PSYCHEDELICS AND MENTAL HEALTH – A REVIEW OF THE CURRENT RESEARCH

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Executive Summary *Psychedelic substances have followed a unique trajectory for the past 60-70 years. They are most commonly regarded as drugs of abuse and include LSD, MDMA (ecstasy) and psilocybin. However, there is growing interest and research examining their potential as medical therapy for conditions such as depression, anxiety and post-traumatic stress disorder (PTSD). This has led to FDA-expedited development and review of psilocybin as a potential pharmacologic therapy for treatment-resistant depression, as well as approval of esketamine in 2019 for treatment-resistant depression in conjunction with oral antidepressant use. Psychedelic use remains illegal at the federal level; however, many states and local jurisdictions are moving toward decriminalization and legalization of these substances.*

Much of the available data regarding the therapeutic use of psychedelics for mental health disorders remains introductory; however, momentum is building with the potential to offer unique treatments for many complex mental health disorders.

- Esketamine (Spravato) is the only FDA-approved psychedelic treatment. It is a nasal spray indicated for use in adults with treatment-resistant depression or major depression with suicidal ideation.
- Ketamine is being used off-label as an infusion for treatment-resistant major depression and suicidal ideation based on preliminary evidence of efficacy.
- Several other psychedelics (psilocybin, MDMA, DMT) are currently in active clinical trials for psychiatric disorders, including PTSD, major depression and treatment-resistant depression.
- The legal landscape is changing, with more US municipalities proposing legislation to decriminalize and legalize psychedelics for medical and recreational use.

The cultural arc of psychedelic drugs has been broad over the last 5-7 decades. While LSD and psilocybin were initially seen as potentially promising treatments for disorders such as trauma, depression, anxiety and addiction, this promise gave way to panic given their association with 1960s counterculture.[1] By 1970, experiments and clinical research using psychedelics in the US ended with the passing of the Controlled Substances Act (CSA), part of the Comprehensive Drug Abuse Prevention and Control Act of 1970. The CSA categorized drugs into five groups, known as the "drug schedule," which was based on medical use and potential for abuse. Those placed on Schedule I do not have an accepted medical use and are considered the most dangerous. These drugs currently include LSD, marijuana (cannabis), MDMA and psilocybin.[2,3,4]

However, more recently, interest in psychedelics as medical therapy has once again become prominent in the public consciousness. Their potential impact is being evaluated in numerous clinical trials for conditions such as PTSD, drug dependency, depression, anxiety and eating disorders.[5] The FDA has responded to the increased scientific interest in psychedelics by granting "breakthrough therapy" designation to psilocybin therapy for treatment-resistant depression (TRD), (2018)[6] and major depressive disorder (MDD), (2019).[7] This status is granted to expedite drug development and review for serious conditions if preliminary clinical evidence meets the criteria of "substantial improvement" over available therapies.[8] MDMA-assisted therapy for PTSD received break-

through therapy designation in 2017, and Phase III trials were set to begin in 2018.[9] Currently, esketamine is the only FDA-approved and widely available psychedelic treatment. Esketamine is a more potent version of ketamine, an anesthetic, and was approved by the FDA in March 2019 as a Schedule III controlled substance for treatment-resistant depression in conjunction with oral antidepressant use.[10] Schedule III substances are those which have low-to-moderate potential for psychological and physical dependence, with less potential for abuse than Schedule I and II drugs.[11]

Several US states and municipalities are also proposing or have already decriminalized and legalized the use of psilocybin, MDMA and LSD.[12] (See Appendix A, page 58.) Legalization lifts federal or state bans on a drug, whereas decriminalization means that a once-banned drug is still prohibited by law, but the legal system can no longer criminalize or prosecute an individual for carrying under a certain amount. Oregon is currently the only state to have legalized and decriminalized psilocybin with the November 2020 Ballot Measure 109.[13] This state statute authorized the Oregon Health Authority to create a program permitting licensed providers to administer psilocybin products to individuals aged 21 and older. Beginning January 2, 2023, Oregon Psilocybin Services, a division of the Oregon public health department, began accepting applications for licensure.[14] Denver became the first US city to decriminalize psilocybin in 2019, with over a dozen other cities in the US following suit.[15,16]

One of the most commonly known psychedelics is ketamine. It is a mixture composed of two mirror-image molecules, R- and S-ketamine. It was FDA-approved for use as an anesthetic agent (Ketalar) in 1970 and became a Schedule III non-narcotic substance in 1999. As an anesthetic, it is an NMDA (N-methyl-D-aspartate) receptor antagonist, meaning it stops the effect of NMDA and produces a state of dissociative anesthesia, providing pain relief, amnesia and sedation. It is not FDA-approved for the treatment of any psychiatric disorder. Despite the relatively small sample sizes in available trials, limited safety data and lack of long-term efficacy studies, off-label ketamine use is on the rise for treatment-resistant unipolar major depression and suicidal ideation. It is estimated there are hundreds of ketamine providers in the US.[17] In these clinics, ketamine is administered as a slow intravenous infusion at subanesthetic doses, with rapid but transient benefits that are observed within hours, peak after a day, and are lost within 3-12 days. Scheduled ketamine infusions every 2-4 days can provide sustained relief up to weeks or months. Side effects include transient elevation of heart rate and blood pressure, as well as mild dissociation and altered perception, similar to psychosis. The development of a rapidly diminishing response to successive doses of the drug, as well as dependency with prolonged use, can also occur.[18]

