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PSILOCYBIN IN PSYCHIATRIC PRACTICE AND PSYCHEDELIC-ASSISTED THERAPY FOR TREATMENT-RESISTANT DEPRESSION

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ABSTRACT

This manuscript comprehensively reviews psilocybin-assisted therapy for major depressive disorder and treatment-resistant depression. It aims to synthesize current understanding regarding its mechanisms, efficacy, safety, costs, and accessibility, comparing it with conventional antidepressant and ketamine treatments. The methodology involved a narrative synthesis of academic literature, drawing from systematic reviews, meta-analyses, and clinical trials identified through targeted database searches.

Key findings indicate that psilocybin therapy demonstrates rapid, robust, and sustained antidepressant effects, with high response and remission rates, often after one or two sessions. Its safety profile is generally favorable, with transient and mild adverse events. Mechanistically, psilocybin primarily acts on serotonin 5-HT2A receptors, modulating brain networks and enhancing neuroplasticity. However, significant challenges exist in terms of high costs, limited accessibility due to the intensive therapeutic model, and regulatory hurdles.

In conclusion, psilocybin-assisted therapy offers a promising alternative for depression, particularly where standard treatments fail, by providing rapid and durable symptom reduction through unique neurobiological pathways. Future research should focus on optimizing treatment protocols, exploring long-term outcomes, identifying predictors of response, and addressing systemic barriers to accessibility and cost-effectiveness to facilitate its integration into broader mental healthcare.

KEYWORDS

Psylocybin, Psilocybin-Assisted Therapy, Depressive Disorder, Treatment-Resistant Depression, Psychedelics, Mental Health

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Introduction

Major Depressive Disorder continues to be a profound global health crisis, with a significant proportion of patients experiencing Treatment-Resistant Depression, where conventional therapies prove ineffective (Haikazian et al., 2023). This therapeutic challenge highlights an urgent need for innovative and more effective interventions (Haikazian et al., 2023; Perez et al., 2023). Existing antidepressant treatments often present limitations such as delayed onset of action, modest efficacy, adverse side effects, and high relapse rates, thereby necessitating the exploration of novel therapeutic avenues (Carhart-Harris et al., 2021; Yao et al., 2024).

In response to this critical gap, psilocybin-assisted therapy has emerged as a promising and rapidly evolving intervention for TRD and other psychiatric conditions (Haikazian et al., 2023; Perez et al., 2023). Psilocybin, acting primarily as a serotonin 5-HT2A receptor agonist, induces altered states of consciousness that are believed to mediate its therapeutic effects (Perez et al., 2023). Clinical research has demonstrated that psilocybin, when combined with supportive psychotherapy, can lead to rapid, robust, and sustained reductions in depressive symptoms, often after only one or two administrations (Davis et al., 2021; Yao et al., 2024; Yu et al., 2022). This potential has garnered significant attention, including breakthrough therapy designations from regulatory bodies for MDD and TRD (Yao et al., 2024).

Despite advancements in pharmacotherapy and psychotherapy, a substantial patient population suffers from TRD, indicating that current treatment paradigms are often insufficient (Haikazian et al., 2023). The inherent limitations of conventional antidepressants necessitate a paradigm shift towards therapies that offer more durable and profound therapeutic effects. The rapid onset, sustained efficacy, and distinct mechanism of action of psilocybin suggest a novel approach to address the underlying pathology of depression, particularly in cases where standard treatments have failed (Davis et al., 2021; Yao et al., 2024; Yu et al., 2022). By reviewing the current evidence, we can better understand its potential to overcome the limitations of existing treatments.

This article aims to critically review the current understanding of psilocybin-assisted therapy for depression, particularly focusing on TRD. We will explore its proposed mechanisms of action, evaluate its efficacy and safety profile as revealed by recent clinical trials, and discuss the associated costs and accessibility challenges, ultimately assessing its potential role in future psychiatric care.

Methodology

This article presents a comprehensive review of the current literature on psilocybin-assisted therapy for depression, particularly focusing on treatment-resistant depression. The methodology employed herein is akin to a narrative review, drawing upon findings from systematic reviews, meta-analyses, and individual clinical trials to synthesize the existing evidence on efficacy, safety, mechanisms of action, cost, and accessibility.

This review is designed as a **narrative synthesis** of existing academic literature. It aims to provide a broad overview and critical discussion of the current state of research on psilocybin-assisted therapy for depression, highlighting key findings, emerging trends, and areas requiring further investigation. This approach allows for the integration of diverse study designs and qualitative insights alongside quantitative data.

Information for this review was primarily gathered through systematic searches of academic databases and the user's curated library of academic works. The search strategy focused on identifying peer-reviewed articles, systematic reviews, and meta-analyses published on the topic of psilocybin and its applications in treating depressive disorders.

Search Strategy:

The primary search terms and concepts included:

- "psilocybin" AND "depression"
- "psilocybin" AND "treatment-resistant depression" OR "TRD"
- "psychedelic-assisted therapy" AND "depression"
- "psilocybin efficacy" AND "depression"
- "psilocybin safety" AND "depression"
- "psilocybin mechanisms of action"
- "cost of psilocybin therapy"
- "accessibility of psychedelic therapy"

Databases utilized for information retrieval included:

- The user's personal library of academic works.
- External academic databases, encompassing relevant scholarly articles and research.

Sources were selected based on their relevance to the stated objectives of this review, prioritizing studies that focused on human clinical trials, systematic reviews, and meta-analyses. No specific publication date restrictions were applied during the initial search to ensure a broad capture of relevant literature, although more recent studies were given particular attention to reflect the latest advancements. Some reviews also used specific frameworks like PRISMA for transparent reporting (Gattuso et al., 2022; Yao et al., 2024).

The collected data were subjected to a narrative synthesis approach. This involved:

1 Extraction of Key Information: Relevant data points were extracted from each identified source, including study design, participant characteristics, interventions, primary and secondary outcomes, reported efficacy and safety data, proposed mechanisms, and discussions on cost and accessibility.

2 Thematic Analysis: Information was grouped and analyzed thematically to identify overarching themes and consistent findings related to psilocybin's therapeutic potential, limitations, and practical implications. This included analyzing data on its rapid onset, sustained effects, and comparison with other therapies.

3 Critical Appraisal: Findings from individual studies, systematic reviews, and meta-analyses were critically appraised to understand the strength of evidence, potential biases (e.g., risk of bias in RCTs assessed using tools like the Cochrane risk-of-bias tool (Feulner et al., 2023)), and generalizability of results. Methodological quality was also considered where reported by the source material, with some studies using scales like the JADAD scale to rate clinical trials (Fluyau et al., 2024).

4 Synthesis and Interpretation: The synthesized information was then interpreted to address the research problem and objectives, forming the basis for the discussions on psilocybin's role in psychiatric care, its benefits, and the challenges it faces regarding cost and accessibility. This often involves pooling psychometric scores and adverse events using random-effects meta-analysis models in systematic reviews to assess effectiveness and tolerability (Bahji et al., 2023).

This comprehensive approach allowed for the integration of diverse perspectives and empirical evidence to provide a holistic understanding of psilocybin-assisted therapy in the context of depression.

Results

Research into psilocybin-assisted therapy for major depressive disorder and treatment-resistant depression has yielded promising results regarding its efficacy, safety, and mechanisms of action.

Efficacy and Clinical Outcomes Psilocybin-assisted therapy has demonstrated significant antidepressant effects, often characterized by rapid onset and sustained benefits (Davis et al., 2021; Yu et al., 2022).

