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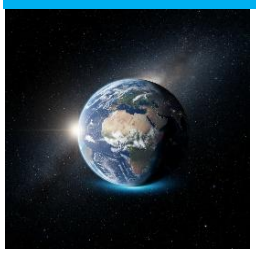

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Psilocybin-Assisted Therapy in Depressive Disorders: Efficacy, Safety, and Persistence of Clinical Effects —A Narrative Review

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ABSTRACT

Introduction and purpose: Depressive disorders, particularly major depressive disorder (MDD) and treatment-resistant depression (TRD), remain major causes of disability worldwide. Conventional treatments are limited by delayed onset, incomplete response, relapse, and adverse effects. This review summarizes current evidence on the efficacy, safety, and durability of psilocybin-assisted therapy in depressive disorders.

Brief description of the state of knowledge: Evidence from randomized trials, open-label studies, follow-up analyses, and meta-analyses indicates that psilocybin-assisted therapy can produce rapid reductions in depressive symptoms, often within days, in carefully selected patients treated in controlled settings. Short-term benefits have been reported in both MDD and TRD, although findings in TRD are less consistent. In a head-to-head trial, psilocybin was not superior to escitalopram on the primary endpoint, while several secondary outcomes favored psilocybin. Follow-up studies suggest that benefits may persist for weeks to months, but longer-term evidence remains limited and heterogeneous. Under supervision, psilocybin was generally well tolerated, with mostly transient adverse effects, including anxiety, nausea, headache, dizziness, and brief cardiovascular activation.

Summary: Psilocybin-assisted therapy appears to be a promising investigational approach for depressive disorders, with rapid onset and possible medium-term benefit in some patients. However, the evidence base remains limited by small samples, heterogeneous designs, restricted comparative data, and delivery in specialized settings. Larger and longer-term studies are needed to clarify comparative efficacy, durability, long-term safety, and feasibility in routine clinical practice.

Keywords: Psilocybin; Major Depressive Disorder; Treatment-Resistant Depression; Psychotherapy; Safety

1. INTRODUCTION AND PURPOSE

Depressive disorders remain a major clinical and public health challenge, with major depressive disorder (MDD) representing one of their most consequential forms because of its recurrent course, functional impairment, and negative impact on quality of life. In addition to persistent low mood, affected patients commonly experience anhedonia, cognitive dysfunction, reduced social and occupational functioning, and diminished overall well-being. The burden of depression is further amplified by chronicity, frequent relapse, and the difficulty of achieving sustained remission in routine clinical practice.

Although currently available treatments, including selective serotonin reuptake inhibitors (SSRIs), other antidepressants, and evidence-based psychotherapies, have improved outcomes for many patients, important limitations remain. Therapeutic onset is often delayed, a substantial proportion of patients achieve only partial response, and relapse is common even after initial improvement. Treatment adherence may also be compromised by adverse effects such as gastrointestinal symptoms, sexual dysfunction, and sleep disturbance. These limitations have sustained interest in therapeutic approaches that may act more rapidly, require less frequent dosing, and engage mechanisms distinct from those of conventional antidepressant strategies [1,2,3].

This unmet need is particularly evident in treatment-resistant depression (TRD), usually defined as inadequate response to at least two appropriate treatment trials. TRD is associated with greater illness chronicity, more severe functional burden, and a reduced likelihood of response to subsequent conventional interventions. In clinical practice, such patients often undergo repeated medication changes, augmentation strategies, or neuromodulatory interventions without achieving durable remission. Accordingly, TRD has become a central focus of contemporary psilocybin research and an important context in which to examine whether a mechanistically distinct intervention may address some of the limitations of standard care [3,4,5,6].

Interest in psychedelic compounds in psychiatry predates the current wave of research. During the 1950s and 1960s, psychedelics were investigated in psychiatric settings for a range of affective and existential indications, but regulatory restrictions and broader sociopolitical factors led to a prolonged interruption of clinical studies. Over the past two decades, this field has re-emerged under more rigorous ethical, methodological, and safety standards, with psilocybin becoming one of the most extensively studied classic psychedelics in affective disorders [7,8,9].

Psilocybin has attracted particular interest as a potential therapeutic option because it combines a distinctive pharmacological profile with a structured psychotherapeutic model. After administration, psilocybin is metabolized to psilocin, which acts primarily through agonism at 5-HT2A receptors and is associated with changes in emotional processing, large-scale brain network dynamics, and neuroplasticity relevant to depressive pathology [8,9,10]. Importantly, in clinical studies psilocybin is not administered as a stand-alone pharmacological intervention, but rather within a framework of psychedelic-assisted therapy that typically includes preparation, a monitored dosing session, and post-session integration. This model reflects the view that therapeutic benefit may arise from the interaction between pharmacological effects, the acute subjective experience, and psychotherapeutic support [11,12,13,14].

Recent clinical studies suggest that psilocybin-assisted therapy may produce rapid antidepressant effects in both MDD and TRD, with benefits that may extend beyond the period of acute drug action and without the need for chronic daily administration [1,2,5,11,15]. At the same time, the available evidence remains heterogeneous with respect to study design, control conditions, durability of response, and safety reporting, which makes careful synthesis necessary [3,16,17,18,19]. Therefore, the aim of this narrative review is to summarize the current state of knowledge on the efficacy, safety, and persistence of clinical effects of psilocybin-assisted therapy in depressive disorders, with particular emphasis on major depressive disorder and treatment-resistant depression.

2. STATE OF KNOWLEDGE

This article is a narrative review based on an analysis of scientific publications indexed in PubMed, Scopus, and Web of Science concerning the therapeutic use of psilocybin in depressive disorders. Particular attention was given to clinical efficacy, safety, durability of antidepressant effects, and the principal limitations of the available evidence

2.1 Clinical efficacy in major depressive disorder

Major depressive disorder (MDD) is a common and disabling mood disorder characterized by persistent low mood, anhedonia, cognitive symptoms, and impaired psychosocial functioning. Although standard treatments such as selective serotonin reuptake inhibitors and psychotherapy are effective for some patients, important limitations remain, including delayed onset of action, incomplete response, residual symptoms, and poor tolerability in a substantial proportion of cases. Against this background, psilocybin-assisted

therapy has attracted interest as a potential alternative treatment model because it is delivered in one or two supervised sessions with psychological support and may produce antidepressant effects more rapidly than conventional daily pharmacotherapy [1,2,11,15].

Early controlled evidence in primary MDD was provided by the waitlist-controlled randomized trial of Davis et al. [11], which enrolled 24 patients and compared immediate psilocybin-assisted therapy with delayed treatment over an 8-week period. In that study, psilocybin was associated with rapid and marked reductions in depressive symptom severity, helping establish proof of concept for this approach in MDD rather than exclusively in treatment-resistant populations [11]. Longer-term follow-up of this cohort by Gukasyan et al. [20] suggested that clinically meaningful improvement was maintained in a proportion of participants over time, with 75% meeting response criteria and 58% meeting remission criteria at 12 months [20]. These findings are encouraging, but they should be interpreted as follow-up data rather than as direct evidence of long-term efficacy from a blinded randomized comparison [11,20].

