implications for research, making investigation into its mechanisms of action and therapeutic potential extremely difficult.[32]

At state and local levels, however, efforts to decriminalize psilocybin have increased in recent years, beginning in Denver, CO in 2019. The substance is now fully decriminalized and legal for medical use under state law in two states, Oregon and Colorado, and decriminalized in select municipalities in California, Massachusetts, Michigan, Washington, D.C., and Washington state. Efforts to decriminalize the substance are continuing, with the number of psychedelic law reform initiatives increasing steadily, from five in 2019 to 36 in 2022, nearly all of which specifically cite psilocybin. A total of 25 states had considered bills during that period.[33]

In an effort to promote innovation in the context of the restrictive drug classification setting, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA) in July 2012, which provided the Food and Drug Administration (FDA) with an expedited drug development tool, termed "breakthrough therapy" designation.[34] The designation recognizes a drug's therapeutic potential, based on preliminary clinical evidence, to treat serious or life-threatening conditions, including for those drugs classified as Schedule I. The designation expands access for research on a drug by enabling the FDA to expedite the development and review process.[35] Two Schedule I psychedelics have been designated breakthrough therapies by the FDA: 3,4-methylenedioxymethamphetamine (MDMA) to treat moderate to severe posttraumatic stress disorder in 2017 and psilocybin to treat severe treatment-resistant depression in 2018 and major depressive disorder in 2019.[36–38]

Efforts to expand access to psilocybin are ongoing, with recent developments on the federal level. The Breakthrough Therapies Act, a proposed bipartisan bill initially introduced in November 2022[39] and again as an updated version in March 2023,[40] aims to "remove regulatory hurdles that inhibit research and compassionate use access to potentially lifesaving treatments that are heavily restricted by Schedule I of the Controlled Substances Act," including by

"expediting the transfer of substances that receive breakthrough therapy designation from Schedule I to Schedule II, which – with DEA oversight – will enable patient access and reduce the burden on further clinical investigation."[41] Perhaps the most significant development in the federal government's recognition of the therapeutic potential of psychedelics to treat psychiatric and substance use disorders, is the FDA's first-of-its-kind draft guidance on designing clinical trials for this drug class in June 2023.[42] In a discussion of the draft guidance, Tiffany Farchione, MD, director of the Division of Psychiatry in the FDA's Center for Drug Evaluation and Research, highlighted psychedelics' "initial promise" in treating such disorders and explained, "By publishing this draft guidance, the FDA hopes to outline the challenges inherent in designing psychedelic drug development programs and provide information on how to address these challenges. The goal is to help researchers design studies that will yield interpretable results that will be capable of supporting future drug applications."[43]

Problems with Current Legality

With more legislation being introduced at the state level to legalize and assert a medical purpose for psilocybin, problems arise concerning its continued classification as an illegal substance on the federal level. This legal conundrum raises important questions for psychiatrists to consider regarding topics of criminality, standard of care, and duty to inform of effective treatments.

Federal Government's Potential Approach

History indicates that psilocybin, despite its legalization at the state level, will be under the control of the federal government. What approach the government takes when it comes to criminality and prosecution remains unclear.

The Commerce Clause of the U.S. Constitution (Article 1, Section 8, Clause 3) gives Congress the power "to regulate commerce with foreign nations, among states, and with Indian Tribes." Historically, the clause has been considered a grant of congressional authority and restriction of states' regulatory authority for interstate commerce.[44] Although the Supreme Court initially focused on the meaning of "commerce," later interpretations in the 1930s focused on Congress's power to regulate commerce, with a resulting ongoing debate in the courts and among judges over the extent of the power of the federal government under the Commerce Clause.[45] On the whole, the definition of commerce has been interpreted broadly by the courts. For example, in *Wickard v. Filburn* (1942), a farmer growing wheat on his own farm to feed his own animals was found to be engaged in interstate commerce, because not selling the wheat on the market affected the international price of wheat.[46] Since the 1990s, the Court has narrowed the scope of the Commerce Clause considerably.[47,48]

