



Psilocybin in Clinical Treatment: Emerging Evidence, Opportunities, and Considerations

Executive Summary

The purpose of this white paper is to provide information about psilocybin, and its use in clinical settings to treat an increasing number of mental health and addiction issues. The paper will define what psilocybin is, how it works in the brain, clinical use, legal concerns, and current legislative action in the State of Indiana. There are several organizations that continue to research psilocybin in the treatment arena. Several will be referenced throughout this paper.

Introduction

Psilocybin originated from fungal species within the genus *Psilocybe*. Psilocybin is an alkaloid that is the main psychedelic ingredient in psychedelic mushrooms. *Psilocybe* mushroom species are pan-tropical, growing around the globe, including regions of the southeastern United States, Central and South America, Southeast Asia, and parts of Africa.¹

Although interest in psychedelics, more specifically psilocybin, has emerged recently within western culture, the traditional and ancestral use of psychedelic mushrooms originated generations ago in Mesoamerica. Civilizations such as the Aztec, Maya, Olmec, and Zapotec have documented the use of psilocybin to evoke altered states of consciousness for healing rituals and religious ceremonies.¹

Psychedelics do not appear to be addictive. Addiction typically means people are taking escalating amounts of a drug in the face of adverse consequences, such as social, financial, legal, and physical. With psychedelics, this common addictive pattern has not been observed. There is growing tolerance, but it does not lead to addictive behaviors. There are substantial risks in the use of psychedelics, but addiction does not appear to be one of them.²

Why Psilocybin?

Johns Hopkins University started the study of psychedelics in 2000 when the late Roland Griffiths, a psychiatry and neuroscience professor, launched the first Food and Drug Administration (FDA)-approved study of psilocybin. Ongoing research at John Hopkins has produced more than 150 peer-reviewed articles. These articles explore the therapeutic benefits of psychedelics in treating a range of conditions including depression, Post Traumatic Stress Disorder (PTSD), addiction disorders, anorexia nervosa, obsessive-compulsive disorder, and more. The Center for Psychedelic & Consciousness Research opened at Hopkins in 2019. As a result, the center has cemented the institution's leadership role in the field.²

Mount Sinai and the James J. Peters VA Medical Center, the Center for Psychedelic Therapy Research examines the therapeutic potential of psychedelic compounds for PTSD and other trauma-related symptoms. More than 70 percent of American adults (about 223.4 million people) have experienced a major traumatic event in their lifetime. Approximately six out of every one hundred people will develop PTSD at some point in their lives. Five percent of the U.S. adult population (seventeen million people) experience PTSD in any given year. Veterans, especially those who deployed to a war zone, are more likely to develop PTSD than non-veterans.³

Although some cognitive behavioral therapies have been designated “gold standard” treatments for PTSD, these treatments are not cure-alls, and there is an urgent need for new pathways to healing and recovery. Psychedelic-assisted psychotherapy is a promising option.

Another area of research is exploring the safety and efficacy of using psychedelics to treat a wider range of concerns, including depression and bulimia. Some of the clinical trials currently taking place are:

- Randomized clinical trial comparing MDMA (Methylenedioxy-Methamphetamine)-assisted therapy with two versus three MDMA sessions in veterans with PTSD in an outpatient Veterans Administration setting.³
- Open label, two-site study of psilocybin for PTSD, conducted at the Center and Kings College London.³
- Study exploring changes in brain functioning associated with MDMA-assisted therapy.³
- Research looking at changes in brain functioning associated with psilocybin-assisted therapy.³

- Assessment, using functional magnetic resonance imaging, of changes in brain functioning associated with treatment (being performed in conjunction with the MDMA-assisted and psilocybin-assisted therapy studies).³
- Long-term follow-up study of veterans following MDMA-assisted therapy.³
- Exploration of psychological and biological changes associated with MDMA-assisted psychotherapy in healthy volunteers.³

The Center for Psychedelic Therapy Research has examined the neurobiological mechanisms of psychotherapy and other treatments for PTSD. They have investigated the effects of psychedelics on brain function and molecular and cellular biology. This is accomplished by obtaining brain images and blood samples before and after psychedelic administration in willing participants for the assessment of well-established biomarkers of PTSD and resilience. Genome-wide epigenetic, gene expression, proteins, metabolites, immune markers, and hormones can be measured before and after treatment. The knowledge gained from these biomarkers will not only allow us to understand biological changes associated with recovery but will also help us understand how recovery with psychedelics may lead to more enduring, transformational changes. In addition, stem cell technology will be used to determine the impact of psychedelics on gene expression networks in neuronal cells reprogrammed from stem cells obtained from persons with and without PTSD.³

How has it been used to treat mental health disorders?