The randomized trial literature in MDD now includes several comparator designs. In the phase 2 double-blind trial by Carhart-Harris et al. [1], 59 patients with MDD received either two 25-mg psilocybin sessions with psychological support or escitalopram with 1 mg psilocybin as an active control. At 6 weeks, the prespecified primary depression outcome did not significantly differ between groups, although several secondary outcomes favored psilocybin [1]. In a placebo-controlled double-blind randomized trial, von Rotz et al. [15] administered a single weight-adjusted psilocybin dose of 0.215 mg/kg versus mannitol placebo in 52 patients and reported a marked reduction in MADRS symptom severity at 14 days, with 54% of psilocybin-treated participants meeting remission criteria and no serious adverse events [15]. Further support comes from the larger double-blind randomized trial by Raison et al. [2], which enrolled 104 patients and compared a single 25-mg psilocybin session plus psychological support with niacin 100 mg within the same therapeutic framework over 43 days. This study also found a rapid antidepressant effect relative to niacin and did not identify evidence of emotional blunting [2].

Taken together, these randomized studies suggest that psilocybin-assisted therapy may reduce depressive symptoms within days to weeks in some patients with MDD [1,2,11,15]. However, effect estimates vary across trials because study designs, comparators, endpoints, and follow-up periods differ [1,2,15]. Short-term remission and response rates were substantial in some studies, including 54% remission at 14 days in the trial by von Rotz et al. [15], whereas longer-term observational follow-up of the Davis cohort suggested continued benefit in a

proportion of participants at 12 months [20]. These findings support a clinically meaningful efficacy signal, but they should not be collapsed into a single pooled estimate without acknowledging differences in study design and time horizon [11,15,20].

Quantitative syntheses broadly reinforce this signal. Meta-analyses by Metaxa et al. [3] and Perez et al. [16] found significant antidepressant effects of psilocybin across depressive populations, with the latter also suggesting a dose-response relationship in which higher doses were associated with greater efficacy [3,16]. The individual-participant-data meta-analysis by Simonsson et al. [17] likewise reported substantial reductions in depressive symptoms [17]. More recent analyses by Swieczkowski et al. [21] and Syed et al. [22] suggested that a 25-mg dose may provide the clearest short-term efficacy signal and that factors such as bodyweight-adjusted dosing and longer integration may influence outcomes [21,22]. Although pooled analyses cannot substitute for individual randomized trials, they support the view that antidepressant effects have been observed across multiple studies rather than in a single isolated dataset [3,16,17,21,22].

Beyond symptom reduction, secondary analyses suggest that psilocybin may influence domains relevant to patients' lived experience. In a 6-month observational follow-up of the escitalopram comparison trial, Erritzoe et al. [23] reported greater reductions in depressive symptoms after psilocybin at one month that were maintained through 6 months, although interpretation is limited by the observational nature of follow-up and the potential influence of additional post-trial treatment [23]. Other secondary analyses reported effects on cognitive bias [24], increased emotional empathy after psilocybin [25], and evidence that escitalopram, but not psilocybin, was associated with blunted brain responsiveness to emotional stimuli [26]. Exploratory work has also suggested that psychological flexibility may mediate antidepressant response [27]. Together, these findings raise the possibility that psilocybin may have a therapeutic profile extending beyond symptom reduction alone, although these analyses should be interpreted as supportive and hypothesis-generating rather than definitive [23,24,25,26,27].

Overall, current evidence suggests that psilocybin-assisted therapy has meaningful antidepressant potential in MDD, with rapid onset and promising short-term effects across several randomized studies [1,2,11,15]. At the same time, comparative conclusions should remain cautious. In the available head-to-head trial, psilocybin did not demonstrate superiority over escitalopram on the prespecified primary outcome, although several secondary and patient-centered outcomes favored psilocybin [1,23,24,26]. Most trials remain modest in size, blinded follow-up periods are relatively short, and the conspicuous psychoactive effects of psilocybin make successful masking difficult [1,2,15]. Expectancy effects and functional unblinding

therefore remain important limitations, even though secondary analyses suggest expectancy may not fully explain observed outcomes [1,2,15,22,28]. Accordingly, current data support psilocybin as a promising intervention for MDD, but larger and longer-duration randomized controlled trials are still needed before its role in routine clinical practice can be defined with confidence [3,16,17,21,22].

2.2 Clinical efficacy in treatment-resistant depression

Treatment-resistant depression (TRD), commonly defined as inadequate response to at least two antidepressant trials, represents a particularly severe and heterogeneous subgroup of depressive illness characterized by chronic symptoms, recurrent relapse, functional impairment, and limited therapeutic options. Within the present evidence base, psilocybin studies in TRD have mainly focused on patients with substantial prior treatment exposure, including cohorts with marked treatment resistance, thereby addressing a clinically important unmet need rather than mild or early-stage depression [4,5,29]. This context is important when interpreting efficacy estimates, because outcomes in TRD would be expected to be less favorable than in less refractory depressive populations, even when an intervention shows clinically meaningful benefit [3,5,30].

Initial proof-of-concept evidence came from open-label studies by Carhart-Harris and colleagues. In the 2016 feasibility study, 12 patients with TRD received psilocybin 10 mg followed by 25 mg with psychological support, and substantial reductions in depressive symptom severity were observed over 3 months [4]. A subsequent 6-month follow-up suggested persistence of benefit in a proportion of participants and reported that acute psychological insight was associated with longer-term improvement [29]. More recent open-label work extended these observations to more clinically complex TRD populations. Aaronson et al. studied 12 patients with severe TRD treated with a single 25-mg dose and reported significant MADRS reductions at both 3 and 12 weeks [30]. Goodwin et al. also reported that 19 TRD patients receiving 25 mg psilocybin adjunctively with an SSRI showed a mean MADRS reduction of 14.9 points at 3 weeks, with 42.1% meeting both response and remission criteria [31]. Taken together, these studies provide supportive feasibility evidence for rapid symptom reduction, but their open-label design limits causal inference [4,29,30,31].

The randomized evidence base is anchored by the phase 2 double-blind trial of Goodwin et al., which remains the largest controlled TRD study in the current dataset (n=233) [5]. Participants with a treatment-resistant major depressive episode received a single administration of 25 mg or 10 mg psilocybin with psychological support, with 1 mg psilocybin

serving as a low-dose control, and were followed for 12 weeks [5]. The principal finding was that the 25-mg dose produced a significantly greater reduction in depressive symptoms over 3 weeks than the 1-mg comparator, with a between-group MADRS difference of -6.6 points [5]. A related secondary analysis further suggested that the 25-mg dose was associated with greater improvement than 1 mg in patient-reported depression severity, anxiety, functioning, and quality of life, indicating that clinician-rated change was accompanied by broader psychosocial benefit [32]. In this resistant population, response and remission outcomes were clinically meaningful but more modest than those reported in less refractory MDD cohorts, with the 25-mg dose associated with approximately 37% response and 29.1% remission at 3 weeks [5,32].