Gonzalez v. Raich (2005) highlights how the federal government could approach the criminality of psilocybin through its ruling on another Schedule I substance: marijuana.[49] In 1996, California passed the Compassionate Use Act, which legalized marijuana for medical use on the state level.[50] The drug remained illegal on the federal level, resulting in the Drug Enforcement Administration (DEA) removing cannabis plants from the homes of two patients who grew them for personal use. The patients, Angel Raich and Diane Monson, sued the federal government, claiming that the Controlled Substances Act (CSA) violated the Commerce Clause.[51] The court filing raised the question as to whether or not the courts considered personal homegrown marijuana to be interstate commerce, which the federal government could then regulate. The court ultimately ruled that the federal government, via the CSA, trumped state laws for marijuana. Although the specific details of medical marijuana were lost within a larger debate of federal or state powers, the ability of the federal government to control and regulate substances under the CSA became clearer. Given they are classified under the same CSA drug schedule, it is reasonable to assume that federal regulation and control of psilocybin will follow that of marijuana. A few years later, in 2009, under President Obama, the Department of Justice announced that the federal government would not prosecute users and distributors of marijuana who had legal authority under state medicinal marijuana laws.[52] The federal government has not yet indicated whether a nonprosecution approach will be taken with psilocybin. States may begin to take a proactive approach, as in California, where a bill was introduced in September 2023 to "prohibit the use of Federal funds from preventing a State from implementing their own laws with respect to psilocybin," i.e., prosecution (Ref. 53, p 1). Although the outcome of the bill remains unknown, a similar amendment for marijuana, known as the Rohrabacher-Farr amendment,

prohibits the Department of Justice from using its funds to prevent various states from implementing their own laws regarding medical marijuana use, distribution, possession, or cultivation and has passed annually since 2014.[54]

Standard of Care

In nearly all states, standard of care is evaluated on a national level.[55] A court attempting to apply a national standard of care may be presented with an impossible task, because different states have different laws regarding the use of psilocybin, leading to different treatment paradigms. Furthermore, the local legality of a treatment does not necessarily mean it follows the national standard of care, and someone could still be liable for malpractice in a jurisdiction following a national standard of care despite following local laws. Given these variations, practitioners should be aware of the standards for psilocybin in their current jurisdiction of practice.

An additional perspective to consider is the leading professional societies' stances on psilocybin. Professional medical societies have developed clinical practice guidelines to help physicians access information about and more readily implement evidence-based medicine. The American Psychiatric Association (APA) provides clinical practice guidelines on the treatment of psychiatric disorders, although it makes clear that they are "not intended to serve or be construed as a 'standard of medical care'" (Ref. 56, p 3). Nevertheless, lawyers have used such practice guidelines in court to argue both for and against malpractice claims.[55] At this time, the APA does not have clinical practice guidelines regarding the use of psilocybin. In the organization's policy statement, it declares support for the ongoing exploration and research of psychedelics but does not endorse their use for treatment.[57] Such a lack of clear professional guidelines may broaden the situations in which patients claim malpractice. Without practice guidelines, either from experts in journals or professional societies, such as the APA, it is harder to define a national standard of care regarding psilocybin treatment. Furthermore, if no organization supports the use of psilocybin to treat psychiatric disorders, members may avoid its use to limit their own professional liability. As with any psychiatric conditions, clear and current guidelines will benefit both patients and psychiatrists in understanding their best treatment options.

Right to Effective Treatment

If psilocybin is awarded FDA approval for treatment of certain psychiatric disorders, psychiatrists must consider their duty to inform patients of the treatment. The legality around whether or not to inform a patient of the availability of the new treatment is outlined in the controversial 1985 ruling in *Osheroff v. Chestnut Lodge*.[58] In this landmark case, the plaintiff, Dr. Raphael Osheroff, had been a patient at Chestnut Lodge in Maryland, a private inpatient psychiatric hospital, for months while receiving treatment for severe depression. Over the duration of the hospitalization, Dr. Osheroff was only offered psychotherapy and not medications, despite there being good evidence of medications available to treat the primary depressive disorder. Upon leaving Chestnut Lodge and initiating treatment at another inpatient hospital, Dr. Osheroff received a combination of phenothiazine and tricyclic (TCA) antidepressants and improved quickly, eventually being discharged and returning to his medical practice. Dr. Osheroff sued the psychoanalytic treatment center for malpractice, the implication being that the patient has a right to effective treatment and that treatment with demonstrated efficacy has priority over alternatives.[59]

The antidepressant medications Dr. Osheroff was treated with were available for years when the case was litigated in the 1980s, with the discovery of phenothiazines in the late 19th century and the first TCA, imipramine, in the 1950s.[60,61] Psilocybin was first isolated and synthesized in 1958 and then used extensively prior to its classification as a Schedule I substance in 1967.[62] If, in many years, the body of evidence were to convincingly show the noninferiority or superiority of psilocybin compared with conventional treatments, then providers will, hypothetically, need to consider whether the substance will be a treatment about which patients should be informed. Depending on legislation at that time, psychiatrists may be faced with the clinical and ethical duty to recommend the treatment in a state where psilocybin is legal but perhaps in conflict with federal law if it remains a Schedule I controlled substance.

Respectable Minority Doctrine

One could imagine that psilocybin may only be prescribed by a select number of psychiatrists initially. Recent studies indicate that mental health providers have favorable views about the therapeutic

potential of psychedelics but have reservations regarding the risks associated with the class of substances.[63–65] Given these views, another perspective to consider regarding the use of psilocybin to treat psychiatric disorders is the "respectable minority doctrine."

