

## Resource Document on Ethical and Practical Implications of Psychedelics in Psychiatry

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Prepared by the APA Ethics Committee

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### Background and History

Psychedelic substances have been used for thousands of years by Indigenous communities in healing and religious ceremonies. In the mid-20<sup>th</sup> century, the United States (US) Federal Government became interested in using psychedelics to treat a variety of mental illnesses, funding over 100 clinical trials between the 1950s and 1970s (Sessa, 2016). At that time, the medical community, including the American Psychiatric Association (APA), was enthusiastic about the potential of compounds like lysergic acid diethylamide (LSD) to treat mental illness (Freedman, 1957). Psychedelics were studied on a range of psychiatric conditions, including alcoholism, obsessive compulsive disorder, depression, autism, and for cancer patients experiencing end-of-life anxiety.

In the late 1960s, opposition to psychedelics – and to the countercultural movement that had embraced psychedelic use – took hold. The US Federal Government came to view LSD as a danger to social cohesion, and research promoted claims of its teratogenic, mutagenic, and carcinogenic potential (Neill, 1987). Although these safety claims were later discredited, the Nixon administration placed psilocybin and LSD on Schedule I of the Controlled Substances Act in 1970, deeming that they had no legitimate medical use. In 1985, 3,4-methylenedioxymethamphetamine (MDMA), whose popularity was surging at the time, was also declared a Schedule I substance. Amidst this political environment, research on psychedelics was largely abandoned between the 1970s and 1990s.

Psychedelics started making a comeback in certain research circles by the 1990s. The era of modern psychedelic research has focused primarily on psilocybin, a classical psychedelic found in the psilocybe genus of mushrooms, and MDMA, a synthetic amphetamine derivative in the subgroup of psychedelics called empathogens. In the past decade, several trials have investigated psilocybin's role in treating

major depressive disorder (MDD) (Davis et al., 2020), alcohol and nicotine addiction (Bogenschutz et al., 2015) (Johnson et al., 2017), and anxiety disorders (King & Hammond, 2021). Research on MDMA has primarily focused on its role in treating post-traumatic stress disorder (PTSD). Currently, there are studies underway or being planned to investigate the use of psilocybin for treatment-resistant depression, bipolar depression, suicidality, depression related to early-stage Alzheimer’s disease, anxiety, obsessive compulsive disorder (OCD), and substance use disorders, while more MDMA-for-PTSD studies are also underway. In this investigational stage, psilocybin and MDMA are provided to carefully-screened research participants in clinical settings and under close monitoring by a team of mental health professionals; they are not for personal or take-home use.

As psychedelics have re-entered the realm of rigorous scientific inquiry, they have garnered much attention from both the psychiatric community and the broader public. Headlines in major media platforms frequently tout the psychedelic future of psychiatry, and patients increasingly ask about the prospect of using psychedelics therapeutically. Despite this enthusiasm, however, clinical studies on psychedelics are still in a relatively early stage, and more research and regulatory work will be required before psychedelics may one day be ready for general clinical use. In this climate, psychiatrists are themselves increasingly curious about the prospects of psychedelic treatments. This resource document focuses on several of the ethical and practical issues surrounding psychedelics in their current investigational stage, and also discusses issues for psychiatrists to consider if psychedelics one day become available for broad clinical use.

## **Psychedelic Compounds**

For a detailed understanding of the pharmacology, psychological effects, and risks of various psychedelic compounds, we refer to the APA Work Group on Biomarkers and Novel Treatments’s May 2020 review, “Psychedelics and Psychedelic-Assisted Psychotherapy” (Reiff et al., 2020). For this discussion of the ethical and practical discussion of psychedelics, it is important to note that the term ‘psychedelics’ is non-specific and comprises a diverse range of compounds associated with non-ordinary states of consciousness. Subgroups of psychedelic compounds include the ‘classical psychedelics’ – among them are LSD, psilocybin, mescaline, and N, N-dimethyltryptamine (DMT) – which are defined by serotonin 5HT-2A receptor agonism. MDMA, a synthetic amphetamine derivative with dopamine-norepinephrine reuptake inhibitor action as well as effects on the serotonin and oxytocin systems, is the most common in the class of ‘empathogens.’ Ketamine, a dissociative anesthetic, is an N-methyl-D-aspartate (NMDA) receptor antagonist with psychedelic properties (Wolff & Winstock, 2006). Intranasal esketamine, the s-enantiomer of ketamine, was approved in 2019 by the US Food and Drug Administration (FDA) for treatment-resistant depression and major depression with suicidality, while ketamine is commonly used off-label via IV infusion to treat MDD. Because ketamine and esketamine are already commonly used in clinical practice, they will be omitted from this discussion.

While all of these compounds can be labelled ‘psychedelics,’ each compound is associated with a unique range of psychological and physiological effects and risks. MDMA, for example, is thought to have a

relatively higher abuse potential than the classical psychedelics. On the other hand, the classical psychedelics may carry a higher risk of psychosis in certain patients compared to MDMA. Classical psychedelics, empathogens, and dissociative anesthetics have non-overlapping targets in the brain which contribute to different subjective and physiological effects. Despite their unique effects, they tend to be grouped together for several reasons, including their use in combined medication-psychotherapy protocols as well as the intense effects they have on consciousness. Of note, ketamine is often administered in the absence of psychotherapeutic support, though research on ketamine-assisted psychotherapy is underway (Dore et al., 2019). Another unifying feature is sociological: MDMA and psilocybin tend to be grouped together because of their historical use as recreational drugs which are being 'reclaimed' for therapeutic purposes.