A second randomized contribution comes from Rosenblat et al., who evaluated repeated-dose psilocybin-assisted psychotherapy in a 30-patient trial including participants with TRD and bipolar II depression [6]. In contrast to the single-dose design used by Goodwin et al., participants received one to three 25-mg psilocybin sessions and were compared with a waitlist control over 6 months [6]. The trial reported a large antidepressant effect size and suggested that repeated dosing may be associated with additional symptom reduction [6]. However, interpretation should remain cautious because the sample was small and diagnostically mixed, so these findings should be considered preliminary rather than definitive evidence for repeated-dose strategies specifically in TRD [6].

Dose-response findings are among the clearer signals in the TRD literature. In the phase 2b randomized trial, the 25-mg dose separated from the 1-mg control, whereas evidence for lower dosing was less compelling [5,32]. This interpretation is broadly consistent with wider meta-analytic evidence. Perez et al. found that higher psilocybin doses were associated with greater antidepressant efficacy across depressive disorders, albeit alongside more dose-related acute adverse effects such as nausea and physical discomfort [16]. Similarly, Swieczkowski et al. identified 25 mg as the dose associated with the clearest short-term symptom reduction in network meta-analysis, with acceptable tolerability [21]. Because these pooled analyses are not restricted exclusively to TRD, they should not be treated as direct confirmation within resistant depression alone; however, they are concordant with the dose gradient observed in the Goodwin trial and support 25 mg as the dose with the clearest efficacy signal in current TRD studies [5,16,21].

Durability remains a central question, particularly because TRD is typically chronic and relapsing. The open-label follow-up by Carhart-Harris et al. documented symptom reduction persisting to 6 months in a subset of patients [29], while Goodwin et al. later reported 52-week observational follow-up data from 58 TRD participants, suggesting that antidepressant benefit

was maintained in some individuals after a single dose [33]. These findings indicate the possibility of sustained benefit in a subset of responders, but they also imply heterogeneity in long-term trajectories, with some patients maintaining gains and others requiring additional intervention [6,29,33]. The repeated-dose findings from Rosenblat et al. are therefore of clinical interest because they raise the possibility that relapse prevention or extension of response in TRD may require strategies beyond a single administration, although this question remains insufficiently resolved by current randomized evidence [6,33].

Special clinical considerations in TRD include concomitant SSRI use and the impact of antidepressant discontinuation. Goodwin et al. provided preliminary open-label evidence that psilocybin can be administered alongside ongoing SSRI treatment, with meaningful 3-week MADRS improvement and no serious treatment-emergent adverse events or increased suicidality in a 19-patient study [31]. Related post-hoc analyses suggested that patients who discontinued prior antidepressants did not show reduced psychedelic effects or diminished therapeutic efficacy compared with unmedicated participants [34], and Chisamore et al. likewise reported comparable antidepressant outcomes between unmedicated patients and those discontinuing medications, with adverse events mostly mild to moderate and no serious adverse events [35]. These findings are clinically relevant because antidepressant tapering can be difficult in TRD, but the available evidence remains preliminary and requires confirmation in larger controlled studies [31,34,35].

Overall, current evidence suggests that psilocybin may have antidepressant potential in TRD, with the most convincing signal observed at the 25-mg dose and the strongest controlled support coming from the 233-patient phase 2b randomized trial [5]. Remission and response rates in TRD appear lower than those reported in less treatment-refractory MDD populations, but they remain clinically notable given the severity of prior treatment failure [5,31]. Strengths of the literature include testing in highly resistant populations, relatively rapid onset of improvement, and a clearer dose-response signal than is available in some other areas of psychedelic research [5,16,21]. At the same time, interpretation should remain cautious because definitions of TRD vary across studies, blinding remains difficult, follow-up within randomized phases is relatively short, and the role of repeated-dosing or maintenance protocols is still not well defined [5,6,16,28]. Accordingly, current data support psilocybin as a promising intervention for TRD, but one that still requires confirmation in larger and methodologically robust trials, as well as further clarification of long-term treatment strategy [5,6,16,21].

Major clinical trial programs of psilocybin-assisted therapy in depressive disorders, together with related follow-up and secondary analyses, are summarized in Table 1.

Table 1. Major clinical trial programs of psilocybin-assisted therapy in depressive disorders and related follow-up/secondary analyses

Program / primary study	Related reports	Pop.	Design	n	Regimen	Comparator	Main finding	FU
Davis 2021 program	Gukasyan 2022 (FU)	MDD	RCT, WC	24	2 sessions, 20–30 mg/70 kg	Delayed treatment	Rapid reduction in depressive symptoms; 12-month follow-up suggested sustained response/remission in a proportion of participants	8 wk RCT; 12 mo FU
Carhart-Harris 2021 program	Erritzoe 2024 (obs. FU); Henry 2025, Jungwirth 2025, Wall 2025, Sloshower 2024, Erritzoe 2024 (sec./anc.)	MDD	DB RCT	59	2 × 25 mg	Escitalopram + 1 mg psilocybin	Primary endpoint neutral; several secondary and patient-centered outcomes favored psilocybin; related obs. FU analyses should be interpreted as extensions of the same trial program	6 wk RCT; up to 6 mo
von Rotz 2022	—	MDD	DB, PC RCT	52	Single dose, 0.215 mg/kg	Mannitol	Marked short-term symptom reduction; 54% remission at day 14; no serious AEs reported	14 d
Raison 2023	—	MDD	DB RCT	104	Single 25 mg	Niacin	Significant antidepressant effect versus control within a structured therapeutic model	43 d
Carhart-Harris 2016 program	Carhart-Harris 2018 (FU)	TRD	OL feasibility study	12	10 mg, then 25 mg	None	Proof-of-concept signal in severe TRD; follow-up suggested persistence in a subset of participants	3 mo; 6 mo FU
Goodwin 2022 program	Goodwin 2023 (sec. analysis); Goodwin 2025 (obs. FU)	TRD	Phase 2b, DB RCT	233	Single 25 mg vs 10 mg vs 1 mg	1 mg psilocybin	Strongest controlled TRD evidence; clearest efficacy signal at 25 mg; later reports extended patient-reported and follow-up data	12 wk RCT; up to 52 wk obs. FU
Goodwin 2023 (concomitant SSRI study)	Chisamore 2025; Marwood 2024	TRD	OL study / 19 related post-hoc analyses		Single 25 mg with ongoing SSRI	None	Preliminary evidence that psilocybin may be administered with concomitant SSRI treatment in selected TRD patients; interpretation remains preliminary	3 wk
Aaronson 2025	—	TRD	OL study	12	Single 25 mg	None	Significant MADRS reduction at 3 and 12 weeks; supportive but uncontrolled evidence	12 wk
Rosenblat 2024	—	TRD / BP-II depression	RCT, WC	30	1–3 × 25 mg	Waitlist	Large antidepressant effect; possible benefit of repeated dosing, but interpretation is limited by small size and diagnostically mixed sample	6 mo
Griffiths 2016	—	Cancer-related depression/distress	DB crossover RCT	51	Single high dose	Low-dose control	Large and sustained antidepressant/anxiolytic effect in advanced-illness context	~6 mo
Ross 2016	—	Cancer-related depression/distress	DB crossover RCT	29	Single high dose	Low-dose control	Rapid and sustained symptom reduction in advanced-illness context	~6 mo
Agrawal 2025	—	Cancer-related depression/distress	Obs. FU	28	Single 25 mg + group therapy	None	Longest follow-up in the review; 50% remission at 24 months should be interpreted specifically in cancer-related populations	24 mo

Abbreviations: Pop., population; FU, follow-up; MDD, major depressive disorder; TRD, treatment-resistant depression; BP-II, bipolar II; RCT, randomized controlled trial; DB, double-blind; OL, open-label; PC, placebo-controlled; WC, waitlist-controlled; obs., observational; sec., secondary; anc., ancillary; AE, adverse event.