The term stems from *Lorenz v. Booth* (1915), a case in which a surgeon was found not liable for malpractice for the treatment of a patient's fractured bone, as "that method did have the approval of at least a respectable minority of the medical profession who recognized it as a proper method of treatment" (Ref. 66, p 9). The term is discussed further in the 1954 court case *Baldor v. Rogers*, in which a patient sued his doctor for malpractice after he recommended injections to treat his malignant lip tumor when other treatments proven to be more effective, including surgical resection and chemotherapy, were available. The court ultimately ruled that, in the absence of a cure and given that the doctor was not indulging in "quackery," the physician could not be held responsible for malpractice. The justices noted, "If the treatment used is approved by a 'respectable minority of the medical profession' that would relieve the defendant of the charge of malpractice. The doctor is obligated only to use reasonable skill and he fulfills his obligation if he uses methods approved by others of the profession who are reasonably skilled" (Ref. 67, p 6-7). This situation has been called a "two schools of thought doctrine," in which one school is the majority view but both have recognition in the community.[68] Thus, a reasonable practitioner might not utilize a given treatment, but it would not necessarily be malpractice for one who did.

One could argue that there is currently no respected minority of practitioners when it comes to using psilocybin as medicine, as it is primarily being utilized in Institutional Review Board (IRB)-approved clinical research studies, and therefore, its use is outside the legal standard of care. There are other indicators that practitioners would satisfy a respectable minority designation and be protected against malpractice claims. Adherence to available treatment and practice guidelines would fulfill the requirement for the minority approach to be established in definite principles. The requirement for minority school practitioners to meet a baseline level of skill and knowledge could be fulfilled by medical licensing or by having completed a specific psilocybin training program. Additionally, psychiatrists would be well equipped to exercise the required reasonable care in diagnosis.[69]

Ethics Challenges

Such rapid developments in the legal and research domains of psilocybin as a treatment for psychiatric disorders raise ethics challenges regarding how the substance is sourced, developed, and administered.

Provider Bias regarding Therapeutic Potential

Controlling for bias is an essential component of investigative drug research.[70] With excitement and development about psilocybin's therapeutic potential, there is risk for increased bias concerning its potential effects by those administering the treatment. Barber and Dike[70] describe such research equipoise, the necessity of researchers and clinicians remaining neutral and unbiased in the assessment of the hypothesis of a drug or therapy's potential, as it applies to psilocybin. They note how the high enthusiasm surrounding this drug, specifically on the governmental and political level, can threaten the maintenance of this scientific principle, given the FDA's and political movement's acknowledgment of its potential.[71] The recent June 2024 vote against the use of MDMA for the treatment of PTSD by an FDA advisory panel serves as a cautionary tale. Panel members raised concerns about the validity of the trial data in part because of allegations of misconduct and bias.[72] In addition, the personal enthusiasm of the individual clinician must also be considered. Anderson and colleagues note the grandiosity and ego inflation that may develop in clinical providers who both personally take and administer psychedelics in psychotherapy sessions, highlighting an overemphasis on the therapeutic potential of the drug class.[73] Within the conversations about right to effective treatment and the duty of the provider to inform the patient of treatment effects, psychiatrists must be vigilant in their assessment of psilocybin before recommending it to their patients. One must also consider whether undue enthusiasm for the treatment could threaten the medical community's view of the therapy as a proper method of treatment and therefore the argument that it is prescribed by a respectable minority.

Patient-Provider Interpersonal Dynamic

The history of psychiatric care is unfortunately fraught with cases in which the provider crossed an ethics boundary. The nature of psilocybin's unique therapeutic potential in the psychotherapy setting,

such as features similar to classical mystical and spiritual experiences[74] and potential to induce personality changes,[15,75] is also what makes ethics practices and standards in its delivery so important. Anderson and colleagues cite the risk of erotic and parental transference in such dynamics, suggesting they are "magnified when a patient's therapist not only administers unconditional acceptance and validation, but also expedites access to experiences of transcendence or profound catharsis via a drug" (Ref. 73, p 830). One could imagine how the risks of boundary crossings and violations in this type of therapeutic relationship could elevate if not carried out by a careful, ethics-oriented practitioner. Vunerable patients seeking this treatment, such as those with serious mental illness who have failed prior treatments, may be particularly at risk.