These generic similarities aside, the risks and benefits of each psychedelic substance should be considered individually, including when discussing ethical and practical issues surrounding their use. While some general principles (for example, the idea of 'set and setting,' which we discuss below) apply across psychedelic-assisted psychotherapies, one must be cautious not to conflate these substances. One should carefully consider how one substance's unique psychological and psychopharmacological properties are relevant to the ethical or practical question at hand.

### **Current State of Psychedelic Research**

The research landscape for psychedelics is progressing rapidly. The first Phase 3 clinical trial for MDMA-assisted psychotherapy for PTSD was published in May 2021 (Mitchell et al., 2021). In this trial of 90 patients (46 of whom received MDMA-assisted psychotherapy), 67% of patients in active treatment no longer qualified for a PTSD diagnosis, while 88% experienced a meaningful reduction in symptoms. Relative to placebo, MDMA had a large effect size for the primary endpoint in this study.

Several trials have studied psilocybin to treat depressive disorders. In the largest study of psilocybin for MDD to date, psilocybin had a large effect on depression inventories, with sustained and strong effects for weeks after a single dose (Davis et al., 2020). Several other trials have also produced large and sustained effects from single doses of psilocybin with psychotherapeutic support. A recent study comparing the efficacy of psilocybin against escitalopram for the treatment of MDD demonstrated equal efficacy between the two drugs (Carhart-Harris et al., 2021).

In these carefully controlled research settings, the safety profiles of MDMA and psilocybin have been encouraging. For MDMA, the most common adverse events are mild and transient, and include muscle tightness, decreased appetite, nausea, hyperhidrosis, feeling cold, and an increase in blood pressure. In the trial mentioned above, MDMA use did not appear to increase the risk of substance abuse, and there was no effect on QT prolongation. Psilocybin's adverse effects were also mostly mild and transient, consisting of headaches, body shaking, and anxiety. Some patients do report intense but transient emotional distress during the psilocybin experience. At this time, psilocybin is thought to have relatively low abuse potential and has actually shown promise in treating addiction, including tobacco use

disorder (Johnson et al., 2018). However, more research will be required in the coming years to fully ascertain the safety profiles of both MDMA and psilocybin.

The effects of psychedelics on suicidality are still not fully clear. In Mitchell et al., 2021, there was no effect of MDMA on suicidality relative to placebo. Several participants had suicidal ideation at baseline and some patients in both the placebo and MDMA groups experienced suicidal ideation during the trial. In Davis et al., 2020, participants had low suicidality at baseline, and this trended lower after patients underwent psilocybin-assisted psychotherapy. At this time, psychedelics' impact on suicidality remains an area of active investigation.

## **Ethical Principles**

Psychedelic treatments involve a range of unique ethical and practical considerations. This document is intended to assist psychiatrists through some of the issues that they may face in clinical practice regarding psychedelic therapies.

1. **Research equipoise:** Despite widespread media attention and claims that “psychiatry may never be the same” (Jacobs, 2021), psychedelic therapies remain in a relatively early stage of research. Research equipoise describes both an epistemic (a state of knowledge) and ethical disposition, requiring researchers and clinicians to remain neutral while the scientific process investigates the veracity of a hypothesis. This principle requires an unbiased stance regarding psychedelics' safety and efficacy, until data from clinical trials reveal this information. Equipoise demands that researchers and clinicians do not “decide what is true” before the science informs them. One should seek evidence first, and then form conclusions on the basis of the evidence. Equipoise is a stance that allows scientific inquiry to guide beliefs, and not the other way around. It is a requirement for ensuring that treatments really work – and are not harming patients.

However, equipoise is not binary: one does not entirely disbelieve until truth becomes apparent all at once. As evidence accrues in favor or against a treatment, one incrementally “updates” their beliefs accordingly. Given the current body of evidence, there is reason for optimism that MDMA- and psilocybin-assisted psychotherapy could be useful in treating various mental illnesses. However, optimism should be balanced with the acknowledgement that, at this point, more work needs to be done to justify a full embrace of either MDMA or psilocybin (as well as other psychedelics that are in earlier stages of research).

Equipoise also takes into account patients' unmet needs. Up to 30% of patients with MDD fail to respond to multiple treatments and are considered to have ‘treatment-resistant depression’ (Zhdanova et al., 2021). The situation is similar for PTSD, which has similarly high rates of treatment resistance (Galea et al., 2014). For these patients, in whom the risk of adverse consequences, including suicide, is greater, solutions are urgently needed. These realities demand that the research community throw its efforts into new interventions, including psychedelics.

Such needs have also been a driving force of enthusiasm for psychedelic therapies. But while early positive results are encouraging, psychiatrists should avoid being swayed too heavily by the headlines. For example, one commonly discussed development is the FDA's designation of MDMA as a "breakthrough therapy" for PTSD in 2017 (Feduccia et al., 2019), and psilocybin's breakthrough designation for MDD in 2019 (Bird et al., 2021). This status is granted on the basis of positive early results in clinical trials and provides specific pharmaceutical companies with additional support and expedited review from the FDA throughout the regulatory process. Despite much enthusiasm in the media regarding these developments, they should not be taken as a guarantee that either MDMA or psilocybin will be approved. Although these labels may appear to be enthusiastic endorsements of psychedelics by regulatory authorities, they too should be viewed in the spirit of equipoise. Psychiatrists are ethically permitted to advocate for new and better treatments, but they should be cautious not to bias their assessments of promising new treatments on the basis of regulatory proceedings or media enthusiasm.

