EMERGING MINDS
JOURNAL FOR STUDENT RESEARCH

ISSN 2976-9094
EMJSR 2026, Vol 4:MH1-MH13
https://doi.org/10.59973/emjsr.317

Received: 2026-01-08
Accepted: 2026-01-15
Published: 2026-01-25

The Evaluation of the Efficacy and Safety of the Use of Psilocybin in the Treatment of Adults with Treatment-Resistant Depression

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Abstract - Treatment-resistant depression (TRD) has been well-researched within scientific literature, although the therapeutic value of psilocybin is not fully understood. The aim of this systematic review is to determine a stable and effective dosage unit to inform health professionals of the benefits of psilocybin, using peer-reviewed literature and meta-analysis. The review will also compare selective serotonin reuptake inhibitors (SSRIs) with psychotherapy to draw conclusions and recommendations of psilocybin therapy to improve day-to-day living for affected patients. PubMed and the University of Portsmouth Discovery online database (EBSCOhost) were individually utilized from December 2024 to March 2025. Five open-label studies and 2 randomized controlled trials (RCTs) were selected to assess psilocybin efficacy and safety. Appraisal checklists along with search criteria were used to determine eligibility and reliability of these data. The random-effects meta-analyses demonstrated that psilocybin at 25 mg within specific integrated sessions was effective at treating TRD compared to 10 mg and 1 mg by comparing clinical trials between two doses and single doses. Psilocybin at 25 mg was found to significantly reduce patients' depressive severity compared to the baseline, which was prevalent in the two-dose studies (n = 5) compared to the single-dose studies (n = 2), due to the number of studies produced. The overall evidence suggests that psilocybin is an effective therapeutic for treatment-resistant depression, with a dosage unit of 25 mg administered as a single capsule per dosing session, with one dose per clinical session. Limitations to the evidence and this review have affected the overall results; therefore, more relevant studies are needed.

Keywords - Treatment-resistant depression; Psilocybin; Major Depressive Disorder.

1 Introduction

Depression is a common mental disorder characterized by persistently low mood that interferes with daily life, with over 300 million people suffering globally [1]. Depression is influenced by gender, age, family history, a history of depression or other mental health conditions, as well as personal, social, and environmental influences. These factors cause mild, moderate, and severe symptoms. The NHS classifies these symptoms into three categories: psychological, physical, and social [2]. Psychological symptoms include persistent emotions of despair, guilt, and worry, which can lead to suicidal thoughts; physical symptoms include delayed speech, mobility, disrupted sleep, and self-harm or

suicide; and depression's social symptoms include failing to pursue hobbies and avoiding or having difficulty communicating with friends and relatives. Depression is treated depending on the type of patient and the severity of their symptoms, using selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and/or psychotherapy. However, some patients do not respond to these interventions and have an increase in their depressive symptoms. This is called treatment-resistant depression (TRD).

TRD is diagnosed in patients when they have an inadequate response to an average of two antidepressants at adequate dosages for at least 6 to 8 weeks [3,4]. TRD patients experience the same symptoms as major depressive patients (MDD), with 30% being diagnosed with TRD and having more severe symptoms, longer depressive episodes, anhedonia, suicidal ideation, or suicide [4]. The causes of TRD are unknown, but are similar to depression, both having many contributing factors. Repetitive transcranial magnetic stimulation (TMS), second-generation antipsychotics, intravenous ketamine, and intranasal esketamine administered alongside an antidepressant have been approved by the Food and Drug administration (FDA) for therapeutic use [5].

SSRIs work as antagonists, boosting serotonin and norepinephrine levels while blocking 5 - hydroxytryptamine receptors (5HT-2) and alpha-1 adrenergic receptor (α1-ARs) activation. 5HT-2 receptors are excitatory serotonin receptors that increase fear and anxiety, but they are blocked by the absorption of SSRIs, which increases the amount of serotonin and relaxes the muscles in the body by concurrently blocking the excitatory α1-ARs [6]. SSRIs have been shown to be more effective and cause fewer side effects than tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) [7,8].

Researchers hypothesize that chronic stress may contribute to TRD by changing the function of the hypothalamus-pituitary-adrenal axis (HPA) [9]; this is the primary stress response system, consisting of a feedback loop between the brain, pituitary, and adrenal glands [10,11]. When HPA is activated by environmental or physical stress, the hypothalamus secretes corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) on the pituitary gland, which increases the release of the adrenocorticotropic hormone (ACTH); this travels via the bloodstream and attaches to receptors on adrenocortical cells, stimulating cortisol synthesis [12]. This equilibrium is maintained through negative feedback, in which receptors in the hypothalamus and hippocampus regulate cortisol levels and instruct the hypothalamus to stop producing CRH [12]. Studies investigating the relationship between the HPA axis and depression have found a direct correlation between depression and increased cortisol production, resulting in a reduced cortisol awakening response (CAR) [13]. Chronic stress can raise cortisol levels, leading to poorer outcomes in MDD, which can progress to TRD [13]. SSRIs, such as escitalopram, can stabilize the HPA axis and steepen cortisol gradients in MDD patients [14]. Psychotherapies such as cognitive behavioral therapy can also modulate the HPA axis by developing human connections and releasing burdened emotions [15]. Due to the biomarkers previously described, SSRIs are not fully effective in TRD patients meaning that the HPA axis in TRD patients is dysregulated and results in an increase in chronic stress and therefore more severe symptoms. However, there has been research into the use of psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine), which may be effective in treating TRD and can help lower severe depressive symptoms [3-15].