Note: Secondary, ancillary, and follow-up publications derived from the same trial program are grouped together to avoid double-counting apparently independent lines of evidence. Cancer-related depression/distress studies are presented separately because their durability data should not be generalized directly to primary MDD or TRD.

2.3 Comparison with conventional antidepressants

Selective serotonin reuptake inhibitors (SSRIs) remain a standard pharmacological treatment for depressive disorders, but their clinical utility is limited by delayed onset of benefit, incomplete response in a substantial proportion of patients, and adverse effects that may include emotional blunting and reduced adherence. Against this background, psilocybin-assisted therapy has emerged as a mechanistically distinct intervention, combining acute 5-HT2A receptor agonism with structured psychological support rather than chronic monoaminergic modulation through daily dosing. Comparative evidence therefore concerns not only antidepressant efficacy, but also differences in onset, treatment burden, emotional processing, and broader patient-centered outcomes [1,2,3,22].

The most informative direct comparison comes from the phase 2 double-blind randomized trial by Carhart-Harris et al., which enrolled 59 patients with major depressive disorder and compared two 25-mg psilocybin sessions plus psychological support with a 6-week course of daily escitalopram, accompanied by very low-dose psilocybin in the comparator arm to support masking [1]. At 6 weeks, the trial did not show a statistically significant between-group difference on the prespecified primary endpoint, namely change in QIDS-SR-16 score [1]. However, several secondary outcomes, including response, remission, and measures of well-being, favored psilocybin [1]. This distinction is important clinically: the study does not establish superiority of psilocybin over escitalopram on its primary outcome, but it does suggest that psilocybin may have a different therapeutic profile across some secondary and patient-centered domains, which warrants further investigation rather than definitive comparative conclusions [1,3,17,23]. Additional analyses from the same comparison program have examined the effects of discontinuing serotonergic antidepressants before psilocybin therapy, highlighting antidepressant withdrawal as a relevant methodological and clinical consideration when interpreting comparative outcomes [36].

Longer-term comparative data remain limited. The 6-month observational follow-up by Erritzoe et al. extended interpretation of the same trial and suggested that improvements in depressive symptoms were sustained in both groups, while the psilocybin arm showed greater reductions in depressive severity from 1 month through 6 months [23]. Psilocybin was also associated with more favorable outcomes in work and social functioning, meaning in life, and psychological connectedness [23]. These findings support the possibility that short-course psilocybin therapy may differ from escitalopram in its broader experiential and functional profile, but the observational nature of follow-up, modest sample size, and potential influence

of additional post-trial treatment preclude firm causal claims about longer-term comparative superiority [1,3,23].

A central difference between psilocybin and conventional antidepressants concerns temporal dynamics and treatment model. Across randomized trials in depression, psilocybin has generally been associated with symptom improvement within days, whereas SSRIs typically require several weeks before clinically meaningful benefit becomes apparent. In addition, psilocybin trials have usually involved one or two supervised dosing sessions rather than continuous daily administration. Meta-analytic evidence also suggests substantial antidepressant effects of psilocybin across depressive populations [3,21,22]. However, broader comparisons with standard antidepressants should remain cautious, because effect sizes are drawn from heterogeneous trial designs, populations, and control conditions, and psilocybin studies typically include intensive psychotherapy that is not directly comparable with routine SSRI prescribing [2,3,11,21,22].

Differences in emotional and cognitive effects may further distinguish psilocybin from SSRIs. Secondary analyses from the escitalopram comparison trial suggest that escitalopram may reduce brain responsiveness to emotional stimuli, whereas psilocybin does not appear to produce the same pattern of emotional blunting [26]. Wall et al. reported reduced emotional responsiveness with escitalopram but not psilocybin, while Henry et al. found differential effects on cognitive bias, and Martens et al. observed that both treatments reduced negative affective bias, although potentially through different psychological or neurocognitive pathways [24,26,37]. Taken together, these findings raise the possibility that psilocybin may relieve depressive symptoms without the emotional dampening often associated with SSRIs, and may instead preserve or facilitate emotional engagement. Nevertheless, these observations are derived from secondary analyses and should be interpreted as hypothesis-generating rather than as definitive mechanistic proof [1,24,26,37].

Comparative differences may also extend to functioning and quality of life. In addition to symptom outcomes, the psilocybin arm in the head-to-head trial showed advantages across several secondary psychosocial measures, and the 6-month observational follow-up suggested stronger gains in social functioning, connectedness, and meaning in life [1,23]. Similar improvements in functioning and quality of life have also been described in patient-reported analyses of psilocybin trials more broadly, suggesting that the intervention may influence domains not fully captured by symptom scales alone [22]. This may be clinically relevant because restoration of functioning and subjective well-being is often a major treatment goal in

depression, particularly in patients who achieve only partial benefit from conventional pharmacotherapy [1,22,23].

From a tolerability perspective, the two approaches appear to differ more in pattern than in absolute burden. SSRIs are associated with chronic adverse effects during daily use, including sexual dysfunction, gastrointestinal complaints, sleep disturbance, and emotional blunting, whereas psilocybin is characterized mainly by acute, transient adverse effects occurring during or shortly after dosing, such as headache, nausea, anxiety, and fatigue [3,19,26]. In the escitalopram comparison trial, adverse events were broadly comparable and no serious adverse events were reported [1]. Even so, the treatment experience differs substantially: psilocybin concentrates adverse effects into supervised treatment sessions, whereas SSRIs distribute them across prolonged administration. For some patients, this difference may be clinically meaningful, but psilocybin also requires greater procedural intensity, specialized monitoring, and psychotherapeutic infrastructure [1,3,19,26].

Overall, current evidence suggests that psilocybin-assisted therapy has a distinct therapeutic profile relative to conventional antidepressants, particularly in terms of speed of action, treatment model, and selected secondary outcomes related to emotional processing and well-being [1,3,22,23,28]. At the same time, available data remain insufficient to regard psilocybin as a replacement for SSRIs. Direct comparison evidence is limited, the key head-to-head trial was neutral on its primary endpoint, and expectancy effects, blinding difficulties, and the absence of large long-term randomized comparisons remain important limitations [1,3,22,23,28]. A balanced interpretation is therefore that psilocybin represents a promising alternative or adjunctive approach with a different clinical profile, but further adequately powered comparative trials are required before its place relative to established antidepressants can be defined with confidence [1,3,22,23,28].

2.4 Persistence of therapeutic effects

Available follow-up data suggest that psilocybin-assisted therapy may produce antidepressant effects extending beyond acute drug exposure, but durability appears heterogeneous and should be interpreted separately across diagnostic populations and study designs. The current evidence base includes short-term randomized follow-up, prospective cohort extensions, and observational analyses, with substantially greater uncertainty at longer time points than in acute efficacy trials [1,2,20,23].

