REVIEW

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# Psychedelic-assisted therapy: An overview for the internist

## ABSTRACT

Preliminary evidence suggests that psychedelic-assisted therapy—the enhancement of psychotherapy with psychedelics such as 3,4-methylenedioxymethamphetamine (MDMA) and psilocybin—may be efficacious for depression, posttraumatic stress disorder, substance use disorders, and other conditions. Therapeutic psychedelic research is advancing steadily, with psilocybin, MDMA, and lysergic acid diethylamide designated breakthrough therapies by the US Food and Drug Administration (FDA). However, in August 2024, the FDA declined to approve a New Drug Application for MDMA and asked its sponsor to conduct another phase 3 trial. Clinicians are urged to prepare for the possible return of psychedelics to medicine.

## KEY POINTS

- Psychedelic-assisted therapy may hold therapeutic potential for some psychiatric conditions and substance use disorders.
- Response can vary, but psychedelics may offer durable effects for months or longer following a single administration.
- Psychedelics have a reassuring safety profile in highly controlled clinical trial settings, though they carry serious risks for some patients.

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Psychedelic compounds such as lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA, or Ecstasy), and psilocybin are drawing interest amid evidence that they may effectively treat psychiatric disorders and substance use disorders.[1] This interest is further fueled by evidence that psychedelics used in a psychotherapeutic setting may improve treatment-resistant conditions and provide benefits that last for months or longer after just 1 treatment session.

Because of the experimental nature of psychedelic-assisted therapy, internists may have little exposure to this modality. However, with possible US Food and Drug Administration (FDA) approval in the coming years and patients increasingly self-treating with psychedelics, the timing is right for clinicians to educate themselves about psychedelic-assisted therapy. This article reviews the potential effects, risks, and therapeutic applications of these powerful drugs, with a focus on MDMA-assisted therapy for posttraumatic stress disorder (PTSD) and psilocybin-assisted therapy for depression.

## OVERVIEW OF PSYCHEDELICS

Psychedelic drugs can significantly alter perception, cognition, mood, affect, social relatedness, and sense of self or meaning. They are unique in that they profoundly affect consciousness without simultaneously inducing delirium.[1] Some of the most notable subjective effects of psychedelics are visual perceptual changes; hallucinations and pseudohallucinations; enhanced feelings of connectedness; and mystical experiences characterized by feelings of unity or oneness,

transcendence of time and space, and deep emotional and spiritual significance. More so than other drugs, the subjective effects of psychedelics are influenced by "set and setting," referring to one's mindset ("set") and the physical environment and social milieu ("setting") of administration.[2]

### Classic vs nonclassic psychedelics

There is debate among researchers about which drugs should be classified as psychedelics. From a phenomenological standpoint, substances with a variety of pharmacologic mechanisms produce psychedelic subjective effects. For example, the effects of LSD are produced via serotonin 2A receptor agonism; ketamine, N-methyl-D-aspartate receptor antagonism; and MDMA, serotonin release into the synaptic cleft. However, some researchers argue that only compounds that produce these effects primarily via serotonin 2A receptor agonism (eg, LSD, psilocybin, dimethyltryptamine) are psychedelics. In a compromise between these competing views, primary serotonin 2A agonists are referred to as *classic* psychedelics, while compounds that exert similar effects via alternate pharmacologic mechanisms are termed *nonclassic* psychedelics.[3]

### Underlying mechanisms are being explored

Over the past 2 decades, numerous studies have explored multiple psychedelic compounds for their effects on various mood, anxiety, and substance use disorders, with promising findings on efficacy and favorable safety profiles in research settings.[1] How psychedelics might be able to treat such diverse conditions remains unclear, but multiple potential explanatory hypotheses are currently under investigation.[4]

Functional neuroimaging studies suggest that psychedelics can disrupt the default mode network, a group of brain regions involved in self-referential thinking and introspection.[4] This network is often overactive in several psychiatric disorders and substance use disorders. Temporarily disrupting the default mode network may enable it to reorganize in a way that fosters more flexible thought patterns, facilitating more adaptive ways of thinking and behaviors.