Informed Consent

The APA describes informed consent as one of psychiatry's primary ethics and professional practices, involving information disclosure, capacity, and avoidance of coercive influences.[76] When it comes to psilocybin, information about the potential changes a patient may experience may be too difficult to communicate if one has not experienced those changes, especially because this is still a novel drug of which the long-term effects in higher risk populations are not yet fully understood.[77] Recommendations to address clinicians' lack of subjective experience with psilocybin include having people who have received psychedelic treatment share their experiences with those who are considering it and utilizing virtual and augmented reality to simulate the perceptual experience.[78,79] And for those clinicians who may consider joining others who have chosen to experience psychedelics firsthand, it has been discussed that the potential epistemic benefit of a personal psychedelic experience should not outweigh the autonomy of the provider's decision to pursue it.[24,80,81] Smith and Sisti recommend a more comprehensive consent process for psilocybin compared with other psychiatric treatments, including the drug's potential to induce shifts in personality and values, associated mental health risks, and possible use of therapeutic touch.[82] Although risk of toxicity and dependence are low for psilocybin, discussion about the potential, albeit currently unclear, risk for future substance use outside of a controlled medical setting is warranted, especially among those with a history of substance use.[83] As a novel psychiatric treatment, additional disclosures concerning longitudinal access to treatment and out-of-pocket costs may be warranted as well.[84]

Potential challenges and pitfalls in obtaining informed consent to the use of a psychedelic drug such as psilocybin necessitate careful assessment of the patient's capacity to give informed consent.[85] For example, a patient with an affective disorder who retains cognitive capacity may still manifest affectively based incapacity to give informed consent.[86] Patients can also be susceptible to magical thinking, by which they may regard a particular medication as either a miracle cure or a dangerous hazard (or both).[87] Patients are at even greater risk for such magical thinking in the case of psychedelic drugs, given how those drugs are popularly conceived. Another dimension of capacity to be assessed is the patient's ability to tolerate uncertainty, which is commonly diminished in depressed or demoralized patients. It is important for the patient to be able to understand that all choices, including medical choices, involve uncertainty, and this particular choice carries with it more uncertainty than most.[88]

Equity and Access

There exists a centuries-, possibly millennial-, long history of ritualistic use of psilocybin and other psychedelics by indigenous people.[89] Such use continues to the present time and has been utilized by nonindigenous people seeking transformational experiences or relief from mental distress. These experiences and knowledge have clearly contributed to our understanding of psychedelics, including psilocybin, as medicine. It is unclear whether a pathway can be accomplished that integrates such practices and practitioners into the potential reality of medically prescribed psychedelics or to even meaningfully acknowledge their contribution. The importance of such integration and acknowledgment is further elucidated in the Zinberg model of psychotropic effects as a product of drug, set, and setting.[90] Therefore, regulators need to proceed with caution regarding the effects of these substances in different settings and with states of mind. A comprehensive psychiatric evaluation to screen for vulnerable states of mind and informed consent processes, with alternatives being presented, must be followed in nonindigenous settings for self-selected populations seeking therapeutic effects rather than religious revelation.

In addition to equity, there is the ethics problem of who will have access to psilocybin treatment. An analysis of 18 psychedelic studies found that over 80 percent of research participants were non-Hispanic White.[91] Such uniformity provides a limited analysis of who psilocybin treatment may benefit and its potentially differential effects among people of different racial and ethnic backgrounds. Numerous contributors to the literature highlight the importance of including a more diverse group of research participants in psychedelic clinical research studies.[72,92–94]

From a cost perspective, an additional area of concern is who will have access to psilocybin treatment in the event that it does receive FDA approval for treatment of psychiatric disorders. Ketamine, an anesthetic that can induce psychedelic experiences and hallucinations, offers insight into the potential financial barriers to treatment with psilocybin.[95] A dose of racemic ketamine used to treat MDD costs one to five dollars.[96] Although racemic ketamine has been shown to effectively treat treatment-resistant depression, it does not have FDA approval for this indication and is not covered by insurance, resulting in patients having to pay large out-of-pocket costs of up to $1,000 per treatment. Conversely, intranasal esketamine, racemic ketamine's S-enantiomer, was approved in 2019 by the FDA for treatment of treatment-resistant depression.[97] One dose of FDA-approved Spravato (esketamine) costs $590–$885 with three doses per week recommended to maintain therapeutic effectiveness.[96] In this form, the drug is covered by some insurance plans and patients can pay as little as $10 per treatment under the manufacturer's copay assistance program.[97] As the contrast between access to ketamine and esketamine illustrates, coverage of psilocybin by insurers, including Medicaid and Medicare, will be essential to ensuring access to psilocybin for those of all socioeconomic backgrounds, rather than only those who have the means to afford it.

Conclusion

Psilocybin is emerging as a novel treatment in psychiatry for a range of psychiatric disorders that preliminary studies indicate it has the potential to effectively treat. Now, as it appears to be on the cusp of approval as a breakthrough treatment by the FDA, psilocybin will be examined and researched on a larger scale. Psychiatrists must be knowledgeable about the potential legal and ethics problems that may arise with respect to this new treatment.

