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PSILOCYBIN AND IMMUNOMODULATION IN MAJOR DEPRESSIVE DISORDER: SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Major depressive disorder (MDD) is a leading cause of disability worldwide. Conventional antidepressants often fail in treatment-resistant cases, and emerging evidence suggests psilocybin-assisted therapy may offer substantial antidepressant effects, possibly via immunomodulatory mechanisms.

Methods: This systematic review and meta-analysis followed PRISMA 2020 standards. Randomized controlled trials (RCTs), controlled clinical trials, and observational studies published between 2016 and 2024 were identified through searches in PubMed, Scopus, and Cochrane. Outcomes evaluated included validated depression scales (MADRS, QIDS, HDRS), response (≥50% symptom reduction), remission rates, and biomarkers related to inflammation and neuroplasticity. Risk of bias was assessed with RoB-2, ROBINS-I, and SYRCLE tools; GRADEpro was used to assess certainty of evidence. Meta-analysis pooled data from five RCTs with homogeneous outcomes.

Results: Psilocybin therapy was associated with a large reduction in continuous depression scores (SMD = −2.08; 95% CI −3.47 to −0.68) and roughly threefold higher odds of response compared with control (OR = 3.10; 95% CI 1.88 to 5.12; $I^2 = 0\%$ for response outcomes). Continuous outcome heterogeneity was high ($I^2 = 95\%$), likely due to variations in depression scales, dosing protocols, and psychological support intensity. Biomarker data (e.g., reductions in IL-6, TNF-α, CRP; increases in BDNF) provided preliminary evidence of immunomodulation. Certainty of evidence was rated moderate for response outcomes and low for continuous change due to inconsistency and imprecision.

Conclusion: This review supports psilocybin-assisted therapy as a promising intervention for MDD, with both clinical and immunological effects, especially among treatment-resistant populations. Future large-scale, multisite RCTs with standardized protocols, active comparators, longer follow-ups, and greater biomarker sampling are needed to clarify mechanisms and long-term safety.

Keywords: psilocybin; major depressive disorder; immunomodulation; randomized controlled trials; biomarkers; treatment-resistant depression.

INTRODUCTION

Major depressive disorder (MDD) is among the leading causes of disability worldwide, affecting more than 280 million people and contributing significantly to global disease burden. Conventional antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are first-line treatments, but up to 30% of patients develop treatment-resistant depression (TRD), experiencing inadequate symptom relief and impaired functioning despite multiple medication trials [1]. The limited efficacy, delayed onset of action, and adverse effect burden of standard therapies have prompted investigation into novel approaches, including psychedelic-assisted interventions.

Recent international research highlights psilocybin-assisted therapy as a promising rapid-acting intervention. A 2024 BMJ meta-analysis concluded that psilocybin significantly improves depressive symptoms with an acceptable tolerability profile [2]. Similarly, a large-scale systematic review and meta-analysis published in *Frontiers in Psychiatry* confirmed that psilocybin produces large effect sizes and sustained improvements in MDD and TRD populations [3]. Beyond symptom relief, neuroimaging studies have shown that psilocybin enhances global brain network integration, potentially reversing pathological hyperconnectivity patterns seen in depression [4].

Emerging work has also explored psychological mechanisms. A 2024 placebo-controlled trial reported that gains in psychological flexibility mediated the relationship between psilocybin use and symptom improvement, suggesting that enhanced emotional processing may be a key therapeutic pathway [5]. Meanwhile, meta-research has identified that control-arm responses in psilocybin trials are often lower than those in SSRI or esketamine studies, raising questions about expectancy effects and the importance of blinding and comparator design [6].

On the local front, while controlled psilocybin trials are still rare in Pakistan, recent reviews have emphasized the urgent need for culturally tailored, evidence-based mental health innovations to address rising rates of depression, especially among youth and post-trauma populations. Feasibility studies on integrative psychotherapies suggest a readiness to explore novel biological-psychological interventions within tertiary care systems in South Asia.