Neurochemically, psychedelics seem to temporarily enhance neuroplasticity—the brain's ability to reorganize and form new neural connections—for weeks after their immediate effects have ceased. This increased neuroplasticity may promote learning and cognitive flexibility, which patients can use to develop new perspectives and facilitate lasting behavioral changes.

## HISTORICAL PERSPECTIVE

### Early medical use of psychedelics and subsequent regulation

Humans have used naturally occurring psychedelics such as psilocybin and mescaline for thousands of years, and knowledge from indigenous peoples' ritualistic use informs the delivery of psychedelic-assisted therapy.[5] Interest in therapeutic applications of psychedelics in Western medicine is not new. After Swiss chemist Albert Hoffman discovered LSD's psychoactive effects in 1943, his employer Sandoz disseminated LSD to physicians to identify potential clinical applications. Clinical use of LSD in the 1950s and 1960s showed promising results for alcohol use disorder, cancer-related psychological distress, and other conditions.[6,7] Hoffman identified psilocybin as the primary psychoactive compound in *Psilocybe mexicana* mushroom samples in 1958 and first synthesized psilocybin in 1959. Sandoz subsequently also disseminated it for psychiatric research.[8]

In the mid-1960s, the FDA began requiring that drugs be subjected to monitored clinical trials to establish safety and efficacy for specific indications. Amid growing public concern about nonmedical use of psychedelics and the patent for LSD expiring in 1965, Sandoz did not pursue these trials, so clinical use of psychedelics drew to a close.[9] In 1970, most psychedelics were designated under the Controlled Substances Act as Schedule I drugs (ie, no accepted medical use and a high potential for abuse) in the United States, erecting significant bureaucratic and cost barriers that essentially halted early research into psychedelics' therapeutic benefits.

Although MDMA was synthesized in 1912 by Merck chemists,[10] the company conducted no human testing, so it was not designated a Schedule I drug in 1970 because its psychoactive effects were still unknown. American chemist Alexander Shulgin re-synthesized MDMA and performed self-trials in 1976,[10] which led to therapists using MDMA as an adjunct in psychotherapy (permissible in some states at the time). Uncontrolled case series from that period suggested MDMA held therapeutic potential for multiple psychiatric conditions.[11] However, in 1984, once it learned of nonmedical use of MDMA, the US Drug Enforcement Administration announced plans to make MDMA a Schedule I drug. MDMA-assisted therapists attempted to halt this action via administrative hearings,[12] and the US Drug Enforcement Administration administrative judge overseeing the case concluded MDMA should be a Schedule III drug. However, the US Drug Enforcement Administration overruled this and placed MDMA into Schedule I in 1985.

**Figure 1.** Psychedelic treatment room, Cleveland Clinic Lutheran Hospital.

## Renewed interest in therapeutic applications

Through considerable efforts of researchers and philanthropists who believed potentially useful medicines had become unnecessary casualties of the "War on Drugs," clinical trials exploring the therapeutic potential of psilocybin and MDMA were revived in the 2000s. Due to positive findings from these trials,[1] numerous biotechnology companies hoping to develop psychedelics as medicines have recently emerged.[13] Psychiatry has also warmed to the notion of psychedelics as medicines, with 81% of psychiatrists in a 2023 national survey agreeing they show promise in treating psychiatric conditions, and over half planning to incorporate psychedelics into their practices upon FDA approval.[14]

Research into therapeutic applications of psychedelics is now progressing after several decades of dormancy due to regulatory requirements and a lack of federal research funding.[15] In a promising sign, the FDA has granted breakthrough therapy status to LSD, MDMA, and psilocybin because they show potential for significant improvement over existing treatments. With this designation, pharmaceutical companies developing psychedelic treatments receive intensive guidance from the FDA on their drug development programs, and the FDA review process is accelerated.

