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REVIEW

Psilocybin Therapy for Major Depressive Disorder: A Systematic Review

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Abstract

Introduction: Major depressive disorder (MDD) is a prevalent and complex mood disorder. Its psychotherapies often involve delayed treatment-response times, while its pharmacotherapies can cause unwanted side effects. In recent years, there has been a resurgence in psychedelic research with a specific interest in the potential of psilocybin for treating MDD. Therefore, this systematic review was performed to evaluate the effectiveness of psilocybin therapy at moderate (15±5 mg/70 kg) to high (25 ± 5 mg/70 kg) doses in the psychiatric treatment of MDD.

Methods: The review included a literature search using PubMed (Medline), SCOPUS, Web of Science, and Medline (Ovid) databases from January 1, 2013, to February 28, 2023. Seven studies were included following the inclusion and exclusion criteria (e.g., moderate to high dosing psilocybin treatment, peer-reviewed, moderate to severe depression, control/delayed treatment groups, and non-directive therapy during psilocybin sessions). Studies were excluded using PRISMA guidelines and appraised using the Critical Appraisal Skills Programme checklists.

Results: The primary outcomes assessed included changes in depression scores on validated diagnostic tools and secondary outcomes that supported depression remission (e.g., improved well-being and rumination scores, and decreased anxiety scores). Psilocybin was found to reduce depression symptoms in moderate single-dose contexts and have minimal reported side effects at high doses. A positive relationship was observed between the quality of psilocybin-induced experiences and the reduction in depressive symptoms. Additionally, a dose-response relationship was found between moderate (15±5 mg/70 kg) and high-dose psilocybin (25 ± 5 mg/70 kg), with greater improvements generally seen in higher dose conditions.

Discussion: This review suggests that psilocybin can be an effective treatment option for MDD. Psilocybin shows meaningful improvements in depression scores with the potential to treat psychiatric conditions concurrent to depression. The non-directive therapy approach during high-dose sessions enabled unique psychedelic and personal experiences, potentially allowing more profound and individualized therapy. Reported side effects were minimal, and suggestions for future studies are provided.

Conclusion: Psilocybin therapy was found to reduce depression levels and improve secondary outcomes that support depression remission, indicating efficacy for MDD and other depressive conditions. Despite seeming promising, further research is required before introducing PAP options to mainstream clinical practice.

Keywords: Major depressive disorder; psilocybin; depression; psilocybin-assisted psychotherapy; acute psychedelic experience; CBT; SSRIs

Introduction

Major depressive disorder (MDD) is a highly prevalent condition, affecting an estimated 280 million people worldwide in 2023 (~3.8% of the global population) [1]. The American Psychiatric Association characterizes MDD as a mental health condition that involves persistent feelings of sadness, loneliness, and loss of interest in once pleasurable activities [2]. Selective serotonin reuptake inhibitors (SSRIs) are the most prescribed antidepressant pharmacotherapy. However, they have limited efficacy, delayed response onsets, and a high incidence of side effects such as drowsiness, nausea, vomiting, fluctuations in weight (±5% change in body weight in a month), decreased sleep quality, and sexual dysfunction [3-5]. Cognitive behavioural therapy (CBT) is a widely-used psychotherapy approach for MDD, which involves identifying and modifying negative thought patterns and behaviours. However, psychotherapies like CBT have a delayed onset of action, typically taking several weeks or months to produce significant improvements in depressive symptoms [6]. Given the high prevalence of MDD and its substantial burden on individuals/society, there is a pressing need for more effective, safer, and faster-acting treatments.

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), an MDD diagnosis can be made with the presence of at least five of the following symptoms: depressed mood, loss of interest or pleasure in activities (anhedonia), weight fluctuation, insomnia or hypersomnia, psychomotor agitation or delay, fatigue or loss of energy, feelings of worthlessness or guilt, diminished ability to think or concentrate, and recurrent thoughts of death or suicidal ideation [2]. Being both the leading cause of disability and suicide worldwide, [7-8] finding an effective solution to MDD is both a pressing public health concern and one that demands immediate attention.

A treatment direction presently garnering traction is called psilocybin-assisted psychotherapy (PAP). Psilocybin is a naturally occurring psychedelic compound found in certain species of *Psilocybe* mushrooms. When administered in moderate to high doses, it can cause acute psychedelic experiences (APE) that are characterized by visual and auditory hallucinations (synesthesia); alterations in perception, thought processes, and emotions; profound changes in mood, cognition, and behaviour; decreased rumination, and; increased introspection and ego-dissolution [9-10]. The substance has a long history, ranging from use by certain cultures in central Mexico to northern Australia for theological/spiritual practices for thousands of years, to wide-stream recreational use in the 1960s United States, [11] to present-day research examining its potential to revolutionize the field of clinical psychiatry.