Individuals who take psilocybin report a wide range of experiences ranging from 4-8 hours depending on the dose. These experiences have been reported as visual imagery of multicolored geometric shapes, vivid imaginative sequences, synesthesia, feelings of bliss and connectedness, dissolution of the self/ego, and mystical-type experiences (i.e., experiences that create lasting change in a person's worldview). Researchers have begun pairing psilocybin with various forms of psychotherapy, called Psilocybin-Assisted Therapy (P-AT), to support mental health conditions.⁴

Although psilocybin has shown efficacy for treating depression, anxiety, and substance use, there has been minimal research on its impact on PTSD symptoms. However, there is great interest in studying the utility of P-AT for treating PTSD given that psilocybin:

- Affects neural networks to create positive changes in personality, increase feelings of connectedness, increased openness, improved perspective, increased psychological flexibility, and an increased sense of well-being.⁴
- Facilitates fear extinction and neurogenesis in animals, which may directly counteract the impaired fear extinction and neurogenesis that play a key role in the development and maintenance of PTSD; and⁴
- Induces emotional breakthrough experiences that have been established as a key mediator in long-term psychological change in treatment for other mental health disorders.⁴

Treatment and Setting Applications

While P-AT findings are promising, there are several challenges with psychedelic research that should be considered when interpreting the evidence. While the double-blind randomized controlled trial (RCT) is considered the gold standard design for identifying treatment-specific effects, the strong physical and psychological effects of psychedelics create difficulties effectively conducting blinded, controlled trials. Participants and investigators can typically tell if the person received the investigational product or a placebo thus breaking the blind. Failing to keep patients (and researchers and staff) uncertain of treatment condition assignment (i.e., maintaining the mask or "masking") introduces expectancy effects. If participants know they have received psychedelic treatment they already believe it will improve their symptoms, this alone can improve clinical outcomes (i.e., the placebo effect).⁴

Conversely, if participants know they received a treatment they already believe is unlikely to improve their symptoms, e.g., an inert placebo, this alone can worsen outcomes. Use of "active" placebos that mimic aspects of the psychedelic experience is essential, as is the use of masked assessors. Study staff also should be masked to the extent possible. The adequacy of masking for both patients and providers should be assessed, along with patients' treatment expectations before treatment. There is a critical need for trial designs with psychedelics to better manage expectancy effects.⁴

Regulatory and Legal Landscape

Psilocybin remains a Schedule I drug, although as of February 2024, Australia, the states of Oregon and Colorado, and the Canadian state of Alberta have legalized psilocybin for medicinal purposes in supervised settings. Similar bills are currently underway in the states of California, Washington,

New Jersey, and Massachusetts. The FDA has been reviewing the evidence for P-AT for mental health treatment, which may lead to legalization of P-AT for this purpose.⁴

The U.S. Food and Drug Administration (FDA) granted “breakthrough therapy” designation to psilocybin-assisted psychotherapy for both major depressive disorder in 2019 and treatment-resistant depression in 2018.

John Hopkins Center for Psychedelic & Consciousness Research recently announced three clinical trials studying the therapeutic effects of psilocybin for Post Treatment Lyme Disease, co-occurring alcohol use disorder and depression, and Obsessive-Compulsive Disorder (OCD).⁵

An Interim Study Committee on Public Health, Behavioral Health, and Human Services was formed on September 25, 2025, in the Indiana legislature. The Committee determined the following findings concerning the topics on mental illness:

1. Many people conflate increased access to psilocybin assisted therapy with the issue of increased access to medical and recreational cannabis. However, the committee hearing made it clear that the evidence for psilocybin assisted therapy is promising and significantly more robust and the two issues are unrelated.
2. Currently, psilocybin is designated as a Schedule I drug. The prevailing view is that psilocybin should not be a Schedule I drug and has proven medical benefits.
3. The Federal Food and Drug Administration has designated psilocybin as a “breakthrough therapy” medication, which recognizes that it has important potential medical benefits and may have more benefits than current therapies can provide. This designation is due to current mainstream research showing benefits. This research comes from major respected institutions and publications, including the New England Journal of Medicine, JAMA, Johns Hopkins, Harvard, and others. Therapeutic uses based on research include treatment of resistant depression, anxiety, PTSD, and the potential for opioid dependence, tobacco and alcohol dependence and others.
4. The robust research and “breakthrough therapy” designation show promise for the use of psilocybin in the treatment of several mental and behavioral health disorders. However, due to regulatory uncertainty and the novel nature of the therapy, a cautious approach is warranted.

The Committee made the following recommendation concerning the topics on mental illness:

The Committee recommends the Indiana General Assembly take an approach that strikes a balance between access, research, and prudence by authorizing the Indiana state research institutions to conduct a pilot clinical study utilizing established therapeutic protocols as a starting point to explore the efficacy, safety, and feasibility of psilocybin assisted therapy in Indiana.⁶

House Enrolled Act 1259 established a Therapeutic Psilocybin Research fund to be administered by the Department of Mental Health and Addiction (DMHA) for continued research. DMHA will ensure that research institutions meet all the following: (1) Has an academic institution that operates an institutional review board (IRB) that oversees research. (2) Publishes the results of previous clinical trials in peer reviewed publications. (3) Has access to a clinical research center and the center's resources, including research dedicated medical staff.

The therapeutic psilocybin research fund is established for the purpose of providing financial assistance to research institutions in Indiana to study, in accordance with the requirements established in House Enrolled Act 1259 for the use of psilocybin to treat mental health and other medical conditions. The bill was ordered engrossed and adopted in January 2024.⁷

Conclusion

The use of psilocybin and other psychedelics offer promise for those struggling with many types of mental health conditions, PTSD, and/or behavioral health problems. Research is ongoing as are the promising results, ethical concerns, and need for guided therapy. It is complex and requires prudence in all areas.

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