- Response and Remission Rates: A systematic review and meta-analysis reported a pooled response rate of 57% and a remission rate of 45% in the psilocybin group, significantly higher than the 22% response and 14% remission rates in control groups (Haikazian et al., 2023). In a study involving cancer patients with comorbid MDD, response rates reached 80% and remission rates 50% (Haikazian et al., 2023).
- Effect Size: A meta-analysis of 9 studies (n=596) yielded a large effect size in favor of psilocybin (Standardized Mean Difference = -0.78; $p<0.001$) (Haikazian et al., 2023).
- Speed of Action: Patients often experience a rapid reduction in depressive symptoms within one day of psilocybin administration, a stark contrast to the weeks typically required for traditional antidepressants to show effects (Yu et al., 2022). This rapid onset of therapeutic action highlights a distinct advantage of psilocybin, offering immediate relief to individuals suffering from severe depressive episodes (Fang et al., 2024).
- Durability of Effects: The antidepressant effects of psilocybin have been shown to be sustained for a substantial period, from 1 week to 6 months after administration (Yu et al., 2022), and even up to 12 months in some long-term follow-up studies (Gukasyan et al., 2022). This sustained benefit after just one or two administrations represents a significant advantage over daily conventional antidepressants (Davis et al., 2021).

Safety and Tolerability Psilocybin-assisted therapy appears to be generally well-tolerated, with most reported adverse events being transient and mild to moderate in nature.

The most frequently reported adverse event is transient headache, usually within 24 hours post-dosing (Carhart-Harris et al., 2021). Other statistically significant acute adverse effects include nausea, anxiety, dizziness, and elevated blood pressure (Yerubandi et al., 2024). These cardiovascular effects are typically self-limiting (Yu et al., 2022).

Serious adverse events, although rare, have been observed, necessitating careful patient selection and monitoring (Fang et al., 2024).

Patient selection and preparation protocols for psilocybin-assisted therapy are crucial for ensuring patient safety and maximizing therapeutic outcomes. These protocols involve comprehensive psychiatric and medical evaluations to identify suitable candidates and mitigate potential risks. This careful screening process ensures that individuals with conditions such as psychosis or severe cardiovascular issues are excluded, as these may contraindicate psilocybin administration.

Patient Selection and Evaluation:

- Psychiatric Screening: A thorough psychiatric evaluation, often using structured clinical interviews, is conducted to identify any contraindicated psychological conditions or history (Davis et al., 2021; Johnson et al., 2008). A consistent exclusion criterion across studies is a personal or family history (first or second degree) of psychotic or bipolar I or II disorders (Carhart-Harris et al., 2018; Davis et al., 2021; Gukasyan et al., 2022; Johnson et al., 2008). Some studies also exclude individuals with a history of alcohol or drug dependence, major depression within a recent timeframe, obsessive-compulsive disorder, dysthymic disorder, panic disorder, dissociative disorder, anorexia nervosa, or bulimia nervosa, especially in non-treatment studies (Johnson et al., 2008).
- Medical Evaluation: Participants must be medically stable with no uncontrolled cardiovascular conditions (Davis et al., 2021). While transient elevations in blood pressure and heart rate can occur during psilocybin administration, these are typically considered non-clinically significant and self-limiting (Psiuk et al., 2022; Ross et al., 2016).
- Medication Washout: To prevent confounding effects and potential interactions, participants are generally required to refrain from using other psychoactive medications, particularly antidepressants (e.g., selective serotonin reuptake inhibitors), for a specified washout period (e.g., at least 5 half-lives or 2 weeks) before screening or psilocybin administration (Carhart-Harris et al., 2018; Davis et al., 2021; Gukasyan et al., 2022; Perez et al., 2023).
- Exclusion Criteria for Generalizability: It is important to note that the strict eligibility criteria often employed in research studies, which exclude individuals with comorbidities, prior treatment failures (like ketamine or ECT), suicide risk, or certain personality disorders, can limit the generalizability of findings to the more complex patient populations encountered in real-world clinical settings (Rosenblat et al., 2024).

Preparation Protocols:

- Preparatory Sessions: Patients undergo several preparatory meetings (typically 2-3 sessions) with trained therapists. These sessions are designed to build trust, provide psychoeducation about the trial design and procedures, explain the potential psilocybin experience, and help participants set intentions for their session (Goodwin, Aaronson, et al., 2023; Goodwin, Croal, et al., 2023; Gukasyan et al., 2022; Perez et al., 2023; Rotz et al., 2023). This meticulous preparation is crucial for ensuring the psychological safety and well-being of the participants and fostering an environment of openness and acceptance (Rotz et al., 2023).
- Support During Administration: During the psilocybin administration session, participants are typically in a calming, non-clinical environment and are accompanied by one or two trained therapists who provide continuous support. The therapists ensure physical and psychological safety, encourage introspection, and allow the subjective experience to unfold naturally, often with minimal active guidance (Goodwin, Aaronson, et al., 2023; Goodwin, Croal, et al., 2023; Rotz et al., 2023). A study psychiatrist is usually available on-site for any necessary consultations (Goodwin, Aaronson, et al., 2023; Goodwin, Croal, et al., 2023).
- Integration Sessions: Following the psilocybin session, patients engage in integration sessions with their therapists. These sessions help participants process their experiences, work through challenging emotions, and facilitate the creation of a meaningful narrative to support adequate behavioral adaptations in everyday life (Perez et al., 2023; Rotz et al., 2023). This comprehensive pre- and post-session support structure is integral to the therapeutic model, extending beyond mere pharmacological intervention to encompass a holistic psychological process (Atiq et al., 2024).

Mechanisms of Action Psilocybin's therapeutic effects are believed to stem from its multifaceted interaction with the brain, primarily through its action on the serotonergic system and its impact on brain networks and neuroplasticity.

- Serotonergic System: Psilocybin and its active metabolite, psilocin, structurally resemble serotonin and primarily exert their effects by binding to and activating 5-HT2A receptors (Psiuk et al., 2022). This modulation of the serotonergic system is considered crucial for its antidepressant action (Perez et al., 2023). Beyond this primary interaction, psilocybin also interacts with other serotonin receptor subtypes, including 5-HT1A, which contributes to its diverse pharmacological profile and therapeutic efficacy (Szafoni et al., 2024). The activation of 5-HT2A receptors is believed to be central to psilocybin's psychedelic effects, yet emerging research suggests a potential dissociation between its hallucinogenic properties and antidepressant mechanisms, opening avenues for novel non-hallucinogenic psychoactive compounds (Kolasa et al., 2024).
- Brain Network Modulation: Studies using fMRI have shown that psilocybin decreases cerebral blood flow in regions such as the amygdala (hyperreactive in depression) and the posterior cingulate cortex, which is involved in emotion and consciousness regulation (Psiuk et al., 2022). Psilocybin also modulates the brain's default mode network, a network often found to be dysfunctional in psychiatric disorders (Psiuk et al., 2022). Furthermore, psilocybin enhances functional connectivity in other brain networks, such as those involved in executive control and salience processing, potentially facilitating improved cognitive flexibility and emotional regulation (Ching et al., 2024). This enhanced connectivity may contribute to the observed improvements in mood and psychological well-being (Szafoni et al., 2024).
- Neuroplasticity: Psilocybin can enhance cortical glutamatergic transmission, activate AMPA receptors, and increase the expression of brain-derived neurotrophic factor (Ross et al., 2016). These effects are associated with neuronal growth, differentiation, and synaptogenesis, suggesting a role in promoting neuroplasticity which may contribute to its antidepressant efficacy (Ross et al., 2016). This enhanced neuroplasticity, specifically in the medial prefrontal cortex, is attributed to postsynaptic effects that stimulate glutamate release and activate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, triggering downstream Brain-Derived Neurotrophic Factor - Tropomyosin Receptor Kinase B and mTOR signaling pathways (Szafoni et al., 2024).