Psilocybin is a hallucinogenic chemical found in gilled mushrooms, or popularly known as magic mushrooms, that when ingested, absorbs rapidly due to its 3-hour half-life [16]. Psilocybin, having a similar molecular structure to serotonin (Fig. 1), can alter mood, perceptions, and thoughts to increase happiness within recipients [16]. The genus Psilocybe, a member of the Hymenogastraceae family, is responsible for the hallucinogenic effects [17]. Well-known species include Psilocybe azurescens, Psilocybe semilanceata, and Psilocybe cyanescens [17,18].

Psilocybin is classified as a class A substance under the UK's Misuse of Drugs Act 1971, due to its significant potential for abuse [19]. Despite this, psilocybin is one of the safest recreational drugs, with few hospital admissions and no withdrawal symptoms when used in illegal recreational settings [20]. When psilocybin is heavily misused, it can cause toxicity and symptoms such as disorientation, hallucinations, paranoia, and muscle weakness [21]. To maximize the benefits of psilocybin therapy,

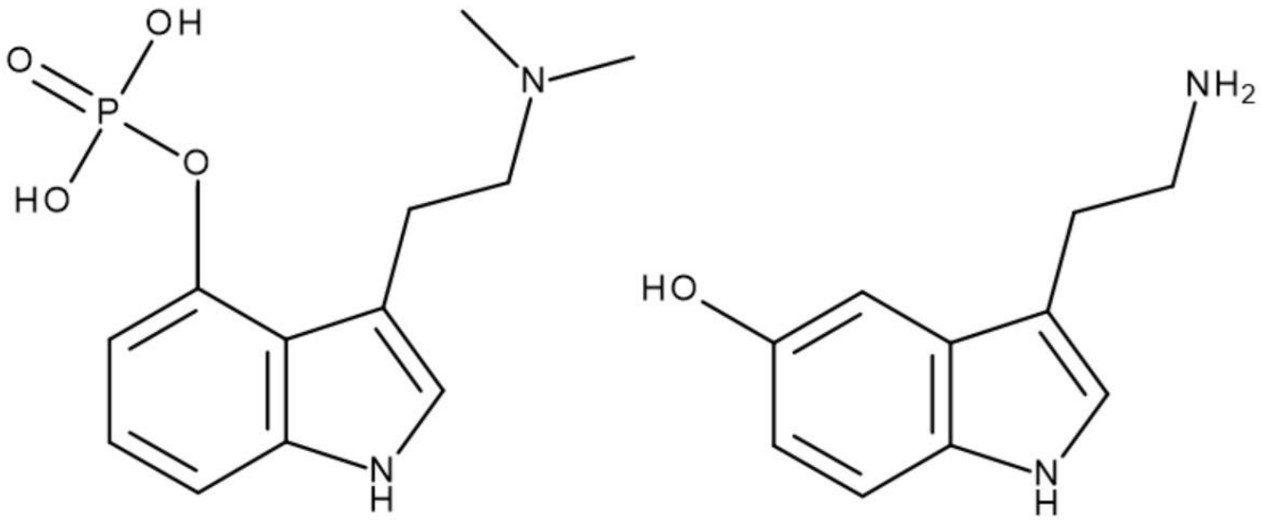

Figure 1: Chemical structures of psilocybin (left) and serotonin (right).

researchers experimented with the psychedelic to discover the safest and most effective dosage while avoiding significant adverse effects.

Recent randomised control trials (RCTs) have shown that high doses of capsulated psilocybin are effective in reducing TRD symptoms, as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale (HDRS) [22]. Severe adverse effects, including suicidal thoughts and self-injury, were observed at higher dosages, whereas milder effects, such as headaches and nausea, were more common. Patients having a history of suicide ideation and self-harm were more likely to encounter stronger side effects compared to those without a history. Research suggests that combining psilocybin with antidepressants can reduce or negate the severity of the effects due to patient familiarity and reaction to existing medication [22]. Nonetheless, psilocybin's effectiveness depends on patient perspectives and experiences. Breeksema et al. (2024) found that a supportive environment, clear expectations, and extensive treatment are necessary for patients to completely benefit from the therapy [1]. Since psilocybin is a hallucinogenic drug, it should be administered in a controlled setting with health professionals, such as in a hospital. However, due to limitations described above, this can be challenging and demotivating for patients to receive the treatment.