## Regulatory approval efforts

The field suffered a notable setback in August 2024, when the FDA declined to approve a New Drug Application for MDMA for PTSD despite positive findings from 2 phase 3 trials and asked its sponsor, Lykos Therapeutics, to conduct another phase 3 trial.[16] The FDA typically does not publicly disclose its reasoning for New Drug Application decisions, and Lykos Therapeutics has not publicly shared the complete text of the FDA's response letter. However, Lykos Therapeutics stated that the letter's contents "echo" critiques raised during a June 2024 meeting of an FDA Advisory Committee that recommended against approving MDMA.[17] Concerns raised about Lykos Therapeutics' trials during that meeting included ineffective blinding due to MDMA's psychoactive effects; failure to collect electrocardiograms, liver function tests, and data on participants' feelings of euphoria (to assess addictive potential); and risk of therapist sexual misconduct after a therapist in a phase 2 clinical trial in Canada engaged in a sexual relationship with a participant.[16]

Prior to this decision, it was believed by many in psychiatry that MDMA would become the first FDA-approved psychedelic. Due to the FDA's requirement of a new phase 3 trial, it now seems more likely that psilocybin will be approved by the FDA first. After a positive phase 2 trial,[18] Compass Pathways is conducting 2 phase 3 trials of psychedelic-assisted therapy for treatment-resistant depression. If these trials are successful, FDA approval could be granted in 2026.

**TABLE 1**
**Essential concepts of psychedelic-assisted therapy**

| | |
|---|---|
| **Set and setting** | One's mindset ("set") and the physical environment ("setting") can strongly influence psychedelic subjective effects. Appropriate preparation by the practitioner, which includes building a strong therapeutic alliance and administering the psychedelic in a supportive environment, will minimize adverse experiences and enhance therapeutic efficacy. |
| **Intention**[24] | Defining and setting an intention for what one hopes to gain from a psychedelic experience may increase the likelihood of a powerful and therapeutic psychedelic experience. |
| **Ego dissolution** | Losing one's sense of self is a key feature of the psychedelic experience that can produce positive effects, such as feelings of unity, or negative effects, such as anxiety. This experience tends to be limited to classic psychedelics (psilocybin, lysergic acid diethylamide) and does not usually occur with MDMA. |
| **Mystical experience** | This transformational state, sometimes elicited by psychedelics, is marked by ineffability, ego dissolution, positive mood, transcendence of time and space, and feelings of unity with ultimate reality. The degree to which participants have a mystical experience has been positively correlated with therapeutic effect with classic psychedelics, but not with MDMA. |
| **Challenging experience, bad trip** | A negative psychedelic experience is marked by fear, dysphoria, paranoia, or confusion. Preparation, setting an intention, and taking a psychedelic under the care of a therapist can reduce the risk. Many who have had a challenging psychedelic experience ultimately report it was helpful, though some report long-term psychological harms. |
| **Neuroplasticity** | In this adaptive process, neuronal connections (eg, dendritic spines, synaptic proteins) change in response to a stimulus or experience. This can lead to formation of new neuronal connections or extinction of previously established ones. Psychedelics may enhance neuroplasticity for weeks after exposure. |
| **Suggestibility**[25] | The quality of readily and uncritically accepting and acting upon others' suggestions is enhanced by psychedelics and may be helpful for psychotherapy. |

MDMA = 3,4-methylenedioxymethamphetamine

The Usona Institute has also reported positive findings in a phase 2 trial of psilocybin for major depressive disorder[19] and launched its first phase 3 trial in March 2024.

## PSYCHEDELIC-ASSISTED THERAPY PARADIGM

Psychedelic-assisted therapy arose from combining LSD and psychotherapy in the 1950s, with the eventual addition of music during sessions.[20] Participants in psychedelic-assisted therapy clinical trials undergo preparation sessions to build therapeutic alliance with their therapists, set intentions for their psychedelic sessions, and receive psychoeducation about psychedelics. During psychedelic treatment sessions, participants are cared for by 1 or 2 psychedelic-assisted therapy–trained therapists. Psychedelic sessions occur in a therapeutically appointed space. Inside the treatment room there typically is calming artwork, a couch or a bed on which the participant may recline, and comfortable seating for the therapists, as sessions can last 6 to 8 hours (**Figure 1**). Patients wear headphones and listen to curated music playlists. Participants are also offered eyeshades to facilitate inward focus, with periodic discussion with their therapists occurring as needed.