Psilocybin's mechanism of action for depression treatment is not yet fully understood; however, extant theories support its action at neurotransmitter and brain-region levels. Psilocybin has been found to have agonist activity on the serotonin 5-HT2A receptor, densely located in several brain regions associated with mood, emotion, and cognition (e.g., prefrontal cortex and hippocampus). When stimulated, serotonin 5-HT2A receptors trigger various signalling cascades responsible for altering the neural activity, enabling its hallucinogenic and other effects (e.g., increasing cortical excitability, increasing glutamate levels likely responsible for ego dissolution; disrupted resting state network) [12-15]. The default mode network (DMN) is a set of interconnected brain regions that are more active when the mind is at rest and not focused on the external environment. Disruptions in this network have been implicated in several psychiatric disorders, including depression and anxiety [16-17]. Carhart-Harris et al. conducted an fMRI study on healthy volunteers and found that psilocybin administration led to a decrease in functional connectivity between the medial prefrontal cortex and posterior cingulate cortex (key regions of the DMN), and an increase in connectivity between the posterior cingulate cortex and other brain regions associated with visual and somatosensory processing [16]. This is important for its therapeutic effects, as it suggests that psilocybin may disrupt the self-referential, habitual, and rigid patterns of thinking that are characteristic of depression and MDD. Through these pharmacodynamic mechanisms, psilocybin has been associated with regulating mood, emotion, and cognition, and reducing symptoms of depression such as fatigue, low motivation, and anhedonia. Furthermore, the use of high-dose psilocybin has been found effective on behalf of its psychological effects. Notably, these effects can include its ability to 1) induce profound episodes of introspection with APEs that can be discussed in psychotherapy sessions; 2) reduce rumination and improve mood after sessions, and; 3) provide patients with an insightful platform to overcome difficult thoughts and emotions [18-20]. These can in turn lead to increased optimism and motivation to engage in activities that can further ameliorate mood. Therefore, psilocybin's unique therapeutic pathway operates through its pharmacodynamic (e.g., effects on 5-HT2A/glutamate receptors; DMN) and psychological activity (e.g., increased receptivity to CBTs; APEs).

The process of PAP is generally conducted through a series of high-dose psilocybin sessions facilitated by specially trained psychotherapists. The sessions are held in a safe and relaxing environment, typically with dim lighting, eyeshades, and calming background music. The sessions are preceded by psychological preparation, intended to help the patient build trust and rapport with the therapist, and create an atmosphere of openness and willingness to address psychological resistance [21-22]. During the psilocybin dosing sessions, therapists provide emotional support and guidance while minimizing interaction, thereby allowing patients to guide their healing process through non-directive therapy. The seven studies examined in this review employed this non-directive therapeutic framework during psilocybin dosing sessions. The non-directive approach aims to facilitate the participant's inner healing process by minimizing directed therapy, rather than imposing a specific therapeutic agenda (e.g. CBT/dialectical behaviour therapy) [23]. Following dosing sessions, integration sessions are held with the same therapists to discuss the patients' experiences and any potentially meaningful insights or details of emotional challenges overcome [19, 24-25]. Therefore, when psilocybin is paired with psychotherapy, there is a symbiotic relationship between them -- each enhance the other's capacity to improve clinical depression outcomes. In the treatment of MDD, it is more fitting to consider psilocybin as a distinct type of drug-assisted psychotherapy, for it neither falls solely under the categories of pharmacotherapy nor psychotherapy interventions.

The purpose of this systematic review is to evaluate the efficacy of PAP compared to control/placebo groups with non-directive psychotherapy conditions for the treatment of MDD. This review analyzes the extant literature to determine PAP's potential as a viable treatment for MDD, while also comparing it to traditional depression therapies (presented as either placebo or delayed treatment conditions who received psychotherapy treatment or antidepressant therapy but no clinically relevant amount of psilocybin).

Methods

Search Strategy and Selection Process

(a) Search strategy: A comprehensive search was conducted for relevant studies published in English from January 1, 2013, to February 28, 2023, using four databases: PubMed (Medline), SCOPUS, Web of Science, and Medline (Ovid). The same search strategy was applied to each of these databases, which was as follows: "psilocybin"[MeSH Terms] OR (psiloc*) AND [(depressive disorder [MeSH Terms]) OR "major depressive disorder." This strategy was used to identify studies pertaining to the use of psilocybin treatment for MDD.

(b) Selection process: Zotero software (Corporation for Digital Scholarship, Vienna, Virginia, USA) was used to manage and organize retrieved articles obtained from the screening process. Covidence (Veritas Health Innovation, Melbourne, Victoria, Australia) was employed to facilitate the screening process. A single reviewer (KV) initially screened titles and abstracts to identify potentially relevant studies. Full texts of the remaining articles were then examined by the same reviewer (KV) to ascertain appropriate studies for inclusion. Duplicate articles and those which violated the inclusion criteria were eliminated as part of the screening process.

Eligibility Criteria

The PICO (patient/population, intervention, comparison, and outcomes) standards were used to develop the following inclusion and exclusion criteria:

(a) Participants: Patients of any gender/race aged 18 years or older who have been diagnosed with depression according to the DSM-5 or validated depression scales (see Table 1.a) were included in this study. Further, studies included were confined to those which excluded patients undergoing antidepressant drug therapy at the time of the trial, which may alter the effectiveness of psilocybin and contribute to internal validity bias.

(b) Intervention: Moderate and high dose psilocybin (ranging from 15±5 mg/70 kg to 25±5 mg/70 kg, respectively) with non-directive psychotherapeutic support.

(c) Comparison: Control groups (placebos or delayed treatment groups) who received either antidepressant pharmacotherapy or traditional psychotherapy (but no clinically relevant amount of psilocybin: ≤1 mg/70 kg).

(d) Outcome: The objective of this study was to assess the efficacy of psilocybin in reducing depressive symptoms of patients with severe depression. To evaluate the effectiveness of the treatment for depression symptom reduction (primary outcome), pre-validated psychometric tools were utilized, including the Beck's Depression Inventory (BDI; score range from 0 to 63, with higher scores indicating more severe depression), Hamilton Depression Rating Scale (HAM-D; a score of ≥17 was required for enrollment), Montgomery–Åsberg Depression Rating Scale (MADRS; score range from 0 to 60, with higher scores indicating more severe depression), and the Self-Reported Quick Inventory of Depressive Symptomatology (QIDS-SR-16; 0 to 27, with higher scores indicating more severe depression; see Table 1.a). Secondary outcomes assessed in this study included the Psychological Insight Scale (PIS-6), Ruminative Response Scale (RRS), White Bear Suppression Inventory (WBSI), and the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS; see Table 1.b).