Despite encouraging findings, several gaps remain. Most studies focus primarily on symptom reduction and short-term outcomes, with fewer evaluating biological mechanisms such as immune and inflammatory biomarkers (e.g., IL-6, TNF-α, CRP) or neurotrophic factors like BDNF. Given growing evidence that systemic inflammation may mediate treatment resistance, understanding psilocybin's immunomodulatory effects could clarify its therapeutic potential.

Therefore, the present systematic review and meta-analysis aimed to (1) synthesize current clinical evidence on psilocybin-assisted therapy in MDD/TRD, (2) explore reported immunological and neuroplastic outcomes, and (3) assess safety, quality of evidence, and research gaps to guide future clinical trials.

2. MATERIAL AND METHODS

2.1 Protocol and Registration

This systematic review and meta-analysis was performed under the Cochrane Collaboration Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines. Registration was conducted prospectively in the International Prospective Register of Systematic Reviews (PROSPERO)

2.2 Search strategy

We systematically searched Pubmed, Scopus and Cochrane Central Register of Controlled Trials with the search strategy combined MeSH terms and free-text keywords, including *"psilocybin," "psychedelic therapy," "major depressive disorder," "treatment-resistant depression," "randomized controlled trial,"* and *"clinical trial."* Boolean operators (AND, OR) were applied to maximize retrieval. Our group manually analyzed the references from all included studies for additional ones. All articles in the databases that met the criteria and their respective references were incorporated into Endnote. Duplicate articles were removed. Two authors (M.K and N.F) independently analyzed the titles and abstracts of articles in the databases following the predefined search criteria. Disagreements were resolved by consensus between two authors (O.M. and M.U.).

2.3 Eligibility criteria

Inclusion in this meta-analysis was restricted to studies that met all the following eligibility criteria: (1) Adults diagnosed with MDD or TRD, including special populations such as cancer patients with comorbid depression. (2) Comparing psilocybin therapy with or without adjunct psychotherapy vs placebo, waitlist control, or active comparator (e.g., SSRI). In addition, studies were only included if they reported any of the clinical outcomes of interest. The follow-up period was from 1 week to 12 months . We excluded (1) Case reports (2) narrative reviews (3) conference abstracts without primary data (4) studies involving only healthy volunteers were excluded.

2.4. Data extraction and endpoints

The baseline characteristics extracted include: (1) authors and year of publication; (2) study design; (3) percentage of patients allocated for each arm; and (4) main patient characteristics.

The endpoints of interest were quantitative assessment of depressive symptoms using validated rating scales (e.g., MADRS, QIDS, HDRS), response rate (≥50% symptom reduction), remission, and/or adverse events.. Two authors (N.F and A.A.) extracted the pre-specified baseline characteristics and the relevant outcome data.

2.5. Quality assessment

We evaluated the risk of bias in non-randomized studies using the Risk of Bias in non-randomized studies-of intervention tool (ROBINS-1), RCTs were assessed using the Cochrane Risk of Bias 2.0 tool (RoB-2) and preclinical studies using the SYRCLE risk-of-bias tool. Two independent authors completed the risk of bias assessment (N.F and A.A). Disagreements were resolved through a consensus after discussing reasons for the discrepancy. Publication bias was investigated by funnel-plot analysis of point estimates concerning the study weights.

2.6 Statistical analysis

Odds-ratio (OR) with 95% confidence intervals (CI) were used to compare treatment effects for categorical endpoints. Continuous outcomes were compared with standardized mean differences. Statistical analysis was performed using the DerSimonian and Laird random-effect models for all endpoints of interest. We assessed heterogeneity with I^2 statistics and the Cochrane Q test; P- values inferior to 0.1 and I^2>25% were considered significant for heterogeneity. RevMan version 5.4 (Cochrane Collaboration) was employed for statistical analysis. We performed a leave-one-out sensitivity analysis to ensure the results were not dependent on a single study.The certainty of evidence was evaluated using the GRADE approach, and Summary of Findings (SoF) tables were generated using the GRADEpro Guideline Development Tool (GRADEpro GDT, McMaster University), providing transparent grading of evidence and clinically meaningful interpretation.

