

# Comparative Efficacy of Psilocybin and MDMA in PTSD Treatment: A Systematic Review of Long-Term Outcomes

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## ABSTRACT

Highly stressful events can lead to post-traumatic stress disorder (PTSD)—a significant public health concern which existing treatments (e.g., psychotherapy and traditional medications) have shown marginal efficacy for. Psychedelics—alternatively called hallucinogens—are psychoactive substances that cause perception, mood, and cognitive changes. Because they are known for their impact on neuron plasticity and the formation of new connections, researchers are exploring psychedelics' therapeutic potential for PTSD. This review compares psilocybin and MDMA's effectiveness in treating PTSD.

## Introduction

Post-traumatic stress disorder (PTSD) is a chronic disorder caused by a stressful and traumatic event characterized by flashbacks, nightmares, severe anxiety, and uncontrollable thoughts about the event.<sup>13</sup> PTSD is a significant public health concern with high burdens on patients and their communities due to its high lifetime prevalence and major consequences.<sup>1</sup> Although psychotherapy is the standard for treatment, PTSD often remains a chronic illness.<sup>8,9</sup> Only two medications, paroxetine, and sertraline, have been approved for the treatment of PTSD thus far—still with limited effects.<sup>2,5</sup> In other words, current treatments such as psychotherapy and traditional medications have shown marginal efficacy.<sup>7,8,9</sup> As such, resources have been allocated to both find and develop alternative treatments for PTSD. One major area of interest is psychedelic science, which focuses on the efficacy of psychedelic medicines—psychoactive substances that cause changes in perception, mood, and cognitive processes—and psychedelic-assisted therapies in treating mental health disorders.<sup>6,14</sup>

Plant- and fungi-derived psychedelics have been part of indigenous cultures and medicinal traditions for millennia.<sup>3</sup> Psychedelics made their mainstream debut in the West after Albert Hofmann first synthesized lysergic acid diethylamide (LSD) in 1938.<sup>4</sup> Soon, psychedelic research began to slow down due to government intervention and social stigma. In more recent decades, psychedelic science has been on the rise due to relief in suppression of psychedelics and their study, as well as growing disenchantment in current

mental health care methods—psychedelic decriminalization has even landed on Massachusetts' ballot this year.<sup>6,11</sup> Through persistent education and advocacy, psychedelic science has opened the gates for exploring psychedelics as an alternative means of healing, particularly in the mental health space.<sup>3</sup> Accordingly, some of these research efforts have been made to explore the therapeutic capabilities of psychedelics in PTSD.<sup>7,8,9,12,13</sup> Many of these research efforts have looked at how psychedelics can be used in conjunction with psychotherapy approaches.

While there has been a recent surge in psychedelic research, gaps remain in understanding their mechanics, risks, and effectiveness in treating PTSD. For example, one study showed that MDMA and ketamine could reopen the social reward learning critical period even when 5-HT<sub>2A</sub> receptors were blocked. The results of such literature call one of the most solidified beliefs about psychedelics into question: the therapeutic effects of psychedelics derive from modulating serotonin 2A receptors. Despite growing research, the mechanisms, benefits, and risks of psychedelics in treating mental health disorders remain poorly understood.

To address the need for a deeper understanding of psychedelics and their role in treating mental health disorders, particularly PTSD, this systematic review evaluates the therapeutic potential of psilocybin and MDMA compared to psychotherapy and traditional medications, focusing on efficacy, safety, and psychological outcomes. One of these psychedelic compounds, psilocybin, is considered a “classic” psychedelic in that it is thought to work on serotonin 2A receptors. On the other hand, MDMA, a “non-classic” psychedelic, does not work on serotonin 2A receptors, as earlier mentioned.

Outcome measures include PTSD symptom improvement over follow-up periods (six months, one year, and two years), changes in psychological mechanisms (e.g., emotional regulation, trauma processing, self-compassion), adverse effects, and safety profiles. By comparing the data across literature on the efficacy and safety of psychedelic-assisted and traditional treatments, this systematic review will clarify psychedelics' current standing and provide an avenue for further research down more promising avenues.