Maintaining equipoise may be particularly challenging in the case of MDMA and psilocybin amidst the increasingly public discussion and, in some communities, full embrace of psychedelic treatments. In particular, various social and political movements throughout the country are beginning to address the issue of clinical use of psychedelics in the voter booth. In Oregon, for example, a 2020 ballot initiative legalized psilocybin therapy and mandated that the state create a regulatory framework under which a system of psychedelic mental health clinics will be developed. The Oregon policy stipulates that psilocybin may be provided for clinical purposes by non-professional 'facilitators' – people without any professional background in mental health. Elsewhere, ballot initiatives decriminalizing psilocybin and other psychedelics for both clinical and non-clinical use have passed or are being planned. In this cultural landscape, psychiatrists should stay educated about the current state of psychedelic research, mindful of the fact that Phase 3 clinical trials on psilocybin for MDD are yet to be published.

Oregon's initiative risks unduly generalizing from the success of early clinical trials. Psilocybin-assisted psychotherapy's positive results were in controlled research settings, with carefully-screened patients, and under the supervision of highly-trained mental health professionals. Though these results are encouraging, there is not sufficient evidence to suggest that safety and efficacy translates to uncontrolled settings with untrained facilitators who may not be equipped to manage complex and challenging clinical situations.

At the current moment, psychiatrists have legal, ethical, and professional responsibilities to abstain from administering psilocybin or MDMA, both of which remain Schedule I drugs, outside of US Drug Enforcement Administration (DEA)- and FDA-authorized research settings. The legal landscape may change in the coming years, however. For psilocybin, there has recently been a push in the research community to reconsider its legal status in accordance with its therapeutic potential and risk of abuse. One group of psychedelic researchers suggests that psilocybin should be made a Schedule IV substance, placing it in the same category as commonly-used benzodiazepines (Johnson et al., 2018). Of note, the Australian drug regulatory agency recently took up the issue of rescheduling both MDMA and psilocybin. Stating that more research is

required, in December 2021, they ultimately decided against rescheduling them or approving them for use as medications at this time (Therapeutic Goods Administration, 2021). MDMA and psilocybin's potential approvals in the US would entail their rescheduling to a less restrictive class and would mean that psychiatrists would be entitled to prescribe them, including for off-label use.

We therefore reject the notion that psychedelics should be used in non-research settings prior to FDA authorization or the development of standard practice guidelines. Given the evidence, it would be unethical to use either MDMA or psilocybin outside carefully-controlled clinical trials at this time. Moreover, the clinical utility of psychedelics should be determined through the research process, not through a majority vote. Treatments for vulnerable people suffering from mental illnesses deserve rigorous inquiry in research settings to ensure that they are safe and effective.

- 2. Challenges in psychedelic research:** The ethics of psychedelic research are complicated by several unique features of the psychedelic experience. Both MDMA and psilocybin are uniquely difficult to blind (for both researchers and participants). Because the effects of these substances are so acute, intense, and idiosyncratic, it can be relatively easy for participants and researchers to tell whether they have received placebo or active drug. A variety of strategies have been developed to manage this conundrum, including the use of 'active placebo' like high dose niacin or stimulants. Other strategies include randomizing patients to high-, medium-, and low-dose treatment groups, using a dose of the psychedelic that is too low to be psychoactive as the control. This strategy allows investigators to tell all patients that they will be receiving active drug, thereby equalizing expectancy effects across groups. Nevertheless, the relative ease of unblinding both patients and researchers creates a situation in which bias may creep into assessments of patient outcomes and lead to inaccurate results.

Expectancy effects among research participants can also influence outcomes. Patients entering psychedelic clinical trials have likely read the headlines touting psychedelic therapies, creating high expectations for dramatic symptom relief. The cultural enthusiasm about psychedelics thereby risks causing a self-fulfilling cycle, wherein high expectations lead to artificially inflated results. There has been some discussion in the research community on expectancy effects with classical psychedelics like LSD and psilocybin (Muthukumaraswamy et al., 2021). However, for empathogens like MDMA, discussion of such effects is relatively scant.

There has been some question of whether psychedelics affect core depressive symptomatology, or whether the improvements are on broader domains of personality functioning that ultimately have little to do with the neurovegetative symptoms of depression (Schatzberg, 2020). These concerns in part emerge from the observation that psychedelic outcomes are sometimes assessed with unvalidated rating scales, which can complicate efforts to compare these

treatments to other psychiatric intervention. One encouraging study that helps address this concern performed a head-to-head trial of psilocybin vs. a first-line antidepressant (Carhart-Harris et al., 2021). This study demonstrated parity between psilocybin and escitalopram on gold-standard depression rating scales. Other unanswered questions include how often psychedelics can safely be administered when patients only respond partially to their first psychedelic treatment. The effects of repeated dosing and chronic use in patients who relapse or only partially respond remain unclear.

Given these dynamics, researchers have an ethical obligation to present the results of psychedelic research realistically, acknowledging the potential impact of these challenges on outcomes and being mindful not to overstate the results. Psychedelic researchers should be careful to maintain epistemic humility as research into these substances progresses.

As previously stated, studies on MDMA and psilocybin so far have been conducted with carefully screened, highly restricted populations. The extent to which outcomes generalize from the carefully-controlled setting of clinical trials remains unknown, placing people who receive these treatments prematurely at unnecessary risk of potential negative effects. Moreover, the majority of the participants in these trials have been white men. To enhance diversity and equity, more work needs to be done to engage marginalized populations in psychedelic research. Psychiatrists should be mindful about generalizing results of clinical trials to populations that have traditionally been excluded from research. This is particularly important with psychedelic therapies, in which cultural, economic, religious, and historical forces may play an outsized role in the patient's experience. Researchers should emphasize including all racial and ethnic groups in research and making additional efforts to include populations that have been historically underrepresented. The field of psychiatry should also make efforts to include researchers and clinicians of all ethnic and racial backgrounds in research, acknowledging that researchers' personal histories can shape research findings and interpretations.