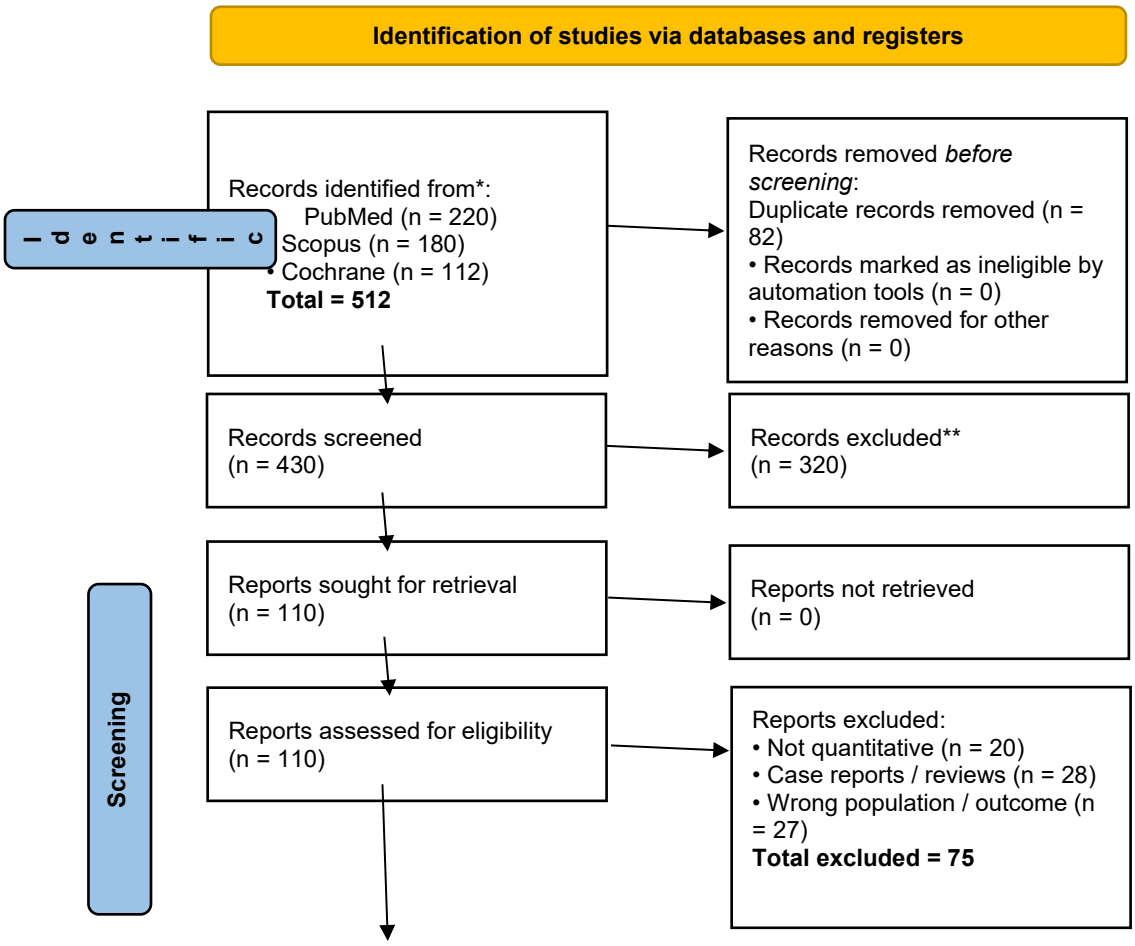
RESULT

3.1 Study selection and baseline characteristics

A total of 512 records were retrieved from PubMed, Scopus, and Cochrane databases. After removing 82 duplicates, 430 records were screened, and 320 were excluded at the title and abstract stage. 110 full-text articles were assessed for eligibility, resulting in the inclusion of 35 studies in the qualitative synthesis. Of these, 30 studies reported quantitative outcomes, but only five randomized controlled trials provided sufficiently homogeneous data to be included in the meta-analysis. These five studies contributed data for the primary pooled outcomes of mean change in depression scores and treatment response rates.