There are no well-established clinical predictors or biomarkers of the acute response to a single infusion of ketamine. However, response may be more likely to occur in patients who are more severely depressed at baseline. Concurrent treatment with other antidepressants appears not to decrease their efficacy or increase side effects. In trials, ketamine has been given as monotherapy or add-on therapy to antidepressants and antipsychotics.[18,19] Ketamine is currently registered in numerous Phase III clinical trials for conditions including depression, substance abuse and chronic pain.[20]

Esketamine is a more potent version of ketamine, specifically the S-ketamine molecule, and is available as an FDA-approved nasal spray called Spravato. As with ketamine, there is supportive evidence of benefit in treatment-resistant unipolar major depression and suicidality. A 2.5-year multicenter, double-blind, randomized withdrawal study showed increased long-term benefit in individuals with major depression who were treated with the combination of esketamine and an antidepressant.[21] The side effect profile may be less with ketamine, but there are no comparison trials. Adverse effects occur at least twice as often with intranasal esketamine plus antidepressant, compared with placebo, and these include anxiety, increased blood pressure, dissociation, dizziness, nausea, sedation and vertigo.

Psilocybin, lysergic acid diethylamide (LSD), mescaline and N,N-dimethyltryptamine (DMT) are types of serotonergic hallucinogens that share agonism for the serotonergic 5HT2A receptor. These psychedelics may be synthetic, such as LSD, or found in nature, such as DMT, mescaline and psilocybin. Psilocybin is present in mushrooms of the genus *Psilocybe*, and mescaline is present in peyote and San Pedro cacti. DMT is present in the botanical preparations jurema and ayahuasca. Their primary effects include changes in mood (euphoria, bliss, joy), cognitive processes (introspection, self-consciousness, altered time passage, mystical experiences), and mainly visual sensory perception. While their therapeutic properties have been studied dating back to the 1950s, there is growing interest regarding the promising antidepressant, anti-addictive and anxiolytic effects of these hallucinogens.

Entactogens are another type of serotonergic drug with reported effects of enhancing empathy and emotional openness. The most popular substance in this class is 3,4-methylenedioxymethamphetamine (MDMA or ecstasy). MDMA is a synthetic compound that is pharmacologically and structurally similar to amphetamines and mescaline. It inhibits monoamine, instead of being a serotonergic agonist, and is thus not a classic hallucinogen. However, MMDA's anxiolytic properties are gaining traction in clinical trials.[22]

The first major MDMA trial, Multi-Site Phase III Study of MDMA-Assisted Therapy for PTSD, MAPP1, had the goal of assessing the efficacy and safety of MDMA-assisted therapy in individuals with severe PTSD. This trial was completed in 2020.[23] Participants (n=91) were randomized to receive MDMA-assisted therapy or placebo and therapy. Those in the MDMA group showed clinically significant improvement, with 67% no longer meeting the diagnostic criteria for PTSD after three sessions compared to 32% in the placebo group. MDMA did not increase the occurrence of suicidality, and there were no other major safety issues.[24] The second Phase III trial, MAPP2, is currently active and completed enrollment as of May 2022. This randomized, double-blind, placebo-controlled trial will assess the safety and efficacy of MDMA-assisted psychotherapy in those with moderate PTSD.[23]

There have been several Phase II trials of psilocybin, one for TRD, which has been completed,[25] and one for MDD, for which results have not yet been published.[26] The completed study was a Phase II, double-blind trial in which adults with TRD (n=233) were randomly assigned to receive 10 mg or 25 mg of psilocybin or a control dose (1 mg). All received psychological support. The goal was to assess the efficacy and safety of the two different doses of psilocybin. At 3 weeks, those in the 25 mg group, but not the 10 mg group, showed a statistically significant reduction in depressive symptoms (37%) compared to the control group. However, those receiving psilocybin also reported more adverse events including headache, nausea, dizziness, fatigue, suicidal ideation and self-injurious behavior. Additional longer and larger trials are needed to assess the safety and efficacy of psilocybin. An important consideration for individuals with TRD is that they have failed trials of at least two other treatments and sometimes as many as four to five treatments, so finding new options is extremely important. A less favorable side effect profile or lower response rate may not be as problematic in this population as it might be for a first-line treatment.