Comparative Analysis of Psilocybin with Other Antidepressant Treatments Psilocybin-assisted therapy represents a distinct and rapidly evolving approach to treating depression, particularly Major Depressive Disorder and Treatment-Resistant Depression. Its characteristics set it apart from conventional antidepressant medications and other emerging rapid-acting treatments such as ketamine or esketamine. The core differences lie in their fundamental mechanisms of action, the speed and durability of their therapeutic effects, their respective safety and tolerability profiles, and the overarching treatment models they employ.

Mechanisms of Action

Conventional antidepressants, such as selective serotonin reuptake inhibitors, primarily function by blocking the presynaptic reuptake of serotonin, thereby increasing its availability in the synaptic cleft (Costagliola et al., 2008; Edinoff et al., 2021). Ketamine and esketamine, on the other hand, operate as NMDA glutamate receptor antagonists, a mechanism that also promotes neuroplasticity by activating the mTOR pathway (Aleksandrova & Phillips, 2021; Psiuk et al., 2022).

Onset and Duration of Antidepressant Effects

One of the most striking differences lies in the temporal dynamics of their antidepressant effects. Psilocybin therapy is notable for its rapid onset of action; patients often report significant reductions in depressive symptoms within a single day of administration (Yu et al., 2022). This swift alleviation of suffering stands in stark contrast to conventional antidepressants, which typically require two weeks or more of consistent daily use before their full therapeutic benefits become apparent (Yu et al., 2022). The psychological impact of such a rapid response for individuals grappling with severe, often chronic, depression cannot be overstated, offering immediate hope and relief. Furthermore, the durability of psilocybin's effects is a significant advantage. A single or a few administrations of psilocybin, combined with therapeutic support, can lead to sustained antidepressant effects for weeks to months, with some studies tracking benefits up to six months (Yu et al., 2022) and even twelve months (Gukasyan et al., 2022).

This contrasts sharply with conventional antidepressants, which necessitate continuous, daily medication for their effects to persist. Discontinuation of SSRIs frequently leads to a relapse or recurrence of MDD, highlighting the chronic management burden and the medication-dependent nature of their efficacy (Peselow et al., 2014; Voderholzer et al., 2024). Ketamine and esketamine also offer a rapid onset of antidepressant effects, often within hours to days (Nigam et al., 2024; Psiuk et al., 2022). However, their therapeutic window is typically much shorter than psilocybin's, with effects often lasting about a week, and requiring repeated use to maintain improvement (Davis et al., 2021; Psiuk et al., 2022). A comparison study even suggested therapeutic advantages of a single, moderate dose psilocybin over ketamine, given that ketamine's response rates have been found to drop significantly after one week (Rotz et al., 2023). The extended duration of action observed with psilocybin after limited sessions thus presents a potentially revolutionary shift from daily pharmacological management to time-limited, intensive interventions that foster lasting change.

Efficacy

The efficacy profiles of these treatments also vary considerably. Psilocybin-assisted therapy has demonstrated compelling results, particularly for patients with TRD. Meta-analyses and systematic reviews report high response rates, with a pooled response rate of 57%, and remission rates, at 45%, in psilocybin groups. These figures are significantly higher than those typically observed in control groups (22% response, 14% remission) (Haikazian et al., 2023). For instance, a study involving cancer patients experiencing comorbid MDD reported response rates as high as 80% and remission rates of 50% (Haikazian et al., 2023). While one study comparing psilocybin to escitalopram (a common SSRI) found no significant difference in the primary measure of depression severity, psilocybin demonstrated superior outcomes across critical secondary measures, including improvements in well-being, anhedonia, and social functioning (Erritzøe et al., 2024; Yu et al., 2022). This suggests that psilocybin may offer a more holistic improvement in patient quality of life beyond just symptom reduction. Conventional antidepressants exhibit variable efficacy, and a significant portion of patients (approximately 30-50%) with MDD do not respond fully to pharmacotherapies, with 10-30% considered treatment-resistant (Davis et al., 2021). About three out of four people with TRD are treated with four or more lines of medication before achieving a tolerable response, underscoring the limitations of current pharmacotherapies for this population (Goodwin et al., 2023). Ketamine and esketamine are recognized for their rapid and potent antidepressant effects, particularly in severe and treatment-resistant cases (Nigam et al., 2024). While they can induce significant reductions in symptoms, their efficacy can be transient, with response rates decreasing after approximately one week, often necessitating repeated dosing regimens (Psiuk et al., 2022; Rotz et al., 2023). The high response and remission rates coupled with the sustained effects of psilocybin suggest its potential to offer a more definitive and transformative therapeutic experience for individuals who have exhausted other options.

Safety and Tolerability

The safety and tolerability profiles also highlight key distinctions. Psilocybin-assisted therapy, when conducted within a carefully structured and supportive therapeutic environment, has generally been found to be safe and well-tolerated (Carhart-Harris et al., 2018). The acute adverse events are typically transient and mild to moderate. These commonly include headache within 24 hours post-dosing (Carhart-Harris et al., 2021), as well as nausea, anxiety, dizziness, and transient elevations in blood pressure (Yerubandi et al., 2024). These physiological changes are generally self-limiting and resolve without intervention (Yu et al., 2022).

Crucially, studies have not reported an increased risk of paranoia or transient thought disorder following psilocybin administration in properly screened individuals (Yerubandi et al., 2024). Furthermore, psilocybin has a very low potential for addiction (Davis et al., 2021), and some studies suggest fewer problematic side effects such as suicidal ideation, decreased sexual drive, or weight gain compared to widely prescribed antidepressants (Davis et al., 2021). Of significant concern, SSRIs carry a black box warning regarding an increased risk of suicidal ideation and behavior, especially in children, adolescents, and young adults (aged 18-24) (Edinoff et al., 2021). The long-term use of these medications can also lead to withdrawal symptoms upon discontinuation, making it challenging for patients to stop treatment (Costagliola et al., 2008). Ketamine and esketamine, while effective, commonly induce mind-altering effects during their administration, which can include dissociation, perceptual disturbances, and disorientation (Psiuk et al., 2022). Although these effects are typically managed in a controlled clinical setting, they can be unsettling for patients. Moreover, repeated administrations of ketamine derivatives, particularly outside of strict medical supervision, can carry a non-trivial potential for abuse (Gukasyan et al., 2022; Psiuk et al., 2022). Therefore, the safety profile of psilocybin, characterized by transient acute effects and low long-term risks when administered responsibly, presents a compelling alternative for many patients.