(e) Study design: Only peer-reviewed clinical trials (e.g., randomized controlled trials (RCT) or open-label clinical studies) published in English were included in this systematic review. Therefore, case series, animal studies, meta-analyses, literature reviews, and systematic reviews were not included. Studies were required to study the effect of moderate to high-dose psilocybin administration in non-directive therapy conditions during dosing sessions.

Table 1.a Comparison of the scoring scales used to measure the primary outcome (depression).

Scale	Description of Primary Outcome
BDI	21-item self-report inventory. Scale is scored from 0 to 63.* BDI≥30 indicates severe depression. Assesses mood, guilt, worthlessness, energy, and appetite.
HAM-D	17-item rating scale. Scale scored 0 to 52.* HAM-D≥17 indicates severe depression. Assesses mood, guilt, suicide ideation, and sleep.
MADRS	10-item rating scale. Scale is scored from 0 to 60.* MADRS≥35 indicates severe depression. Assesses sadness, tension, sleep, appetite, and energy levels.
QIDS-SR	16-item self-report scale. Scale is scored from 0 to 27.* QIDS-SR≥16 indicates severe depression. Assess mood, energy, concentration, and sleep.

**Higher scores indicate more severe depression*

Table 1.b Comparison of the scoring scales used to measure the secondary outcomes (factors supporting depression improvement).

Scale	Description of Secondary Outcome
PANAS	The 20-item Positive and Negative Affect Schedule was used to measure well-being through positive and negative emotions; scores range from 10-50 for both sections.
PIS-6	The 6-item Psychological Insight Scale was used to measure the psychological insight after an acute psychedelic experience.
RRS	The 22-item Ruminative Response Scale scores range 22-88 measures the degree to which a patient experiences rumination, a symptom of depression.
WBSI	15-item White Bear Suppression Inventory scores range from 15-75; higher scores indicate greater tendency to suppress thoughts.
WEMWBS	14-item Warwick- Edinburgh Mental Wellbeing Scale; scores range from 14-70; higher scores indicate higher well-being) was used to measure perceived well-being.

Critical Appraisal

Studies were assessed for risk of bias using the Critical Appraisal Skills Programme Randomised Controlled Trial Checklist [26]. The studies included were all classified as low risk of bias, indicating that risk of bias was minimized and that the results were likely to be reliable. The studies were judged to be of good quality and the results can likely be trusted. The most common sources of bias (e.g., inadequate randomization, allocation, concealment, blinding) were all addressed in the included studies. Furthermore, all the studies included adequate follow-up, with minimal evidence of attrition bias.

Data Extraction

A single reviewer (KV) conducted the data extraction. The data extraction table (Table 2) includes the seven studies displaying each study's authors, intervention(s), and primary and secondary experimental outcomes. Through a thematic analysis of the seven studies, primary outcomes (i.e., impact of psilocybin therapy on depression scores) and secondary outcomes (i.e., the impact of psilocybin therapy on other factors that influence depression scores, such as changes in well-being and anxiety scores) were generated for inclusion in the results. Data were extracted from the seven included studies in a systematic manner, including information on the authors, year of publication, study design, sample size, dose(s) of psilocybin, primary and secondary outcomes, and reported results (see Table 2).

Data Synthesis

Data synthesis for this systematic review was conducted using both qualitative thematic analysis and quantitative methods. Qualitative thematic analysis was used to identify themes and patterns that emerged from the studies included in the review. This involved coding the data from the studies and then analyzing the coded data to identify patterns and commonalities across the studies which are discussed in the results section. The quantitative methods used for data synthesis included comparing the results of different studies and effect size calculations, which were used to estimate the magnitude of the effects of psilocybin on depression. These results were presented tabularly and used to compare the results of the different studies and to determine the overall effect of psilocybin on depression. In addition, a narrative synthesis was performed to summarize the results of the studies and to provide an overview of findings. This involved summarizing the results of the studies, highlighting the commonalities and differences between the studies, and drawing conclusions about the overall effects of psilocybin on depression.

Results

This systematic review examined the efficacy of psilocybin for the treatment of MDD. When conducting the literature search, 316 studies were identified using four databases. After the removal of duplicates, screening, and full-text inclusion/exclusion review, seven articles were retained for synthesis (Figure 1). Primary outcomes assessed in this review were changes in depression scores (e.g., QIDS-SR-16, MADRS, HAM-D, and BDI; Table 1.a) and secondary outcomes were changes in well-being scores (e.g., WEMWBS, PANAS), and other clinically relevant outcomes for improving depression scores (e.g., PIS-6, changes in anxiety symptoms, the role of the APE; Table 1.b).

