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REVIEW

Therapeutic Effects of Low-Dose Psilocybin in Depression and Other Mental Disorders: A Systematic Review

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Abstract

Introduction: High-dose psilocybin has shown potential in treating various psychiatric disorders, but its perceptual and cognitive effects, along with the risk of adverse events, highlight the need for alternative treatment approaches. One such approach is the use of low-dose psilocybin, which does not significantly alter cognition or perception. While low-dose psilocybin has garnered growing interest in the psychiatric community, its therapeutic efficacy remains unclear and warrants further investigation. This systematic review aims to evaluate the efficacy and safety of low-dose—whether in the form of microdosing or low-dose control conditions in clinical trials—psilocybin for mental disorders.

Methods: We conducted a systematic review of all empirical evidence involving low-dose psilocybin in human subjects for psychiatric treatment from inception to June 2024. We also searched for relevant registered clinical trials on clinicaltrials.gov.

Results: We identified five registered clinical trials and six publications, including randomized controlled trials (RCTs) (3, 50%), secondary outcome studies (2, 33%), and case report (1, 16%). Four studies (66%) included concurrent psychotherapy. Doses ranged from 1–3 mg per 70 kg as a single dose or 0.1–0.2 g of dried psilocybin-containing mushrooms every 3 days for up to 3 years. Two RCTs studied treatment-resistant depression with 1, 10, and 25 mg psilocybin doses. In the 1 mg group, 18% of participants showed a significant response, 8% achieved remission, and the Montgomery–Åsberg Depression Rating Scale score improved by −5.4 (95% confidence interval [CI]: −8.1 to −2.7) at week 3, though only 10% maintained this by week 12.

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Another study found transient improvements in anxiety and cognitive function with 1 mg. One trial reported no significant improvement with 1–3 mg doses, though 12% achieved anxiety remission and 16% depression remission. An RCT comparing 25 mg to 1 mg plus escitalopram found higher response rates with 25 mg than 1 mg group, although no significant difference in rumination or thought suppression between groups was observed.

Conclusion: The empirical evidence for the efficacy of low-dose psilocybin in treating mental disorders is limited. The current research is constrained by a lack of well-designed studies that compare low-dose psilocybin to placebo. To better understand its potential, future research should include large, rigorous RCTs specifically focused on assessing low-dose protocols.

Keywords: psilocybin, psychiatric disorder, systematic review, psychedelics

Introduction

Psilocybin is a naturally occurring psychedelic compound produced by mushrooms of the *Psilocybe* genus.[1] It is one of the earliest psychedelics, with its uses dating back thousands of years to pre-Columbian Mesoamerican cultures in spiritual and religious contexts.[2] Recreational and therapeutic interest in psilocybin grew in the 1950s–1960s,[3] and a recent resurgence of research—often termed the "psychedelic renaissance"—has led to renewed scientific exploration of its effects on psychiatric disorders, including depression, anxiety, and substance use disorders.[4] Psilocybin is a prodrug that is biotransformed into psilocin in the gastrointestinal tract and liver through dephosphorylation.[5] Given its structural similarity to serotonin, psilocin functions as a partial agonist at 5-hydroxytryptamine (5-HT) receptors, particularly 5-HT_{2A} receptors.[3] Due to its lipophilicity, psilocin crosses the blood-brain barrier and accesses the central nervous system (CNS), leading to dose-dependent alterations in cognition and mood.[6–9]

Therapeutic research on psilocybin generally explores two dosing strategies: "high dosing" and "low dosing".[10] High dosing involves administering a large amount of psilocybin, typically exceeding 10 mg of pure psilocybin, which induces pronounced effects often characterized by functional or cognitive changes, profound alterations of one's conscious experience and sense of self [also referred to as a "high" or a "trip"].[10,11] This approach has been central to psilocybin-assisted psychotherapy, where the induced altered state of consciousness is thought to enhance psychological flexibility and facilitate therapeutic insights.[12–14] However, high-dose psilocybin is associated with adverse events (AEs), ranging from mild to severe. Common AEs include transient anxiety (22–31%), headaches (10–20%), nausea (10–15%), and elevated blood pressure (5–10%).[15–17] More concerning effects, such as severe anxiety or, in rare cases, suicidal ideation, have also been reported. These risks, along with the intensive therapeutic infrastructure required, can limit accessibility.[18]

In contrast, therapeutic low-dose psilocybin encompasses two primary applications: (1) low-dose control conditions in clinical trials, and (2) microdosing, a repeated administration regimen often used outside clinical trial settings.[10–12] In clinical trials, low-dose psilocybin (typically 1–5 mg of pure psilocybin) is administered as a single or limited number of doses, often serving as a control condition to evaluate the effects of higher doses.[19–21] These doses do not typically induce significant alterations in perception or cognition.[19] In contrast, microdosing involves the repeated administration of very low doses of psilocybin (typically ≤1 mg of pure psilocybin) on a regular schedule (e.g., every other day or a few times per week), often without supervision.[19–21] This practice, popularized by anecdotal reports and researchers such as Fadiman and Stamets, is hypothesized to confer cognitive or mood-enhancing benefits while avoiding overt psychedelic effects.[19–21]

While substantial research has focused on the therapeutic potential of high-dose psilocybin, therapeutic effects of low-dose psilocybin—whether in the form of microdosing or low-dose control conditions in clinical trials—remains understudied.[12] Given the need for alternative psilocybin dosing strategies that balance therapeutic benefit with safety, further investigation is warranted. In this review, we aim to synthesize the current literature on therapeutic effects of low-dose psilocybin—whether in the form of microdosing or low-dose control conditions in clinical trials–focusing on its efficacy, safety, and clinical protocols. Clarifying the therapeutic potential of low-dose psilocybin could inform future clinical trials and guide clinical decision-making.