Treatment Model

The treatment models for these interventions differ profoundly. Psilocybin-assisted therapy employs a highly structured, multi-stage process that extends beyond mere drug administration. It typically involves several preparatory meetings (often 2-3 sessions) with trained therapists. These sessions are crucial for building rapport, providing comprehensive psychoeducation about the psilocybin experience, managing expectations, and helping patients set intentions for their session. This meticulous "set and setting" preparation is paramount for ensuring the psychological safety and well-being of the participant (Rotz et al., 2023). During the actual psilocybin administration session, patients are typically in a comfortable, non-clinical environment and are continuously supported by one or two trained therapists who ensure physical and psychological safety, while encouraging introspection and allowing the subjective experience to unfold naturally (Rotz et al., 2023). A study psychiatrist is usually available on-site for any necessary consultations (Goodwin et al., 2023). Following the psilocybin session, integration sessions with therapists are vital. These sessions help patients process their profound experiences, work through challenging emotions, and translate insights gained during the psychedelic state into meaningful behavioral changes and psychological adaptations in their daily lives (Perez et al., 2023). This comprehensive pre-, during-, and post-session support structure is integral to the therapeutic model, emphasizing a holistic psychological process rather than just pharmacological intervention (Atiq et al., 2024). This integrated approach fosters deep introspection and emotional processing, facilitating profound cognitive shifts that contribute to sustained remission from depressive symptoms, a critical advantage over traditional pharmacotherapy. Conventional antidepressants, by comparison, are typically prescribed as daily oral medications, often managed through brief, routine medical appointments. While psychotherapy may be an important adjunct, it is not inherently integrated into the medication administration process itself. The focus is primarily on sustained pharmacological effect. Ketamine and esketamine treatments usually involve repeated administrations in a clinical setting, such as intravenous infusions or nasal spray. These sessions require medical supervision and monitoring, particularly during and immediately after the administration due to their acute psychotropic effects, but typically do not involve the same intensive preparatory and integrative psychotherapy components as psilocybin therapy (Psiuk et al., 2022).

Interaction with SSRIs

An important consideration for psilocybin therapy is its interaction with concurrently used SSRIs. While most previous trials for psilocybin-assisted therapy included antidepressant drug withdrawal as a standard procedure (Goodwin et al., 2023), a recent study examined the co-administration of psilocybin (COMP360 25mg) with SSRIs for treatment-resistant depression (Goodwin et al., 2023). This study found that the safety and efficacy of psilocybin were not compromised when administered adjunct to an SSRI, suggesting that antidepressant drug withdrawal is not necessarily a prerequisite for a therapeutic response to psilocybin in this patient group (Goodwin et al., 2023). However, reports suggest that the subjective psychedelic effects, which are often considered integral to the therapeutic process, might be diminished in individuals taking SSRIs (Goodwin et al., 2023). This interaction necessitates careful management and further research is needed to examine whether outcomes of psilocybin as a monotherapy or as an adjunct to SSRIs remain comparable in longer term follow-up (Goodwin et al., 2023). For conventional antidepressants, interactions with other psychoactive medications are a common clinical consideration, requiring careful review by prescribing physicians to prevent adverse drug events. Ketamine, on the other hand, can be used as an adjunct to oral antidepressants, and in some cases, may even augment their effects (Psiuk et al., 2022). The precise guidelines for managing SSRI use in the context of psilocybin therapy are an active area of clinical research.

Cost and Accessibility

The financial and logistical barriers to psilocybin-assisted therapy present a significant impediment to its widespread adoption. The intensive nature of the treatment model, demanding extensive time from highly trained clinicians across multiple preparatory, administration, and integration sessions, drives costs remarkably high. Estimates for a full course of psilocybin therapy in the US, particularly for TRD, range from **$3,000 to over $20,000** (Avanceña et al., 2025; Haikazian et al., 2023). For example, one cost-effectiveness analysis estimated that treatment could cost around $11,537 USD per patient (Haikazian et al., 2023). Similar concerns about the "very expensive" nature of psilocybin therapy and its high staffing requirements have been voiced by psychiatrists in Europe. This substantial upfront financial burden places PAP beyond the reach of many patients, especially without comprehensive insurance coverage. This contrasts sharply with conventional antidepressants, which are generally more accessible and often covered by health insurance, making their daily use financially viable for most individuals, even if long-term costs accumulate. Even for ketamine and esketamine, while still costly, off-label generic ketamine can sometimes offer a lower-cost alternative, although it may not always be covered by insurance. However, even with cost reductions for therapist support and psilocybin price, PAP shows promise for cost-effectiveness compared to other therapies (McCrone et al., 2023). From a societal perspective, cost-effectiveness of psilocybin can be even more favorable (McCrone et al., 2023). Group therapy models could also significantly reduce clinician costs and increase access, with estimates suggesting savings of $981 per patient for psilocybin-MDD treatment in group settings (Marseille et al., 2023).

Compounding the cost issue are several other accessibility challenges. There is a critical shortage of therapists adequately trained and certified to deliver this specialized form of psychotherapy (Williams et al., 2021). Regulatory hurdles further restrict access; psilocybin's classification as a Schedule I substance in many jurisdictions, including the US, has historically severely limited research and clinical implementation (Beau et al., 2024). Strict eligibility criteria in current clinical trials, which often filter out individuals with significant comorbidities, a history of suicidality, prior experiences with other rapid-acting treatments like ketamine or electroconvulsive therapy, or certain personality disorders (Rosenblat et al., 2024; Shore et al., 2019; Villiger, 2024), mean that the generalizability of research findings to real-world, more complex patient populations is limited. These factors underscore a significant disparity in access compared to widely available conventional treatments. To ensure equitable access to this potentially transformative treatment, robust policy reforms, the development of affordable and scalable service delivery models (such as group therapy (Marseille et al., 2023)), and innovative reimbursement strategies are urgently needed. Furthermore, distinguishing between clinical therapeutic models and supported adult use models, as highlighted in policy discussions, is crucial to avoid confusion and ensure ethical practice (McGuire et al., 2024). Integrating PAP into existing healthcare systems will require significant investment in training a new generation of psychedelic therapists, developing appropriate treatment infrastructure, and establishing reimbursement models that reflect the intensive nature and potential long-term benefits of the therapy.

Generalizability of Findings

Finally, the generalizability of findings from current research varies across these treatment modalities. Conventional antidepressants have been extensively studied across diverse patient populations, making their findings broadly applicable. In contrast, psilocybin-assisted therapy research, while promising, has largely relied on highly controlled clinical trials with very strict inclusion and exclusion criteria. These criteria often filter out individuals with significant comorbidities, a history of suicidality, prior experiences with other rapid-acting treatments like ketamine or electroconvulsive therapy, or certain personality disorders (Rosenblat et al., 2024; Shore et al., 2019; Villiger, 2024). For example, one trial noted that 97% of its participants with higher levels of treatment resistance would have been excluded from another similar trial, highlighting the differences in patient populations studied (Rosenblat et al., 2024). While necessary for initial safety and efficacy evaluations, this practice limits the direct applicability of the positive results to the broader, more complex patient populations typically encountered in everyday clinical practice. Future research will need to cautiously expand these inclusion criteria to study more diverse groups, allowing for a better understanding of PAP's effectiveness and safety in real-world scenarios (Davis et al., 2021; Perez et al., 2023). Ketamine research also faces similar generalizability challenges, though arguably to a lesser extent, as it has been studied in a wider range of treatment-resistant populations.

Discussion

The accumulated research on psilocybin-assisted therapy for depression, particularly treatment-resistant depression, presents a compelling case for its therapeutic potential while simultaneously highlighting significant challenges for its widespread adoption. The findings reveal a treatment modality characterized by rapid, robust, and sustained antidepressant effects, distinct mechanisms of action, but also high costs and substantial accessibility barriers.

Significance of Efficacy and Safety Data

The most significant finding is PAP's remarkable efficacy in reducing depressive symptoms, often leading to high response and remission rates (Haikazian et al., 2023). The pooled response rate of 57% and remission rate of 45% demonstrate a considerable impact, especially in patient populations where conventional treatments have failed (Haikazian et al., 2023). The rapid onset of action, often within hours to days, fundamentally differentiates PAP from traditional antidepressants, which typically require weeks to exert their full effects (Carhart-Harris et al., 2021; Yu et al., 2022). Furthermore, the durability of these effects, lasting for weeks to months after just one or two administrations, suggests a potential paradigm shift from chronic daily medication to time-limited, intensive interventions (Davis et al., 2021; Gukasyan et al., 2022; Yu et al., 2022).

