Review Article

The therapeutic efficacy of psilocybin in major depressive disorder: A review of recent clinical and mechanistic evidence

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Abstract

This review examines the therapeutic efficacy of psilocybin for major depressive disorder by integrating findings from clinical trials, meta-analyses, and mechanistic research. A comprehensive literature search across major scientific databases identified empirical studies evaluating psilocybin's effects on depressive symptomatology, safety, and underlying neurobiological mechanisms. Psilocybin's primary pharmacological action as a 5-HT2A receptor agonist leads to alterations in brain connectivity, particularly within networks associated with self-referential processing and emotional regulation. These receptor-level effects are accompanied by neuroplastic changes, including enhanced synaptogenesis and functional reorganization, which contribute to the rapid and sustained antidepressant outcomes observed in clinical settings. Neuroimaging studies further support these mechanisms by demonstrating reductions in amygdala activity and modifications within default

mode and executive networks following administration. Clinical evidence consistently indicates that psilocybin produces substantial reductions in depressive symptoms, with meta-analyses reporting large effect sizes and durable benefits lasting from several weeks to as long as one year. Randomized controlled trials highlight its rapid onset of action, with remission rates notably higher than those achieved with conventional treatments, including in populations with treatment-resistant depression. Open-label studies reinforce the durability of these effects and emphasize the essential role of psychotherapeutic support in optimizing therapeutic outcomes. Across studies, psilocybin demonstrates a favorable safety profile, with adverse events being mild, transient, and predictable. Despite these promising findings, methodological limitations such as small sample sizes, high heterogeneity, and variability in treatment protocols underscore the need for larger, standardized Phase III trials. Future research should also include direct comparisons with established antidepressants and efforts to identify biomarkers that may guide personalized treatment approaches.

Key words

Psilocybin, Major depressive disorder, Psychedelic therapy, Neuroplasticity, Clinical trials, Meta-analysis.

Introduction

Major depressive disorder (MDD) is one of the most prevalent mental health conditions worldwide, contributing substantially to the global burden of disease and disability. Its functional, social, and economic impact is considerable, as the disorder is associated with reduced quality of life, increased healthcare expenditures, and a significant loss of productivity that affects individuals and societies at multiple levels [1, 2]. Despite the availability of conventional therapeutic options, current treatments show important limitations. Traditional antidepressants often require several weeks to exert their effects and are frequently associated with adverse events that compromise adherence. Moreover, approximately 30% of patients do not respond adequately to these interventions, underscoring the need for more effective and faster-acting therapeutic strategies [2, 3].

This context highlights the growing interest in exploring new therapeutic avenues, including psychedelic compounds, within psychiatric care. Psilocybin has demonstrated notable potential in treating depression, particularly in individuals with treatment-resistant forms of the disorder, by producing rapid and sustained reductions in symptom severity and showing a more favorable adverse-effect profile compared to standard treatments. Its antidepressant effects are believed to arise from its serotonergic and glutamatergic properties, which operate through mechanisms distinct from those targeted by traditional pharmacotherapies [4, 5]. Unlike antidepressants that primarily inhibit serotonin reuptake, psilocybin acts as a 5-HT2A receptor agonist, altering patterns of brain connectivity and promoting increased cognitive flexibility. This mechanism may interrupt maladaptive rumination and facilitate emotional breakthroughs, offering a therapeutic pathway that differs substantially from conventional approaches [2, 6].

Clinical evidence further supports the therapeutic promise of psilocybin. Multiple trials have shown significant improvements in depressive symptoms following psilocybin administration, with effect sizes indicating substantial reductions in symptomatology compared to placebo [5, 7]. Additionally, psilocybin-assisted therapy has been found to outperform psychotherapy alone, suggesting that the combined pharmacological and psychological components enhance overall treatment outcomes [3]. Mechanistic studies align with these clinical findings. Neuroimaging research indicates that psilocybin modifies

functional activity within several neural regions, potentially increasing synaptogenesis and altering cerebral blood flow in structures such as the amygdala and prefrontal cortex, changes that may underpin its rapid antidepressant effects [1, 8].

Despite this promising evidence, the broader implementation of psilocybin as a therapeutic modality faces several challenges. Persistent stigma surrounding psychedelic substances, existing legal restrictions, and the potential risks associated with unregulated use represent significant barriers to widespread clinical adoption [3].

The objective of this review is to critically examine and synthesize the current evidence on the therapeutic efficacy of psilocybin for major depressive disorder, focusing on its clinical outcomes, underlying neurobiological mechanisms, comparative advantages over traditional antidepressant treatments, and the challenges that influence its potential integration into clinical practice.