Methods

Literature search

We conducted a systematic review, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines,[13] on three databases (APA PsycInfo, Embase, and MEDLINE through OVID) from inception until June 2024. This review was registered in

PROSPERO (CRD42024562382). The following search terms were used: (psilocybin OR psilocibin OR psilocybine OR silocybin OR psiloc* OR shrooms OR magic mushrooms OR mushies) AND (mental disorder OR mental illness OR psychiatric disorder OR depression OR treatment resistant depression OR major depressive disorder OR depressive disorders OR anxiety OR social anxiety OR social anxiety disorder OR generalized anxiety OR generalized anxiety disorder OR personality disorder OR schizophrenia OR bipolar disorder OR bipolar OR post traumatic stress disorder OR substance abuse disorder OR substance abuse OR obsessive compulsive disorder OR acute stress disorder OR adjustment disorder). We found further relevant articles using Google Scholar and manual searches of references of included articles. We also conducted a search for registered clinical trials on ClinicalTrials.gov (https://clinicaltrials.gov/). The search terms "psilocybin" and "microdose" were used. The search was conducted in June 2024.

Selection criteria and study selection

The following inclusion criteria were used to assess relevant studies: (1) original studies; (2) evaluated the efficacy of low-dose (sub-perceptual)–whether in the form of microdosing or low-dose control conditions– psilocybin; (3) in patients with at least one diagnosed mental disorder in both clinical and non-clinical settings as either a primary or secondary outcome; and (4) published in English. Furthermore, the following exclusion criteria were also applied: (1) involved non-human subjects; (2) used psychedelics other than psilocybin; (3) systematic reviews, narrative reviews, letters to the editor, editorials, or commentaries; and (4) non-peer reviewed. Furthermore, observational studies that included participants with self-reported mental health diagnoses but were limited to cross-sectional designs were excluded due to their inability to assess causality or treatment effects over time.

The process of study selection was carried out by two reviewers on Covidence (H.F., R.S.H.), who first independently assessed the titles and abstracts during the first level screening and then the full texts of each article during the second level. Conflicts between the two reviewers were resolved in meetings and discussions between the reviewers until a consensus was reached.

Data extraction

Two independent reviewers (H.F., R.S.H.) reviewed the full text of the included studies and extracted the following variables: first author, year of publication, study design, aim of study, participant characteristics, study population, dose, psychotherapy principles (if available), outcomes, outcome measures, protocol, results, and conclusion.

Quality assessment

We used Covidence's quality assessment tool to assess the risk of bias (RoB) of included papers.[14] Specifically, we evaluated the following six domains: selection and recruitment, sequence allocation, blinding, placebo controls, data transparency, and other sources of bias.

Results

Search results

The literature search resulted in 2854 records. After removing the duplicates (n = 899), 1955 articles had their titles and abstracts screened, resulting in 1841 being excluded for irrelevance. The 114 remaining studies were then full-text screened with 108 exclusions, for reasons shown in Figure 1. Finally, a total number of six studies involving 134 participants (31% female) were included in our systematic review. The results of RoB assessment can be found in Supplementary Table S1. Detailed characteristics of included studies can be found in Figures 2 and 3 and Tables 1 and 2. We also identified five registered clinical trials that had not yet been published; detailed characteristics can be found in Table 3.

Characteristics of included published studies

Out of the six included articles, three were randomized controlled trials (RCTs), one was a case report and two were secondary outcomes publications.[15–18,29,30] Three of the six articles had concurrent psychotherapy before, at the time of psilocybin administration and after administration.[15–18,29,30] The administered doses included 1 mg or 1–3 mg per 70 kg, given as a one-time administration, and 0.1–0.2 g of dry weight administered every 3 days or a single dose of 1 mg. Notably, one study used a low-dose psilocybin regimen following a microdosing protocol, while the remaining studies employed low doses as control conditions in trials.

Case report on low-dose psilocybin (microdosing protocol)

Lyons (2022) reported on a 43 year old male's experience of self-treating his adolescence-onset treatment-resistant depression (TRD) with home-grown *Psilocybe* mushrooms.[29] He had previously undergone various forms of pharmacological interventions (including selective serotonin reuptake inhibitors-SSRIs, selective norepinephrine reuptake inhibitors-SNRIs, antipsychotics, and mood stabilizers), transcranial magnetic stimulation, electroconvulsive therapy (ECT) and psychotherapy (including cognitive-behavioural therapy); however, no meaningful or sustained effects were observed. The patient reported orally consuming 0.1–0.2 g dry weight (the approximate equivalent of