Alongside research into the effects of psilocybin in TRD, psychotherapy has also been researched to identify which type of psychotherapies are congruent and effective with psilocybin. One study explored the effects of psychotherapy and the importance of the sessions being able to facilitate emotional processing, supportive change, and acceptance in both the patients and the relationships around them [23]. Cognitive behavioral therapy (CBT) is commonly used for depressive patients. It is a time-limited and structured-based approach that is determined by the patient's behavior and their cognitions [23]. The sessions are designed to help the patient identify, analyze, and change their thoughts, behavior and negative thinking patterns. Interpersonal psychotherapy (IPT) incorporates elements of various psychotherapies to improve social support and emotional processing while minimizing interpersonal stress [23]. Intensive short-term dynamic psychotherapy (ISTDP), as CBT and IPT, employs psychoanalysis to identify and address the patient's defensive response, which can lead to an increase in depressive symptoms [23]. The sessions themselves assist the patient in reducing anxiety, developing insight into repressed emotions and attachments, unraveling maladaptive coping mechanisms, and changing their behavior.

Psychotherapy is necessary while TRD patients are being treated with psilocybin, since the psychedelic can invoke emotions that are trauma-centered that intensify their environment and sensory experiences.

Although clinical evidence suggests that psilocybin can be a viable therapy option for TRD, there are numerous gaps in the existing knowledge that must be addressed. Markers such as side effects, concurrent administration of psilocybin with antidepressants or psychotherapy, and an established effective dosage must be investigated to educate health professionals and the public about psilocybin's full potential. This systematic review will assess the full efficacy of psilocybin using escitalopram as an example SSRI and compare two types of psychotherapy to determine the most successful and safest treatment approach.

The hypotheses in this work are:

- Null Hypothesis: There is no evidence that psilocybin can be used to treat TRD effectively.
- Alternative Hypothesis: There is clear evidence that psilocybin can be used to treat TRD effectively.

This study aims to evaluate the safety and efficacy of psilocybin for treating TRD in adults and update the existing literature to push for more clinical trials and legality in the UK. This will be achieved with the following objectives, to: (a) systematically review peer-reviewed literature through eligibility protocol, inclusion and exclusion criteria and search methods; (b) use an appropriate statistical and analytical software tool to meta-analyze these data and evaluate the results; (c) use databases to critically analyze relevant and specific studies to establish a full consensus of the effectiveness of psilocybin.

2 Methods

The systematic review was conducted through the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. The PICO (Population, Intervention, Comparison, Outcome) framework [25] was applied to ensure precise search results and provide high-quality peer-reviewed evidence to specify the research question (Table 1).

Table 1: The four components of the PICO framework used in this study.

Population	Intervention	Comparison	Outcome
Adult patients with TRD	Treatment with psilocybin	Psychotherapy vs SSRIs	Treatment of TRD and improvement in day-to-day life for patients

Open-label studies and RCTs were included and found through electronic databases (PubMed and the University of Portsmouth Discovery online database, EBSCOhost). The search terms included psilocybin, treatment-resistant depression and clinical trials using the added Boolean operators and filters (Table 2).

Table 2: Search strategy for psilocybin in treatment-resistant depression.

Key Word Search
'psilocybin' AND 'Treatment-resistant depress*' OR 'Treatment resistant depress*' OR 'TRD'
'psilocybin' AND 'Treatment-resistant depress* OR 'Treatment resistant depress* AND TRD' AND 'clinical trials*'
'Psilocybin' AND ('treatment resistant depression or TRD') NOT (major depressive disorder OR MDD OR major depression*) AND ('clinical trials OR clinical research OR clinical study')

The screening of the studies was performed using various inclusion and exclusion criteria (Table 3). The filters used were the same for each database; these were: peer-reviewed journal articles, past

8 years, source: academic journals, and papers written in English. Relevant studies included adult patients who only suffered from TRD regardless of ethnicity, sex and gender. Excluded studies contained individuals who were not diagnosed with TRD and were below the age of 18 years old. Individuals in clinical trials who have undergone the following psilocybin administration as comparators against each other: psilocybin at 1, 10 or 25 mg per dose at a time within specified sessions. Two trials with patients receiving psilocybin at 25 mg alongside escitalopram were recorded. Outcomes were extracted from studies that reached a viable conclusion on the exact dosage of psilocybin regarding side effects and population.

Table 3: Inclusion and exclusion criteria.