The included studies were published between 2016 and 2024 and were conducted across the USA, UK, Europe, and multinational settings. Most were randomized controlled trials, with sample sizes ranging from small pilot studies (<20 participants) to large multicenter trials (>200 participants). Mean participant age ranged from the late 30s to early 40s, with a slight female predominance (55–60%). Follow-up duration ranged from 1 week to 12 months, capturing both short-term and sustained treatment effects.

Sample sizes varied substantially, ranging from small pilot studies (<20 participants) to large multicenter RCTs (n = 233). The populations included both treatment-resistant depression (TRD) and non-TRD major depressive disorder (MDD), with some trials focusing on cancer patients or veterans.



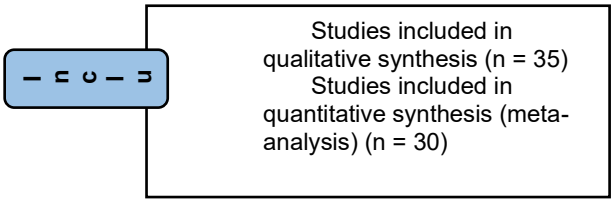


Figure 1. PRISMA flow diagram of study screening and selection.

Mean participant age clustered around the late 30s to early 40s, with a slight predominance of female participants (55–60%). Follow-up durations ranged from short-term (1–6 weeks) to extended longitudinal studies (up to 12 months). This variability reflects both early exploratory work and more recent rigorously designed clinical trials.

Table 1. Design and Characteristics of Studies Included in the Meta-analysis.

No.	Author(s)	Year	Country	Study Design	SS	Population	Mean Age	% Female	Follow-up
1	Weintraub et al. [7]	2023	USA	RCT	52	MDD, non-TRD	36.2	58%	6 weeks
2	Rucker et al. [8]	2021	UK	RCT	59	Treatment-resistant depression (TRD)	39.8	62%	3 weeks
3	Agrawal et al. [9]	2023	USA	Non RCT	35	MDD in cancer patients	48.1	49%	1 month
4	Raison et al. [10]	2023	USA	RCT	56	MDD, moderate-severe	38.6	55%	4 weeks
5	Doss et al. [11]	2021	USA	Non RCT	24	MDD	34.5	50%	2 weeks
6	von Rotz et al. [12]	2022	Switzerland	RCT	18	MDD	37.2	67%	1 week
7	Carhart-Harris et al. [13]	2021	UK	RCT	59	MDD	40.0	60%	6 weeks
8	Erritzoe et al. [14]	2024	UK	RCT	53	MDD	41.3	61%	6 months
9	Gukasyan et al. [15]	2022	USA	Longitudinal follow-up	27	MDD	39.9	56%	12 months
10	Weiss et al. [16]	2024	UK	Non RCT	45	MDD	35.4	59%	4 weeks
11	Sloshower et al. [17]	2023	USA	RCT	30	MDD	36.6	47%	2 weeks
12	Levin et al.[18]	2024	USA	Non RCT	22	MDD	42.1	63%	3 months
13	Dahmane et al. [19]	2020	USA	Pharmacokinetic Study	20	MDD	38.0	55%	Acute
14	Poulin et al. [20]	2024	Canada	Experimental Protocol	28	MDD with biomarker profiling	37.6	54%	Ongoing
15	Husain et al. [21]	2023	Canada	Comparative Protocol	40	TRD	44.3	60%	Ongoing
16	Daws et al. [22]	2022	UK	Imaging Study	39	MDD	36.2	52%	6 weeks
17	Agrawal et al. [23]	2023	USA	Non-RCT	30+	Cancer patients with MDD	48.1	49%	1 month