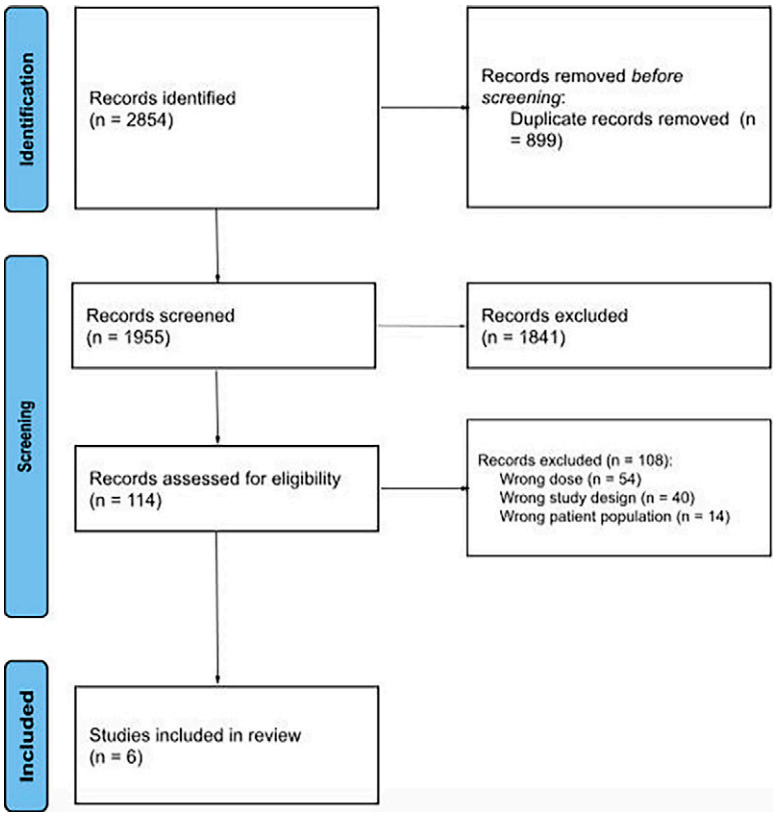

Fig. 1. PRISMA diagram.

1–2 mg pure psilocybin)[31] of home-grown mushrooms every 3 days for a total of 3 years. He took one capsule containing psilocybin powder on the morning of Day 1, followed by 2 days without dosing (Day 2 and Day 3). He then took another capsule on Day 4, followed by another 2-day break (Day 5 and Day 6). This pattern of dosing every third day continued for 8 weeks. After completing the 8-week cycle, the patient took a 4-week break from microdosing before starting the next 8-week cycle. The patient initially began dosing at 0.1 g and, after 1-week, titrated to 0.2 g, which he maintained as his standard dose. He followed this regimen consistently over 3 years, completing multiple 8-week cycles interspersed with 4-week breaks. Depression symptoms were measured using the clinician-rated Hamilton Depression Rating Scale (HDRS). At baseline, he presented with very severe depression (HDRS = 27). He experienced significant improvements in his depression symptoms after 6 months (HDRS = 11) and had complete remission at 2 years (HDRS = 7). He experienced significant improvements in his depression symptoms (HDRS down to 11) after 6 months and had complete remission at 2 years. The patient reported mild instances of nausea after the first two doses that subsequently subsided.[29]

RCTs using low-dose psilocybin as a control condition

Both publications by Goodwin et al. (2022 and 2023)[15,16] reported on the same multinational clinical trial (n = 233) sponsored by Compass Pathways. The study compared the outcomes of a single administration of three different doses (1, 10, and 25 mg) of a proprietary psilocybin formulation (COMP360) among individuals with TRD. Follow-up sessions, where patients were re-evaluated, were conducted at weeks 1, 3, 6, 9, and 12 after administration. The 2022 publication by Goodwin et al. assessed 1 mg psilocybin's efficacy in improving depression symptoms using the Montgomery–Åsberg Depression Rating Scale (MADRS).[15] At 3 weeks, 18% of participants in the 1 mg group experienced a clinically significant response (defined as a reduction of at least 50% in the MADRS score from baseline) with 8% of participants experiencing complete remission. The least-squares mean change in the MADRS score at week 3 was −5.4 (95% confidence interval [CI]: −8.1 to −2.7), however, this improvement was only sustained in 10% of patients at week 12. Similarly, Goodwin et al.'s 2023 publication of the same trial assessed a more diverse group of outcomes, including anxiety, optimism and pessimism, disability, quality of life, and cognitive function.[16]

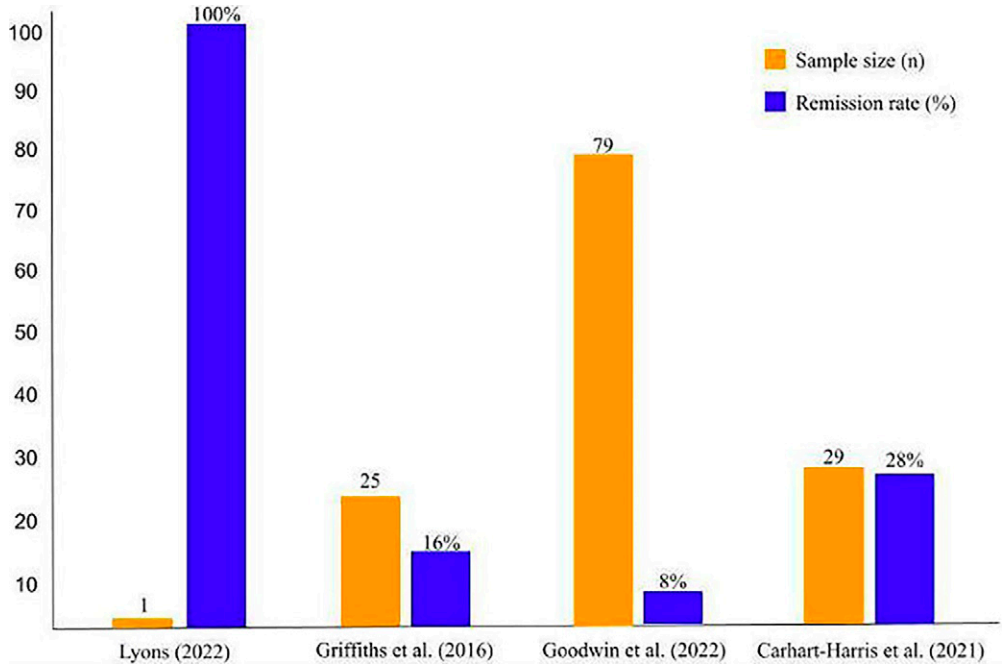

Fig. 2. Depression remission rates across included studies. Bar graph illustrating the complete remission rates of depression in the included studies and their corresponding sample sizes. Lyons 2022 reported on a single patient's complete remission from his treatment-resistant depression after 2 years of self-microdosing under the Fadiman protocol. Griffiths et al. 2016 had 25 patients and a remission rate of 16% whereas Goodwin et al. 2022 saw 8% of patients experience remission in 79 patients. Carhart-Harris et al. 2021 had 29 patients and a remission rate of 28%.