2.4.1 MDD follow-up

In major depressive disorder (MDD), randomized trials indicate that antidepressant benefits can remain detectable beyond the immediate dosing period. In the phase 2 trial comparing psilocybin with escitalopram, improvement was maintained through 6 weeks, although the prespecified primary endpoint did not significantly differ between groups and several secondary outcomes favored psilocybin [1]. Similarly, the niacin-controlled trial by Raison et al. showed rapid benefit sustained through 43 days, supporting persistence beyond the acute psychedelic window in at least some patients [2].

Longer-term MDD follow-up data suggest sustained improvement in a proportion of participants, but these findings derive primarily from prospective and observational extensions rather than long-term randomized comparisons. In the 12-month follow-up of the Davis cohort, Gukasyan et al. reported that 75% of participants met response criteria and 58% met remission criteria at one year; among those who had responded at 1 month, 71% continued to meet response criteria at subsequent assessments [11,20]. In the 6-month observational follow-up of the escitalopram comparison trial, both treatment groups maintained improvement, but the psilocybin group showed greater reductions in depressive symptoms from 1 month onward that were sustained to 6 months, together with broader psychosocial gains [23]. A secondary analysis from the same MDD program further suggested that stronger therapeutic alliance was associated with better long-term outcomes, although this does not itself establish durability [12].

These MDD findings should not be generalized beyond this population. Interpretation is limited by attrition over time and by the frequent use of additional treatment during follow-up: 33% of participants in the 12-month cohort initiated a new course of daily antidepressants, and 62.7% of participants in the 6-month comparative follow-up sought additional therapy or medication [12,20,23]. Accordingly, MDD follow-up studies support the possibility of sustained benefit in some participants, but not durable remission independent of ongoing care [12,20,23].

2.4.2 TRD follow-up

In treatment-resistant depression (TRD), available evidence suggests maintenance of response in some participants, but the follow-up dataset is smaller and methodologically more heterogeneous than in MDD [4,6,29,33]. Early open-label studies reported sustained symptom reduction at 3 months and follow-up to 6 months after psilocybin administered with

psychological support, indicating that clinically meaningful improvement may extend beyond the acute phase in a subset of patients with more refractory illness [4,29].

At the same time, durability estimates in TRD remain less certain. In the 6-month Carhart-Harris follow-up, 6 of 9 initial responders maintained response whereas 3 relapsed, suggesting partial maintenance rather than uniform persistence [29]. More recent observational follow-up from the phase 2 TRD program reported maintenance of antidepressant effect up to 52 weeks in a subset of participants after a single dose, but these longer-term data are uncontrolled and therefore vulnerable to selection and follow-up bias [33]. Interpretation is further complicated by heterogeneity in resistance severity and treatment protocols, including repeated-dose designs such as Rosenblat et al., which are not directly comparable with single-dose studies [6,29,33].

Overall, TRD follow-up findings support the possibility of sustained benefit in some participants, but certainty remains lower than in MDD because long-term data are based mainly on open-label or observational designs, with smaller samples and greater clinical heterogeneity [4,6,29,33].

2.4.3 Cancer-related depression and advanced illness

In patients with cancer-related depression or distress associated with advanced or life-threatening illness, follow-up studies also suggest sustained benefit in some participants, but these data should be interpreted within the context of secondary depression in medically serious illness rather than extrapolated directly to primary MDD or TRD [38,39]. The double-blind crossover trials by Griffiths et al. and Ross et al. showed substantial antidepressant and anxiolytic improvement maintained for approximately 6 months after psilocybin-assisted treatment [38,39].

Importantly, the longest follow-up durations in the current dataset are derived from studies in patients with cancer-related distress. In Agrawal et al., 50% of depressed participants remained in remission at 24 months after a single 25-mg psilocybin session with group therapy [40]. This 24-month durability signal should therefore be attributed specifically to cancer-related depression or advanced-illness populations rather than presented as a general estimate for depressive disorders overall [38,39,40]. Even in this cohort, however, only 25% maintained symptom improvement without any additional psychiatric medication or psychedelic treatment, indicating that long-term benefit was not universal and often coexisted with further care [40].

Overall, follow-up evidence supports the possibility of sustained antidepressant benefit after limited psilocybin dosing, but durability should not be presented as guaranteed or uniform

across populations [20,23,29,33,40]. Interpretation of long-term effects remains limited by the observational nature of most follow-up data, participant attrition, small sample sizes, selection effects favoring participants who remained engaged in follow-up, heterogeneity of dosing and psychotherapeutic support, and the frequent use of additional interventions such as antidepressants or psychotherapy during follow-up periods [20,23,29,33,40]. Long-term randomized controlled evidence remains scarce; therefore, current data are best interpreted as suggesting sustained improvement in a proportion of participants rather than definitive or treatment-independent remission durability [20,23,29,33,40].

2.5 Safety and adverse effects

Across contemporary clinical studies, psilocybin-assisted therapy appears to be generally well tolerated under controlled conditions, with an adverse-effect profile dominated by transient psychological and somatic reactions rather than persistent medical toxicity [16,19,21,41]. This conclusion, however, applies primarily to carefully selected participants treated in highly structured research environments that include preparatory sessions, continuous monitoring during dosing, and post-session support [1,2,5,15]. Accordingly, the available evidence supports an acceptable safety profile in clinical settings, but not an assumption of inherent or unconditional safety outside those settings [17,18,19].

The most consistently reported acute adverse effects are psychological phenomena occurring during or shortly after the dosing session. Meta-analytic and trial-level data indicate that anxiety, fear, confusion, and transient psychological distress are among the most common acute reactions, particularly at the peak of psychoactive intensity [16,19]. These experiences are clinically important because they may be distressing even when they are self-limited and manageable with reassurance and therapeutic support [1,4,5,19]. In controlled trials, such reactions typically resolved as the acute drug effects subsided, and prolonged psychiatric destabilization was uncommon [1,4,15]. This pattern suggests that the principal acute risks are psychological rather than toxicological, but it also underscores that tolerability is closely linked to supervision, preparation, and interpersonal containment during the session [17,19].

Physiological adverse effects are also frequent, although they are generally mild to moderate and self-limited. Meta-analyses have identified headache, nausea, dizziness, and other forms of physical discomfort as the most common somatic events, with evidence of a dose-response relationship for some adverse effects, particularly nausea and general physical discomfort [16,19]. Randomized trials likewise reported commonly occurring but usually transient symptoms such as headache, nausea, fatigue, and dizziness, without clear evidence of

severe systemic toxicity [1,6]. In the head-to-head trial versus escitalopram, adverse events such as headache and nausea were broadly comparable across groups, while the large phase 2 trial in treatment-resistant depression did not suggest a pattern of prolonged medical complications [1,5]. Overall, the physiological adverse-effect burden appears clinically manageable, but it is not negligible and should be reported transparently rather than minimized [16,18,19].