The safety profile, characterized by generally transient and mild to moderate adverse events, is also significant. While psychological support is crucial during the acute psychedelic experience, the absence of an increased risk of paranoia or transient thought disorder is reassuring (Yerubandi et al., 2024). This combination of high efficacy and acceptable safety positions PAP as a strong contender for addressing the unmet needs of individuals with TRD.

Implications of Mechanisms of Action

Understanding the mechanisms of action is critical for refining PAP and integrating it into clinical practice. Psilocybin's primary action on 5-HT2A receptors, coupled with its modulation of brain networks like the default mode network and its capacity to enhance neuroplasticity, offers a unique therapeutic pathway (Psiuk et al., 2022; Ross et al., 2016). The reduction of activity in regions such as the amygdala (often hyperactive in depression) and the promotion of neuronal growth suggest a fundamental reorganization of brain function, rather than merely symptom suppression (Psiuk et al., 2022; Ross et al., 2016). This mechanistic insight supports the potential for lasting change and could inform the development of future psychiatric treatments.

Challenges of Cost and Accessibility

Despite the clinical promise, the high cost and limited accessibility of PAP are substantial impediments to its broad implementation. The intensive therapeutic model, which necessitates multiple highly trained clinicians and extensive patient time, drives up costs significantly. With estimated costs ranging from $3,000 to over $20,000 per course in the US, and similar concerns about high expense in Europe, PAP is currently out of reach for many patients (Avanceña et al., 2025; Garel et al., 2023; Žuljević et al., 2024). This financial burden is compounded by a shortage of trained therapists, strict eligibility criteria in research, and restrictive

regulatory frameworks, particularly psilocybin's Schedule I classification in the US (Beau et al., 2024; Haikazian et al., 2023; Marseille et al., 2023; Szafoni et al., 2024).

The contrast with conventional antidepressants, which are widely accessible and often covered by insurance, highlights the disparity. While long-term costs of chronic antidepressant use accumulate, the upfront cost of PAP remains a major barrier. Even for ketamine/esketamine, which can also be costly, off-label generic ketamine offers a potentially lower-cost alternative, though often without insurance coverage (Crane et al., 2023; Nigam et al., 2024). These accessibility issues underscore the need for innovative service delivery models (e.g., group therapy (Marseille et al., 2023)), policy reforms, and robust reimbursement strategies to ensure equitable access to this potentially transformative treatment.

Implications for the Field

The findings have several profound implications for the field of psychiatry:

1 Paradigm Shift in Depression Treatment: PAP offers the potential to shift the treatment paradigm for TRD from chronic, daily medication to a time-limited, intensive therapeutic process. This could significantly improve quality of life for patients burdened by long-term medication side effects and limited efficacy.

2 Integration of Psychotherapy and Pharmacotherapy: PAP inherently integrates pharmacotherapy with intensive psychotherapy, underscoring the critical role of psychological support in maximizing therapeutic outcomes. This challenges models that primarily focus on medication management alone. This integrated approach fosters deep introspection and emotional processing, facilitating profound cognitive shifts that contribute to sustained remission from depressive symptoms, a critical advantage over traditional pharmacotherapy (Europe, 2023).

3 Policy and Regulatory Reform: The promising data necessitates continued re-evaluation of drug scheduling and regulatory frameworks to facilitate research, clinical development, and eventual patient access. Breakthrough Therapy designations, like those granted by the FDA, are critical steps in this direction (Belouin et al., 2022).

4 Healthcare System Adaptation: Integrating PAP into existing healthcare systems will require significant investment in training a new generation of psychedelic therapists, developing appropriate treatment infrastructure, and establishing reimbursement models that reflect the intensive nature and potential long-term benefits of the therapy. Furthermore, addressing the prohibitive costs associated with psychedelic-assisted psychotherapies necessitates exploring alternative funding mechanisms and promoting the use of generic compounds where therapeutically appropriate, as seen with ketamine (Joshi et al., 2024).

5 Focus on Personalized Medicine: While effective, PAP is not a panacea. Future research needs to refine patient selection criteria, optimize dosing regimens, and explore combination therapies to personalize treatment approaches. This includes investigating genetic, phenotypic, and environmental markers that may predict treatment response and adverse effects. Such individualized strategies are crucial for maximizing therapeutic benefits and minimizing risks, ultimately enhancing the safety and efficacy of psychedelic-assisted therapies across diverse patient populations (Brennan & Belser, 2022).

Conclusions

Psilocybin-assisted therapy represents a significant development in treating Major Depressive Disorder and Treatment-Resistant Depression. Its efficacy, rapid action, and neurobiological underpinnings are notable, but it also faces considerable barriers related to cost and access.

- Efficacy and Rapid Onset: PAP demonstrates significant and rapid antidepressant effects. A meta-analysis involving 596 patients yielded a large effect size (Standardized Mean Difference = -0.78; $p<0.001$) in favor of psilocybin for reducing depression severity (Haikazian et al., 2023). Reductions in depressive symptoms can occur within days of administration (Haikazian et al., 2023). These effects can also be sustained over time (Yu et al., 2022).
- Safety and Tolerability: Psilocybin therapy, when administered with psychological support in a controlled setting, appears to be safe. Studies indicate that it can be given safely, even in severe cases of depression (Carhart-Harris et al., 2018). Acute adverse events are typically transient and mild to moderate (Yerubandi et al., 2024).
- Mechanisms of Action: Psilocybin exerts its effects primarily through activation of serotonin 5-HT2A receptors (Perez et al., 2023; Psiuk et al., 2022). It modulates key brain networks, such as decreasing cerebral blood flow in regions like the amygdala (hyperactive in depression) and influencing the default mode network (Psiuk et al., 2022). Furthermore, psilocybin has been shown to increase neuroplasticity by enhancing cortical glutamatergic transmission and promoting the expression of brain-derived neurotrophic factor (Ross

et al., 2016). Studies also suggest that psilocybin therapy is associated with decreased brain network modularity, which correlates with antidepressant effects (Daws et al., 2022).

- Cost and Accessibility Challenges: The intensive nature of PAP, which requires extensive clinician time and multiple sessions, results in high costs, with estimates ranging from $3,000 to $20,000 per course in the US for TRD (Avanceña et al., 2025; Haikazian et al., 2023). This cost, along with the requirement for multiple qualified therapists, creates a significant financial burden for patients and limits access (Haikazian et al., 2023). Current clinical trials often use strict eligibility criteria, excluding patients with comorbidities, prior treatment failures (e.g., ketamine or ECT), suicide risk, or other significant psychiatric conditions, which limits the generalizability of findings to real-world settings (Rosenblat et al., 2024; Shore et al., 2019; Villiger, 2024). Regulatory classification, such as psilocybin's historical status as a Schedule I substance, has also been a barrier to research and broader implementation (Beau et al., 2024; Haikazian et al., 2023).

Potential Directions for Future Research To overcome current limitations and facilitate the responsible integration of PAP into mental healthcare, future research should prioritize the following areas:

1 Optimizing Treatment Protocols:

- Dose-Response and Repeated Dosing: Further research is needed to determine the optimal psilocybin doses for various conditions and to understand the impact and necessity of repeated administrations (Haikazian et al., 2023; Perez et al., 2023).
- Therapeutic Models: Investigations should explore the most effective psychotherapeutic frameworks to accompany psilocybin, including the role of different psychological variables and the efficacy of lower doses or group-based models to enhance scalability and affordability (Carhart-Harris et al., 2018; Marseille et al., 2023; Shore et al., 2019).
- Broader Patient Populations: Clinical trials should cautiously expand inclusion criteria to study more diverse patient populations, including those with comorbidities or greater treatment resistance, to improve generalizability to real-world settings (Davis et al., 2021; Rosenblat et al., 2024; Villiger, 2024).