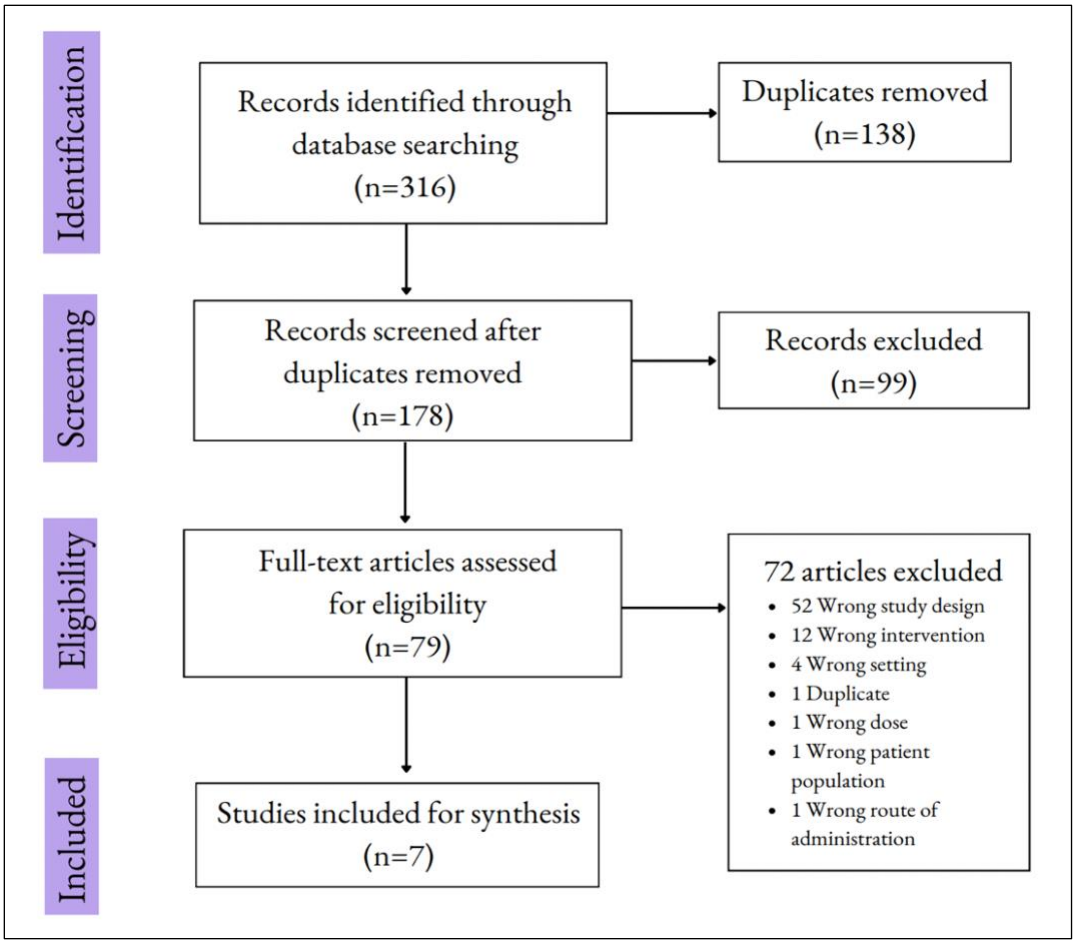

Figure 1. PRISMA flowchart of research papers screened from identification to inclusion created using Covidence.

The first study examined was a double-blind RCT (n=59) comparing high-dose (25 mg) psilocybin to escitalopram, a commonly prescribed SSRI, conducted by Carhart-Harris et al. [3]. They found that at the 6-week endpoint, the psilocybin treatment group (PTG) and the escitalopram group both showed a decrease in QIDS-SR (depression) scores, although there was no statistically significant change in depression outcomes between the groups. However, psilocybin was favoured for its secondary outcomes. This included the PTG reporting greater improvements in emotion and ability to feel compassion and pleasure, less drowsiness and rumination, and greater improvements in WEMWBS (well-being) scores than the escitalopram treatment group [3]. Barba et al. conducted a follow-up study using the data generated from Carhart-Harris et al. [3] to examine the impacts of psilocybin on rumination, a common symptom of MDD (criterion A7 in DSM-5) [2, 18]. They found that the PTG experienced a significant decline between baseline and endpoint RRS (rumination) scores (with a moderate effect size, d = 0.63), while the SSRI group did not (d = 0.1) [18]. They further noted that in the PTG, there was a significant correlation between PIS-6 scores (ratings of insight after a psychedelic experience) and ΔRRS (change in rumination scores), as well as significant correlation between PIS-6 scores and ΔWBSI (change in thought suppression scores). This indicates that higher levels of psychological insight following APEs were strongly correlated with improved rumination and thought suppression symptoms [18].

A double-blind RCT (n=52) conducted by von Rotz et al. studied the efficacy of moderate dose psilocybin administration (0.215 mg/kg, rounded to nearest integer; therefore 15.05 mg/70 kg rounds to 16 mg/70 kg) for the treatment of MDD [27]. They found that at the 14-day endpoint, the PTG had decreased MDD scores by 13.0 points on the MADRS (d = 0.97) and 13.2 points on the BDI (d = 0.67), which was significantly larger than the placebo group scores [27]. This translated into 54% of patients being in remission under the MADRS (score <10 points; PTG: 14/26 vs. placebo: 3/26) and 46% in remission under the BDI (BDI score <10 points; PTG: 12/26 vs. placebo: 3/26) at the end of their study [27]. These findings suggest that the divergent treatment conditions experienced by the PTG, particularly the psilocybin-induced APE (e.g., oceanic boundlessness (OBN) or ego dissolution), played a critical role in the study's clinical outcomes.

In their phase 2 double-blind RCT (n=233), Goodwin et al. found a dose-response relationship between very low- (1 mg; control), moderate- (10 mg), and high-dose (25 mg) psilocybin on depression outcomes, with higher doses producing greater symptom relief when paired with non-directive therapy [28]. At the 3-week endpoint, the 25 mg PTG had superior MADRS and QIDS-SR-16 score improvement from baseline measurements compared to the 1 mg control and 10 mg PTG [28]. At the endpoint, this dose-response relationship was further supported by improved secondary outcomes. These included proportional decreases in Generalized Anxiety Disorder 7 Scale (GAD-7) and Zung Self-Rating Depression Scale (SDS) scores, as well as improved PANAS (well-being) scores as psilocybin levels increased. [28]