Serious adverse events appear uncommon in controlled settings, but they cannot be considered impossible. Across randomized and follow-up studies, reports of psychosis, severe behavioral disturbance, or prolonged psychiatric reactions have been rare, and several trials explicitly reported no serious adverse events related to psilocybin administration [1,6,15,20]. Early feasibility work in treatment-resistant depression similarly described transient anxiety, confusion, or nausea without prolonged psychotic symptoms [4,29]. At the same time, the absence of frequent events in relatively small and highly selected samples should not be interpreted as proof that such events do not occur [17,18]. Suicidal ideation or behavioral worsening has been reported rarely in severe depressive populations, warranting careful monitoring and cautious interpretation rather than categorical reassurance [17,31,34]. The most balanced conclusion is therefore that serious psychiatric or behavioral complications appear uncommon in controlled clinical environments, but cannot be excluded [17,18].

A related concern is whether psilocybin may worsen depressive symptoms or destabilize patients during follow-up. The most informative evidence comes from the individual participant data meta-analysis by Simonsson et al., which found generally low risks of symptom worsening and no signal that psilocybin-assisted therapy carried a greater risk of deterioration than comparator conditions, including conventional treatment approaches [17]. Trial-level observations are broadly consistent with this conclusion, as comparative and secondary analyses did not show increased baseline-adjusted suicidality or worsening attributable to psilocybin relative to controls [1,17,34]. These findings are reassuring, but they should still be interpreted in light of strict trial screening and limited power to detect uncommon harms [17,18].

Cognitive safety has also emerged as an important area of interest, particularly given concerns about possible neuropsychological sequelae after intense psychedelic experiences. Current evidence does not indicate cognitive decline in depressed cohorts treated with psilocybin. In a post-hoc analysis of patients with treatment-resistant depression, Johnson et al. found no evidence of cognitive deterioration and, on the contrary, observed short-term improvements on cognitive measures after treatment [42]. Although these findings are preliminary and based on limited follow-up, they are consistent with the broader absence of evidence for cognitive toxicity in contemporary therapeutic studies [17,42]. Nevertheless,

longer-term and more systematically assessed neurocognitive outcomes remain insufficiently characterized.

Cardiovascular and broader physiological safety data suggest that psilocybin produces transient sympathomimetic effects, most notably short-lived increases in blood pressure and heart rate [16,19]. These changes have generally been mild, predictable, and self-limited in controlled trials, resolving as acute drug effects wore off [16,19]. Clinical studies in depression have not identified a consistent pattern of serious cardiovascular complications, but this likely reflects both medical prescreening and exclusion of higher-risk participants [1,5,15]. Consequently, available data support the view that cardiovascular effects are usually manageable in appropriately screened individuals, while reinforcing the need for caution in patients with significant cardiovascular disease [18,19].

The apparent safety of psilocybin in trials is inseparable from rigorous screening and the therapeutic importance of set and setting. Most studies excluded individuals with psychotic disorders, strong psychosis vulnerability, or significant cardiovascular illness, and treatment was embedded in a structured framework of preparation, monitored administration, and psychological support [1,2,5,15]. This design likely mitigates acute panic, disorganization, and medically significant autonomic responses [17,19]. Safety, therefore, should be understood as a property of psilocybin administered within a clinical system, not of the compound in isolation.

Several limitations constrain interpretation of the current safety literature. Most trials remain relatively small, reducing the ability to detect rare but clinically significant adverse events [17,21,41]. Long-term safety data are limited, especially outside specialized follow-up cohorts [17,20]. Importantly, Marinis et al. identified inconsistent and low-quality reporting of side effects across psilocybin trials, highlighting substantial heterogeneity in harms documentation and the need for standardized reporting frameworks [18]. Finally, controlled trial conditions differ substantially from real-world use, where screening, supervision, and crisis management may be absent [17,18,19].

In summary, current evidence indicates that psilocybin-assisted therapy has a generally acceptable safety profile in carefully controlled clinical settings [17,19,21,41]. Adverse effects are typically transient and are more often psychological than physiological, with anxiety, confusion, headache, nausea, dizziness, and short-lived cardiovascular activation representing the most characteristic events [16,19]. Serious complications appear uncommon but cannot be excluded, particularly given limited sample sizes and imperfect adverse-event reporting [17,18]. Thus, the available literature supports cautious optimism: psilocybin may be generally well

tolerated under controlled conditions, but its safety depends fundamentally on patient selection, structured administration, and skilled clinical supervision [1,5,17,18].

The adverse-effect profile reported in clinical studies is summarized qualitatively in Table 2, with emphasis on the consistency of reporting and the clinical context of individual safety signals.

Table 2. Qualitative synthesis of adverse effects reported in clinical studies of psilocybin-assisted therapy for depressive disorders

Adverse effect / safety domain	Typical timing or context	Typical clinical characterization in the reviewed literature	Strength/consistency of signal	Key source types supporting this summary
Anxiety, fear, acute psychological distress	During peak psychedelic effects or shortly thereafter	Commonly described acute psychological reactions; usually transient and manageable with reassurance, preparation, and therapist support in controlled settings	**Consistently reported**	Trial-level reports and meta-analytic/systematic evidence [1,4,5,16,19]
Confusion / disorientation	During acute intoxication phase	Usually transient; resolves as drug effects subside; clinically relevant mainly because it may be distressing during the session	**Moderately consistent**	Trial-level reports and safety reviews [4,16,19]
Headache	Most often post-session or later on dosing day	One of the most frequently described somatic adverse effects; generally mild to moderate and self-limited	**Consistently reported**	Meta-analytic and randomized trial evidence [1,16,19]
Nausea / gastrointestinal discomfort	During or soon after dosing	Common somatic adverse effect; appears dose-related in pooled analyses; usually transient	**Consistently reported**	Meta-analytic and trial evidence [1,16,19]
Dizziness / physical discomfort / fatigue	During or shortly after the session	Usually mild to moderate and self-limited; part of the broader acute somatic burden rather than a serious toxicity signal	**Moderately consistent**	Trial-level and pooled safety data [1,6,16,19]
Transient increases in blood pressure and heart rate	Acute dosing period	Short-lived sympathomimetic effects; generally manageable in screened participants under monitoring; relevance increases in patients with cardiovascular vulnerability	**Consistently reported in supervised settings**	Safety reviews and pooled analyses [16,18,19]
Suicidal ideation, symptom worsening, or clinical deterioration	During follow-up rather than the acute dosing window	Reported rarely; current pooled analyses do not show a clear excess risk relative to comparators, but available studies are underpowered for uncommon harms	**Limited but important signal**	Individual participant data meta-analysis, secondary analyses, and follow-up studies [17,31,34]
Psychosis, prolonged psychiatric reaction, severe behavioral disturbance	Acute or early post-acute period	Rare in screened clinical populations; cannot be excluded; risk estimates remain uncertain because of small samples and exclusion of vulnerable individuals	**Rare but uncertain**	Follow-up studies, safety reviews, and harms-reporting analyses [17,18,19]
Cognitive deterioration	Short-term follow-up	Current evidence does not suggest cognitive decline in treated depressed cohorts; available data remain limited	**Insufficient evidence for harm signal**	Post-hoc cognitive analysis and broader safety synthesis [17,42]

Note: This table provides a qualitative synthesis of the adverse-effect profile reported in clinical studies and meta-analyses. Frequency descriptors are not expressed as pooled numerical incidence ranges because harms reporting across psilocybin trials remains heterogeneous and incompletely standardized. Serious adverse events appear uncommon in screened, therapist-supported clinical settings, but cannot be excluded.