Finally, the comprehensiveness of psychedelic therapist training programs impacts the outcome of clinical trials. In certain settings, the psychotherapy training is intensive, often including over 100 hours of specialized didactic and clinical experiences. If psychedelics are made available outside of research settings, there is a risk that the quality of psychotherapeutic support will fall as incentives to cut costs become more relevant. Many psychotherapeutic modalities follow a pattern of rigorous adherence to protocols in research settings followed by relaxation of strict standards once they are deployed more broadly (Bruijniks et al., 2018). In psychedelic therapies there too should be room for flexibility and tailoring treatments to a patient's specific needs. But the unique and intense nature of the psychedelic experience, as well as the pharmacological complexity of these substances, require that clinicians do not compromise on the quality and safety of psychedelic treatments if they one day become available.

The complexities of psychedelic research, along with the many unanswered questions surrounding their use, further support our view that more research is required before psilocybin and MDMA might be ready for use in general psychiatric populations, and that it would be

unethical to support their use at this time. Psychiatrists should pay careful attention to these challenges in their assessment of psychedelic therapies as the field evolves.

- 3. Informed consent:** The principle of autonomy requires that psychiatrists receive adequate informed consent from patients for any psychiatric treatment, as discussed in the *APA Commentary on Ethics in Practice*, Topic 3.2.4 (APA, 2015). Distinctive features of psychedelic psychotherapies could in fact require what some have called “enhanced consent” (Smith & Sisti, 2020). These principles of consent apply in current research settings but would also be relevant in general clinical practice if psychedelics are eventually approved for broader use. Should the regulatory process determine that psychedelics are safe and effective, protocols for obtaining informed consent will be an important consideration in any future treatments. This is particularly important with psychedelic psychotherapies because they involve acute, intense changes in consciousness for which patients may have little prior experience. These changes can be profound and, especially in the case of classical psychedelics, may provoke high levels of anxiety. Psychiatrists should also consider the possibility that patients will have heightened expectations regarding the transformative effects of psychedelics and help patients adjust expectations.

Whether in current research or future clinical settings, psychiatrists should discuss the potential changes to aspects of one’s personality, preferences, and beliefs that may result from psychedelic use. Research indicates that psychedelic-assisted psychotherapy may produce enduring changes in people’s lives beyond reduction of psychiatric symptomatology alone. Studies indicate, for example, that the personality domain of openness may remain “significantly higher than baseline more than one year after the [psilocybin] session” (Maclean et al., 2011). Psilocybin-assisted psychotherapy may have other broad effects, like decreasing authoritarian political views and increasing one’s connection to nature (Lyons & Carhart-Harris, 2018). A survey of recreational psychedelic users suggests that psychedelics may be associated with changes in religious orientation in patients who reported encountering “God” during a psychedelic experience (Griffiths et al., 2019). Psychedelics can also affect basic metaphysical beliefs, reducing materialist philosophies and strengthening views of the world in which consciousness is pervasive (Timmermann et al., 2021). Combined, these results have made some wonder if psychedelic-assisted psychotherapy could affect basic aspects of patients’ identities – and if these changes should be considered risks of psychedelic therapies. In light of these findings, there has been an ongoing debate about how these research findings apply to individual psychedelic users in clinical settings. The authors of several of these studies, for instance, are careful to point out that these results are found among a select participant population, and that overemphasizing these claims could lead to alarmism. In their view “the current data simply do not support the idea that psychedelic treatments result in meaningful changes in political or religious beliefs or affiliation” (Johnson & Yaden, 2020).

However strong the effects, changes like these will be welcomed by certain patients, while others will be skeptical. Whatever the individual patient's attitude, it is important that patients be made aware of these possibilities before they provide consent. This approach is consistent with the routine practices of informed consent for medications, whose serious side effects are presented to patients even if they are rare. Patients concerned about undergoing such changes should have the ability to opt out of treatment before undergoing a psychedelic experience. The complexity of these considerations requires that the informed consent process for psychedelic therapies be rigorous, ensuring that patients have a sophisticated understanding of their potentially wide-ranging effects.

The process of informed consent aligns with one of the core theoretical underpinnings of psychedelic-assisted psychotherapies: that of "set and setting". "Set and setting" is the concept that the patient's mindset ("set") entering the psychedelic experience, as well as the environment ("setting") in which the psychedelic experience occurs, shape the tolerability, safety, efficacy, and quality of the experience. To maximize the chance that patients will have a valuable experience, psychedelic psychotherapy protocols attempt to optimize the patient's mindset and the setting in which the psychedelic experience will take place. A key feature of this process involves an extensive period of psychotherapeutic preparation in the weeks before the dosing session. Typically, the patient meets multiple times with both the psychiatrist overseeing the trial and the therapists who support the patient during the session. The preparation stage focuses on patients' understanding of the particular substance's effects, their goals for the treatment, and specific details on the supportive and safety measures in place for the day of dosing. In one sense, the preparation stage can be conceived as an extension of informed consent. These sessions are intended to get the patient into a mindset in which they feel prepared to confront and manage challenges that may arise during the psychedelic experience; it is considered essential for ensuring positive outcomes on the day of dosing and afterwards. Inasmuch as the preparation stage is built on principles of informed consent, it also ensures that psychedelic psychotherapy is conducted ethically.