Each of these functional characteristics was measured through validated scales. The least-squares mean (standard error) of the Quick Inventory of Depressive Symptomatology 16-item Self-Report (QIDS-SR-16) total score for the 1 mg group was −3.6 (0.67). Furthermore, the 1 mg psilocybin group was associated with statistically significant slight-to-moderate, but transient, improvements in anxiety, attitudes in life, cognitive function, and quality of life.

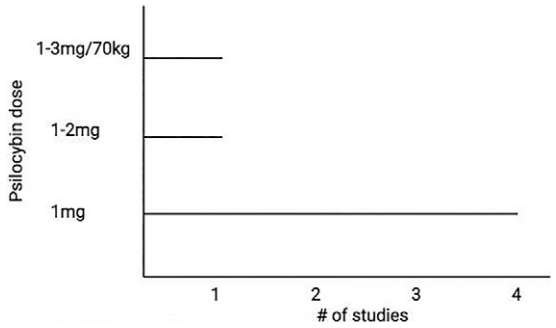

Fig. 3. Psilocybin dose across included studies.

Furthermore, Griffiths et al. (2016) examined psilocybin's efficacy in reducing depression and anxiety in patients with life-threatening cancer (n = 56) using a randomized crossover trial design where each participant received both a low-dose (1 – 3 mg/70 kg) and a macrodose (22 – 30 mg/70 kg) of psilocybin with a washout period of 5 weeks in between.[18] Clinical outcomes, which included depression and anxiety symptoms, quality of life, and death acceptance, were measured. These metrics were collected at various time points, including immediately after trial enrollment, immediately after each administration, 5 weeks after each administration, and 6 months following the second administration. The authors did not observe statistically significant improvements in any of the measured outcomes in the 1–3 mg/70 kg dose condition. However, they reported non-significant trends toward improvement across all metrics. The 12% remission rate for depression on the GRID-HDRS-17 (GRID-HAMD-17) was observed at the 6-month follow-up, representing a quantitative change in the primary measure for major depressive disorder (MDD). Remission was specifically defined as a score of ≤7 on the GRID-HAMD-17 and a reduction of ≥50% from baseline. In contrast, data on anxiety, assessed with the Hamilton Anxiety Rating Scale

Table 1. Characteristics of Included Studies

Author(s) (year)	*Study design*	*Aim of study*	*Number of participants, mean age, % female*	*Study population*	*Psilocybin dose*	*Psychotherapy*
Carhart-Harris et al. (2021)[35]	Phase II, double-blind, randomized, controlled trial	To compare antidepressant effects of psilocybin with escitalopram over a 6-week period.	1 mg + escitalopram: $n = 29$ Mean age: 39.1 % female: 31	Aged of 18 and 80 years with long-standing, moderate-to-severe MDD	25 mg of psilocybin 3 weeks apart plus 6 weeks of daily placebo (psilocybin group) or two separate doses of 1 mg of psilocybin 3 weeks apart plus 6 weeks of daily oral escitalopram (escitalopram group)	Preparatory therapeutic session + active support + integration session
Barba et al. (2022)[37]		To assess the comparative effect of escitalopram, and psilocybin, on rumination and thought suppression in major depressive disorder.	25 mg: $n = 30$ Mean age: 43.3 % female: 37			
Griffiths et al. (2016)[32]	Phase II, double-blind, crossover randomized controlled trial Within-subject comparison	To study the effects of psilocybin in cancer as it pertains to the relief of anxiety and depression symptoms.	Low-dose group: $n = 25$ Mean age: 56.1 % female: 48 High-dose group: $n = 26$ Mean age: 56.5 % female: 50	Adult patients with a diagnosis of life-threatening (including recurrent) cancer AND at least one DSM-IV axis I diagnosis.	Low-dose: 1–3 mg/70 kg High-dose: 22–30 mg/70 kg Group 1: low-dose first, high-dose second[a] Group 2: high-dose first, low-dose second	Not available
Lyons (2022)[36]	Case report Within-subject comparison	To report on a single patient's experience in self-treating their TRD with home-grown psilocybin.	$n = 1$ Mean age: 43 % female: 0	A single 43 year old Caucasian male with PMHx of HTN and TRD (since 17 years old).	Dry weight: 0.1–0.2 g Dried home-grown *Psilocybe cubenesis* ground into powder and encapsulated One capsule every three days for three years	No, but the patient had previously received extensive psychotherapy to no effect and did not continue after the start of self-treatment with psilocybin.
Goodwin et al. (2022)[b,33]	Phase II, multinational, double-blind, randomized controlled trial Between- *and* within-subject comparison	To study the safety and efficacy of a proprietary synthetic form of psilocybin (manufactured by COMPASS, termed COMP360) in TRD.	1 mg: $n = 79$ Mean age: 38.1 % female: 46 10 mg: $n = 75$ Mean age: 40.6 % female: 55	Adult patients with a DSM-V diagnosis of TRD/MDD (single *or* recurrent episodes) without psychotic features and other comorbidities.	Single dose Group 1: 25 mg Group 2: 10 mg Group 3: 1 mg (microdose)	Preparatory sessions and active support
Goodwin et al. (2023)[b,34]		To study the effects of the aforementioned COMP360 on cognitive and functional outcomes in TRD patients.	25 mg: $n = 79$ Mean age: 40.2 % female: 56			

[a]The authors have provided baseline measurements as well as measurements after each session (two total for each participant); by comparing the scores after the first session from group one to their baseline scores, we were able to only examine the effects of microdoses.