References

1. Lamkin M. Prescription psychedelics: The road from FDA approval to clinical practice. Am J Med. 2022 Jan; 135(1):15–6
2. Ling S, Ceban F, Lui LMW, *et al*. Molecular mechanisms of psilocybin and implications for the treatment of depression. CNS Drugs. 2022 Jan; 36(1):17–30
3. Siegel JS, Subramanian S, Perry D, *et al*. Psilocybin desynchronizes the human brain. Nature. 2024 Jul; 632:131–8
4. Carhart-Harris R, Giribaldi B, Watts R, *et al*. Trial of psilocybin versus escitalopram for depression. N Engl J Med. 2021 Apr; 384(15):1402–11
5. Gukasyan N, Davis AK, Barrett FS, *et al*. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. J Psychopharmacol. 2022 Feb; 36(2):151–8
6. von Rotz R, Schindowski EM, Jungwirth J, *et al*. Single-dose psilocybin-assisted therapy in major depressive disorder: A placebo-controlled, double-blind, randomised clinical trial. EClinicalMedicine. 2022 Dec; 56:101809
7. Goldberg SB, Pace BT, Nicholas CR, *et al*. The experimental effects of psilocybin on symptoms of anxiety and depression: A meta-analysis. Psychiatry Res. 2020 Feb; 284:112749
8. Goodwin GM, Aaronson ST, Alvarez O, *et al*. Single-dose psilocybin for a treatment-resistant episode of major depression: Impact on patient-reported depression severity, anxiety, function, and quality of life. J Affect Disord. 2023 Apr; 327:120–7
9. Yu C-L, Yang F-C, Yang S-N, *et al*. Psilocybin for end-of-life anxiety symptoms: A systematic review and meta-analysis. Psychiatry Investig. 2021 Oct; 18(10):958–67
10. Kelmendi B, Kichuk SA, DePalmer G, *et al*. Single-dose psilocybin for treatment-resistant obsessive-compulsive disorder: A case report. Heliyon. 2022 Dec; 8(12):e12135
11. Lugo-Radillo A, Cortes-Lopez JL. Long-term amelioration of OCD symptoms in a patient with chronic consumption of psilocybin-containing mushrooms. J Psychoactive Drugs. 2021 Apr-Jun; 53(2):146–8
12. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J Clin Psychiatry. 2006 Nov; 67(11):1735–40
13. Wilcox JA. Psilocybin and obsessive compulsive disorder. J Psychoactive Drugs. 2014 Nov-Dec; 46(5):393–5
14. Catlow BJ, Song S, Paredes DA, *et al*. Effects of psilocybin on hippocampal neurogenesis and extinction of trace fear conditioning. Exp Brain Res. 2013 Aug; 228(4):481–91
15. MacLean KA, Johnson MW, Griffiths RR. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. J Psychopharmacol. 2011 Nov; 25(11):1453–61
16. Weiss B, Ginige I, Shannon L, *et al*. Personality change in a trial of psilocybin therapy v. escitalopram treatment for depression. Psychol Med. 2024 Jan; 54(1):178–92
17. Bogenschutz MP, Forcehimes AA, Pommy JA, *et al*. Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. J Psychopharmacol. 2015 Mar; 29(3):289–99
18. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol. 2014 Nov; 28(11):983–92
19. Peck SK, Shao S, Gruen T, *et al*. Psilocybin therapy for females with anorexia nervosa: A phase 1, open-label feasibility study. Nat Med. 2023 Aug; 29(8):1947–53
20. Jairaj C, Rucker JJ. Postpartum depression: A role for psychedelics? J Psychopharmacol. 2022 Aug; 36(8):920–31