Methodology

The literature search was carried out using major scientific databases, including PubMed, Science Direct, JAMA, BMJ, PsycINFO, and the Cochrane Library. The search strategy employed predefined keywords such as Psilocybin, major depressive disorder, psychedelic therapy, neuroplasticity, clinical trials, meta-analysis, ensuring a comprehensive retrieval of studies relevant to the therapeutic use of psilocybin in major depressive disorder. The drafting and organization of this methodological section were supported by artificial intelligence tools, which facilitated the synthesis and structuring of the information without altering the original content of the sources consulted.

The inclusion criteria comprised clinical trials particularly randomized controlled trials involving psilocybin administration in individuals diagnosed with major depressive disorder. Recent meta-analyses and systematic reviews were also considered, as well as studies evaluating efficacy, duration of therapeutic effects, safety outcomes, and underlying neurobiological mechanisms. Only empirical studies published in English or Spanish were included.

Exclusion criteria were applied to refine the selection process. Non-clinical studies, including animal and in vitro research, were excluded except when referenced solely to contextualize mechanistic explanations. Reports lacking quantitative data were omitted, along with studies addressing depression secondary to other conditions that did not provide independent analyses specific to major depressive disorder.

Study selection and analysis involved classifying the retrieved literature according to study design, including meta-analyses, randomized controlled trials, and open-label studies. When applicable, methodological quality and risk of bias were assessed using tools such as the Cochrane Risk of Bias instrument and the GRADE framework. Data extraction focused on variables such as psilocybin dosage, sample size characteristics, outcome measures, and follow-up duration, allowing for a structured synthesis of the available clinical evidence.

Pharmacological basis and mechanisms of action

Psilocybin exerts its primary pharmacological effects through serotoninergic modulation, acting as a 5-HT2A receptor agonist that is fundamental to both its antidepressant and psychedelic properties. Activation of this receptor induces alterations in brain connectivity, particularly within the default mode network and in regions associated with emotional processing, such as the amygdala. These changes reflect a disruption of rigid neural patterns that often characterize depressive states and contribute to the therapeutic action of the compound [9, 10].

Beyond receptor-level interactions, accumulating evidence indicates that psilocybin promotes neuroplastic changes that may underlie its sustained antidepressant effects. Studies suggest that the compound facilitates both functional and synaptic reorganization, supporting longer-term improvement in depressive symptoms. These neuroplastic processes are closely associated with psilocybin's capacity to modulate serotonin and glutamate receptor activity, ultimately enhancing synaptogenesis and promoting adaptive neural remodeling [8].

Neuroimaging findings further reinforce these mechanistic insights. Reductions in blood flow to the amygdala have been observed following psilocybin administration, a change that correlates with decreases in depressive symptomatology and improved emotional regulation. Additionally, alterations in connectivity within the default mode and executive networks have been reported, suggesting widespread functional reorganization that supports enhanced emotional modulation and increased cognitive flexibility [8, 11].

Emerging perspectives propose that some of psilocybin's effects may extend beyond classical neurotransmitter interactions, potentially involving metabolic or mitochondrial pathways. Although these hypotheses remain preliminary and are still under investigation, they represent a developing area of interest within the broader effort to understand the full spectrum of psilocybin's therapeutic mechanisms [4].

Results

Meta-analytic evidence consistently supports the therapeutic efficacy of psilocybin in major depressive disorder, with studies reporting large effect sizes that range from Hedges' g = 0.70 to 1.47, indicating substantial reductions in depressive symptoms compared to control groups [5, 7]. These analyses also identify an approximate effective dose of 24.68 mg/70 kg for primary treatment, with therapeutic benefits typically emerging within 4 to 8 weeks and, in some cases, persisting for 6 to 12 months [12, 13]. Across these investigations, psilocybin demonstrates a favorable safety profile, with adverse events generally mild and transient most commonly headaches, nausea, and short-lived anxiety and no serious adverse events reported [7, 14].

Randomized clinical trials further reinforce these conclusions, showing that even a single or double dose of psilocybin can induce rapid antidepressant effects within 1 to 7 days, a markedly faster response compared to traditional pharmacotherapies. Sustained therapeutic outcomes have also been documented, with remission achieved in up to 58% of participants at 12 months in studies conducted by Johns Hopkins [15]. Comparisons with placebo or active control conditions consistently favor psilocybin, reflecting significant reductions in symptom severity and higher remission rates across diverse clinical populations [16]. Importantly, psilocybin has demonstrated efficacy in treatment-resistant depression, offering a promising alternative for individuals who have not responded adequately to conventional treatments [3].