[b]The two studies use data from the same clinical trial, however, both the questionnaires used and endpoints measured are different (the original 2022 article focuses on safety and efficacy whilst the 2023 article focuses on cognitive and functional outcomes).

DSM, Diagnostic and Statistical Manual of Mental Disorders; HTN, hypertension; MDD, major depressive disorder; PMHx, past medical history; TRD, treatment-resistant depression.

Table 2. Results of Included Studies

Author(s) (year)	*Outcomes*	*Outcome measures*	*Protocol*	*Results*	*Conclusion*
Carhart-Harris et al. (2021)[35]	MDD symptoms	QIDS-SR-16	Patients were assigned in a 1:1 ratio to receive two separate doses of 25 mg of psilocybin 3 weeks apart plus 6 weeks of daily placebo (psilocybin group) or two separate doses of 1 mg of psilocybin 3 weeks apart plus 6 weeks of daily oral escitalopram (escitalopram group). The primary clinical outcome was the change from baseline in the score on the QIDS-SR-16 scores range from 0 to 27, with higher scores indicating greater depression) at 6 weeks.	The mean (±SE) change from baseline in the score on the QIDS-SR-16 at week 6 was −8.0 ± 1.0 − 6.0 ± 1.0. A QIDS-SR-16 response at 6 weeks occurred in 14 patients (48%). QIDS-SR-16 remission at week 6 occurred in 8 patients (28%).	This trial comparing psilocybin with escitalopram in a selected group of patients showed that the change in scores for depression at 6 weeks did not differ significantly between the trial groups.
Barba et al. (2022)[37]	Rumination and thought suppression	RRS WBSI	Patients were assigned in a 1:1 ratio to receive two separate doses of 25 mg of psilocybin 3 weeks apart plus 6 weeks of daily placebo (psilocybin group) or two separate doses of 1 mg of psilocybin 3 weeks apart plus 6 weeks of daily oral escitalopram (escitalopram group). RRS and WBSI were administered at baseline and week 6.	No significant changes in RRS (mean difference post — pre: −1.00, $p = 0.16$, $d = 0.1$) or WBSI (mean difference post — pre: −2.85, $p = 0.162$, $d = 0.32$) from baseline to 6-week scores in the escitalopram group.	Relative to 1 mg psilocybin, 25 mg psilocybin had a significantly greater impact on both thought suppression and rumination.
Griffiths et al. (2016)[32]	Measures of depressed mood, anxiety, quality of life, attitudes, and behaviour	Clinician-rated GRID-HAM-D-17 (depression) and HAM-A (anxiety) Variety of self-rated scores: BDI (depression), HADS (anxiety), STAI (trait anxiety), POMS (mood), BSI (general psychiatric symptoms), MQOL (quality of life), LOT-R (illness optimism), LAP-R DA & DTS (death acceptance), PLT (life meaningfulness), LAP-R Coherence (understanding of self) Community-rated (family, friends, colleagues, etc.) scores for attitudes, behavior, psychosocial functioning, etc. through the community observer questionnaire	This randomized cross-over study design involved one group who received the low-dose first, then the high-dose and another group who received the high-dose first, then the low-dose. The two doses were separated by a period of five weeks. Outcomes were measured at baseline upon enrolment (4 weeks prior to first session), on the day of each session, 5 weeks after each session, and 6 months after the last session.	No statistically significant improvement in *any* of the measured traits either immediately after or 5 weeks after the low-dose. However, there were non-significant improvements in all depression and anxiety scores, quality of life, and death acceptance.	Single microdoses of psilocybin in the range of 1 − 3 mg/70 kg did not lead to statistically significant improvements in depression and anxiety symptoms nor did it improve patient's quality of life, attitudes, and behaviors in clinician-, self-, or community-rated outcomes. However, there were non-significant improvements in all of these measures.
Lyons (2022)[36]	MDD symptoms	Clinician-rated HDRS	The patient took 0.1–0.2 g of homegrown psilocybin every three days (Fadiman protocol) for a total of 3 years prior to the publication of the case report.	Significant decrease in the HDRS from 27 (baseline) to 20 (after 3 doses) to 11 (6 months after therapy start) to 7 (3 years after therapy start)	In the case of this singular patient, a regimen of 0.1–0.2 g every 3 days was effective at improving depression symptoms.

(*continued*)

Table 2. (Continued)

Author(s) (year)	*Outcomes*	*Outcome measures*	*Protocol*	*Results*	*Conclusion*
Goodwin et al. (2022)[33]	Depression symptoms and safety	Depression symptoms were measured with the MADRS and safety was measured through the recording of adverse events and changes in vital signs, clinical laboratory testing, and electrocardiography.	This randomized 1:1:1 parallel assignment study used a stratified (based on country and previous psilocybin use) randomization technique to assign participants into either 25, 10, or 1 mg of a proprietary psilocybin formulation to be administered once.	The microdose (1 mg) led to a significant reduction in MADRS score by 5.4 (95% CI: −8.1 to −2.7) from baseline three weeks after administration. Serious adverse events occurred in 1% of patients.	Single microdose psilocybin reduced depression symptoms in this study, however, the effect was relatively non-sustained. Serious adverse events rarely occurred, indicating a relatively good safety profile.
Goodwin et al. (2023)[34]	Depression severity, anxiety, optimism/pessimism, disability, quality of life, and cognitive function	A variety of clinician- and self-rated scoring systems were used: GAD-7 (anxiety), QIDS-SR-16 (depression), PANAS (optimism and pessimism), SDS and WSAS (disability and functioning), EQ-5D-3L (daily quality of life), and the DSST (cognitive function).	Efficacy outcomes were measured at baseline (one day prior to administration session), 1 day after, and at weeks one, three, six, nine, and 12. Safety outcomes were continuously monitored during the entirety of the trial.	The following changes at week three were statistically significant ($p < 0.05$): −3.6 in QIDS-SR-16, −3.5 in PANAS, −3.3 in GAD-7, −1.1 in SDS days lost, −4.1 in WSAS, +0.14 in EQ-5D-3L, and +4.8 in DSST. At week 12, the following changes were statistically significant ($p < 0.05$): −5 in QIDS-SR-16, −4.4 in GAD-7, −1.2 in SDS days lost, −9.3 in WSAS, +0.15 in EQ-5D-3L, and +4.6 in DSST.	Administration of a single microdose (1 mg) of psilocybin led to slight to moderate improvements in depression and anxiety symptoms, attitudes in life, cognitive function, and quality of life.