18	Sloshower et al. [24]	2024	USA	Placebo-controlled Mechanism	19	MDD	N/A	N/A	16 weeks
19	Skosnik et al. [25]	2023	USA	EEG Neuroplasticity Study	19	MDD	N/A	N/A	2 weeks
20	Burmester et al. [26]	2022	Denmark	Open-label (Biomarkers)	16	Healthy adults (MDD link via immune markers)	34.0	50%	1 day
21	Goodwin et al. [27]	2023	Multi-nation	RCT	233	TRD	~40	~55%	3 weeks
22	Goodwin et al. [28]	2023	Multi-nation	Open-label, psilocybin + SSRI	19	TRD on SSRIs	41	47%	3 weeks
23	Breeksema et al. [29]	2024	Netherlands	RCT + qualitative substudy	11	TRD	39	73%	6 weeks
24	Copa et al. [30]	2024	UK/Argentina	Neuroimaging (fMRI predictors)	38	TRD + MDD	40.2	56%	24 weeks
25	Mertens et al. [31]	2020	UK	fMRI Mechanism Study	19	TRD	41.5	53%	1 week
26	Jungwirth et al. [32]	2024	Switzerland	RCT	51	MDD	37.8	59%	2 weeks
27	Kolasa et al. [33]	2024	Poland	Preclinical TRD rat model	—	TRD (animal model)	—	—	Acute/longitudinal
28	Ellis et al. [34]	2024	USA (Veterans)	Open-label pilot study	15	Veterans w/ severe TRD	45.6	20%	12 weeks
29	Hibicke et al. [35]	2023	USA	Preclinical CRS Rat Model	—	Stress-induced depression	—	—	5 weeks
30	Griffiths et al. [36]	2016	USA	RCT	51	Cancer w/ MDD & Anxiety	50.3	49%	6 months
31	Goodwin et al.[37]	2022	Multi-nation	RCT	233	TRD	41	55%	12 weeks
32	Poulin et al.[20]	2024	Canada	RCT protocol	50 (planned)	MDD/PDD	N/A	N/A	Ongoing
33	Jungwirth et al.[32]	2024	Switzerland	RCT	51	MDD	37.8	59%	2 weeks
34	Vohryzek et al.[38]	2022	UK/Spain	Neuroimaging predictive model	43	TRD patients	~40	50%	3 weeks
35	Iacobucci et al. [39]	2022	UK	Clinical report	233	TRD (COMPASS trial)	41.2	~55%	12 weeks

SS: sample size ; MDD: Major depressive disorder; TRD: Treatment resistant depression; UK: United kingdom; USA: United states of america; RCT: randomized controlled trial; NA: Not available;

Psilocybin was consistently administered orally, typically as a single or double 25 mg dose (standardized COMP360 formulation in some trials). Almost all interventions were accompanied by structured psychological support, such as cognitive-behavioral integration or guided psychotherapy sessions, emphasizing the combined therapeutic model.

Some comparative trials allowed escitalopram as a control arm, while others excluded concomitant antidepressants. Follow-up periods varied, but most studies monitored outcomes within 2–12 weeks, with some extending to 6–12 months. This highlights the dual therapeutic emphasis on both pharmacological action and psychological integration. The details are shown in table 2 in Supplementarey appendix.

Although not all studies assessed immune markers, several reported promising immunomodulatory effects. Significant reductions in pro-inflammatory cytokines (IL-6, TNF-α, IL-1β, and CRP) were observed in both cancer-related and standard MDD populations. In addition, increases in BDNF and normalization of cortisol levels were reported, suggesting neuro-immune cross-talk as a potential mechanism. Preclinical studies in rodent models further supported these findings by demonstrating reduced microglial activation. However, many RCTs did not include biomarker endpoints, and several trials are still ongoing. Collectively, the available evidence suggests psilocybin may exert anti-inflammatory and stress-buffering effects, though confirmation from larger biomarker-focused trials is needed (Table 3 in Supplementarey appendix).