The subjective effects of psychedelics vary widely, though it is not unusual for participants receiving high doses to report dramatic experiences, such as being reborn or being in the presence of God. Many trial participants report that psychedelic-induced mystical experiences are among the most meaningful and spiritually significant experiences of their lives.[21] Vital signs are collected throughout psychedelic treatment sessions, and participants undergo medical evaluations toward the session's end to ensure appropriateness for discharge. Once cleared, participants are released into the care of a responsible adult and instructed not to drive until the following day.

In the days to weeks after a psychedelic session, participants return for integration sessions to process their psychedelic experiences and consider how to translate resulting insights into durable behavioral change. For

**TABLE 2**
**Potential acute effects and pharmacology of orally administered MDMA and psilocybin**

| | MDMA[30,31] | Psilocybin[18,19,48] |
|---|---|---|
| **Potential acute psychological effects** | Sense of well-being, relaxation, reduced anxiety, stimulation, euphoria, prosocial effects, heightened introspection, increased self-esteem, reduced fearfulness, increased empathy, altered sense of time, mystical experience | Elevated mood, stimulation, enhanced introspection, illusions, visual perceptual changes, hallucinations (auditory, olfactory, tactile, gustatory, and visual), synesthesia, alterations in sense of time, enhanced feelings of connectedness, anxiety, fatigue, affective lability, mystical experience |
| **Potential acute physical effects[28,29]** | Mydriasis; diaphoresis; increases in blood pressure, temperature, and heart rate; slight impairment in psychomotor performance; dry mouth; jaw clenching; bruxism | Mydriasis, elevated or slowed heart rate, elevated or decreased blood pressure, nausea, increased or decreased tendon reflexes, tremor, dysmetria |
| **Most common adverse effects** | Anxiety, jaw clenching, muscle tightness, reduced appetite, nausea, dizziness, excessive sweating, restlessness, feeling jittery, blurred vision, pyrexia, irritability, panic attack | Headache, nausea, visual perceptual effects, dizziness, fatigue, euphoric mood and mood alteration, anxiety, and paresthesia |
| **Time to peak effects** | 1–2 hours | 1–2 hours |
| **Elimination half-life** | 8–9 hours | 2–3 hours |
| **Duration of acute effects** | 4–6 hours | 6 hours |
| **Primary neurotransmitters affected** | Serotonin, norepinephrine, dopamine | Serotonin |
| **Metabolism** | Primarily hepatic, via cytochrome P450 (mainly CYP2D6) | Rapidly undergoes hepatic first-pass metabolism and dephosphorylation into psilocin (psychoactive metabolite); psilocin then undergoes phase I and phase II (primary) metabolism in the small intestine and liver, with metabolites eventually excreted renally |

MDMA = 3,4-methylenedioxymethamphetamine

weeks after treatment, psychedelics appear to reopen critical periods for social learning[22] and enhance neuroplasticity.[23] This provides a rationale for the potential importance of integration sessions for prolonging therapeutic efficacy, although this claim requires further investigation. The number of psychedelic sessions in a treatment course typically ranges from 1 to 3 over several weeks, depending on the protocol and condition being treated.

Essential psychedelic-assisted therapy concepts are outlined in **Table 1**.[24,25]

## MDMA-ASSISTED THERAPY FOR PTSD

MDMA is a nonclassic psychedelic; it acts primarily as a releaser and reuptake inhibitor of serotonin, norepinephrine, and, to a lesser extent, dopamine.[26] MDMA's effects tend to be less intense than those of classic psychedelics, despite frequently catalyzing powerful emotional experiences. It typically produces an increased sense of well-being accompanied by increased extraversion, empathy, and feelings of closeness with others. MDMA lends itself to enhanced introspection without the distraction of significant alterations in perception, body image, or sense of self.[27] Mild elevations in blood pressure, body temperature, and heart rate are expected during treatment sessions.[28]