Inclusion	Exclusion
Published in English from 2016 to the present – to maintain relevance in up-to-date research	Articles that were not published in English and were prior to 2016
Adult patients who solely suffered from TRD	Studies that were systematic reviews, meta-analyses, non-peer-reviewed, and contained animal studies
Study types: qualitative studies, clinical trials (RCTs and open-label studies), and peer-reviewed literature	Non-adult patients who did not solely suffer from TRD
Full-text articles only that were academic journals	Non-academic journals and journals that only included the abstract

3 Results

3.1 Data extraction

The search from two databases (PubMed and EBSCOhost) yielded 489 articles (base value). There were no duplicates, but from the 489 articles that were screened, 476 were excluded based on the title and abstract. This led to 14 studies that were subjected to the final screening step by full-text reading. A further 7 studies were excluded as they contained systematic reviews and therefore did not meet the eligibility criteria. From this, the total number of articles that passed the full screening was 7 (Fig. 2).

3.2 Study characteristics

A total of 377 participants were included in the studies (Table 4). The female percentage was recorded as the male participation was generally lower. In most cases, the patients experienced moderate to severe symptoms of TRD. All dose values (1 mg, 10 mg, 25 mg) denote milligrams per dosing session, with one capsule administered per clinical session, rather than a daily dose. Two of the 7 relevant studies investigated single doses, including a comparison of 1 mg as a control from Goodwin et al. (2022), while the remaining 5 investigations employed 2 doses of psilocybin within tailored sessions. All the studies included classical music to help participants relax while receiving the prescribed psilocybin dose. The integration sessions were also the same, with each trial involving a lead therapist who prepared the participants for the session and an assisting therapist in case the lead therapist needed further assistance or had to leave the session. A trial psychiatrist was also present for consultation, and at the conclusion of the session, an interview with the lead therapist was held to encourage patients to reflect on their sessions and report any issues. The detailed characteristics of the studies are shown in Tables 5 and 6.

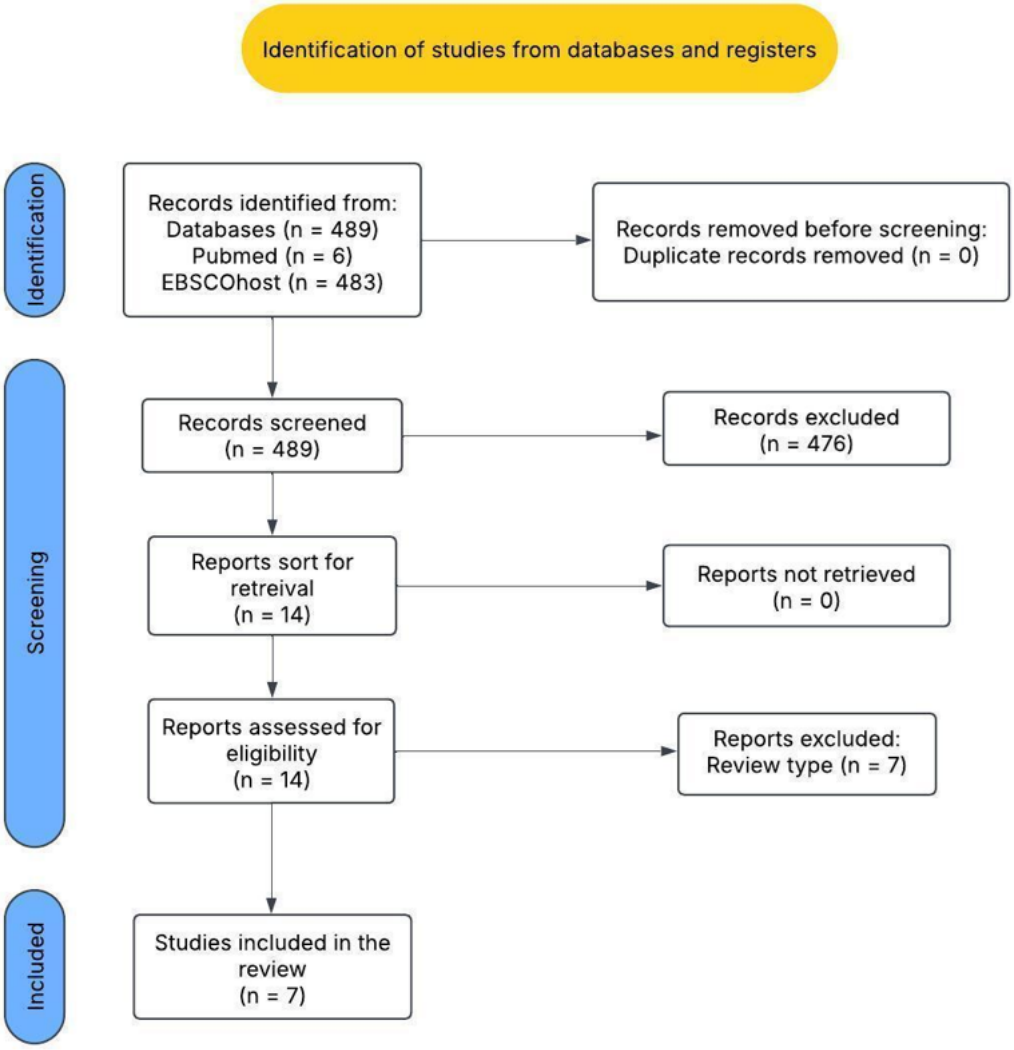

Figure 2: Identification and screening of studies through the PRISMA flow diagram.