2 Long-term Safety and Efficacy:

- Extended Follow-up: Longer-term follow-up studies are essential to fully ascertain the durability of therapeutic effects and the long-term safety profile of psilocybin therapy, especially given the current limited follow-up periods in many trials (Davis et al., 2021; Li et al., 2024).
- Specific Safety Concerns: Continued investigation into potential risks, such as the emergence of psychosis or the impact on suicidality in at-risk individuals, is critical (Davis et al., 2021; Villiger, 2024).

3 Neurobiological Mechanisms and Predictors of Response:

- Biomarker Identification: Identifying specific neurobiological markers that predict treatment response or non-response can help personalize PAP and optimize outcomes for individual patients (Daws et al., 2022).
- Mechanism Refinement: Further research into how psilocybin acutely and chronically affects brain function, connectivity, and neuroplasticity will deepen our understanding of its therapeutic action (Daws et al., 2022).

4 Accessibility, Training, and Policy:

- Cost-Effectiveness Analyses: Comprehensive economic analyses are crucial to understand the real-world costs and benefits of PAP and to develop strategies for more affordable access, such as exploring group therapy models (Marseille et al., 2022, 2023).
- Workforce Development and Training: Robust training programs and certification for psychedelic therapists are necessary to address potential clinician shortages and ensure high-quality, standardized care (Dorval et al., 2025; Williams et al., 2021).
- Regulatory Frameworks: Research should inform policy and regulatory bodies on the safe and equitable integration of psilocybin into healthcare systems, considering aspects like drug scheduling, patient eligibility, and reimbursement models (Beau et al., 2024; Belouin et al., 2022; Dorval et al., 2025). This includes differentiating between clinical models and supported adult use models to avoid confusion (McGuire et al., 2024).

REFERENCES

1. Aleksandrova, L. R., & Phillips, A. G. (2021). Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics [Review of *Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics*]. *Trends in Pharmacological Sciences*, *42*(11), 929. Elsevier BV. https://doi.org/10.1016/j.tips.2021.08.003
2. Atiq, M. A., Baker, M., Voort, J. L. V., Vargas, M. V., & Choi, D. (2024). Disentangling the acute subjective effects of classic psychedelics from their enduring therapeutic properties [Review of *Disentangling the acute subjective effects of classic psychedelics from their enduring therapeutic properties*]. *Psychopharmacology*. Springer Science+Business Media. https://doi.org/10.1007/s00213-024-06599-5
3. Avanceña, A. L. V., Vuong, L. N., Kahn, J. G., & Marseille, E. (2025). Psilocybin-assisted therapy for treatment-resistant depression in the US: a model-based cost-effectiveness analysis. *Translational Psychiatry*, *15*(1), 330. https://doi.org/10.1038/s41398-025-03556-4
4. Bahji, A., Lunsky, I., Gutiérrez, G., & Vázquez, G. (2023). Efficacy and Safety of Four Psychedelic-Assisted Therapies for Adults with Symptoms of Depression, Anxiety, and Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis [Review of *Efficacy and Safety of Four Psychedelic-Assisted Therapies for Adults with Symptoms of Depression, Anxiety, and Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis*]. *Journal of Psychoactive Drugs*, 1. Taylor & Francis. https://doi.org/10.1080/02791072.2023.2278586
5. Beau, K., Michelle, P., Rajeev, R., C., R., Rhianna, Ben, S., & Keytin, P. (2024). Considering Alternatives to Psychedelic Drug Prohibition. In *RAND Corporation eBooks*. https://doi.org/10.7249/rra2825-1
6. Belouin, S. J., Averill, L. A., Henningfield, J. E., Xenakis, S. N., Donato, I., Grob, C. S., Berger, A. M., Magar, V., Danforth, A., & Anderson, B. (2022). Policy considerations that support equitable access to responsible, accountable, safe, and ethical uses of psychedelic medicines [Review of *Policy considerations that support equitable access to responsible, accountable, safe, and ethical uses of psychedelic medicines*]. *Neuropharmacology*, *219*, 109214. Elsevier BV. https://doi.org/10.1016/j.neuropharm.2022.109214
7. Brennan, B., & Belser, A. B. (2022). Models of Psychedelic-Assisted Psychotherapy: A Contemporary Assessment and an Introduction to EMBARK, a Transdiagnostic, Trans-Drug Model. *Frontiers in Psychology*, *13*. https://doi.org/10.3389/fpsyg.2022.866018
8. Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Martell, J., Blemings, A., Erritzoe, D., & Nutt, D. J. (2021). Trial of Psilocybin versus Escitalopram for Depression. *New England Journal of Medicine*, *384*(15), 1402. https://doi.org/10.1056/NEJMoa2032994
9. Carhart-Harris, R. L., Bolstridge, M., Day, C. M. J., Rucker, J., Watts, R., Erritzoe, D. E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Curran, H. V., & Nutt, D. J. (2018). Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology*, *235*(2), 399. https://doi.org/10.1007/s00213-017-4771-x
10. Ching, T. H. W., Amoroso, L., Bohner, C., D'Amico, E. J., Eilbott, J., Entezar, T., Fitzpatrick, M., Fram, G., Grazioplene, R., Hokanson, J., Jankovsky, A., Kichuk, S. A., Martins, B., Patel, P., Schaer, H., Shnayder, S., Witherow, C., Pittenger, C., & Kelmendi, B. (2024). Safety, feasibility, tolerability, and clinical effects of repeated psilocybin dosing combined with non-directive support in the treatment of obsessive-compulsive disorder: protocol for a randomized, waitlist-controlled trial with blinded ratings. *Frontiers in Psychiatry*, *14*. https://doi.org/10.3389/fpsyt.2023.1278823
11. Costagliola, C., Parmeggiani, F., Semeraro, F., & Sebastiani, A. (2008). Selective Serotonin Reuptake Inhibitors: A Review of its Effects on Intraocular Pressure [Review of *Selective Serotonin Reuptake Inhibitors: A Review of its Effects on Intraocular Pressure*]. *Current Neuropharmacology*, *6*(4), 293. Bentham Science Publishers. https://doi.org/10.2174/157015908787386104
12. Crane, M. A., DiStefano, M. J., & Moore, T. J. (2023). False or Misleading Claims in Online Direct-to-Consumer Ketamine Advertising in Maryland. *JAMA Network Open*, *6*(11). https://doi.org/10.1001/jamanetworkopen.2023.42210
13. Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2021). Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*, *78*(5), 481. https://doi.org/10.1001/jamapsychiatry.2020.3285
14. Daws, R. E., Timmermann, C., Giribaldi, B., Sexton, J. D., Wall, M. B., Erritzoe, D., Roseman, L., Nutt, D., & Carhart-Harris, R. (2022). Increased global integration in the brain after psilocybin therapy for depression. *Nature Medicine*, *28*(4), 844. https://doi.org/10.1038/s41591-022-01744-z
15. Dorval, M., Chang, S.-L., Farzin, H., Nguyen, O., Stephan, J.-F., Tapp, D., Deschamps, P., Joly, Y., Moureaux, F., Foxman, R., Masse-Grenier, M., & Fallu, J. (2025). Roadmap for Equitable Access and Responsible Use of Psilocybin-Assisted Psychotherapy in Palliative Care. *Palliative Medicine Reports*, *6*(1), 153. https://doi.org/10.1089/pmr.2024.0108
16. Edinoff, A. N., Akuly, H. A., Hanna, T. A., Ochoa, C., Patti, S. J., Ghaffar, Y. A., Kaye, A. D., Viswanath, O., Urits, I., Boyer, A. G., Cornett, E. M., & Kaye, A. M. (2021). Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review [Review of *Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review*]. *Neurology International*, *13*(3), 387. PAGEPress (Italy). https://doi.org/10.3390/neurolint13030038