2.6 Neuropharmacology and mechanisms of action of psilocybin

Psilocybin appears to exert its effects through a multilevel mechanism linking receptor pharmacology, large-scale brain network modulation, neuroplasticity, and psychologically meaningful subjective experiences. As a prodrug, psilocybin is rapidly converted to psilocin, which acts primarily as an agonist at serotonin 5-HT2A receptors, although it also interacts with other serotonergic targets. Available mechanistic evidence suggests that 5-HT2A receptor

activation is central not only to the acute psychedelic state, but also to downstream neural and psychological processes that may contribute to antidepressant effects. In particular, the intensity of subjective drug effects has been reported to correlate with neocortical 5-HT2A receptor occupancy and plasma psilocin levels, supporting a biologically plausible link between pharmacokinetics, receptor engagement, and phenomenology. Taken together, pharmacological and neuroimaging studies suggest that psilocybin may initiate a cascade extending from serotonergic receptor stimulation to altered cortical signaling, emotional processing, and subsequent symptom improvement [8,9,10,43,44].

A key proposed mechanism involves modulation of large-scale brain networks, especially the default mode network (DMN), which is strongly implicated in self-referential thought, autobiographical processing, and depressive rumination. Acute psilocybin administration has been associated with desynchronization and reduced integrity of major DMN hubs, including the medial prefrontal cortex and posterior cingulate cortex, consistent with the concept of transient network "disintegration" during the psychedelic state. This acute disruption may relax rigid top-down patterns of self-focused cognition that characterize depression. Importantly, the post-acute phase appears neurobiologically distinct: rather than persistent destabilization, studies suggest a subsequent reorganization marked by decreased network modularity, increased global integration, and normalization of previously maladaptive connectivity patterns. These findings have been interpreted as a possible functional "reset," although this remains a heuristic model rather than an established mechanism, and may reflect a shift away from entrenched depressive cognition toward greater flexibility and adaptive processing [43,44,45,46,47,48].

Neuroplasticity provides a complementary explanatory framework for the persistence of effects beyond the drug's relatively short-lived pharmacological presence. Mechanistic summaries in the current literature describe psilocybin as a candidate psychoplastogenic intervention capable of inducing rapid and sustained changes in neuronal structure and function. Following 5-HT2A activation, intracellular signaling pathways involving brain-derived neurotrophic factor (BDNF) and TrkB are thought to be upregulated, promoting synaptogenesis, dendritic spine growth, and functional remodeling in brain regions relevant to executive control and emotion regulation. These processes are clinically relevant because depression is associated with rigid neural and cognitive patterns, reduced adaptability, and impaired stress-related plasticity. By opening a transient window of enhanced neural flexibility, psilocybin may facilitate revision of maladaptive schemas and behaviors, particularly when embedded within psychotherapy. Thus, neuroplasticity may help explain why one or two dosing sessions can be

followed by improvements lasting weeks or months rather than only hours, although the causal contribution of these mechanisms in humans remains incompletely defined [3,8,46,47,48].

Psilocybin also appears to alter emotional processing in ways that may differ meaningfully from conventional antidepressants. Limbic and frontolimbic imaging studies indicate that psilocybin changes amygdala responsivity and prefrontal-amygdala coupling after treatment. In treatment-resistant depression, increased right amygdala responses to emotional faces one day after psilocybin have been associated with subsequent clinical improvement, while reduced ventromedial prefrontal-amygdala connectivity has been linked to decreased rumination. Rather than dampening emotional salience, psilocybin may restore access to emotional material that had previously been avoided or blunted. This profile contrasts with SSRI-associated emotional blunting, a distinction further supported by secondary analyses showing reduced brain responsiveness to emotional stimuli with escitalopram but not with psilocybin, as well as by studies demonstrating increased emotional empathy after psilocybin therapy. Additional work on affective bias suggests that psilocybin may reduce negative interpretive bias while preserving or enhancing emotional responsiveness, which could be therapeutically relevant in depression [25,26,37,49,50].

Beyond neural circuitry, emerging evidence suggests that psilocybin's antidepressant action may be mediated in part by cognitive and psychological change processes. Among these, psychological flexibility has become a particularly important candidate mechanism. Exploratory mechanistic work indicates that gains in flexibility may mediate symptom improvement, suggesting that psilocybin does not simply suppress depressive symptoms but may help patients relate differently to distressing thoughts and emotions. Related constructs such as emotional breakthrough, insight, acceptance, and connectedness also recur across the literature as plausible therapeutic processes. These psychological shifts are clinically relevant because depression is often characterized by cognitive rigidity, experiential avoidance, and narrowed self-referential processing. By loosening these patterns, psilocybin-assisted therapy may enable new perspectives, more adaptive emotional engagement, and improved integration of previously avoided experiences [13,14,27,51].

The subjective psychedelic experience itself may be more than an epiphenomenon. Several studies indicate that the quality and intensity of the acute experience correlate with antidepressant outcomes, particularly when the experience includes mystical-type features, oceanic boundlessness, emotional intensity, or acute insight. Conversely, more dysphoric or fearful acute states appear less consistently associated with sustained benefit. This pattern supports the view that therapeutic efficacy may depend partly on how receptor-level and

network-level changes are translated into personally meaningful psychological experiences. Notably, therapeutic alliance has also been associated with stronger acute mystical effects and better long-term outcomes, indicating that subjective experience and psychotherapeutic context likely interact rather than operate independently. Accordingly, the psychedelic session may function as a catalyst through which neurobiological destabilization is transformed into emotional and cognitive change with antidepressant relevance [12,14,27,51].

Taken together, current evidence supports an integrated but still provisional model of psilocybin's action in depressive disorders. At the receptor level, psilocin engages 5-HT2A signaling and may initiate acute cortical destabilization. At the systems level, this has been associated with transient DMN disintegration, increased brain network flexibility, and altered emotional processing. At the psychological level, the acute experience may facilitate insight, emotional breakthrough, connectedness, and greater psychological flexibility. Rather than demonstrating a single established pathway, the current literature suggests that psilocybin's antidepressant effects likely emerge from the interaction of pharmacological action, network-level reorganization, subjective experience, and psychotherapeutic context [8,9,10,12,13,14,25,26,27,34,37,43,44,45,46,47,48,49,50,51].

2.7. Clinical implementation considerations

Psilocybin for depressive disorders should not be conceptualized as a standalone pharmacological intervention, but rather as a structured model of psychedelic-assisted therapy in which drug administration is embedded within a psychotherapeutic framework. Across clinical trials in this area, psilocybin has consistently been paired with preparatory sessions, therapist-supported dosing, and post-session integration, regardless of whether the design was open-label, waitlist-controlled, placebo-controlled, or comparator-based against escitalopram [1,2,5,11,15,20,31,52]. This three-phase model appears to be a defining feature of contemporary clinical implementation and may contribute both to safety and to antidepressant outcomes [1,2,5,11,15,20,31,52].