BDI, beck depression inventory; BSI, brief symptom inventory; DSST, digit symbol substitution test; DTS, death transcendence scale; EQ-5D-3L, EuroQol quality of life questionnaire; GAD-7, generalized anxiety disorder-7; GRID-HAM-D-17/HDRS, Hamilton Depression Rating Scale; HADS, hospital anxiety and depression scale; HAM-A, Hamilton Anxiety Rating Scale; LAP-R DA, revised life attitude profile death acceptance; LOT-R, revised life orientation test; MQOL, McGill quality of life; PANAS, positive, and negative affect schedule; PLT, purpose in life test; POMS, profile of mood states; QIDS-SR-16, quick inventory of depressive symptomatology self-report 16 Questions; RRS, Ruminative Response Scale; SDS, Sheehan disability scale; STAI, state-trait anxiety inventory; WBSI, White Bear Suppression Inventory; WSAS, work and social adjustment scale.

Table 3. Characteristics of Registered Clinical Trials

Clinical trials.gov identifier	*NCT06450210*	*NCT05042466*	*NCT05252598*	*NCT05832255*	*NCT05259943*
Trial status	Not yet recruiting	Not yet recruiting	Withdrawn	Suspended	Recruiting
Country	USA	USA	Canada	Canada	Canada
Study characteristic	Phase 1 Interventional, sequential assignment, single masking	Phase 1 Interventional, non-randomized, single group assignment, triple masking	Phase 1 Interventional, single group assignment, quadruple masking	Phase 2 Interventional, single group assignment, open label	Phase 2 Interventional, crossover assignment, triple masking
Projected sample size	20	30	0	10	50
Participants	21 to 60 years old	History of trauma	Healthy participants	Fragile X syndrome	MDD
Protocol	Microdoses of psilocybin trihydrate will be administered to participants (1.2 mg, 2.0 mg, 3.0 mg, and 4.2 mg).	1 gram to 1.5 g of psilocybin every other day for 5 days then moving into a M/W/F dose ranging in the enhanced micro-dose levels of 0.15G. thru 0.33 for 8 weeks	1mg encapsulated psilocybin.	Blister packs will contain five capsules of the study drug, Psilocybin 1.5 mg. Subjects will be given blister packs with weekly doses at each visit including baseline (day 1), day 8, day 15, day 21, and day 28.	8 doses of 2 mg psilocybin
Outcome measure	Number of participants with normal or abnormal psychological status as assessed by a psychiatric mental status exam Agree that for one week before each drug session, he/she will refrain from taking any nonprescription medication, nutritional supplement, or herbal supplement	PLC-5	Use of validated questionnaires to assess drug-effects on mood, sleep, memory, cognition, anxiety, and depression.	Use of validated questionnaires to assess drug-effects on mood, sleep, memory, cognition, anxiety, and depression.	Health questionnaire somatic-anxiety-depression

PCL-5, PTSD checklist for DSM-5; MDD, major depressive disorder.

(HAM-A), showed limited clinical relevance, as anxiety outcomes were not consistently discussed in the preceding sections. To maintain focus on the primary depression outcome, details on anxiety remission rates were omitted.[18]

Carhart-Harris et al. (2021) conducted an RCT and randomized patients ($n = 59$) with MDD to two separate doses of 25 mg psilocybin 3 weeks apart plus 6 weeks of daily placebo or two separate doses of 1 mg psilocybin 3 weeks apart plus 6 weeks of daily oral escitalopram.[17] The primary outcome of this study was changes in QIDS-SR-16 from baseline to week 6. Initially, the mean QIDS-SR-16 scores were 14.5 in the psilocybin group and 16.4 in the escitalopram group. Over the course of 6 weeks, the mean changes in scores from baseline were -8.0 ± 1.0 points for the psilocybin group and -6.0 ± 1.0 for the escitalopram group (difference, −2; 95% CI, −5.0 to 0.9; $p = 0.17$). A response on the QIDS-SR-16 scale was observed in 70% of patients in the psilocybin group compared to 48% in the escitalopram group, indicating a between-group difference of 22 percentage points (95% CI, −3 to 48). Remission rates were 57% and 28% (difference, 28.1% points; 95% CI, 2.3 to 53.8), respectively.[17] Barba et al. (2022) used Carhart-Harris et al. (2021) to evaluate the comparative effect of escitalopram + 1 mg psilocybin, and 25 mg psilocybin, on rumination and thought suppression in MDD.[30] Rumination and thought suppression were measured using the Ruminative Response Scale (RRS) and White Bear Suppression Inventory (WBSI), respectively. The results of this study indicated no significant changes in RRS and WBSI scores from baseline to week 6 in the escitalopram + 1 mg psilocybin group.[30]

Characteristics of included registered clinical trials

We found five registered clinical trials of which two were located in the United States and three in Canada. One USA trial involved 20 participants aged 21 to 60 using a low-dose of synthetic psilocybin trihydrate (1.2, 2.0, 3.0, and 4.2 mg) in Phase 1. Another USA trial involved 30 participants using dried psilocybin-containing mushroom doses (0.15–0.33 g, and 1–1.5 g monthly) over 8 weeks in Phase 1. A Canadian trial, which was withdrawn, planned to use 1 mg encapsulated psilocybin with no participants enrolled. The other Canadian trial, which is suspended, involved 10 participants using 1.5 mg psilocybin in weekly doses via blister packs in Phase 2. Finally, a Canadian trial involving 50 patients with MDD aims to evaluate the effect of 8 doses of 2 mg psilocybin on depressive symptoms.