21. Kooijman NI, Willegers T, Reuser A, *et al*. Are psychedelics the answer to chronic pain: A review of current literature. Pain Pract. 2023 Apr; 23(4):447–58
22. Schindler EAD, Gottschalk CH, Weil MJ, *et al*. Indoleamine hallucinogens in cluster headache: Results of the clusterbusters medication use survey. J Psychoactive Drugs. 2015 Nov-Dec; 47 (5):372–81
23. Sewell RA, Halpern JH, Pope HG Jr. Response of cluster headache to psilocybin and LSD. Neurology. 2006 Jun; 66(12):1920–2
24. Brennan W, Jackson MA, MacLean K, Ponterotto JG. A qualitative exploration of relational ethical challenges and practices in psychedelic healing. J Humanist Psychol [Internet]; 2021 Sep. Available from: https://journals.sagepub.com/doi/10.1177/00221678211045265
25. Effinger A. Oregon's appetite for psilocybin is being fed outside the law in the mushroom underground [Internet]; 2023. Available from: https://www.wweek.com/news/2023/04/26/oregons-appetite-for-psilocybin-is-being-fed-outside-the-law-in-the-mushroom-underground. Accessed July 10, 2024
26. Michienzi A, Hamlin J, Farah R, Bazydlo L. Notes from the field: Schedule I substances identified in nootropic gummies containing Amanita muscaria or other mushrooms - Charlottesville, VA, 2023-2024. MMWR Morb Mortal Wkly Rep. 2024 Jul; 73(28):628–30
27. United States Drug Enforcement Administration. The DEA years [Internet]. Available from: https://www.dea.gov/sites/default/files/2021-04/1970-1975_p_30-39_0.pdf. Accessed August 19, 2023
28. 21 U.S.C. § 812 (2023)
29. United States Drug Enforcement Administration. Drug scheduling [Internet]. Available from: https://www.dea.gov/drug-information/drug-scheduling. Accessed August 19, 2023
30. Indiana Department of Health. 5 scheduled drug categories defined [Internet]. Available from: https://www.in.gov/health/overdose-prevention/general-information/drug-schedules-1-5/. Accessed August 19, 2023
31. van Amsterdam J, Opperhuizen A, van den Brink W. Harm potential of magic mushroom use: A review. Regul Toxicol Pharmacol. 2011 Apr; 59(3):423–9
32. Nutt DJ, King LA, Nichols DE. Effects of Schedule I drug laws on neuroscience research and treatment innovation. Nat Rev Neurosci. 2013 Aug; 14(8):577–85
33. Siegel JS, Daily JE, Perry DA, Nicol GE. Psychedelic drug legislative reform and legalization in the US. JAMA Psychiatry. 2023 Jan; 80(1):77–83
34. 21 U.S.C § S.3187 (2023)
35. United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry [Internet]. Silver Spring, MD: Food and Drug Administration; 2014. Available from: https://www.fda.gov/media/86377/download. Accessed August 19, 2023
36. Multidisciplinary Association for Psychedelic Studies. Grant - breakthrough therapy designation [Internet]; 2017. Available from: https://maps.org/wp-content/uploads/2017/08/2017.08.15-IND063384GrantBreakthroughTherapyDesignation1_Redacted.pdf. Accessed August 20, 2023
37. Compass Pathways. Compass pathways receives FDA breakthrough therapy designation for psilocybin therapy for treatment-resistant depression [Internet]; 2018. Available from: https://compasspathways.com/compass-pathways-receives-fda-breakthrough-therapy-designation-for-psilocybin-therapy-for-treatment-resistant-depression/. Accessed August 19, 2023
38. Business Wire. FDA grants Breakthrough Therapy Designation to Usona Institute's psilocybin program for major depressive disorder [Internet]; 2019. Available from: https://www.businesswire.com/news/home/20191122005452/en/FDA-grants-Breakthrough-Therapy-Designation-to-Usona-Institutes-psilocybin-program-for-major-depressive-disorder. Accessed October 24, 2024
39. Booker C, Rand P. S.5123: To amend the Controlled Substances Act to modify the registration requirements relating to research, and for other purposes [Internet]; 2022. Available from: https://www.congress.gov/117/bills/s5123/BILLS-117s5123is.pdf. Accessed January 8, 2024
40. Booker C, Paul R. S.689: To amend the Controlled Substances Act to define currently accepted medical use with severe restrictions, and for other purposes [Internet]; 2023. Available from: https://www.congress.gov/118/bills/s689/BILLS-118s689is.pdf. Accessed January 8, 2024
41. Booker C. Booker, Paul, Mace, Dean introduce bipartisan legislation to promote research and access to potential life saving drugs [Internet]; 2023. Available from: https://www.booker.senate.gov/news/press/booker-paul-mace-dean-introduce-bipartisan-legislation-to-promote-research-and-access-to-potential-life-saving-drugs. Accessed August 19, 2023
42. United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Psychedelic drugs: Considerations for clinical investigations [Internet]. Silver Spring, MD: Food and Drug Administration; 2023. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/psychedelic-drugs-considerations-clinical-investigations. Accessed August 19, 2023
43. United States Food and Drug Administration. FDA issues first draft guidance on clinical trials with psychedelic drugs [Internet]; 2023. Available from: https://www.fda.gov/news-events/press-announcements/fda-issues-first-draft-guidance-clinical-trials-psychedelic-drugs. Accessed August 19, 2023
44. Cornell Law School. Commerce clause [Internet]; 2022. Available from: https://www.law.cornell.edu/wex/commerce_clause. Accessed August 20, 2023
45. Constitution Annotated. ArtI.S8.C3.1 Overview of commerce clause [Internet]. Available from: https://constitution.congress.gov/browse/essay/artI-S8-C3-1/ALDE_00013403/. Accessed August 26, 2023
46. Wickard v. Filburn, 317 U.S. 111 (1942)
47. United States v. Lopez, 514 U.S. 549 (1995)
48. United States v. Morrison, 529 U.S. 598 (2000)
49. Gonzales v. Raich, 545 U.S. 1 (2005)
50. Cal. Health and Safety Code § 11362.5 (2023)
51. Rosenbaum S. Gonzales v. Raich: Implications for public health policy. Public Health Rep. 2005 Nov-Dec; 120(6):680–2
52. Stout D, Moore S. US won't prosecute in states that allow medical marijuana. The New York Times [Internet]; 2009 Oct 19. Available from: https://www.nytimes.com/2009/10/20/us/20cannabis.html. Accessed January 1, 2024
53. Garcia R. H.R.5592: To prohibit the use of federal funds from preventing a state from implementing their own laws with respect to psilocybin [Internet]; 2023. Available from: https://www.congress.gov/118/bills/hr5592/BILLS-118hr5592ih.pdf. Accessed June 7, 2024
54. Chaffee TA. We[ed] the people: How a broader interpretation of the Rohrabacher-Farr Amendment effectuates the changing social policy surrounding medical marijuana. U Cin L Rev. 2023; 91(3):856–88
55. Cooke BK, Worsham E, Reisfield GM. The elusive standard of care. J Am Acad Psychiatry Law. 2017 Sep; 45(3):358–64
56. American Psychiatric Association. Practice Guidelines for the Psychiatric Evaluation of Adults, Third Edition. Arlington, VA: American Psychiatric Association; 2016
57. American Psychiatric Association. Position statement on the use of psychedelic and empathogenic agents for mental health conditions [Internet]; 2022. Available from: https://www.psychiatry.org/getattachment/d5c13619-ca1f-491f-a7a8-b7141c800904/Position-