Open-label studies with extended follow-up periods provide additional support for the durability of psilocybin's antidepressant effects. Such studies have shown sustained improvements up to one year following treatment, suggesting that the compound may facilitate long-term therapeutic change beyond the acute dosing window [15]. Qualitative reports highlight the importance of subjective experiences such as emotional breakthroughs and altered self-perception as well as the integral role of psychotherapeutic support in shaping clinical outcomes, reinforcing the view that psilocybin-assisted therapy is a multifaceted intervention [17]. These findings further illustrate how the therapeutic process relies not only on the pharmacological action of psilocybin but also on its interaction with guided psychological support.

Overall, psilocybin is generally well tolerated, and its adverse effects are predictable and transient, with headaches and dizziness being the most frequently reported symptoms [16]. The importance of a controlled therapeutic environment remains a consistent theme across studies, as the setting and the presence of trained clinicians are essential for ensuring safety and optimizing therapeutic outcomes [18].

Discussion

The interpretation of psilocybin's efficacy in the treatment of major depressive disorder reveals a pattern of rapid and sustained antidepressant effects, with several studies demonstrating effect sizes that exceed those of conventional treatments such as SSRIs and esketamine, often by more than twofold [19]. Evidence consistently shows significant reductions in depressive symptoms, including a standardized mean change of -1.24 from baseline in patients treated with psilocybin, highlighting its substantial therapeutic impact [5]. This level of efficacy is particularly noteworthy in treatment-resistant depression, a population in which traditional pharmacotherapies frequently fail to produce meaningful clinical improvement [20].

The strengths of the existing evidence reinforce these conclusions. Meta-analytic findings report large effect sizes, such as a Hedge's g of -0.89, underscoring the magnitude of psilocybin's clinical impact [7]. The consistency observed between outcomes derived from randomized controlled trials and those aggregated in meta-analyses further strengthens the evidence base, demonstrating a high degree of convergence across methodologies and study designs [16, 17]. Additionally, psilocybin's therapeutic benefits extend beyond depressive symptoms, as several studies document significant improvements in anxiety, contributing to a broader positive psychological profile [18].

Despite these promising findings, several methodological limitations must be considered when interpreting the data. Many psilocybin studies have been conducted with small sample sizes, limiting the generalizability of their conclusions [5]. Furthermore, the high heterogeneity reported across studies, exemplified by an I² value of 70.19%, complicates the synthesis of results and may reflect variability in study designs, populations, or dosing strategies [7]. Another important challenge is the influence of psychotherapeutic components accompanying psilocybin administration. The lack of standardized protocols makes it difficult to disentangle pharmacological effects from therapeutic context, posing a methodological complexity that has been widely acknowledged [21].

The clinical implications of these findings suggest that psilocybin may serve as a valuable adjuvant or alternative therapy, particularly for individuals with treatment-resistant depression who have not benefited from existing interventions [4]. However, regulatory, ethical, and logistical challenges remain significant, including legal restrictions governing psychedelic substances and the requirement for controlled therapeutic environments staffed by trained specialists [1]. The importance of specialized psychotherapeutic support is consistently emphasized, as it appears to enhance the therapeutic process and may contribute substantially to clinical outcomes [21].

Looking ahead, several priority areas for future research have been identified. Phase III clinical trials with broader demographic representation are essential to validate psilocybin's efficacy across diverse populations and ensure its applicability beyond highly selected study cohorts [5]. Direct comparisons with established antidepressants, including SSRIs and fast-acting agents such as ketamine, are needed to determine psilocybin's relative therapeutic value [19]. Furthermore, studies investigating repeated dosing strategies and the identification of biomarkers predictive of therapeutic response may help refine treatment protocols and support

the development of personalized psychedelic-assisted therapies [17].

Conclusion

The evidence synthesized in this review demonstrates that psilocybin produces rapid, robust, and sustained antidepressant effects, supported by consistent findings across meta-analyses, randomized controlled trials, and long-term observational studies. Its capacity to significantly reduce depressive symptoms even in individuals with treatment-resistant depression highlights its therapeutic potential and distinguishes it from conventional pharmacotherapies that often yield slower or insufficient responses.

Mechanistic research reinforces these clinical findings by showing that psilocybin's effects are mediated through serotoninergic modulation, neuroplastic changes, and alterations in brain connectivity that support emotional regulation and cognitive flexibility. The convergence between neurobiological insights and clinical outcomes strengthens the rationale for psilocybin-assisted therapy as a multifaceted intervention in which pharmacological action and psychotherapeutic support jointly contribute to its effectiveness.

Despite its promise, the current body of evidence remains limited by methodological constraints, including small sample sizes, high heterogeneity, and variability in psychotherapeutic protocols. Addressing these limitations through larger, more rigorous Phase III trials, standardized treatment frameworks, and comparative studies with established antidepressants will be essential for determining psilocybin's definitive role in clinical practice and for guiding its safe, ethical, and regulated implementation.

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