17. Erritzøe, D., Barba, T., Greenway, K. T., Murphy, R., Martell, J., Giribaldi, B., Timmermann, C., Murphy-Beiner, A., Jones, M. B., Nutt, D., Weiss, B., & Carhart-Harris, R. (2024). Effect of psilocybin versus escitalopram on depression symptom severity in patients with moderate-to-severe major depressive disorder: observational 6-month follow-up of a phase 2, double-blind, randomised, controlled trial. *EClinicalMedicine*, *76*, 102799. https://doi.org/10.1016/j.eclinm.2024.102799
18. Europe, T. L. R. H. –. (2023). Psychedelic-assisted psychotherapy: hope and dilemma. *The Lancet Regional Health - Europe*, *32*, 100727. https://doi.org/10.1016/j.lanepe.2023.100727
19. Fang, S., Yang, X., & Zhang, W. (2024). Efficacy and acceptability of psilocybin for primary or secondary depression: A systematic review and meta-analysis of randomized controlled trials [Review of *Efficacy and acceptability of psilocybin for primary or secondary depression: A systematic review and meta-analysis of randomized controlled trials*]. *Frontiers in Psychiatry*, *15*. Frontiers Media. https://doi.org/10.3389/fpsyt.2024.1359088
20. Feulner, L., Sermchaiwong, T., Rodland, N., & Galarneau, D. (2023). Efficacy and Safety of Psychedelics in Treating Anxiety Disorders. *Ochsner Journal*, *23*(4), 315. https://doi.org/10.31486/toj.23.0076
21. Fluyau, D., Kailasam, V. K., & Revadigar, N. (2024). Rapid and prolonged antidepressant and antianxiety effects of psychedelics and 3, 4-methylenedioxy-methamphetamine. A systematic review and meta-analysis [Review of *Rapid and prolonged antidepressant and antianxiety effects of psychedelics and 3, 4-methylenedioxy-methamphetamine. A systematic review and meta-analysis*]. *medRxiv (Cold Spring Harbor Laboratory)*. Cold Spring Harbor Laboratory. https://doi.org/10.1101/2024.06.17.24308787
22. Garel, N., Drury, J., Lévesque, J. T., Goyette, N., Lehmann, A., Looper, K., Erritzøe, D., Dames, S., Turecki, G., Rej, S., Richard-Devantoy, S., & Greenway, K. T. (2023). The Montreal model: an integrative biomedical-psychedelic approach to ketamine for severe treatment-resistant depression. *Frontiers in Psychiatry*, *14*. https://doi.org/10.3389/fpsyt.2023.1268832
23. Gattuso, J. J., Perkins, D., Ruffell, S., Lawrence, A. J., Hoyer, D., Jacobson, L. H., Timmermann, C., Castle, D., Rossell, S. L., Downey, L. A., Pagni, B. A., Galvão-Coelho, N. L., Nutt, D., & Sarris, J. (2022). Default Mode Network Modulation by Psychedelics: A Systematic Review. *International Journal of Neuropsychopharmacology*, *26*(3), 155. https://doi.org/10.1093/ijnp/pyac074
24. Goodwin, G. M., Aaronson, S. T., Alvarez, O., Atli, M., Bennett, J. C., Croal, M., DeBattista, C., Dunlop, B. W., Feifel, D., Hellerstein, D. J., Husain, M. I., Kelly, J. R., Lennard-Jones, M. R., Licht, R. W., Marwood, L., Mistry, S., Páleníček, T., Redjep, O., Repantis, D., … Malievskaia, E. (2023). Single-dose psilocybin for a treatment-resistant episode of major depression: Impact on patient-reported depression severity, anxiety, function, and quality of life. *Journal of Affective Disorders*, *327*, 120. https://doi.org/10.1016/j.jad.2023.01.108
25. Goodwin, G. M., Croal, M., Feifel, D., Kelly, J. R., Marwood, L., Mistry, S., O'Keane, V., Peck, S. K., Simmons, H., Sisa, C., Stansfield, S. C., Tsai, J., Williams, S., & Malievskaia, E. (2023). Psilocybin for treatment resistant depression in patients taking a concomitant SSRI medication. *Neuropsychopharmacology*, *48*(10), 1492. https://doi.org/10.1038/s41386-023-01648-7
26. Gukasyan, N., Davis, A. K., Barrett, F. S., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., & Griffiths, R. R. (2022). Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. *Journal of Psychopharmacology*, *36*(2), 151. https://doi.org/10.1177/02698811211073759
27. Haikazian, S., Chen-Li, D. C. J., Johnson, D. E., Fancy, F., Levinta, A., Husain, M. I., Mansur, R. B., McIntyre, R. S., & Rosenblat, J. D. (2023). Psilocybin-assisted therapy for depression: A systematic review and meta-analysis. *Psychiatry Research*, *329*, 115531. https://doi.org/10.1016/j.psychres.2023.115531
28. Johnson, M., Richards, W., & Griffiths, R. (2008). Human hallucinogen research: guidelines for safety. *Journal of Psychopharmacology*, *22*(6), 603. https://doi.org/10.1177/0269881108093587
29. Joshi, K., Liberman, J. N., Parab, P., Darer, J., & Harding, L. (2024). Barriers to Esketamine Nasal Spray Treatment Among Adults With Treatment-Resistant Depression. *The Journal of Clinical Psychiatry*, *85*(2). https://doi.org/10.4088/jcp.23m15102
30. Kolasa, M., Nikiforuk, A., Korlatowicz, A., Solich, J., Potasiewicz, A., Dziedzicka-Wasylewska, M., Bugno, R., Hogendorf, A. S., Bojarski, A. J., & Faron-Górecka, A. (2024). Unraveling psilocybin's therapeutic potential: behavioral and neuroplasticity insights in Wistar-Kyoto and Wistar male rat models of treatment-resistant depression. *Psychopharmacology*. https://doi.org/10.1007/s00213-024-06644-3
31. Li, L., Yu, M., Shi, Z.-M., Huang, X., Ning, Y.-P., Wu, H., Yang, X.-H., & Zheng, W. (2024). Psilocybin for major depressive disorder: a systematic review of randomized controlled studies [Review of *Psilocybin for major depressive disorder: a systematic review of randomized controlled studies*]. *Frontiers in Psychiatry*, *15*, 1416420. Frontiers Media. https://doi.org/10.3389/fpsyt.2024.1416420
32. Marseille, E., Bertozzi, S., & Kahn, J. G. (2022). The economics of psychedelic-assisted therapies: A research agenda [Review of *The economics of psychedelic-assisted therapies: A research agenda*]. *Frontiers in Psychiatry*, *13*, 1025726. Frontiers Media. https://doi.org/10.3389/fpsyt.2022.1025726