In an open-label study (n=20) study on unipolar treatment-resistant depression (TRD) patients, Roseman et al. used moderate (10 mg) and high (25 mg) doses of psilocybin with non-directive therapy support [19]. At the 5-week mark, 47% (n=9) of participants experienced a decrease of ≤50% in their QIDS-SR scores (indicating a clinically relevant response) [19]. Their study on the quality of APE found that participants with "complete" oceanic boundlessness (threshold: OBN > 0.6 score on 0-1.0 scale) had superior clinical outcomes at the 6-month follow-up than those with non-complete OBN (complete: ΔQIOS-SR 9.18 ± 6.4 and ΔBDI 19.54 ± 9.7; non-complete: ΔQIOS-SR 4.37 ± 7.7 and ΔBDI 8.62 ± 14.6) [19]. OBN (oceanic boundlessness) refers to a profound sense of expansiveness, unity, and dissolution of boundaries often experienced by patients during psilocybin-induced psychedelic experiences, whereas dread of ego dissolution (DED) refers to the fear or anxiety that arises when patients face the potential loss of their sense of self/personal identity during APEs. Roseman et al. conducted a regression analysis on the week-5 data, using OBN and DED as independent variables, while the dependent variable was the QIDS-SR score. The results showed that these two variables together accounted for 54% of the variance in depressive scores at week 5 (adjusted r^2 = 0.54) [19]. In a follow-up study to Roseman et al., [19] Carhart-Harris et al. [29] reported that at all 6 post-treatment time points, QIDS-SR16 scores significantly decreased from baseline [29]. BDI scores reduced significantly at 1 week (−22.7 points), 3 months (−15.3, points), and 6 months post-treatment (−14.9 points), showing profound and sustained relief on the Beck's Depression Inventory [29]. There was reasonable correspondence between HAM-D and QIDS-SR16 scores at 1-week post-treatment, with a strong relationship between QIDS-SR16 and BDI (r = 0.81) [29]. Finally, it was observed that the maximum alleviation of MDD symptoms was achieved at the 5-week mark [29].

The last study retained for synthesis was conducted by Gukasyan et al., [30] which involved a clinical trial on patients with MDD. In this trial, two high doses of psilocybin (20 mg/70 kg and 30 mg/70 kg) were administered with a two-week interval between each dose [30]. They found that at the 1-week mark, 75% of patients showed a clinical response rate on GRID-HAM-D scale (≥50% reduction from pre-treatment) and 58% of patients were in remission (GRID-HAM-D score≤7) [30]. At 12 months post-treatment, 75% of patients had a positive treatment response and 58% were in remission (GRID-HAM-D ≤ 7, QIDS ≤ 5, BDI-II ≤ 9). Mean GRID-HAM-D scores decreased significantly from 22.8 at baseline (pre-treatment) to 8.7 at week-1, 8.9 at week-4, 9.3 at month-3, 7.0 at month-6, and 7.7 at month-12 (endpoint; post-treatment) [30]. This data shows a significant decrease in depression scores immediately following treatment, with sustained long-term results over the course of 12 months.

Table 2. Data extraction table for the seven studies included in this review, displaying the intervention used, and primary (i.e., depression scores) and secondary outcomes (i.e., other factors that contribute to improved depression scores) associated with each treatment.

Study	Intervention	Primary outcome(s)	Secondary outcome(s)
Carhart-Harris et al., 2021 [3] Double blind RCT	Drug: 2x 25 mg doses 3 weeks apart (PTG, n=30); 2x 1mg (placebo) doses three weeks apart with sustained escitalopram use at 10mg/day for first 3 weeks then 20mg/day for next 3 weeks (escitalopram group, n=29)	QIDS-SR-16 change at week 6 (endpoint): ▪ PTG: -8.0±1.0 (baseline: 19.2±2.3) ▪ Escitalopram group: -6.0±1.0 (baseline: 18.4±3.4)	▪ Week 6 mean change in WEMWBS score: PTG: 15.4±1.9, escitalopram group: 7.3±1.9. ▪ PTG showed greater perceived improvements in emotion, compassion, and pleasure compared to escitalopram group. ▪ PTG reported less drowsiness compared to escitalopram group.

Study	Intervention	Primary outcome(s)	Secondary outcome(s)
Barba et al., 2022 [18]	Same as Carhart-Harris et al., 2021 [3]	▪ No significant changes found in escitalopram group when comparing baseline & week-6 RRS scores (mean ΔRRS = -1.00, $p = 0.16$, $d = 0.1$). ▪ PTG demonstrated significant difference in RRS scores between baseline and week-6 (mean difference: -7.76, $p < 0.001$, Cohen's $d = 0.63$).	▪ Significant correlation between baseline scores on RRS and WBSI in PTG (r(28) = 0.48, $p = 0.006$). ▪ Baseline QIDS-SR-16 scores had significant correlation with baseline RRS (r(28) = 0.42, $p = 0.02$) and baseline WBSI scores (r(28) = 0.39, $p = 0.04$) in PTG. ▪ In PTG, significant correlation between ΔRRS and PIS-6 scores (r(28) = -0.69, $p < 0.001$) and between ΔWBSI and PIS-6 scores (r(28) = -0.56, $p < 0.001$).
von Rotz et al., 2022 [27] Double blind RCT	Single moderate dose psilocybin (0.215 mg/kg rounded to the nearest integer, e.g., 15.05→16 mg/ 70 kg). Nondirected therapy approach; participants listened to music (both psilocybin & placebo groups).	▪ Symptom severity in PTG decreased significantly at 14-day endpoint: -13.0 points (Cohen's $d = 0.97$; $p = 0.0011$; MADRS) and -13.2 points (Cohen's $d = 0.67$; $p = 0.019$; BDI), surpassing placebo group. ▪ Remission rates at endpoint: 54% of patients in remission according to MADRS (PTG: 14/26 vs. placebo: 3/26; $p = 0.0023$), and 46% in remission according to BDI (PTG: 12/26 vs. placebo: 3/26; $p = 0.013$).	▪ Significant interaction effects found between treatment condition and time for MADRS ($F(5,250) = 11.8$, $p < 0.0001$, $\eta 2G = 0.058$) and BDI ($F(5,250) = 10.4$, $p < 0.0001$, $\eta 2G = 0.050$). ▪ Psilocybin has the potential to reduce depressive symptoms with a single, moderate dose, similar to higher doses used in prior studies, with fewer side effects and improved tolerability.
Goodwin et al., 2023 [28] Phase 2 double blind RCT	233 TRD participants were randomized in 1:1:1 ratio to receive 25mg, 10mg, or 1mg (serving as the placebo) doses of psilocybin. Therapists present to ensure safety and support; let experience unfold naturally. Patients listened to music with eyeshades.	▪ 25 mg PTG demonstrated statistically significant changes in MADRS score compared to the 1 mg control at Week 3 (endpoint) compared to baseline. ▪ The least squared mean (LSM) for QIDS-SR-16 showed a difference of -2.8 (95% CI: -4.6 to -0.9) between the 25 mg PTG and 1 mg control from baseline to endpoint. ▪ The difference in QIDS-SR-16 LSM between 10 mg PTG and 1 mg control was -1.6 (95% CI: -3.5 to 0.3).	▪ Decreased GAD-7, SDS, and PANAS scores. ▪ Exploratory efficacy endpoint measures showed dose-response relationship, with 25 mg PTG improving more than 10 PTG group compared to 1 mg control.
Roseman et al., 2018 [19] Open label clinical trial	Two psilocybin-assisted therapy sessions, one week apart (1st: low dose, 10mg; 2nd: high-dose, 25mg). Non-directive, supportive psychotherapy approach to allow uninterrupted introspection.	▪ At week-5, 47% of participants (n=9) achieved a reduction ≥50% in QIDS-SR scores. ▪ Patients who experienced OBN (n=11) showed greater improvements in ΔQIDS-SR scores at the 6-month endpoint compared to those who did not experience complete OBN (n=8) (9.18 ± 6.4 vs. 4.37 ± 7.7).	▪ OBN is a statistically significant, more efficient predictor of depression remission than visual restructuring and auditory alterations (z scores of 1.64 and 2.01, $p < 0.05$). ▪ Patients with "complete" OBN (threshold: OBN > 0.6) had superior clinical outcomes. ▪ High OBN paired with low DED predicted long-term, positive clinical outcomes on depression.