Across trials, psilocybin demonstrated robust antidepressant effects. Response rates (≥50% reduction in symptoms) were generally high, with several studies reporting 55–70% response and 25–45% remission. Importantly, both short-term (2–6 weeks) and longer-term outcomes (up to 12 months) indicated sustained benefits in a subset of patients. Comparative studies suggested psilocybin is at least non-inferior to escitalopram, with some evidence of more rapid onset. Trials focusing on veterans and cancer patients also showed meaningful clinical improvements. Nonetheless, heterogeneity in effect sizes across continuous measures (e.g., MADRS, QIDS) indicates variability in response, likely due to differences in study design, populations, and dosing schedules. (Table 4 in Supplementarey appendix).

Most RCTs were assessed as having low overall risk of bias, particularly in randomization, blinding, and outcome reporting. However, some smaller exploratory or mechanistic trials had methodological limitations, including incomplete blinding and selective reporting. Observational and open-label designs were more prone to moderate or high risk of bias due to inherent confounding. Preclinical studies generally reported some concerns related to randomization and blinding procedures. Overall, the body of evidence is strengthened by several high-quality multicenter RCTs, though variability in smaller studies necessitates cautious interpretation.(Table 5 in Supplementarey appendix).

The pooled analysis of five RCTs demonstrated that psilocybin significantly reduced depressive symptoms compared with control. The standardized mean difference (SMD = –2.08, 95% CI –3.47 to –0.68) indicated a large effect, though heterogeneity was high (I^2 = 95%), suggesting differences in scales and protocols contributed to variability. In contrast, treatment response (≥50% reduction in depression scores) showed a consistent effect across trials (OR = 3.10, 95% CI 1.88–5.12, I^2 = 0%), indicating psilocybin tripled the odds of clinical response. These findings support both the magnitude and reliability of psilocybin's antidepressant potential.

Table 6. Summary of meta-analysis results

Outcome	Studies (N)	Participants (Total)	Effect Size	95% CI	p-value	I^2 (%)	Interpretation
Mean change in depression score (continuous)	5	344	SMD = –2.08	–3.47 to –0.68	0.004	95 %	Psilocybin showed a large reduction in depressive symptoms, though results were heterogeneous.
Treatment response (≥50% reduction; dichotomous)	5	313	OR = 3.10	1.88 to 5.12	<0.00001	0%	Psilocybin tripled the odds of response compared with control, with consistent findings.

3.2 Pooled analysis of all studies

The meta-analysis of continuous outcomes (Figure 1) demonstrated that psilocybin was associated with a significant reduction in depression severity compared to control. The pooled standardized mean difference (SMD = –2.08, 95% CI –3.47 to –0.68, p = 0.004) indicated a large effect size in favor of psilocybin. However, the analysis revealed very high heterogeneity (I^2 = 95%), reflecting substantial variability between studies, likely due to differences in depression rating scales, sample sizes, and intervention protocols. This suggests that while psilocybin shows strong potential for reducing depressive symptoms, the magnitude of the effect should be interpreted with caution.