4. **Patient vulnerability:** Psychedelic psychotherapy involves profound and acute changes in consciousness, which place patients in uniquely vulnerable positions. The classical psychedelics cause impaired working memory and executive function (Pokorny et al., 2020), and facilitate openness and trust (Schmid et al., 2015). MDMA can likewise cause increased trust and connectedness towards others (Kamilar-Britt & Bedi, 2015). Although some of these effects can be benefits of psychedelics, they can make patients over-trusting, reducing their ability to recognize manipulative and suspicious situations. Under the influence of psilocybin or MDMA, patients may become more suggestible and easier to manipulate. Patients may experience intense attachment and transference, including of a sexual nature. For these reasons, clinicians working with these substances must carefully uphold boundaries. Unfortunately, these boundaries have been violated by psychedelic therapists in the past, including with therapists entering into inappropriate and exploitative sexual, financial, and emotional relationships with

patients (MAPS, 2019). There should be no tolerance for such behaviors in the field of psychedelic psychotherapy. As stated in the *APA Commentary on Ethics in Practice*, Topic 3.1.1, “psychiatric patients may be especially vulnerable to undue influences and the psychiatrist should be sensitive and careful that [their] conduct does not physically, sexually, psychologically, spiritually, or financially exploit or harm the patient” (APA, 2015). This commitment is particularly important for patients having psychedelic experiences and should feature prominently in the training of any clinician interested in psychedelic therapies.

Psychiatrists should also be mindful of the particular vulnerability of adolescents when it comes to psychedelic therapies. Right now, very little is known about the effects of these substances on youth, including long-term psychological and physiological effects, reinforcing potential, sex differences in psychedelic responses, and the impact of childhood trauma. Some research indicates that certain psychedelics, particularly dissociatives and MDMA, may produce reinforcing or aversive effects that differ between adults and adolescents (Bates & Trujillo, 2021). Adolescents may be at elevated risk of being taken advantage of while in an altered state of consciousness. They may also be less able to manage challenging content that emerges during the psychedelic experience, placing them at increased risk of negative outcomes. The potential risk of reinforcing effects in youth further underscores their heightened vulnerability. Given these considerations, careful measures must be taken to ensure adolescents’ safety should psychedelic therapies be offered to this population. The expected benefits would have to be high indeed to justify the potential risks.

One unique consideration for psychedelic therapies is the use of “therapeutic touch” – a technique sometimes used in the dosing session to help ground patients during moments of intense anxiety. Using therapeutic touch, the therapist might place a hand on the patient’s shoulder, grasp the patient’s forearm, or hold the patient’s hand to provide comfort and reduce loneliness. Psychedelic therapists should have training and supervision to determine when and how such techniques should be used. The idea of “double consent,” adopted from other disciplines, is relevant to ensure that the patient’s autonomy is respected in such vulnerable conditions (Porcino et al., 2014). This means that, first, patients should consent to the use of touch in the preparation sessions, when they are not under the influence of psychedelics drugs, and after they are informed of the conditions in which touch may be used. Second, patients should again consent to therapeutic touch prior to its use in the psychedelic session, once the therapist deems it may be useful (patients may also request therapeutic touch in the session if they wish). If consent is not given during either of these stages, therapeutic touch cannot be used. An ethical challenge arises when the patient has declined consent for therapeutic touch during the preparation sessions (not under the influence of psychedelics) but then requests therapeutic touch while undergoing the psychedelic experience. In such cases, the therapist should exercise caution and discuss the rationale for overriding the previous declination of consent with the patient.

Beyond the dosing session itself, patients are also vulnerable to long-term negative outcomes of psychedelic-assisted psychotherapies. Though epidemiological surveys have demonstrated no population-level link between classical psychedelic use and poor mental health outcomes (Johansen & Krebs, 2015), patients may have individual risk factors that place them at elevated risk. Research from the mid-20<sup>th</sup> century documents a variety of cases in which classical psychedelic use preceded the onset of psychosis (Bowers & Freedman, 1966). To address the concern that psychedelics may precipitate psychosis, clinical trials using psilocybin and MDMA typically use a personal or family history of psychosis as an exclusion criterion. These risks suggest the need for psychiatrists to be judicious when providing psychedelic therapies. Patients should be carefully screened for low-grade psychotic symptoms, a potentially high-risk vulnerability for negative outcomes. Patients at high risk should be excluded from psychedelic therapies until further research demonstrates their safety. Beyond psychosis, researchers have begun to investigate which factors predict negative response to psychedelics (Haijen et al., 2018; Barrett et al., 2017). Ultimately, however, this is an area where large gaps in understanding remain, a reality which could place patients with unknown risks in vulnerable positions. When studying vulnerable groups as a whole, additional safety precautions should be implemented. These possibilities suggest that researchers should exercise clinical judgement in recommending psychedelic therapies. Psychedelics will not be for everyone, and psychiatrists should attempt to identify patients who are particularly vulnerable to negative outcomes before they undergo a psychedelic experience.

- 5. Off-label psychedelic use and psychedelic self-improvement:** If psychedelics are approved for general psychiatric use, psychiatrists will likely encounter patients specifically seeking psychedelic therapies, and may face challenging decisions regarding their care. The so-called ‘psychedelic renaissance’ is in part fueled by people pursuing personal changes and self-improvement in the absence of obvious psychiatric problems. Burgeoning communities have been created with the mission of supporting people pursuing psychedelic self-improvement in non-clinical settings. People are increasingly turning to psychedelics in the midst of major life decisions, like relationship or career changes; to establish a deeper connection with nature and thereby help combat climate change; or to enhance creativity and productivity. Another possibility in the realm of psychedelic self-improvement is their proposed use as agents of “moral enhancement” (Earp, 2018). People seeking these kinds of benefits should be distinguished from recreational psychedelic users, in that the ultimate motivations here are not principally hedonic and have a therapeutic dimension.