Discussion

In this systematic review, we collected, analyzed, and synthesized all available studies that used low-dose psilocybin in the treatment of psychiatric disorders. The resulting studies primarily examined the efficacy of psilocybin in the context of improving anxiety and depression symptoms. With the exception of a case report that used a low dose as microdosing, other studies focused on large doses, with low-dose usually included as a comparator. RCTs reported minimal clinical improvements with one or two low-dose; however, the case report documented significant and long-lasting benefits with regular microdose administration. There were zero peer reviewed clinical studies evaluating regular, chronic psilocybin low-dose dosing practices that occur in naturalistic settings. Hence, the efficacy of low-dose regimens in those with psychiatric disorders remains to be empirically tested.

The Fadiman protocol is a popular microdosing regimen used by individuals who engage in self-administration of microdose psilocybin. It involves consuming the substance on day zero, followed by a two-day period of introspection and reflection, before administering a second dose on day three. This cycle is repeated every third day for 4 to 8 weeks, after which a 2 to 4-week break is taken before restarting the next microdosing cycle.[32] Interestingly, several reviews have identified a pattern where individuals following this prolonged protocol report significantly better and more consistent improvements in mood and mental health.[14,33] In our review, while most studies focused on single administrations of low-dose psilocybin as a control group, one case report examined the microdosing protocol approach and found notable improvements in the individual's depressive symptoms. However, further research is needed to explore the long-term effects and efficacy of this protocol. Despite growing interest in microdosing for its potential therapeutic effects, particularly for enhancing cognition, and mood, current evidence remains inconclusive. Studies such as those by Szigeti et al. (2021) and Murphy et al. (2023) highlight mixed results.[34,35] The largest placebo-controlled trial on microdosing, conducted by Szigeti et al., (2021) found no significant differences between the microdose and placebo groups, suggesting that reported improvements may be due to the placebo effect.[34] Murphy et al. (2023)'s review of controlled studies on microdosing with LSD showed acute effects such as mood and cognition changes, but no lasting benefits from repeated low doses.[35] While microdosing appears to be safe with no serious adverse effects reported, the lack of sustained improvements raises questions about its efficacy as a treatment for psychiatric disorders. These findings underscore the need for more rigorous, longitudinal studies to better understand the long-term effects and therapeutic potential of microdosing. Until then, its benefits remain speculative and unsubstantiated by clinical evidence.

In general, improvements in mood, confidence, self-acceptance, and general mental health are observed following sub-perceptual doses of serotonergic psychedelics.[14,34,36–38] Research evaluating the role of these psychedelics beyond anxiety and depression has found beneficial outcomes in the context of addiction and pain, however, we did not find any studies examining the role of low-dose psilocybin in these disorders.[37,38] Some reviews have also identified discrepancies in findings between studies, particularly in cognition and mood. These discrepancies were particularly obvious between different study designs, such as naturalistic observational studies (which often involve self-reported microdosing), retrospective cohort studies, and more.[14,33] Notably, controlled studies have generally not observed benefits in mood, which further highlights the inconsistencies between different types of research methodologies. The lack of observed mood benefits in controlled settings contrasts with the positive outcomes reported in some observational and cohort studies, suggesting that factors such as placebo effects, self-selection bias, or other confounding variables may play a significant role in the perceived benefits reported by participants in less controlled settings.

In comparison with reviews on high-dose psilocybin for psychiatric disorders, our review suggests comparatively inferior and more transient outcomes with low-dose administrations. There is extensive literature documenting high-dose psilocybin's role in treating various psychiatric disorders, particularly depression, substance use disorders, and anxiety.[36–38] Compared to low-dose, the administration of high-dose psilocybin has been linked with more enduring responses, characterized by notably high rates of complete remission of depression.[36,37] By contrast, low-dose administration has been linked to more variable outcomes, with less evidence for sustained therapeutic benefits. While some high-dose studies have identified rare instances of serious AEs, such as increased suicidal ideation,[37,39] our review of low-dose also noted these concerns. For example, Griffiths et al. (2016) reported a suicide in the 1 mg group though this event was not directly attributed to the substance and occurred later. Other studies have also noted that low-dose psilocybin is not without potential risks.[40] Despite this, concerns remain regarding the safety of repeated administration, especially given the limited data available, particularly in clinical populations.[41] This suggests that it is too early to determine whether low-dose psilocybin is entirely safe and suitable for all populations. In addition, it is important to consider possible contraindications, such as interactions (e.g., Lithium).[42] Furthermore, the potential risk of valvular heart disease warrants attention.[41] The uncertainty about whether such contraindications might also affect low-dose underscores the need for further research. Investigating these interactions is crucial to understanding the comprehensive safety profile of low-dose psilocybin, particularly in patients with preexisting conditions or those on specific medications.