Study	Intervention	Primary outcome(s)	Secondary outcome(s)
Carhart-Harris et al., 2017 [29]	Same as Roseman et al., 2018 [19]	▪ QIDS-SR-16 scores significantly decreased from baseline at all 6 post-treatment time points, with the maximum effect observed at 5 weeks (primary endpoint) (−9.2, 95% CI: -11.8 to -6.6, t=-7.2, $p < 0.001$, Cohen's $d = 2.3$). ▪ BDI scores showed significant reductions at 1 week (-22.7, 95% CI: -17.6 to -27.8, $p < 0.001$), 3 months (-15.3, 95% CI: -8.7 to -21.9, $p < 0.001$), and 6 months post-treatment (-14.9, 95% CI -8.7 to -21.1, $p < 0.001$).	▪ HAM-D and QIDS-SR-16 scores exhibited reasonable correspondence (r = 0.61, $p < 0.001$) at 1-week post-treatment. ▪ A strong correlation was observed between QIDS-SR-16 and BDI scores (r = 0.81, $p < 0.001$). ▪ Sustained responses observed at 6-month follow-up. ▪ Reduction in depressive symptoms at primary endpoint was predicted by strength and quality of APE.
Gukasyan et al., 2022 [30] Open label RCT	Participants given 2 doses of psilocybin, 20mg/70kg and 30mg/70kg, spaced ~2 weeks apart. Nondirective therapy approach during APE.	▪ Week 1 Results: 74% of patients (17 out of 24) showed a clinical response rate on the GRID-HAM-D scale (≥50% reduction from pre-treatment), and 14 out of 24 participants were in remission (GRID-HAM-D score ≤ 7). ▪ 12-Month Results: 75% of patients had a treatment response, and 58% were in remission (GRID-HAM-D ≤ 7, QIDS ≤ 5, BDI-II ≤ 9). ▪ Significant decrease in GRID-HAM-D scores (SD) from baseline (pre-treatment) to various time points (post-treatment): 1 week: 8.7 (7.6); 4 weeks: 8.9 (7.4); 3 months: 9.3 (8.8); 6 months: 7.0 (7.7); 12 months: 7.7 (7.9). ▪ All p-values were > .001 based on adjusted paired t-tests with Bonferroni correction.	▪ No significant difference in average GRID-HAM-D and overall wellbeing scores at 12 months between individuals who started taking daily antidepressants and those who didn't (n=8). ▪ The grand means (SDs) of overall wellbeing scores as a percentage of the maximum possible score were 63.9 (22.6), 60.0 (21.3), 59.0 (24.0), and 65.0 (20.0) at the 1-, 3-, 6-, and 12-month follow-up time points, respectively. ▪ A significant correlation observed at week-4 between MEQ30 scores (measuring mystical experiences) and improved GRID-HAM-D scores, indicating that the quality of mystical experiences influenced depression and overall wellbeing outcomes.

*Please see Table 1.a & 1.b for list of acronyms (scale names and ranges) used in this table

Discussion

The results of this review regard psilocybin therapy as an effective form of drug-assisted psychotherapy for major depressive disorder treatment at moderate and high doses. Considering both the qualitative and quantitative elements of this review, the studies assessed have shown that psilocybin can reduce depression symptoms in those with MDD and lead to sustained remission rates. This can be through its biological mechanisms of actions or via its ability to produce insightful APEs, increased introspection, decreased rumination/thought suppression, and improved receptivity to cognitive therapies following dosing sessions. Psilocybin research continues to show promise for the psychiatric treatment of MDD. Noticeable and statistically significant reductions in depressive symptoms compared to placebo/delayed treatment conditions at various time points were observed, providing increasing evidence for PAP viability in clinical practice. The seven studies examined provide considerable evidence suggesting that as a molecular entity, psilocybin possesses the potential for further clinical trials and drug development. The most consistent finding was decreased depression scores in psilocybin treatment groups compared to the non-treatment groups. While Carhart-Harris et al. [3] found no statistically significant change in depression scores between the psilocybin and escitalopram groups, they noted that the PTG reported greater improvements in terms of secondary outcomes such as increased well-being scores and

decreased anxiety scores. The other trials examined in this review found significant changes in depressive symptoms, further bolstering PAP's validity for depression treatment.