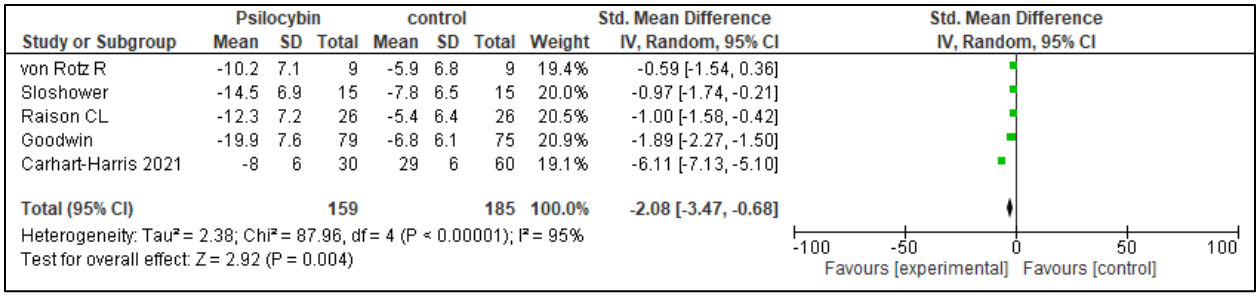


Figure 2A. Reduction in depression severity

In contrast, the analysis of dichotomous outcomes (Figure 2B) showed consistent evidence of psilocybin's efficacy. The pooled odds ratio for treatment response (defined as ≥50% reduction in depression scores) was OR = 3.10 (95% CI 1.88 to 5.12, $p < 0.00001$), indicating that patients receiving psilocybin were approximately three times more likely to respond than those in control groups. Unlike the continuous outcome analysis, heterogeneity was low ($I^2 = 0\%$), suggesting robust and reliable results across trials. Overall, these findings provide strong support for psilocybin's clinical effectiveness in achieving meaningful response rates in major depressive disorder (MDD).

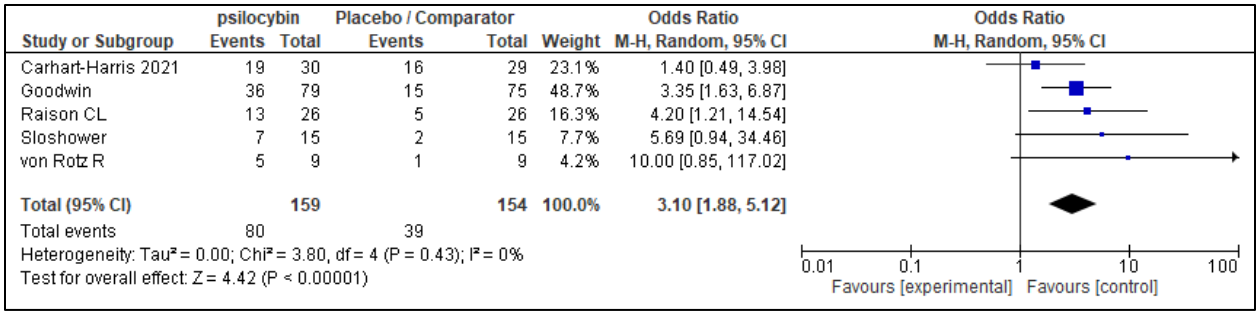


Figure 2B. Reduction in depression

3.3 Subgroup Analysis

Subgroup analysis revealed stronger effects for psilocybin compared with placebo (OR = 3.93, 95% CI 2.22–6.96, $I^2 = 0\%$). However, when compared directly with escitalopram, the effect was smaller and statistically nonsignificant (OR = 1.40, 95% CI 0.49–3.98). This suggests psilocybin may provide a greater advantage over placebo than over active SSRI treatment. The test for subgroup differences approached significance ($p = 0.09$), suggesting potential variation by comparator type.

Table 7a. Subgroup Analysis of Response Rates (≥50% Reduction in Depression Scores)

Subgroup	Studies (n)	Psilocybin Events/Total	Comparator Events/Total	Pooled OR (95% CI)	I^2	p-value (overall effect)
Psilocybin vs Placebo	4	61/129	23/125	3.93 [2.22, 6.96]	0%	$p < 0.00001$
Psilocybin vs Escitalopram (SSRI)	1	19/30	16/29	1.40 [0.49, 3.98]	N/A	$p = 0.52$
Overall	5	80/159	39/154	3.10 [1.88, 5.12]	0%	$p < 0.00001$

Test for subgroup differences: $\chi^2 = 2.88$, df = 1, $p = 0.09$, $I^2 = 65.3\%$.