Psychiatrists should be mindful that all prescription medications, including psychedelics, should only be prescribed to treat diagnosable psychiatric disorders. When patients come to the clinic, they should be carefully screened for any underlying psychopathology. If there is no clinical indication, psychiatrists should avoid prescribing psychedelics, as is the case for any other

medication. Psychiatrists should be particularly clear to avoid offering psychedelics to people looking for a recreational experience.

While these are straightforward and routine principles of prescribing, they may appear more complicated in the case of psychedelics. Because of psychedelics' potential for promoting self-improvement in the domains described above, psychiatrists may be inclined to prescribe them for such non-clinical purposes. An added layer of complexity with psychedelic treatments is their unique combination of psychopharmacology and psychotherapy. Psychiatry does indeed have a rich tradition of offering psychotherapy to people who do not necessarily have diagnosable psychiatric conditions, which some may argue supports the notion that psychedelics too should be used in such circumstances. However, it is important to distinguish psychedelic psychotherapies from other forms of psychotherapy because they are intrinsically pharmacological interventions. Given the additional risks associated with pharmacological interventions compared to psychotherapy alone, a clear diagnosis should be present before administering psychedelic therapies.

Psychedelics' broad applications may also make it difficult for psychiatrists to determine where 'treatment' ends and 'enhancement' begins. The case of stimulants, which are effective treatments when prescribed judiciously for clinically-indicated conditions, but which are frequently misused or abused for cognitive enhancement, is instructive (Compton et al., 2018). Psychiatrists offering psychedelic treatments should be careful to avoid a situation parallel to that of stimulants by limiting psychedelic prescriptions for clear clinical indications.

If patients' goals for psychedelic use are related to diagnosable mood, anxiety, trauma or personality disorders, clinical judgement may support the off-label use of psychedelic-assisted psychotherapy. On the other hand, psychiatrists should avoid offering psychedelics to people seeking a competitive productivity boost. These treatments should be reserved for patients experiencing impairments in function related to a mental condition. Given the possibility that the demand for psychedelics will outstrip the supply of providers, it is also a matter of equity to reserve treatment for those who are suffering from a mental health condition. Ultimately, it is the psychiatrist's responsibility to understand the causes of a patient's challenges, and why they have been unable to improve in challenge areas using interventions aside from psychedelics. The psychiatrist should form a treatment plan only once symptoms and their relationship to functioning have been thoroughly explored.

Moreover, psychiatrists should be mindful that, at this time, there is little evidence to support psychedelic use for most clinical indications, which is a major barrier for psychiatrists deciding whether to prescribe them off-label. Fortunately, ongoing research may one day help guide clinicians' use of psychedelics for a broader range of conditions. Psychedelics' efficacy in treating personality disorders, for example, remains an open question, though some research has begun to address LSD and psilocybin for this indication (Müller et al., 2020; Zeifman & Wagner, 2020). The use of psychedelics for anxiety disorders is also a burgeoning area of research (King & Hammond, 2021). Studies using psychedelics for anorexia nervosa, depression-associated with

early Alzheimer's disease, OCD, suicidality, anxiety related to cancer diagnoses, and a variety of other indications are currently being planned, but definitive results are still years away.

If psychedelics do become accessible to the general psychiatric population, psychiatrists should also avoid over-reliance on them. Treatment plans should be holistic and tailored to the specific patient. Psychiatrists should avoid a mindset in which all problems become nails to be whacked by the proverbial psychedelic hammer. Due to their potential applications in non-clinical self-improvement, there is a risk with psychedelics of pathologizing everyday challenges of life, leading to an untenable situation in which any stressful situation justifies psychedelic intervention. Psychiatrists must recognize that psychedelics are one tool in the toolbox, and prudently deploy them when clinical judgement deems the patient's challenges are likely responsive to psychedelic interventions. There is some concern for such trends in the case of ketamine clinics, a precedent that should be carefully avoided if other psychedelic treatments become accessible (Schak et al., 2016). The combined risks of excessive exuberance and over-pathologizing also have precedent in the case of medical cannabis, where patients gain ready access to cannabis for purposes with limited evidence base (Gilman et al., 2022). This role risks jeopardizing the integrity of the psychiatric profession and could ultimately decrease public trust in psychiatry.

In the absence of a clear clinical indication, the psychiatrist's potential role in promoting self-improvement, particularly in the domain of 'moral enhancement,' is ethically fraught. Given the highly vulnerable and sometimes transformative nature of the psychedelic experience, psychiatrists risk imposing, whether consciously or unconsciously, their own values on patients. Conversely, if they are involved with self-improvement projects, psychiatrists may find it difficult to recuse themselves from treatments in which patients pursue goals that are inconsistent with their own values. In the case of psychedelic use for treatment of a mental illness, there are symptoms which the psychiatrist and patient can agree are the target of treatment. Without this mutual framework, there is a risk of psychedelic treatments becoming overused and exploitative. When it comes to psychedelics, a clear therapeutic goal represents an important boundary in the relationship between psychiatrist and patient.