Table 4: Summary of the demographics and characteristics from all the included studies. *MDD = Major Depressive Disorder, TRD = Treatment Resistant Depression, BDI = Beck Depression Inventory, HAMD = Hamilton Rating Scale for Depression, MADRS = Montgomery-Åsberg Depression Rating Scale, QIDS = Quick Inventory of Depressive Symptomatology, DS = Standard Deviation.*

Article	Sample Size (n)	% Female	Age, Mean (DS)	Severity of Diagnosis
Carhart-Harris et al., 2016 [26]	12	50	42.6 (10.2)	TRD: moderate-severe, HAMD = 19.2
Carhart-Harris et al., 2017 [27]	19	21	42.8 (10.1)	TRD: severe, QIDS = 18.9
Carhart-Harris et al., 2018 [28]	20	30	44.1 (11)	TRD: severe, BDI = 34.5
Lyons and Carhart-Harris, 2018 [29]	15	27	45.4 (2.9)	TRD: moderate-severe, BDI = 34.3
Carhart-Harris et al., 2021[30]	59	34	41.2	MDD: moderate-severe, BDI = 29.1
Goodwin et al., 2022 [31]	233	52	39.8 (12.2)	MDD/TRD: moderate (30%), severe (68%)
Goodwin et al., 2023 [23]	19	58	42.2 (10.8)	TRD: moderate. MADRS = 31.7

Table 5: Summary of the characteristics of the studies where single-dose psilocybin were used. *MADRS = Montgomery-Åsberg Depression Rating Scale, QIDS = Quick Inventory of Depressive Symptomatology.*

Article	Study design	Treatment	Psilocybin dosage / mg	Control (dosage) / mg	Scale	Effects
Goodwin et al., 2022 [31]	RCT	3 preparatory meetings: One with 1 dose of psilocybin and music. Two psychological integrated sessions.	10 or 25	1	MADRS	3 weeks after treatment: First group (25 mg): mean MADRS score decreased by 12 points. Second group (10 mg): 7.9 points. Third group (1 mg): 5.4 points.
Goodwin et al., 2023 [23]	Open-label	3 preparatory meetings: A single session with 1 dose of psilocybin and music. Two integrated sessions.	25	-	MADRS, QIDS	3 weeks after treatment: Mean MADRS scores decreased by 14.9 points.

3.3 Assessment of each study

The critical appraisal skills program (CASP) systematic review checklist [32] was utilized to assess the quality of the peer-reviewed literature. A general systematic review checklist was chosen because the data came from various types of studies, so therefore, the questions asked within the checklist were accurate and appropriate. All the studies passed the checklist and were eligible to be included in the meta-analysis.

3.4 Single-dose psilocybin effects on depressive symptoms

In the double-blind dose-finding parallel-group randomized trial, Goodwin et al. (2022) divided the subjects with MDD into three groups: the first group (n = 79, 56% female, mean age: 40.2 ± 12.2) received a 25 mg dose of psilocybin; the second group (n = 75, 55% female, mean age: 40.6 ± 12.8) received a 10 mg dose; and the third group (n = 79, 46% female, mean age: 38.7 ± 11.7), which acted as a placebo, received a 1 mg dose of psilocybin. Three weeks following the intervention, the first group (25 mg), the second group (10 mg), and the third group (1 mg) all showed decreases of 12 points, 7.9 points, and 5.4 points from baseline on the MADRS scale. When comparing the first and third groups after treatment, the mean difference was statistically significant (mean difference: -6.6, 95% CI [-10.2; -2.9], $p < 0.001$), but not the second and third groups (mean difference: -2.5; 95% CI [-6.2; 1.2], $p = 0.18$). A follow-up open-label fixed-dose exploratory trial was carried out by the same research group on 19 TRD patients who were already on SSRIs in addition to a single 25 mg dosage of psilocybin. Three weeks following treatment, the MADRS showed a decrease of 14.9 points (95% CI [-20.7; -9.2]). Additionally, the degree of the patients' depression symptoms improved two days after therapy and continued to do so for the duration of the three-week follow-up.