Use-of-Psychedelic-Empathogenic-Agents.pdf. Accessed November 18, 2023
58. Osheroff v. Chestnut Lodge, Inc., 490 A.2d 720 (Md. Ct. Spec. App. 1984)
59. Klerman GL. The psychiatric patient's right to effective treatment: Implications of Osheroff v. Chestnut Lodge. Am J Psychiatry. 1990 Apr; 147(4):409–18
60. López-Muñoz F, Alamo C, Cuenca E, *et al*. History of the discovery and clinical introduction of chlorpromazine. Ann Clin Psychiatry. 2005 Jul-Sep; 17(3):113–35
61. Domino EF. History of modern psychopharmacology: A personal view with an emphasis on antidepressants. Psychosom Med. 1999 Sep-Oct; 61(5):591–8
62. Rucker JJH, Iliff J, Nutt DJ. Psychiatry & the psychedelic drugs. Past, present & future. Neuropharmacology. 2018 Nov; 142: 200–18
63. Barnett BS, Siu WO, Pope HG Jr. A survey of American psychiatrists' attitudes toward classic hallucinogens. J Nerv Ment Dis. 2018 Jun; 206(6):476–80
64. Davis AK, Agin-Liebes G, España M, *et al*. Attitudes and beliefs about the therapeutic use of psychedelic drugs among psychologists in the United States. J Psychoactive Drugs. 2022 Sep-Oct; 54 (4):309–18
65. Kim A, Suzuki J. Addiction specialists' attitudes toward psychedelics: A national survey. Am J Addict. 2023 Nov; 32(6):606–9
66. Lorenz v. Booth, 147 P.31 (Wash 1915)
67. Baldor v. Rogers, 81 So. 2d 658 (Fla 1954)
68. Weil Z, Gruber D. The doctrine of two schools of thought–a shield or a sword. Med L. 2000; 19(4):663–702
69. Kapley D, Appel JM, Resnick PJ. Mental health innovation vs. psychiatric malpractice: Creating space for "reasonable innovation". Faulkner L Rev. 2013; 5(1):131–63
70. United States Food and Drug Administration. Step 3: Clinical research [Internet]; 2018. Available from: https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#The_Investigational_New_Drug_Process. Accessed February 3, 2023
71. Barber GS, Dike CC. Ethical and practical considerations for the use of psychedelics in psychiatry. Psychiatr Serv. 2023 Aug; 74(8): 838–46
72. Stone W. FDA advisors reject MDMA therapy for PTSD, amid concerns over research [Internet]; 2024. Available from: https://www.npr.org/sections/shots-health-news/2024/06/04/nx-s1-4991112/mdma-therapy-ptsd-fda-advisors. Accessed June 5, 2024
73. Anderson BT, Danforth AL, Grob CS. Psychedelic medicine: Safety and ethical concerns. Lancet Psychiatry. 2020 Oct; 7(10): 829–30
74. Griffiths RR, Richards WA, Johnson MW, *et al*. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. J Psychopharmacol. 2008 Aug; 22(6):621–32
75. Erritzoe D, Roseman L, Nour MM, *et al*. Effects of psilocybin therapy on personality structure. Acta Psychiatr Scand. 2018 Nov; 138(5):368–78
76. American Psychiatric Association. APA commentary on ethics in practice [Internet]; 2015. Available from: https://www.psychiatry.org/file%20library/psychiatrists/practice/ethics/apa-commentary-on-ethics-in-practice.pdf. Accessed October 7, 2023
77. Smith WR, Appelbaum PS. Novel ethical and policy issues in psychiatric uses of psychedelic substances. Neuropharmacology. 2022 Sep; 216:109165
78. Appelbaum PS. Informed consent to psychedelic treatment—A work in progress. JAMA Psychiatry. 2024 Jun; 81(6):543–4
79. Marks M, Brendel RW, Shachar C, Cohen IG. Essentials of informed consent to psychedelic medicine. JAMA Psychiatry. 2024 Jun; 81(6):611–7