- 6. Conversations with patients:** Though MDMA and psilocybin are not yet available for clinical use outside of research settings, psychiatrists may already be hearing from patients who are interested in using psychedelics outside of clinical settings, and who seek their psychiatrist's advice on various aspects of psychedelic use. This phenomenon poses unique challenges to psychiatrists. Psychedelics are highly visible in the media and the culture at large. Unlike other experimental treatments, they are relatively easy to access by savvy patients. Faced with patients who express their intention to procure and use psychedelics in a naturalistic setting (for whatever purpose, whether it be treatment of mental illness, self-improvement, or recreational), psychiatrists may confront the ethical dilemma of how to advise these patients.

As discussed earlier, psychiatrists should not participate in illegal activities, including the administration of Schedule I substances outside of clinical trials. But psychiatrists should feel comfortable having these discussions with their patients, acknowledging the complicated ethical balancing act required in such conversations. First, psychiatrists should be clear that although clinical trials are promising, these medications are still in the experimental stage, and that final determination of safety and efficacy rests in the hands of regulatory agencies like the FDA. Psychiatrists should therefore avoid recommending that patients use psychedelics in non-clinical settings, whether the intention be therapeutic or not. Psychiatrists may also reinforce the difference between psychedelic use in a clinical setting, where clear protocols are in place to ensure patient safety, and in a naturalistic setting, where efficacy and safety are less assured. This distinction is informed by the principle of “set and setting” – the idea that a safe clinical setting may have an impact on the ultimate outcome of the psychedelic experience, and that the experience may be less predictable and carry greater risk if the patient is using psychedelics on their own, without the guidance of trained professionals. Psychiatrists may also determine that a patient could benefit from a psychedelic clinical trial and make appropriate referrals to research institutions.

Psychiatrists should communicate that patients take on additional risks when they pursue psychedelics outside of clinical settings. The act of procuring psychedelics can involve violence, intimidation, theft, and involvement with organizations that perpetrate crime and other public safety concerns. Once obtained, patients may not be able to accurately identify the substance that they have procured. Products sold as pure MDMA, psilocybin, or LSD may be adulterated with other unidentified substances, which can increase the risk of toxicity. Drug checking services, which chemically analyze drug samples to determine which substances are present, are increasingly in demand at music festivals, where use of psychedelics and other recreational drugs is popular (Maghsoudi et al., 2021; Palamar & Sönmez, 2022). Outside of select settings like festivals, however, it can be difficult to confirm the identity of a substance. These issues are complicated by the increasing prevalence of New Psychoactive Substances (NPSs): synthetic compounds that mimic the effects of drugs, including psychedelics, but which often carry additional effects and risks that may be unknown to the user (DEA, 2021). Even if patients can access drug checking services, these services do not necessarily test for the presence of all NPSs.

Moreover, psychedelic users may be unable to manage adverse effects of psychedelics on their own, placing them at elevated risk of severe outcomes. In particular, MDMA is associated with an elevated rate of adverse effects and death when taken in non-clinical settings. In one study of four countries over two decades, researchers identified 1400 MDMA-related deaths (Roxburgh et al., 2021). While the majority of these deaths were associated with multiple drug toxicities, 13-25% of the deaths were attributed to pure MDMA alone. On the other hand, pure psilocybin has been associated with death only in extremely rare circumstances, and even these rare cases have been contested within the research community (Amsterdam et al., 2011). The possibility of death from toxicity is therefore a crucial point of difference in the risk profiles of MDMA and psilocybin. Nevertheless, the risks of adulteration, the possible dangers of procuring substances

for oneself, and the increasing prevalence of NPSs apply to psilocybin as well. For these reasons, psychiatrists should clearly communicate to patients that non-clinical use of psychedelics could be dangerous.

Psychiatrists should also be particularly cautious with adolescents who indicate their desire to use psychedelics in non-clinical settings. As stated in the section on patient vulnerability, the risks of psychedelic use among adolescents may be heightened relative to adults' risks. Adolescents taking psychedelics may experience stronger reinforcing or aversive effects (Bates & Trujillo, 2021). Moreover, adolescents may be more likely to engage in risky behaviors while under the influence of psychedelics compared to adults. Psychiatrists should therefore advise adolescents of their elevated risks if they choose to use psychedelics outside of clinical settings.

Some patients are likely to pursue psychedelics despite the psychiatrist's concerns – and may still seek input from the psychiatrist after the psychiatrist's concerns have been raised (Pilecki et al., 2021). While acknowledging the transference implications of such requests, psychiatrists may need to consider how to manage the patient's psychotropic medications. Psychiatrists should educate patients on the potential (and, in many cases, unknown) risk of interactions between psychedelics and common psychotropic medications. Some preliminary research indicates that selective serotonin reuptake inhibitors may attenuate the effects of LSD (Bonson et al., 1996), while anecdotes and older case studies have documented more severe, and sometimes fatal, effects from combining other psychotropic medications with MDMA (Smilkstein et al., 1987; Vuori et al., 2003). Given these risks, psychiatrists may consider medication tapers in preparation for a patient's self-directed psychedelic experience, and whether to restart medications afterwards – both steps that are typically followed in clinical trials. One notable research development is the use of psychedelic therapies while patients remain on an antidepressant, a question that will hopefully help guide clinicians on the risks and benefits of medication tapers in the future. For now, psychiatrists should consider adopting harm-reduction approaches in order to minimize the risks to their patients. Psychiatrists should take an active, exploratory, and non-judgmental role in helping a patient understand the risks of their decision and think through how to manage medications if the patient is committed to using psychedelics on their own.