The studies also suggest that higher doses (e.g., 25 ± 5 mg/70 kg) of psilocybin are generally more effective than lower doses (e.g., 5-10 mg /70 kg) in the context of PAP. For instance, Goodwin et al. used exploratory efficacy endpoint measures to demonstrate a dose-response relationship, wherein the high-dose (25 mg) group experienced improved clinical outcomes compared to the lower dose (10 mg) group, but both PTGs had improved MDD outcomes compared to the control group (1 mg) [28]. The dose-response relationship wed with the sustained improvements in depression could be explained by the occurrence of stronger acute psychedelic experiences at higher doses [19]. Moderate and high doses of psilocybin in PAP can lead to APEs capable of facilitating profound and meaningful introspection and self-realizations, bearing psychological insights and improvements [19, 25, 27]. Psilocybin's capacity to generate these constructive APEs at higher doses (even if the patient had a difficult experience or high DED)[1] can be used alongside established psychotherapy techniques in post-treatment (e.g., CBT) to help patients integrate their psychedelic experiences into quotidian life to improve depression long-term.

It is important to consider the significance of the therapeutic approach employed in PAP and its potential influence on depression treatment outcomes. During dosing sessions, non-directive therapy approaches were used, enabling unique (albeit difficult to quantify) experiences under psilocybin conditions, permitting more individualized patient care in post-treatment settings. Most studies included did not emphasize the importance of the therapeutic framework used during integration and talk therapy sessions. Beyond a brief report of the therapists' role in the trials, the studies largely were limited in their analysis of the impact that the type of psychotherapy used in pre- and post-psilocybin sessions had on depression outcomes. The therapeutic framework used in PAP, however, is important for sustained remission. Sloshower et al. investigated the implementation of acceptance and commitment therapy (ACT) as the therapeutic framework in PAP for MDD and found that ACT approaches can improve clinical outcomes by enhancing psychological flexibility, mindfulness, and acceptance [31]. Therefore, to improve external validity in future studies, a standardized psychotherapy framework should be established (e.g., ACT/CBT/other) and thoroughly explained in the study's methods section.

Though beyond the focus of this paper, psilocybin has a relatively strong drug safety profile with minimal negative side effects on both the user and others [32]. Across dose sizes, the studies reported few adverse drug reactions (ADRs), which largely presented as either mild/transient headaches or increased systolic and diastolic blood pressure. This suggests that patients who have underlying cardiovascular conditions or headache disorders may be at a higher risk of these psilocybin ADRs, however, Carhart-Harris et al. considered them statistically insignificant compared to the placebo conditions and the ADRs generally resolved within five hours [3]. In illicit use contexts, psilocybin (alike other serotonergic drugs) could elevate the risks of people taking SSRIs to experience serotonin toxicity (serotonin syndrome). Malcolm et al. found serotonin syndrome very uncommon for psilocybin (compared to other tryptamine psychedelics), and psilocybin was found to have no remarkable interactions with monoamine oxidase inhibitors (a strong class of antidepressants) [33]. The studies excluded patients taking antidepressants due to potential result biases or drug-drug interactions, however, as PAP becomes more widely studied as an acute MDD treatment with antidepressants (and behavioural therapies) to sustain long-term results, the drug toxicology/interactions must be better understood. Additionally, the trials excluded patients with a predisposition to psychotic disorders for patient safety concerns. Patients with underlying psychotic disorders are typically excluded from such trials due to the risk of exacerbating their symptoms or inducing a psychotic episode. The altered states of consciousness associated with moderate/high-dose psilocybin can involve intense emotional experiences, vivid hallucinations, and changes in sensory perception, which may be overwhelming for individuals with psychotic disorders. Additionally, APEs (specifically distressing experiences such as DED), may be more difficult to manage, interpret and integrate for individuals with pre-existing psychotic disorders. While excluding such patients from PAP trials is a precautionary measure to ensure the safety and well-being of all patients, it restricts the possible research for a particularly high-risk class of people who suffer from depression [34].

It is imperative to acknowledge that, despite the encouraging findings presented in these studies, several limitations must be considered. First and foremost, the sample sizes in the studies reviewed were relatively small, largely ranging from 20 to 59 participants, with only one study having a sample size of 233 patients [28]. This can be problematic for several reasons, such as reduced statistical

[1] For instance, achieving a successful resolution to a conflict (e.g., high DED during APE) can lead to gaining insight and relief, whereas failure to do so can prolong suffering. Rossman et al. explained that high OBN (e.g., mystical experiences) and low DED (e.g., acute anxiety during the APE) predicted long-term, positive clinical outcomes on depression,[19] further supporting the use of high-dose psilocybin in PAP.