80. Aday JS, Skiles Z, Eaton N, *et al*. Personal psychedelic use is common among a sample of psychedelic therapists: Implications for research and practice. Psychedelic Medicine. 2023 Mar; 1(1): 27–37
81. Emmerich N, Humphries B. Is the requirement for first-person experience of psychedelic drugs a justified component of a psychedelic therapist's training? Camb Q Healthc Ethics. 2023 Mar; 2:1–10
82. Smith WR, Sisti D. Ethics and ego dissolution: The case of psilocybin. J Med Ethics. 2021 Dec; 47(12):807–14
83. de Veen BTH, Schellekens AFA, Verheij MMM, Homberg JR. Psilocybin for treating substance use disorders? Expert Rev Neurother. 2017 Feb; 17(2):203–12
84. Haeusermann T, Chiong W. Ethical considerations in rapid and novel treatments in psychiatry. Neuropsychopharmacology. 2024 Jan; 49(1):291–3
85. MacIntyre MR, Nair M, Bursztajn HJ. Ketamine and psychedelics: The journey from magical mystery to informed consent. Psychiatr Times [Internet]; 2023. Available from: https://www.psychiatrictimes.com/view/ketamine-and-psychedelics-the-journey-from-magical-mystery-to-informed-consent. Accessed January 4, 2024
86. Bursztajn HJ, Harding HP Jr., Gutheil TG, Brodsky A. Beyond cognition: The role of disordered affective states in impairing competence to consent to treatment. Bull Am Acad Psychiatry Law. 1991; 19(4):383–8
87. Bursztajn H, Gutheil TG, Brodsky A, Swagerty EL. "Magical thinking," suicide, and malpractice litigation. Bull Am Acad Psychiatry Law. 1988; 16(4):369–77
88. Bursztajn HJ, Feinbloom RI, Hamm RM, *et al*. Medical Choices, Medical Chances: How Patients, Families, and Physicians Can Cope With Uncertainty. New York, NY: Routledge; 1990
89. Van Court RC, Wiseman MS, Meyer KW, *et al*. Diversity, biology, and history of psilocybin-containing fungi: Suggestions for research and technological development. Fungal Biol. 2022 Apr; 126(4):308–19
90. Zinberg NE. Drug, Set, and Setting: The Basis for Controlled Intoxicant Use. New Haven, CT: Yale University Press; 1984
91. Michaels TI, Purdon J, Collins A, Williams MT. Inclusion of people of color in psychedelic-assisted psychotherapy: A review of the literature. BMC Psychiatry. 2018 Jul; 18(1):245
92. Smith DT, Faber SC, Buchanan NT, *et al*. The need for psychedelic-assisted therapy in the black community and the burdens of its provision. Front Psychiatry. 2022 Jan; 12:774736
93. Thrul J, Garcia-Romeu A. Whitewashing psychedelics: Racial equity in the emerging field of psychedelic-assisted mental health research and treatment. Drugs (Abingdon Engl). 2021 Apr; 28 (3):211–4
94. Williams MT, Davis AK, Xin Y, *et al*. People of color in North America report improvements in racial trauma and mental health symptoms following psychedelic experiences. Drugs (Abingdon Engl). 2021 May; 28(3):215–26
95. Krupitsky EM, Grinenko AY. Ketamine psychedelic therapy (KPT): A review of the results of ten years of research. J Psychoactive Drugs. 1997 Apr-Jun; 29(2):165–83
96. Moghaddam B. Ketamine. Cambridge, MA: MIT Press; 2021
97. Brendle M, Robison R, Malone DC. Cost-effectiveness of esketamine nasal spray compared to intravenous ketamine for patients with treatment-resistant depression in the US utilizing clinical trial efficacy and real-world effectiveness estimates. J Affect Disord. 2022 Dec; 319:388–96