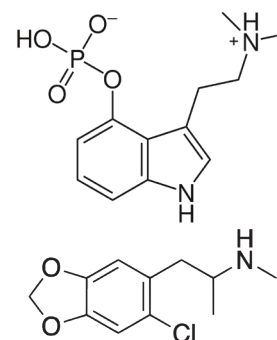


Figure 1. Chemical Structures of Psilocybin (top) and MDMA (bottom)

## Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.<sup>10</sup>

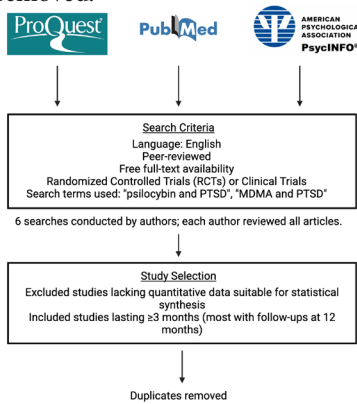
### A. Data Sources and Search

The databases used in this study were APA PsycInfo, PubMed, and ProQuest. Studies lasted from three months to two years, including follow-ups. The articles were limited to those written in English, peer-reviewed, available in free text, and further filtered only to provide results that were

randomized controlled trials or clinical trials. Specific search phrases were: psilocybin and PTSD, MDMA and PTSD. A total of six searches were conducted. Each search was done by one author, and each author read all articles.

## B. Study Selection

This systematic review excluded any studies that did not include quantitative data that could be used for statistical synthesis. Due to a specific interest in long-term outcomes, it included studies that spanned at least three months, with most studies following up after 12 months. After compiling a list of research articles, duplicates from different databases were removed.



**Figure 2. Data Sources, Search, and Study Selection**

## C. Data Extraction

Data was used for analysis if the researchers utilized a method that could show changes in PTSD severity (e.g., changes in CAPS-IV or CAPS-V scores). Data showing changes in a measure that corresponds with PTSD severity (e.g., depression and anxiety) was also included. This was due to the researchers not finding any currently published studies done on psilocybin and PTSD.

Data extraction was done by two reviewers who communicated about which data would be extracted or included. If data was unclear or incomplete, it was not used for analysis. Research articles that had been retracted by their author(s) were also not used for analysis.

# Results

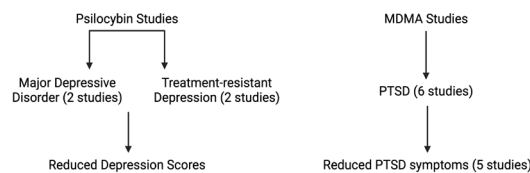
## A. Psilocybin Studies

All four identified studies examining psilocybin's potential relevance to PTSD treatment specifically focused on depression. Two studies focused on treatment-resistant depression, while the other two focused on major depressive disorder. These studies all reported reductions in depression

scores among participants, measured using validated scales. Two studies employed the Montgomery-Åsberg Depression Rating Scale, and the other two utilized the GRID-Hamilton Depression Rating Scale.

## B. MDMA Studies

Six studies examined MDMA as a direct treatment for PTSD, employing either the CAPS-IV or CAPS-V scales to assess PTSD symptom severity. Five of these studies demonstrated statistically significant decreases in PTSD symptoms, while the remaining study approached statistical significance ( $p = .066$ ).



**Figure 3. Results Summary**

## C. Safety Considerations

Both psilocybin and MDMA treatments were associated with transient physical side effects. One MDMA study (Mitchell et al., 2021) documented temporary increases in vital signs—including systolic and diastolic blood pressure, heart rate, and elevated body temperature (up to about 38.1°C) in two participants. Importantly, no lasting physical symptoms were found.

# Discussion

These findings collectively suggest that both psilocybin and MDMA have promising therapeutic potential for addressing PTSD symptoms, either directly (in the case of MDMA) or indirectly through alleviating associated depressive symptoms (in the case of psilocybin). Given that about 5% of the U.S. population experiences PTSD annually, identifying effective treatments is crucial for public health. However, due to the absence of direct research evaluating psilocybin specifically in treating PTSD, it remains unclear whether MDMA or psilocybin is more effective for treating the disorder.

These promising yet preliminary results highlight the importance of further research into both substances' therapeutic efficacy

and safety profiles. Future studies directly comparing MDMA and psilocybin for PTSD could clarify their relative effectiveness and inform clinical practice. In addition, given the observed transient physical effects, safety monitoring should remain of utmost priority in future research to ensure patient well-being during psychedelic-assisted therapy.

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