power, the potential for selection bias (which may limit the generalizability of the findings to larger populations), and decreased quantifiability of the individualistic responses to each patient in the PTG. Additionally, all of the clinical trials included occurred under controlled settings, which may not accurately represent PAP efficacy among the broader population in practice [35]. The first and second study analyzed in this review compared psilocybin to the antidepressant escitalopram with a 6-week examination period [3, 18]. A potential source of error in this study design is the delayed effects seen with escitalopram (and other antidepressant drugs more broadly). Escitalopram requires 4-6 weeks to achieve its full therapeutic effects, [36] potentially limiting the ability of researchers to make a fair comparison between psilocybin and escitalopram efficacy. The follow-up periods in the studies included were relatively brief, ranging from 2-12 weeks, except for two studies with respective follow-ups at 6 and 12 months. Another potential limitation is the lack of a standardized depression scale designated to measure outcomes in PAP trials. Changes in depression scores were measured principally using four scales (BDI, HAM-D, MADRS, and QIDS), which could be a source of error in this review, for there may be variance/incongruities between scales since they each measure slightly different criteria (see Table 1). There have, however, been several studies that have found strong/very strong correlations and convergent validity between these scales [37-40]. The studies did not explicitly consider confounding factors such as (changes in) lifestyle, diet, and comorbidities during their MDD treatment periods. Henceforth, to enhance the internal and external validity of future investigations, it is recommended to extend the observation periods, augment the sample sizes, intensify control over confounding variables, and establish a standardized depression assessment tool (e.g., MADRS/BDI/other) to evaluate alterations in depression status within the context of psilocybin trials. Finally, the studies all had a high proportion of Caucasian patients (>87% average across studies included). Conducting psychedelic clinical trials mainly on White populations from North America and Western Europe overlooks the potential impact of ethnic, racial, and cultural factors on individual responses to PAP, which hinders the generalizability of findings. Increasing the use of ethnopsychopharmacology in PAP research (the study of how different cultures/societies use and understand psychoactive substances in the context of mental health) can raise awareness of the specific and diverse needs of people from different ethnicities in mental health settings, improving clinical outcomes for racial/ethnic minority groups [41].

Progressing beyond the purview of MDD, compelling evidence has indicated that psilocybin exhibits favourable therapeutic outcomes in various other psychiatric conditions including anxiety, post-traumatic stress disorder, eating disorders, and substance use and concurrent disorders (SUCD), potentially given their overlapping neural circuitry and functional connectivity [42-44]. Depression and substance use disorders are among the most common concurrent psychiatric disorders (odds ratio=3.80), [45] so integrating PAP into the treatment of substance use and concurrent disorders could provide additional positive downstream effects on depression outcomes in people with comorbid substance abuse issues SUCD patients. Thus, the incorporation of PAP into other domains of clinical psychiatric research presents an exciting avenue for future research in the field of psilocybin-assisted therapy and mental health treatment.

Applications of this Systematic Review

This review found that psilocybin-assisted psychotherapy can significantly alleviate symptoms of depression and may be a viable treatment option when administered in a safe and supportive environment with appropriate psychological assistance. This paper synthesized and compared clinical trials, analyzing primary and secondary outcomes of psilocybin-assisted psychotherapy, thereby serving as a valuable reference for those involved in the treatment and rehabilitation of MDD. The importance of high-quality acute psychedelic experiences for optimal results through introspection and self-reflection is also emphasized. Despite its low propensity to cause physical or psychological addiction, [46-47] further research is necessary to comprehend the long-term effects of psilocybin and establish effective protocols for its therapeutic use and research.

Conclusions

In conclusion, this systematic review provides evidence surrounding the efficacy of psilocybin and psilocybin therapy (PAP) for the treatment of MDD. The studies included in the review suggest that psilocybin is associated with clinically meaningful reductions in depression scores, and that higher doses were largely more effective than lower doses. The findings also suggest that psilocybin-induced acute psychedelic experiences may be associated with improved long-term, positive clinical outcomes on depression. A dose-effect relationship was observed, minimal adverse drug reactions were reported, and there were statistically significant decreases in depression scores on validated scales. Therefore, psilocybin and psilocybin-assisted psychotherapy should be further investigated as a novel approach to mitigating the devastating impacts of major depressive disorder. As the prevalence of depression and accessibility of life-ending measures from mental illnesses continues to increase, there is a need for effective and innovative approaches to treat depression. With promising results from recent studies, further research on psilocybin could be revolutionary for the field of clinical psychology and psychiatry.

List of Abbreviations Used
ACT: acceptance and commitment therapy
ADR: adverse drug reaction
APE: acute psychedelic experience
CBT: cognitive behavioural therapy
DED: dread of ego dissolution
DMN: default mode network
DSM: Diagnostic and Statistical Manual of Mental Disorders
MDD: major depressive disorder
OBN: oceanic boundlessness
PAP: psilocybin-assisted psychotherapy
PRISMA: preferred reporting items for systematic reviews and meta-analyses
PTG: psilocybin treatment group
RCT: randomized controlled trial
SSRI: selective serotonin reuptake inhibitor
SUCD: substance use and concurrent disorder

Conflicts of Interest
The author declares no conflicts of interest.

Ethics Approval and/or Participant Consent
This paper is a systematic review, therefore no ethics approval was required.

Authors' Contributions
KV: was the sole and principal author of this review, including the design and research of the work, drafting, and finalizing the manuscript, collection/analysis of the data, and final approval of publication.

Acknowledgements
I would like to express my gratitude to Ms. Jane Kim from the University of British Columbia for her mentorship with the URNCST initiative. Further, I would like to convey my appreciation for the valuable counsel I received from Dr. Ron Saulnier from the University of Ottawa, as well as Mr. Ricky Chow from York University. Lastly, I would like to acknowledge the URNCST Journal Administration and Editors and thank them for the opportunity to publish my work.

Funding
This paper received no funding.

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Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Jane Kim, Ricky Chow
Article Dates: Received Apr 10 23; Accepted May 26 23; Published Jul 19 23

Citation
Please cite this article as follows:
Venugopal KL. Psilocybin therapy for major depressive disorder: A systematic review. URNCST Journal. 2023 Jul 19: 7(7). https://urncst.com/index.php/urncst/article/view/489
DOI Link: https://doi.org/10.26685/urncst.489