**Table 2** summarizes MDMA pharmacology, potential acute effects,[28,29] and the most commonly reported adverse events in clinical trials.[30,31]

### Rationale for investigation of MDMA-assisted therapy

PTSD is marked by intrusion symptoms such as nightmares or flashbacks; avoidance of trauma-related thoughts, feelings, or external reminders; negative alterations in cognition and mood; and changes in

arousal and reactivity in people exposed to traumatic events. While trauma-focused therapies are considered first-line treatment, response rates are variable, dropout rates are high, and evidence quality of trials is generally poor.[32] Further, only 20% to 30% of patients respond to treatment with sertraline or paroxetine, the only 2 FDA-approved medications for PTSD.[32] Therefore, there is need for novel PTSD treatments.

MDMA may enhance therapeutic alliance via its prosocial effects while also facilitating a less-threatening experience of traumatic memories. It reduces activity in brain regions associated with fear and anxiety, which may allow severe emotional reactions to traumatic memories to be unlearned.[33,34] Similar to classic psychedelics, MDMA may also enhance or reopen critical periods of learning, which can facilitate behavioral change.

### Functional unblinding in trials a challenge

Clinical trials of MDMA-assisted therapy for PTSD typically involve 2 or 3 treatment sessions, along with preparation and integration sessions. In randomized controlled trials, participants receive the same number of psychotherapy sessions whether they receive MDMA or placebo. Given the strong psychoactive effects of psychedelics, a common criticism of this line of research has been that most participants can easily distinguish whether they have received active drug or placebo (functional unblinding). In the most recent phase 3 trial of MDMA-assisted therapy for PTSD, 94% of participants receiving MDMA guessed they had received it, while 75% of participants in the placebo group were aware they had received placebo.[34]

Importantly, functional unblinding can occur due to a drug's psychoactive effects or side effects as well as its efficacy. This challenge is not unique to psychedelics; high rates are reported in trials of many commonly used psychiatric medications, including stimulants, benzodiazepines, antidepressants (primarily older ones due to more prominent side effects),[35] and antipsychotics.[36] Early MDMA trials used low-dose MDMA as an active placebo to reduce functional unblinding, but later studies switched to inactive placebo after low-dose MDMA was found to worsen PTSD symptoms for some participants. Low-dose MDMA also led to increased anxiety and re-experiencing of trauma during therapy without the emotional breakthrough necessary for processing conferred by high-dose MDMA, with some participants requiring benzodiazepine rescue treatments.[37]

### Promising efficacy results

In a 2022 systematic review and meta-analysis,[30] all 5 eligible randomized controlled trials of MDMA-assisted therapy from 2011 to 2021 used the Clinician-Administered PTSD Scale (CAPS) to evaluate treatment effects (score range 0–80, with higher scores indicating more severe PTSD symptoms; CAPS score ≥ 50 signifies severe PTSD).[38] These trials involved 175 participants with baseline CAPS scores ranging from 44.0 ± 6.0 to 94.4 ± 20.2. Assessment of the primary end point occurred from 3 weeks to 2 months after the last MDMA session, with a 22-point greater reduction in baseline CAPS score occurring in participants receiving MDMA-assisted therapy than in controls (mean difference −22.03; 95% confidence interval [CI] −38.53 to −5.52).[30]

In a recent confirmatory randomized, placebo-controlled phase 3 trial of MDMA-assisted therapy for moderate or severe PTSD, after 3 treatment sessions, response rates at 18 weeks after baseline (6–8 weeks after MDMA session 3) were 86.5% and 69.0% for MDMA and placebo, respectively, while remission rates were 46.2% and 21.4%.[34] This translated to an effect size of 0.70 for MDMA vs placebo. (Effect size is a statistical measure used to quantify the magnitude of a difference between 2 groups' means, which provides a measure of the practical significance of study results. It is calculated as the difference between the 2 means divided by the pooled standard deviation, and is generally interpreted as follows: 0.2 small effect, 0.5 medium effect, and 0.8 or higher large effect.)