Table 6: Summary of the characteristics of the studies where two-doses of psilocybin were used. Treatment A = 4 h of preparatory sessions. 2 doses of psilocybin with music and 2 integration sessions, all 1 week apart. *BDI = Beck Depression Inventory, HAMD = Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, QIDS = Quick Inventory of Depressive Symptomatology.*

Article	Study design	Treatment	Psilocybin dosage / mg	Second psilocybin dosage / mg	Control (dosage) / mg	Scale	Effects
Carhart-Harris et al., 2016 [26]	Open-label	Treatment A	10	25	-	QIDS, BDI, HAMD, MADRS	1 week after treatment: QIDS score decreased compared to the baseline (-11.8). 3-month follow up showed a decrease in mean QIDS scores (-9.2).
Carhart-Harris et al., 2017 [27]	Open-label	Treatment A	10	25	-	QIDS	5 weeks after treatment: QIDS score decreased compared to the baseline (-8.0).
Carhart-Harris et al., 2018 [28]	Open-label	4 h of preparatory sessions. 2 doses of psilocybin with music 1 week apart. Integrative sessions were applied after each dose.	10	25	-	QIDS, BDI, HAMD	1, 2, 3, 5 weeks and 5 months after treatment: QIDS score decreased compared to the baseline. BDIs scores significantly decreased compared to baseline at 1 week, 3 months and 6 months after treatment.
Lyons and Carhart-Harris, 2018 [29]	Open-label	Treatment A	10	25	-	BDI, HAMD	1 week after treatment: Decrease in BDI scores (-22.2) compared to baseline.
Carhart-Harris et al., 2021[30]	RCT	3 h of preparation sessions. 3 weeks apart: 2 doses of psilocybin and escitalopram.	25	25	1	QIDS, BDI, HAMD, MADRS	Escitalopram group: Mean QIDS change score was -6.0 at 6 weeks. Psilocybin group: -8.0 QIDS change score.

3.5 Two-dose psilocybin effects on depressive symptoms

Carhart-Harris et al. (2016) conducted an open-label feasibility trial with 12 patients with moderate-to-severe TRD, administering two oral psilocybin dosages (10 and 25 mg) seven days apart. Psilocybin

therapy significantly reduced depressive symptoms at one week compared to baseline (mean difference: -11.8, 95% CI [-14.35; -9.15], g = 3.1, $p < 0.01$). Even after a 3-month follow-up, patients' clinical conditions improved significantly (mean difference: -9.2, 95% CI [-12.71;- 5.69], g = 2, $p < 0.01$). Using the same intervention modalities as previously described and collecting self-reported clinical findings, the same research team conducted a second pre-post neuro-imaging study on 19 patients with TRD. When compared to baseline, they demonstrated that the administration of two psilocybin dosages effectively decreased the intensity of patients' depressed symptoms five weeks following therapy (mean difference: -8, t = -6.3, $p < 0.001$). In a third open-label single-arm trial, Carhart-Harris et al. (2018) recruited 20 TRD patients who were given two psilocybin doses (10 mg and 25 mg), separated by seven days. Here, baseline, one week, two weeks, three weeks, and five weeks following treatment, as well as at the three- and six-month follow-up, were used to determine the severity of depressive symptoms. At all time-points, QIDS scores showed a substantial decline from baseline, with the largest impact size occurring at 5 weeks (t = -7.2, $p < 0.001$, d = 2.3). Additionally, all 19 of the patients who finished the follow-up showed a decrease in the severity of their depression after the first week, and for most of them, this clinical improvement lasted for 3 to 5 weeks.

Lyons and Carhart-Harris (2018) conducted a second open-label pilot study with 15 participants with TRD. They were given two dosing sessions: a safety dose (10 mg) and a treatment dose (25 mg) one week later. One week after psilocybin treatment, clinical patients' BDI scores dropped significantly compared to baseline (t = 7.9, 95% CI [16.17; 28.23], $p < 0.001$, g = 1.9). In contrast to the previous research, Carhart-Harris et al. (2021) recruited 59 people with moderate-to-severe MDD in a double-blind randomized controlled trial. Participants were split into two separate groups: the active control group (n = 29, 31% female, mean age: 41.2 ± 11.7) received two placebo doses, also three weeks apart, but with daily escitalopram, while the treatment group (n = 30, 30% female, mean age: 43.3 ± 9.7) received two 25 mg doses of psilocybin, three weeks apart, along with a daily placebo for six weeks. The treatment group's mean QIDS scores decreased from baseline by 8 points and the active control groups by 6 points six weeks after the intervention. This resulted in a non-statistically significant 2-point (95% CI [-5.0; 0.9]) between-group difference.

3.6 Comparison of single-dose and double-dose on depressive symptoms

The random-effects meta-analysis through the forest plot (Fig. 3) and funnel plot (Fig. 4) shows that psilocybin considerably reduces TRD patients' depression symptoms when compared to the baseline. Despite the two-dose psilocybin treatment had a larger effect, the effects were observed in both cases. However, because of a sampling error and impact size variability and distribution, the total heterogeneity was high. The funnel plot showed signs of asymmetry and outliers due to the large number of studies conducted; however, the asymmetry was not statistically significant.

3.7 Side effects of single-dose and two-dose psilocybin administration

Tests for the subgroup analysis and difference in the side effects of psilocybin could not be conducted through a random-effects meta-analysis due to the low number of studies found; therefore, the analysis was evaluated manually.