The preparation phase serves several clinical purposes, including psychological screening, expectation setting, development of trust, and establishment of a therapeutic alliance strong enough to contain the altered state induced by psilocybin. Qualitative and psychotherapy-focused evidence suggests that patients often enter treatment with marked vulnerability, uncertainty, and anticipatory anxiety, making preparatory work central rather than ancillary [1,2,4,5,11,13,15,20,31]. Available syntheses indicate that building trust and managing expectations before dosing are important for navigating the acute experience, while

trial protocols have consistently incorporated structured psychological support before administration [1,2,4,5,11,13,15,20,31].

During the dosing session itself, psilocybin is administered in a controlled clinical environment with continuous monitoring by trained therapists or facilitators. The therapeutic stance is generally supportive and non-directive, encouraging an inward-directed experience rather than conventional verbal psychotherapy during the peak drug effect. In this context, “set and setting” remains a clinically meaningful construct: set refers to the patient’s mindset, intentions, and expectations, whereas setting encompasses the interpersonal and physical environment in which the session occurs. The importance of this framework is supported indirectly by the consistency of therapist-supported dosing across trials and more directly by psychotherapy-oriented analyses suggesting that extra-pharmacological variables are closely intertwined with treatment response [1,2,4,5,6,12,13,15,20,52].

Integration constitutes the third phase of the model and is intended to help patients translate acute experiences into enduring psychological change. Rather than treating the psychedelic session as self-sufficient, contemporary protocols assume that post-session psychotherapy is needed for meaning-making, consolidation of insight, and incorporation of emotional material into everyday functioning. This emphasis is supported by follow-up work showing that acute insight, emotional breakthrough, and related experiential variables are associated with longer-term antidepressant outcomes, as well as by meta-analytic signals suggesting that longer integration sessions may be associated with greater efficacy [12,22,23,29,51]. Integration may therefore represent one mechanism through which brief pharmacological exposure yields effects that outlast the presence of the drug [12,22,23,29,51].

The therapeutic alliance appears to be one of the more clinically relevant relational variables in implementation. Levin et al. reported that stronger alliance was associated with more intense acute mystical-type experiences and predicted better long-term depression outcomes, suggesting that the patient-facilitator relationship may be more than a supportive background variable [12,20]. This interpretation is consistent with qualitative reports of increased trust, acceptance, and interpersonal openness after treatment, as well as with protocol-based studies in which close therapist presence is maintained throughout the intervention [12,13,14,20]. Taken together, these findings suggest that therapist competence should be understood as part of the intervention itself rather than merely as a delivery variable [12,13,14,20].

Several psychological mechanisms of change identified in the current literature also have direct implementation relevance. Sloshower et al. found that psychological flexibility

mediated antidepressant effects, supporting the view that psilocybin-assisted therapy may work partly by loosening rigid avoidance-based patterns that maintain depression [27]. Complementary evidence indicates that treatment may be associated with increased connectedness and acceptance, while analyses of the acute experience suggest that emotional breakthrough and mystical-type or peak experiences may predict more durable improvement [2,14,25,26,27,51]. Additional secondary analyses showing preserved emotional responsiveness and increased empathy after psilocybin, in contrast to emotional blunting with escitalopram, further support a model in which therapeutic benefit may depend on emotional engagement rather than suppression [2,14,25,26,27,51].

Expectancy and suggestibility remain important methodological and clinical considerations, but the available evidence suggests that their role may differ from that seen with conventional antidepressants. Szigeti et al. found that high expectancy predicted better outcomes with escitalopram but did not predict response to psilocybin, while Weiss et al. similarly reported moderation of escitalopram response by expectancy [1,28,53]. These findings do not eliminate concerns about blinding in psychedelic trials, but they suggest that psilocybin's antidepressant effects may not be reducible to expectancy alone [1,28,53]. From an implementation standpoint, this supports careful expectation management during preparation while also underscoring the need for rigorous trial designs and standardized therapist behavior to minimize bias [1,28,53].

Practical translation into routine psychiatry remains challenging. The treatment models used in trials are resource-intensive, requiring multiple preparatory and integration visits, prolonged monitored dosing sessions, specialized therapist training, and structured screening procedures [12,14,34,51]. These features distinguish psilocybin-assisted therapy from standard outpatient pharmacotherapy and imply that implementation would depend on dedicated infrastructure, workforce development, and careful patient selection rather than simple medication adoption [12,14,34,51].

Overall, current evidence supports a clinical implementation model in which psilocybin is delivered as a therapist-supported, three-phase intervention centered on preparation, supervised dosing, and integration [12,13,14,18,22,27,28]. The available literature suggests that set and setting, therapeutic alliance, psychological flexibility, and post-session meaning-making are not peripheral features but plausible determinants of antidepressant benefit [12,13,14,18,22,27,28]. At the same time, the intensity, cost, and standardization demands of this model raise important questions about feasibility in routine care. Future work should therefore focus not only on efficacy, but also on manualized protocols, therapist training

standards, medication management pathways, and service models capable of integrating psilocybin-assisted therapy into mainstream psychiatric practice [12,13,14,18,22,27,28].

2.8. Limitations of current evidence

Several limitations constrain interpretation of the current evidence base. Many trials remain relatively small, and even the larger randomized studies are modest in scale compared with the evidence base for established antidepressants [1,2,5,6,11,15]. Randomized follow-up periods are often short, whereas longer-term data are usually observational and therefore more vulnerable to attrition, additional treatment exposure, and selection bias [20,23,29]. Heterogeneity across dosing models, psychotherapeutic support, outcome measures, and control conditions further complicates cross-study comparison and limits the precision of broader conclusions [3,16,17,18,21]. Blinding also remains a persistent methodological challenge because the subjective effects of psilocybin can compromise masking and increase susceptibility to expectancy-related influences [17,19]. Finally, most safety data derive from carefully screened participants treated in specialized settings, which limits generalizability to broader clinical populations and routine psychiatric practice [17,19,21,41].

3. SUMMARY

Current evidence suggests that psilocybin-assisted therapy is a promising emerging intervention for depressive disorders, particularly major depressive disorder and treatment-resistant depression. Across the available clinical literature, psilocybin has been associated with rapid antidepressant effects and clinically meaningful reductions in symptom severity in a proportion of participants. Follow-up studies further suggest that benefit may persist beyond acute drug action in some cases, although the extent and duration of this persistence vary across populations and study designs. Importantly, the strongest 12-month follow-up data come from MDD cohorts, whereas the longest 24-month observations derive from studies in cancer-related depression or distress; these findings should therefore not be generalized across depressive disorders as a whole.

At the same time, therapeutic use should be understood within a structured clinical framework rather than as a stand-alone pharmacological intervention. In controlled settings, psilocybin appears to have an acceptable safety profile, with adverse effects that are typically transient and manageable. Careful patient selection, preparatory support, supervision during dosing, and post-session integration remain essential to minimizing psychological and medical risks.

Taken together, current findings suggest that psilocybin-assisted therapy may represent a clinically relevant option for selected patients with major depressive disorder and, in particular, for those with treatment-resistant depression, where unmet therapeutic needs remain substantial. However, the present evidence base is limited by relatively small samples, heterogeneity of treatment protocols, blinding challenges, reliance on observational follow-up for longer-term outcomes, and a lack of large long-term randomized trials. Further large-scale, methodologically rigorous, and longer-term studies are needed before psilocybin can be integrated into routine psychiatric practice with confidence.

DISCLOSURE

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