While no clinical trials have directly compared MDMA-assisted therapy with sertraline or paroxetine, at the primary end point of phase 3 trials for those medications, the effect sizes were smaller (0.45–0.56 for paroxetine and 0.31–0.37 for sertraline) than the effect size of MDMA in phase 2 trials (0.90) or the 2 phase 3 trials (0.91 and 0.70).[34,39] There have been no trials directly comparing MDMA-assisted therapy with traditional trauma-focused therapies. However, meta-analysis of randomized trials of trauma-focused therapies that included a control condition, rather than waitlist or treatment as usual, showed an effect size of 0.96 after 14 to 27 weeks of treatment.[40]

A dropout rate of 6.8% was observed among participants who received MDMA in phase 2 trials.[39] In contrast, in a recent randomized trial that evaluated 2 trauma-focused therapies for PTSD—prolonged exposure and cognitive processing therapy—dropout rates were 56% and 47%, respectively.[41] It is also notable that phase 2 trials for MDMA-assisted therapy included only participants who had previously been intolerant of or unresponsive to available treatments.[39] Therefore, MDMA-assisted therapy might offer the most public health benefit for PTSD in its potential for patients

not helped by existing PTSD treatments. Only head-to-head trials can provide an accurate assessment of comparative efficacy due to differences in study designs and study populations. Caution is warranted in any comparison of outcomes without head-to-head trials.

### Low risk in clinical trial settings

MDMA has been well tolerated in clinical trials. Although adverse events are common, they have been primarily mild to moderate in severity. Serious adverse events have been rare. One clinical trial participant with a history of premature ventricular contractions experienced worsening contractions after receiving MDMA and was hospitalized, with full resolution and without long-term sequalae.[42]

Given that antidepressants can rarely worsen or induce suicidality, suicidal ideation and suicidal behaviors are important safety outcomes for psychedelic clinical trials. There have been no suicide attempts or completed suicides in clinical trials of MDMA. One trial participant with a history of suicide attempts was hospitalized for suicidal ideation 13 days after their second MDMA session and went on to complete the study.[30,42] In the most recent phase 3 trial of MDMA for PTSD, 2 participants in both the MDMA and placebo groups reported treatment-emergent suicidal ideation, and 1 participant in each group engaged in posttreatment nonsuicidal self-injuring behavior.[34]

MDMA appears to be physiologically safer in controlled settings than in recreational settings. While nonmedical MDMA use has caused rare deaths from hyperthermia or hyponatremia-related seizures, these are typically associated with multiple drug toxicity and dancing in high-temperature environments with likely overhydration.

MDMA's misuse potential is low compared with other commonly used psychoactive drug classes, but somewhat higher than that of classic psychedelics.[43] The existence of addiction to MDMA has been questioned.[44] Elements of addiction, including tolerance, cravings, and psychological dependence, have been reported with MDMA, but physical withdrawal symptoms such as dysphoria appear minor. Questions have been raised about whether these symptoms more accurately reflect subacute "comedown" effects rather than withdrawal. Clinical trials thus far have not yielded evidence of MDMA misuse among participants. While neuroimaging studies of nonmedical users of MDMA have raised concerns about serotonergic neurotoxicity, participants have typically been unusually heavy MDMA users. These studies have also suffered from likely confounding by use of multiple drugs and questions of purity, and have had only limited replicability.[45] Further investigation is necessary, but it is currently thought unlikely that exposure to a small number of MDMA-assisted psychotherapy sessions should cause appreciable risk in this regard.