Carhart-Harris et al. (2016) found no significant side effects among patients receiving psilocybin at 10 and 25 mg, with common minor effects such as headaches and nausea appearing one day after the psilocybin session and passing within 1-2 days [26]. Mild and transient paranoia was reported in one patient during the administration of 10 mg psilocybin, and the researchers hypothesized that this could be attributable to either the trial's withdrawal of antidepressants or low-level therapist contact between dosage sessions. Carhart-Harris et al. (2018) conducted a 6-month follow-up and found the same effects [28]. One patient became uncommunicative during the 25 mg dosing period but was stabilized after the drug effects decreased. This was due to the patient's overwhelming emotions despite their experience being regarded as 'blissful.' Carhart-Harris et al. (2021) reported another experiment that compared escitalopram and psilocybin [30]. Similarly to the previous research, no serious adverse effects were recorded in the 1 mg and 25 mg groups. Within 24 hours of the

dosage, 83-87% of participants had adverse responses, with 83% of patients taking oral escitalopram experiencing increased anxiety and dry mouth. The study concluded that psilocybin was favorable over escitalopram, but the low duration of the escitalopram treatment hindered the results and could have had a better outcome if the treatment was extended.

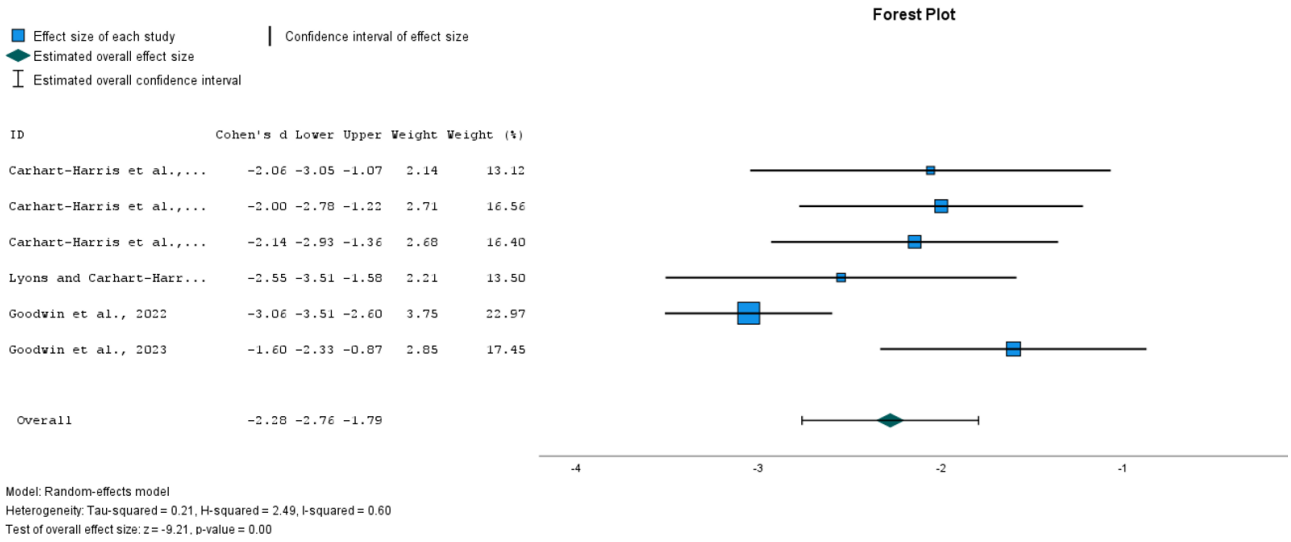

Figure 3: Forest plot of the studies with heterogeneity, confidence interval, and effect size. *Abbreviations: SD = Standard Deviation, SMD = Standardized Mean Difference, 95% CI = 95% Confidence Interval.*