33. Marseille, E., Stauffer, C. S., Agrawal, M., Thambi, P., Roddy, K., Mithoefer, M. C., Bertozzi, S., & Kahn, J. G. (2023). Group psychedelic therapy: empirical estimates of cost-savings and improved access. *Frontiers in Psychiatry*, *14*. https://doi.org/10.3389/fpsyt.2023.1293243
34. McCrone, P., Fisher, H., Knight, C., Harding, R., Schlag, A. K., Nutt, D., & Neill, J. C. (2023). Cost-effectiveness of psilocybin-assisted therapy for severe depression: exploratory findings from a decision analytic model. *Psychological Medicine*, *53*(16), 7619. https://doi.org/10.1017/s0033291723001411
35. McGuire, A. L., Cohen, I. G., Sisti, D., Baggott, M. J., Celidwen, Y., Devenot, N., Gracias, S., Grob, C. S., Harvey, I., Kious, B. M., Marks, M., Mithoefer, M. C., Nielson, E. M., Öngür, D., Pallas, A., Peterson, A., Schenberg, E. E., Summergrad, P., Waters, B., … Yaden, D. B. (2024). Developing an Ethics and Policy Framework for Psychedelic Clinical Care: A Consensus Statement. *JAMA Network Open*, *7*(6). https://doi.org/10.1001/jamanetworkopen.2024.14650
36. Nigam, K., King, F., & Forcén, F. E. (2024). Advancing ketamine in the treatment hierarchy for refractory depression. *The British Journal of Psychiatry*, 1. https://doi.org/10.1192/bjp.2024.217
37. Perez, N., Langlest, F., Mallet, L., De Pieri, M., Sentissi, O., Thorens, G., Seragnoli, F., Zullino, D., Kirschner, M., Kaiser, S., Solmi, M., & Sabé, M. (2023). Psilocybin-assisted therapy for depression: A systematic review and dose-response meta-analysis of human studies. *European Neuropsychopharmacology*, *76*, 61. https://doi.org/10.1016/j.euroneuro.2023.07.011
38. Peselow, E. D., Tobia, G., Karamians, R., Pizano, D., & IsHak, W. W. (2014). Prophylactic efficacy of fluoxetine, escitalopram, sertraline, paroxetine, and concomitant psychotherapy in major depressive disorder: Outcome after long-term follow-up. *Psychiatry Research*, *225*(3), 680. https://doi.org/10.1016/j.psychres.2014.11.022
39. Psiuk, D., Nowak, E. M., Dycha, N., Łopuszańska, U., Kurzepa, J., & Samardakiewicz, M. (2022). Esketamine and Psilocybin—The Comparison of Two Mind-Altering Agents in Depression Treatment: Systematic Review. *International Journal of Molecular Sciences*, *23*(19), 11450. https://doi.org/10.3390/ijms231911450
40. Rosenblat, J. D., Meshkat, S., Doyle, Z., Kaczmarek, E., Brudner, R. M., Kratiuk, K., Mansur, R. B., Schulz-Quach, C., Sethi, R., Abate, A., Ali, S., Bawks, J., Blainey, M. G., Brietzke, E., Cronin, V., Danilewitz, J., Dhawan, S., Di Fonzo, A., Di Fonzo, M., … McIntyre, R. S. (2024). Psilocybin-assisted psychotherapy for treatment resistant depression: A randomized clinical trial evaluating repeated doses of psilocybin. *Med*, *5*(3), 190. https://doi.org/10.1016/j.medj.2024.01.005
41. Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S. E., Belser, A., Kalliontzi, K., Babb, J., Su, Z., Corby, P., & Schmidt, B. L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *Journal of Psychopharmacology*, *30*(12), 1165. https://doi.org/10.1177/0269881116675512
42. Rotz, R. von, Schindowski, E. M., Jungwirth, J., Schuldt, A., Rieser, N. M., Zahoranszky, K., Seifritz, E., Nowak, A., Nowak, P., Jäncke, L., Preller, K. H., & Vollenweider, F. X. (2023). Single-dose psilocybin-assisted therapy in major depressive disorder: a placebo-controlled, double-blind, randomised clinical trial. *eClinicalMedicine*, *56*. https://doi.org/10.1016/j.eclinm.2022.101809
43. Shore, R., Ioudovski, P., Goldie, C., McKeown, S., & Dumont, É. C. (2019). Mapping Psilocybin-Assisted Therapies: A Scoping Review [Review of *Mapping Psilocybin-Assisted Therapies: A Scoping Review*]. *medRxiv (Cold Spring Harbor Laboratory)*. Cold Spring Harbor Laboratory. https://doi.org/10.1101/2019.12.04.19013896
44. Szafoni, S., Gręblowski, P., Grabowska, K., & Więckiewicz, G. (2024). Unlocking the healing power of psilocybin: an overview of the role of psilocybin therapy in major depressive disorder, obsessive-compulsive disorder and substance use disorder. *Frontiers in Psychiatry*, *15*. https://doi.org/10.3389/fpsyt.2024.1406888
45. Villiger, D. (2024). How to Make Psychedelic-Assisted Therapy Safer. *Cambridge Quarterly of Healthcare Ethics*, 1. https://doi.org/10.1017/s0963180124000604
46. Voderholzer, U., Barton, B. B., Favreau, M., Zisler, E. M., Rief, W., Wilhelm, M., & Schramm, E. (2024). Enduring effects of psychotherapy, antidepressants and their combination for depression: a systematic review and meta-analysis [Review of *Enduring effects of psychotherapy, antidepressants and their combination for depression: a systematic review and meta-analysis*]. *Frontiers in Psychiatry*, *15*, 1415905. Frontiers Media. https://doi.org/10.3389/fpsyt.2024.1415905
47. Williams, M. L., Korevaar, D., Harvey, R., Fitzgerald, P. B., Liknaitzky, P., O'Carroll, S., Puspanathan, P., Ross, M., Strauss, N., & Bennett–Levy, J. (2021). Translating Psychedelic Therapies From Clinical Trials to Community Clinics: Building Bridges and Addressing Potential Challenges Ahead. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/fpsyt.2021.737738
48. Yao, Y., Guo, D., Lu, T.-S., Liu, F.-L., Huang, S.-H., Diao, M.-Q., Li, S.-X., Zhang, X.-J., Kosten, T. R., Shi, J., Bao, Y.-P., Lu, L., & Han, Y. (2024). Efficacy and safety of psychedelics for the treatment of mental disorders: A systematic review and meta-analysis. *Psychiatry Research*, *335*, 115886. https://doi.org/10.1016/j.psychres.2024.115886
49. Yerubandi, A., Thomas, J. E., Bhuiya, N. M. M. A., Harrington, C., Villa Zapata, L., & Caballero, J. (2024). Acute Adverse Effects of Therapeutic Doses of Psilocybin: A Systematic Review and Meta-Analysis. *JAMA Network Open*, *7*(4). https://doi.org/10.1001/jamanetworkopen.2024.5960

50. Yu, C.-L., Liang, C.-S., Yang, F.-C., Tu, Y.-K., Hsu, C.-W., Carvalho, A. F., Stubbs, B., Thompson, T., Tsai, C.-K., Yeh, T.-C., Yang, S.-N., Shin, J. I., Chu, C.-S., Tseng, P.-T., & Su, K.-P. (2022). Trajectory of Antidepressant Effects after Single- or Two-Dose Administration of Psilocybin: A Systematic Review and Multivariate Meta-Analysis. *Journal of Clinical Medicine*, *11*(4), 938. https://doi.org/10.3390/jcm11040938
51. Žuljević, M. F., Breški, N., Kaliterna, M., & Hren, D. (2024). Attitudes of European psychiatrists on psychedelics: a qualitative study. *Frontiers in Psychiatry*, *15*. https://doi.org/10.3389/fpsyt.2024.1411234