## PSILOCYBIN-ASSISTED THERAPY FOR DEPRESSION

Psilocybin primarily exerts its psychoactive effects via partial agonism at the serotonin 2A receptor. Depending on the dose, psilocybin can cause potentially intense perceptual alterations, with prominent effects on visual perception. Psilocybin can elevate mood, enhance introspection, and elicit vivid recollection of distant memories.[46] Heightened feelings of connectedness can also occur, but psilocybin tends to produce more of an inwardly focused experience compared with MDMA, with a higher rate of mystical experiences.[47]

Psilocybin elevates blood pressure and heart rate. While elevations are typically mild, self-limiting severe blood pressure elevations have been reported.[28] **Table 2** summarizes psilocybin's pharmacology and acute effects.[18,19,48]

### Rationale for investigation of psilocybin-assisted therapy

Depression involves decreased mood; anhedonia; loss of motivation; disruptions in appetite, sleep, and functionality; and sometimes suicidal ideation or suicide. While antidepressants and psychotherapy are effective for many patients with depression, they are unhelpful or only partially helpful for a substantial minority, and symptomatic improvement is slow. Further, antidepressants can cause problematic adverse effects, including sexual dysfunction and emotional blunting. Treatment-resistant depression, most commonly defined as 2 failed antidepressant treatments, affects approximately one-third of patients with depression.[49] Modalities such as electroconvulsive therapy, transcranial magnetic stimulation, and ketamine or esketamine can be effective for patients with treatment-resistant depression, but there are multiple barriers to their use. Novel rapid-acting agents that produce durable antidepressant effects after only a few administrations would provide considerable improvement in comparison.

### Significant efficacy findings

A meta-analysis of 9 clinical trials of psilocybin-assisted therapy for depression (1 or 2 treatment sessions) included 596 participants and evaluated antidepressant efficacy using multiple instruments, including the Hamilton Depression Rating Scale and the Montgomery-

**TABLE 3**
**Conditions commonly excluded in psychedelic-assisted therapy trials**

| |
|---|
| **Psychiatric conditions** |
| Bipolar disorder (personal or close family history) |
| Personality disorder (eg, antisocial, borderline, schizoid) |
| Psychotic disorder (personal or close family history) |
| Suicidal ideation (with intent or plan) or recent suicidal behavior |
| **Nonpsychiatric conditions** |
| Arrhythmia (clinically significant) |
| Type 1 diabetes, type 2 diabetes (uncontrolled) |
| Hepatic dysfunction, depending on psychedelic metabolism |
| Uncontrolled hypertension |
| Myocardial infarction (lifetime history) |
| Pregnancy or breastfeeding |
| QTc prolongation |
| Seizure disorder |
| Stroke (lifetime history) |
| Tachycardia |
| Unstable thyroid disease |

Asberg Depression Rating Scale.[50] The standardized mean difference in depression outcomes between experimental and control arms was –0.78 (95% CI −1.06 to −0.51, $P < .00001$), signifying a large effect of psilocybin. The pooled response rate at primary end point (which, across included trials, ranged from 1 to 7 weeks after psilocybin administration) was 57% for psilocybin vs 22% for control. Remission was also higher in the psilocybin group compared with the control group (45% vs 14%). Large, statistically significant effect sizes for psilocybin were also observed in 2 open-label trials that had 6- and 12-month follow-ups (1.4 and 2.4, respectively).

### Reassuring safety results

Adverse events are frequently reported in participants receiving psilocybin, though they are usually mild to moderate in severity. Serious adverse events have been rare in clinical trials. One participant sought psychiatric hospitalization for worsening depression after psilocybin treatment.[50] While recent research suggests psilocybin-assisted therapy reduces suicidality,[51] treatment-emergent suicidality remains an important area of interest.

The largest study of patients with treatment-resistant depression to date is a double-blind, randomized controlled phase 2 trial of a single psilocybin-assisted therapy session with 25 mg, 10 mg, and 1 mg (placebo dose) involving 233 participants.[18] From day 2 (first day after psilocybin) to week 3, incidence of suicidal ideation for the 25-mg, 10-mg, and 1-mg groups was 6%, 5%, and 3%, respectively. Incidence of nonsuicidal intentional self-injury during that period was 3%, 1%, and 0%, respectively. From week 3 to week 12, suicidal behavior was reported by 4% of participants in the 25-mg group (all had a history of suicidal behavior or nonsuicidal self-injury), compared with none in the other groups. The incidence of nonsuicidal intentional self-injury during that period for the 25-mg, 10-mg, and 1-mg groups was 0%, 1%, and 1%, respectively. Although not statistically significant, these differences warrant continued investigation into the potential for psilocybin-induced suicidality.