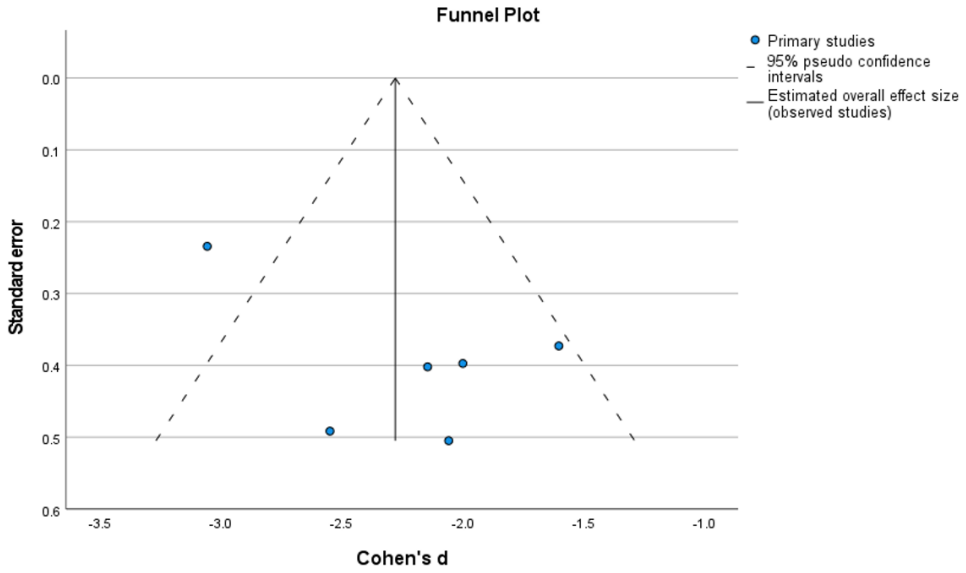

Figure 4: Funnel plot of the studies with the effect size and pseudo confidence intervals.

Goodwin et al. (2022) reported adverse effects in the 25, 10 and 1 mg in the single-dose psilocybin trial [31]. The adverse reactions were higher in the 25 mg group (84%) after 1 day, but from day 2 to week 3, severe adverse effects such as suicidal ideation and self-harm were observed in the same group (9%), and after weeks 3-12, 3% of the 25 mg group experienced these severe effects again, including symptoms of anxiety and depression. All the patients who produced these severe reactions had a history of suicidal behavior and self-injury, and the psilocybin seemed to either increase or bring back these behaviors.

3.8 Psychotherapy

Psychotherapy is necessary for TRD patients as a supportive measure. Crowe et al. (2023) summarized that IPT and ISTDP aligned with psilocybin therapy as it reflects and supports patients' experiences with psilocybin [23]. In all the clinical trials mentioned, general psychotherapy was used, but there

were some limitations that the participants raised in the questionnaire by Breeksema et al. (2024) [1]. The general themes were mistrust in the healthcare system, due to negative previous experiences; limited psilocybin sessions that prevented familiarization and efficacy; trust in onsite therapists, as there was a lack of genuine connection which felt forced at times; and limited preparation time before the integrative sessions, which made the participants feel rushed and pressured to produce results. A unique concern that was frequently brought up was the choice in music that all the participants received. Classical music was used in all the trials, but some patients felt that they were in a 'graveyard' due to the heavy music, whilst other patients enjoyed the music because it made them feel calm and relaxed.

4 Discussion

The purpose of this systematic review was to summarize, assess, and compare the current evidence on the therapeutic effects of single and two-dose psilocybin administration in TRD patients. The seven studies demonstrated psilocybin's significant efficacy in the treatment of TRD. Both single and two-dose treatments were beneficial in lowering the severity of depression symptoms when compared to the baseline. Integrated psychotherapy sessions lowered TRD patients' mild and severe adverse reactions. Therefore, the current evidence does support the alternative hypothesis but has some limitations that affected the results.

4.1 Limitations and recommendations

The main limitation identified in the literature was the sample size, which did not allow for clearer conclusions and comparisons, affecting the overall validity of the investigations. The population margins were not equal, with the female participants producing more data than male participants. The authors classified 5 open-label studies as having a moderate risk of bias, highlighting the lack of RCTs in the research topic and current literature. There was insufficient evidence on the side effects of psilocybin, which did not reflect the consensus of the studies, and only one publication explored psilocybin-assisted psychotherapy.

In terms of psilocybin dosage, 25 mg appears to be the most appropriate dose, but due to the lack of reporting described above, the question remains as to whether it is safe to use long term, as well as comparisons of single and two-dose psilocybin therapeutics to evolve current clinical trials. Furthermore, studies evaluating the effect of SSRIs on psilocybin are sparse, with just one specific antidepressant compared and found in the literature. Along with additional study, SNRIs must also be evaluated and compared to reach an accurate conclusion.

Music therapy should also be researched so that patients can reap the full benefits of the treatment. Although it is impossible to customize music to each individual participant in terms of the future sample size, developing questionnaires and interviewing patients following clinical trials may assist researchers in establishing a trend and improving future integrative sessions. In both the integrative and integrated sessions, IPT and ISTDP should be applied or trialled and then compared to general psychotherapy to determine which is more beneficial with psilocybin. Following the overall theme, additional study into psychotherapy is needed, as TRD patients require support and a care system. Therefore, further research and clinical trials are necessary to fully evaluate the efficacy and safety of psilocybin in TRD so that it can be used in the UK in the future or at least create a discussion within parliament to inform the general public of the options available and the evidence.

5 Conclusions

The findings of the clinical studies analyzed in this systematic review and meta-analysis emphasize the efficacy of psilocybin in the treatment of TRD patients, establishing psilocybin as a viable therapy option. Both single and two-dose psilocybin treatment significantly reduced the intensity of depression symptoms when compared to the baseline. However, further clinical trials, systematic reviews, and meta-analyses are needed to advance this research subject.

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