Psilocybin's underlying mechanism of action, and its relationship to dose response, is not fully understood. Previous studies have reported that high-dose psilocybin administration can lead to increases in trait mindfulness, openness, and other metrics of mental wellbeing.[43] These findings suggest that the therapeutic properties of psilocybin may be associated with subjective experiences and the insights derived from these altered states of consciousness, which in turn contribute to the beneficial outcomes.[44,45] However, given that high-doses do not elicit the same cognitive alterations, but have been shown, at least in animal models to reach a level of target engagement at the 5-HT2A receptor, whether these subjective changes can explain microdose psilocybin's potential improvements in psychiatric symptoms is still debated.[32] It is a possibility that psilocybin could simply work through its 5-HT receptor agonistic effects, similar to the downstream effects of increased 5-HT agonism of traditional SSRIs.[46,47] However, the fact that psilocybin leads to rapid improvements in symptoms suggests the involvement of additional mechanisms. Animal and *in vitro* studies have found psilocybin to act on other neurotransmitters.[46,47] Besides augmenting serotonin levels, 5-HT2A receptor agonism on presynaptic neurons by psilocybin has also been shown to lead to the release of glutamate.[48] This observation has been particularly well-characterized in the prefrontal cortex and in areas near the dopamine reward center.[49,50] Predictably, this rise in released glutamate is also linked to elevated levels of dopamine in these regions following psilocybin administration.[49,50] The nucleus accumbens and the ventral tegmental area within the dopamine reward center emerge as two key regions experiencing the most pronounced increases in dopamine levels. This suggests a plausible link between psilocybin's indirect influence on the dopaminergic system and the observed enhancements in mood and associated symptoms.[50,51] Interestingly, 5-HT2A receptors are also located on some γ-aminobutyric acid neurons.[52] Experimental evidence has found psilocybin to lead to inhibitory neuronal activity in some parts of the brain.[49] Thus, psilocybin modulates neuronal activity in the CNS through neurotransmitter-dependent changes, leading to the observed changes in psychiatric symptoms.

Psilocybin has also been found to promote neurogenesis and increase synaptic density through various conserved pathways.[8] For example, the cortical elevation of glutamate through 5-HT2A receptor signaling increases mRNA transcripts of brain-derived neurotrophic factor (BDNF), which signals through tropomyosin receptor

kinase B (TrkB) to directly increase neuronal growth and plasticity. Moreover, recent research has shown that psilocybin can also directly promote neuroplasticity through direct binding to TrkB independent of BDNF. Given that psychiatric disorders including depression are often characterized by neuronal atrophy in the cortex, psilocybin may achieve antidepressant effects through its ability to restore neuronal growth and increase plasticity.

Future low-dose psilocybin studies must adopt rigorous methodologies to enhance their validity and reliability. This includes implementing transparent statistical practices by involving independent experts and adhering to open science principles, such as pre registration and data sharing. Studies should incorporate well-structured control groups, ensure adequate sample sizes to avoid selection bias, and systematically report safety and AEs with independent assessments.[53] Long-term follow-up is essential to evaluate sustained effects, while efforts must be made to address and report blinding efficacy, placebo effects, and participants' expectations. In addition, research should focus on understanding mechanisms of action through high-powered replication studies and exploring various therapeutic techniques.[53] By addressing these comprehensive aspects, future studies will yield more reliable and generalizable insights into the effects of low-dose psilocybin.

To the best of our knowledge, this is the first systematic review that evaluated the efficacy of low-dose psilocybin in the treatment of psychiatric disorders. However, our review has several limitations. Given that low-dose psilocybin is a relatively new and unexplored field, our review is primarily limited by the small number of studies included. No RCTs evaluated the therapeutic effect of low-dose psilocybin as a primary intervention in individuals with mental disorders. Most studies using low-dose psilocybin as part of microdosing protocols have been conducted in non-clinical settings, placing them outside the scope of this review. The majority (four out of six) of our included studies were primarily structured to evaluate the impacts of high-dose psilocybin, employing low-dose psilocybin as an active control. Consequently, these studies utilized protocols and dosing regimens (e.g., one or two administrations) unsuited for low-dose, thereby potentially influencing the outcomes observed. Furthermore, the lack of a standardized low-dose protocol also implies a difference in the specific doses and schedules used. Besides, performing a meta-analysis was not possible due to the heterogeneity of the study outcomes.

In conclusion, the current evidence for the efficacy of low-dose psilocybin, including both microdosing and low-dose administration in clinical trials, in mental disorders is far from conclusive. The strongest support for these effects comes from a single self-administered microdosing protocol case report, and the existing RCTs using low-dose as control have generally failed to demonstrate significant beneficial outcomes. This limitation may be attributed to the use of single administrations rather than more frequent, microdose-specific protocols. Notably, there remains a lack of longitudinal research on microdosing in clinical populations or individuals with self-reported mental health disorders, further hindering our understanding of its long-term efficacy and safety. To address these limitations, high-quality double-blind RCTs with repeated low-dose regimens—such as the Fadiman microdosing protocol—are needed to clarify efficacy. Future studies should directly compare high-dose protocols with low-dose and investigate the placebo effect, using larger, more diverse samples with longer follow-up periods. In addition, research should explore low-dose psilocybin's potential in other psychiatric (e.g., substance use disorders, posttraumatic stress disorder, anorexia nervosa) and neurological conditions (e.g., chronic pain, migraine, neurodegenerative diseases).

Authors' Contributions

V.B.: Conceptualized the article and contributed to the overall design. S.M.: Contributed to the concept, overall design, article selection, review, study quality appraisal, article preparation, and submission. H.F. and R.S.-H.: Contributed to article selection, study quality appraisal, and article preparation. All the authors contributed to the review and editing. All the authors have approved the final article, and note that this is the authors' original work.

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Supplementary Material

Supplementary Data
Supplementary Table S1

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