Psilocybin misuse has not been reported in clinical trials.

## POST–REGULATORY APPROVAL CONSIDERATIONS

Should the FDA eventually approve a psychedelic, psychiatry will need to build the infrastructure and train the workforce necessary to deliver psychedelic-assisted therapy—a task that will likely take years. FDA Risk Evaluation and Mitigation Strategies for psychedelics will almost certainly require administration in a clinician's office with in-person monitoring by at least 1 licensed and trained psychedelic therapist. Due to logistical demands and training requirements, an initial bottleneck of psychedelic therapists should be expected.

With a round of MDMA-assisted psychotherapy expected to cost between $10,000 and $15,000,[52] coverage by insurers will also be essential to ensuring access.

While MDMA and psilocybin have favorable safety profiles in research settings, numerous populations with real and suspected risk of serious adverse effects from psychedelics are excluded from contemporary psychedelic clinical trials based on established safety guidelines (**Table 3**).[53] There is a significant need for clinical trials to determine the safety of psychedelic-assisted therapy in these populations, as it is unclear whether many of the potential exclusion criteria are necessary or simply based on theoretical but inaccurate risk appraisals.

Other issues to be addressed in trials include the following:

- Determine whether co-administering psychedelics and antidepressants affects efficacy and safety
- Identify psychedelic-assisted therapy's place in psychiatric treatment algorithms
- Incorporate personalized medicine into psychedelic-assisted therapy.

There is also considerable debate about the quantity and nature of psychological support that is necessary and sufficient during the psychedelic experience, as well as who should deliver it, a matter that could significantly impact treatment costs and access.

## NONPSYCHIATRISTS' ROLE IN PSYCHEDELIC-ASSISTED THERAPY

If approved by the FDA, psychedelic-assisted therapy will be practiced primarily by mental health practitioners, but psychedelic-assisted therapy practitioners will likely look to internists, primary care physicians, and other physicians for guidance on the safety of psychedelics in older patients and patients with conditions that have been exclusionary in clinical trials. Oncologists and palliative care physicians may seek to become trained in psychedelic-assisted therapy themselves due to an increasing number of studies indicating psychedelics' potential to treat psychological distress associated with serious medical conditions.[1]

Further, since functional disorders are frequently seen across medicine and psychedelics may treat some of them,[54] there may be an important role for other specialists in conducting psychedelic-assisted therapy trials for these conditions and potentially delivering psychedelic-assisted therapy clinically someday. Notably, clinical trials are investigating psychedelic-assisted therapy for common pain disorders treated by internists, such as fibromyalgia, migraines, and irritable bowel syndrome.

## LAST WORD

Psychedelic-assisted therapy may be a potentially significant medical advance, offering the possibility of durable therapeutic benefits with rapid onset for some patients with PTSD and depression following only a small number of psychedelic treatments. No psychedelic is currently FDA approved, but psilocybin could possibly gain approval in less than 2 years. If approved, it may be the first of many psychedelics to rejoin psychiatrists' armamentarium over the next decade. However, we have much to learn about optimizing these treatments in clinical settings and real-world patient populations.

## DISCLOSURES

Dr. Barnett has disclosed serving as an advisor or review panel participant for CB Therapeutics, COMPASS Pathways, Cerebral, DynaMed, and Janssen Pharmaceuticals; ownership interest (stock, stock options in a privately owned company) in CB Therapeutics; serving as a research principal investigator for COMPASS Pathways and MindMed; consulting for Janssen Pharmaceuticals and TD Cowen; teaching and speaking for TD Cowen; and other activities from which remuneration is received or expected (editorial services- monetary reimbursement) for DynaMed. Dr. King has disclosed ownership interest (stock, stock options in a publicly owned company) in COMPASS Pathways. Dr. Mauney has disclosed serving as a research co-principal investigator for Tryp Therapeutics.

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