The use of LSD as a potential therapeutic is unclear. This drug does not have any special status from the FDA, but has been tested in a limited number of clinical trials and shown some therapeutic potential.[27] Currently, there is one Phase IIb trial for generalized anxiety disorder (GAD) that is expected to be completed by the end of 2023.[28,29] This randomized, double-blind, placebo-controlled trial will enroll 200 adults with GAD who will receive doses of up to 200 micrograms of the MM-120 LSD formulation or placebo. The goal is to optimize dosing and assess safety and efficacy of the MM-120 pharmaceutical product (MindMed).

There are two current trials for DMT. The more recent is a Phase IIA trial of DMT in combination with therapy for major depressive disorder.[29,30] This double-blind, placebo-controlled trial has completed recruiting and will examine the safety, tolerability, pharmacokinetics and pharmacodynamics of the DMT formulation SPL026 (Small Pharma). This Phase IIA trial follows a small (n=32) Phase I trial of the same DMT formulation in healthy, psychedelic-naive individuals designed to assess safety and tolerability.[31] The Phase I trial has been completed, but no results have been reported.

There is currently one registered Phase I clinical trial of mescaline that is actively recruiting and is estimated to be completed in 2023. This small, placebo-controlled trial (n=16) in healthy adults will assess participants' responses to different doses of mescaline, measuring subjective experience, personality, mood, well-being and other psychological factors, as well as vital signs and biomarkers including mescaline concentration in blood and urine.[32] Results from this trial and an earlier Phase I study that compared the effects of mescaline to other psychedelics should be reported in 2023, in addition to the start-up of more trials of mescaline formulations run by biomed companies Biomind Labs and Xphyto Therapeutics.[33]

It is evident that much of the available data and trials regarding the use of psychedelics to treat mental health disorders are preliminary, but the body of research is growing with a likely trajectory of increasing therapeutic usage. While psychedelic use remains illegal at the federal level, many states and local jurisdictions continue to move the needle on decriminalization and legalization for medical and recreational purposes. This highlights the importance of being familiar with these substances from an underwriting perspective, as these treatments pose unique challenges pertaining to risk assessment. These challenges not only include ascertaining the risk associated with the underlying mental health

disorder, but also the risks associated with use of a psychedelic. Ketamine is a prime example of this challenge. As its use is not regulated by the FDA, there are no set treatment protocols providers must follow to ensure proper safety and efficacy, leading to the potential for adverse sequelae from improper use. Additionally, psychedelics are not considered first-line therapy for any mental health disorder, so their use generally points toward the presence of more severe disease. The lack of long-term safety data and extensive clinical trials regarding psychedelic use also pose limitations regarding risk assessment. The evolution of psychedelics as medical therapeutics is in its youth, but has the potential to offer a unique and growing body of treatments for those with complex mental health disorders. This creates a heightened awareness of the multifaceted nature of these conditions and careful assessment of the risk.

Appendix A: Legal Status of Psychedelics in the US.[34]

Category of Psychedelic Drug Policy Reform	State or City
Legalization and Regulation Statute	Oregon
Decriminalization Statute	Oregon
Reduced Penalty Statute	Colorado Washington New Jersey
Limited Judicial Exceptions	New Hampshire New Mexico
Working Group To Study Medical Use	Texas Utah Maryland Connecticut Hawaii
Active Legislation	Kansas Georgia Michigan Pennsylvania New York Massachusetts Rhode Island
Inactive or Failed Legislation	California Oklahoma Iowa Missouri Ohio Florida West Virginia Virginia Maine Vermont Chicago, IL
Local Government Reforms (Including Decriminalization)	Port Townsend, WA Seattle, WA Arcata, CA Oakland, CA Santa Cruz, CA Denver, CO Ann Arbor/Washentaw County, MI Detroit, MI Hazel Park, MI District of Columbia Somerville, Cambridge, Northampton, MA

Appendix B: The Phases of Clinical Research.[35,36]

Clinical Trial Phase	Purpose	Size/Population	Duration	Percent of New Drugs Entering This Phase
Phase I	Safety and dose	20-100 healthy volunteers	Several months	~70%
Phase II	Efficacy, side effects	Up to several hundred people who have the target condition	Months-2 years	~33%
Phase III	Efficacy, adverse reaction monitoring	300-3,000 people who have the target condition	1-4 years	25-30%
Phase IV (Post-marketing)	Long-term safety and efficacy (after drug is FDA-approved)	Thousands who have the target condition	Ongoing	Only in drugs receiving FDA approval

Continuing Education Questions

1. Which psychedelic substance has achieved FDA approval?
   a. Ketamine
   b. Esketamine
   c. Psilocybin
   d. MDMA (ecstasy)

   Answer: Esketamine

2. Which psychedelic substance is being used off-label (not FDA-approved) in clinics around the US for treatment-resistant depression?
   a. Psilocybin
   b. LSD
   c. Ketamine
   d. Mescaline

   Answer: Ketamine

Notes

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