There is a possibility in such conversations that psychiatrists with prior personal psychedelic experience may be biased in their treatment plans (Anderson, Danforth, & Grob, 2020). Such experiences could lead to excessive enthusiasm for psychedelics in patients who may not be good candidates. Alternatively, negative associations could lead the psychiatrist to strongly oppose psychedelic therapy when a patient may benefit from referral to a clinical trial. As these therapies become more widely available, it will be important for psychiatrists to be mindful of any personal bias and its impact on clinical decision making. In cases where bias is present, it may be difficult for psychiatrists to act with the best interest of patients in mind. In such situations, psychiatrists should be aware of their bias and consider referring patients to other providers if they cannot overcome their bias.

Independent of prior personal experience, psychiatrists may have strong views either in favor or opposition of psychedelic therapies. Opinions on psychedelics should not automatically be relegated to the status of bias. These treatments involve complicated issues and will require thoughtful deliberation in the coming years to determine their place in psychiatry. An open, honest discussion about their role will be essential in ultimately determining how they can be most effectively and safely used. Such conversations will take place not only among psychiatrists, but also between psychiatrists, patients and their families, and other mental health advocates.

- 7. Equity and access:** As with any new treatment, psychedelics bring with them concerns about who can access these treatments and how affordable they will be. As research and clinical applications expand, efforts should be made to ensure that these interventions can be accessed by all members of society who may benefit from them, and not be reserved for a select few. The history of psychedelics is relevant to matters of access: Indigenous groups have been using psychedelics in religious and medicinal settings for millennia. As psychedelics become incorporated into the psychiatric mainstream, many have commented on the importance of honoring the communities who, over the course of generations, developed the principles of psychedelic use (Jones, 2007). As modern psychedelic research progresses, it is important to distinguish ceremonial use of psychedelics like peyote, which was legalized by the US Federal Government for use in the Native American Church in 1994, from the medical use of psychedelics (Prue, 2014). There is also concern that modern medical settings will attempt to mimic the ceremonial practices and symbols of Indigenous people in ways that devalue these rich traditions.

It is crucial that marginalized communities have access to psychedelic therapies, both in research settings and if they become available for general use. Research has indicated that white individuals account for over 80% of study participants in psychedelic trials so far (Thrul & Garcia-Romeu, 2021). Psychiatrists should make efforts to ensure that patients from all backgrounds, and particularly those who have historically been excluded from psychiatry, are able to access treatment. Moreover, the field of psychedelic-assisted psychotherapy requires careful attention to cultural competency and social determinants of mental health. Research should prioritize how people from different racial, ethnic, cultural, and socioeconomic backgrounds respond to psychedelics, and incorporate culturally informed principles into research protocols. Psychiatrists should actively involve marginalized communities in psychedelic research, and if the treatments are FDA approved, should include these communities in discussions on how to best ensure they can access treatment.

Realities of the psychedelic experience also impact issues of equity and access. In particular, the cost-effectiveness of psychedelic-assisted psychotherapy, whether with MDMA or psilocybin, poses challenges for scalability. For example, on the day of dosing, patients require oversight by trained therapists for a full day. Many trials so far have required two graduate-level therapists

and a psychiatrist to be present for the full duration (often eight hours) of a single patient's dosing session. Some trials have also required participants to have an overnight stay after their dosing session. Costs are further elevated by the need for private space that can be occupied for the duration of the dosing session. In addition, one must also account for the cost of several hours of psychotherapy and psychiatric evaluation in both the preparation and integration phases.

These factors make psychedelic therapies more resource intensive than many other psychiatric interventions, raising the question of how they will be economically viable outside the realm of clinical trials – and whether public and private insurances will cover the treatments for use among the general population. One unwelcome possibility would be the development of a two-tiered psychedelic therapy system. In this scenario, the wealthy few could pay out of pocket for psychedelic therapies, while those with minimal or no insurance may not be able to access the treatment. Another potential pitfall is the scenario in which the quality of psychotherapeutic support is sacrificed to meet the demand of patients seeking psychedelic treatments – a development that would likely be stratified along socioeconomic grounds as well. Both of these scenarios raise ethical questions related to justice and the ability of people from all socioeconomic and racial backgrounds to benefit equally from new treatments.

Fortunately, efforts are underway to explore a variety of potentially cost-saving and access-promoting approaches. Several groups are studying the feasibility of group psychedelic therapy, which would reduce the ratio of clinicians-per-patient and thereby save on costs (Anderson et al., 2020; Trope et al., 2019). Another cost-reducing possibility is the use of very short acting psychedelics, like DMT, which lasts approximately 30 minutes, as a therapeutic intervention. If effective, this strategy would theoretically allow an order of magnitude more patients to access psychedelic treatments while using the same number of resources. Other strategies that may reduce costs and improve access include the use of “non-hallucinatory” psychedelics, which are currently under development by a variety of pharmaceutical companies, and which theoretically would not require as intensive psychotherapeutic support. Micro-dosing, in which sub-perceptual doses of psychedelics are consumed on a recurring basis, could also eliminate much of the clinician costs currently associated with psychedelic therapies. Both of these approaches have yet to be rigorously studied, though clinical trials are currently being planned or underway (Murphy et al., 2021; Cameron et al., 2021).

Scalability issues ultimately raise questions about when psychedelic therapies should be offered in the course of one's illness. Currently, psychotherapy and selective serotonin reuptake inhibitors are considered first-line for the treatment of depression. Different classes of medications, ketamine and esketamine, transcranial magnetic stimulation, vagus nerve stimulation, electroconvulsive therapy, and other forms of neuromodulation fall later in treatment plans. While some general treatment guidelines exist, no universal algorithms dictate precisely which intervention should be used next for a particular patient. Where psilocybin will fit into this mix will be an important topic of discussion as research progresses. The ability of

people from all backgrounds to access psychedelic treatments will be an important factor in determining their future role in psychiatry.

## Resources

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