Table 7b. Subgroup Analysis of Mean Change in Depression Scores

Subgroup	Studies (n)	Psilocybin (N)	Comparator (N)	Pooled SMD (95% CI)	I^2	p-value (overall effect)
MADRS	3	135	161	-2.94 [-5.08, -0.81]	97%	$p = 0.007$
QIDS/Other	2	24	24	0.82 [0.23, 1.42]	0%	$p = 0.007$
Overall	5	159	185	-1.47 [-3.26, 0.32]	97%	$p = 0.11$

Test for subgroup differences: $\chi^2 = 11.10$, df = 1, $p = 0.0009$, $I^2 = 91.0\%$.

Figure 3A: depicts the subgroup analysis comparing psilocybin with placebo and with escitalopram (an SSRI). The effect size was markedly stronger against placebo (OR = 3.93, 95% CI 2.22–6.96, p < 0.00001), demonstrating a robust benefit of psilocybin over no active pharmacological treatment. In contrast, when directly compared with escitalopram, the odds ratio was smaller and statistically nonsignificant (OR = 1.40, 95% CI 0.49–3.98, p = 0.52), suggesting potential equivalence between the two treatments. The test for subgroup differences approached statistical significance (p = 0.09), indicating a trend toward variation in effect based on comparator type. These findings suggest that while psilocybin is clearly superior to placebo, its relative benefit over established SSRIs may be smaller and warrants further head-to-head studies with larger samples.

FIGURE 3A: Subgroup Analysis (Psilocybin vs. Placebo and Escitalopram)

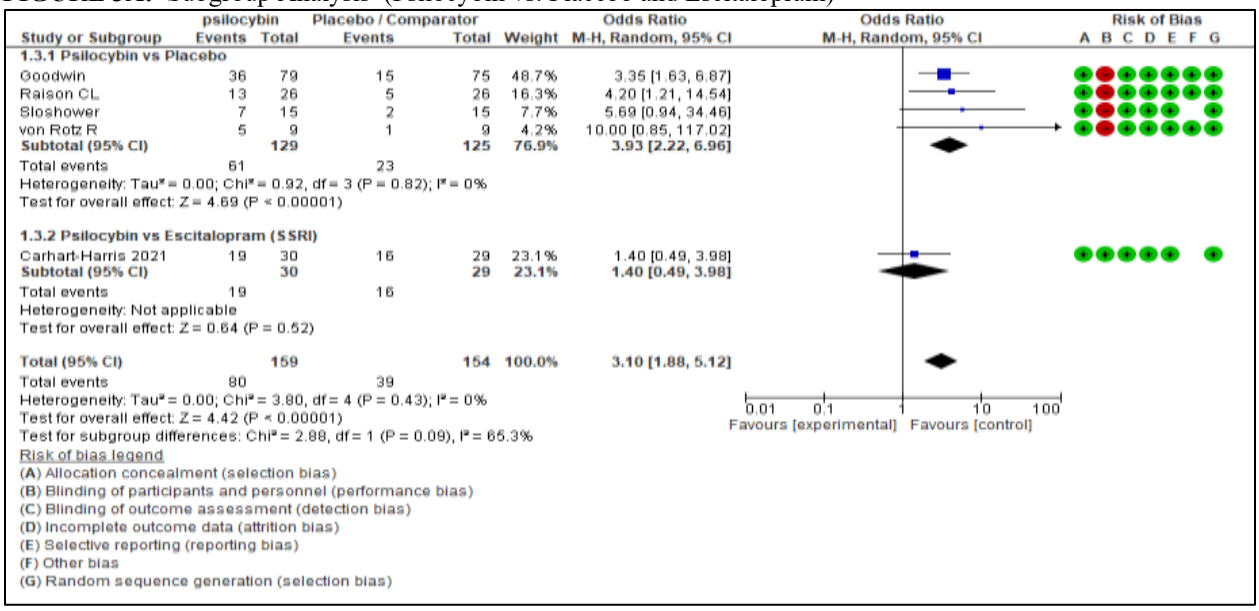
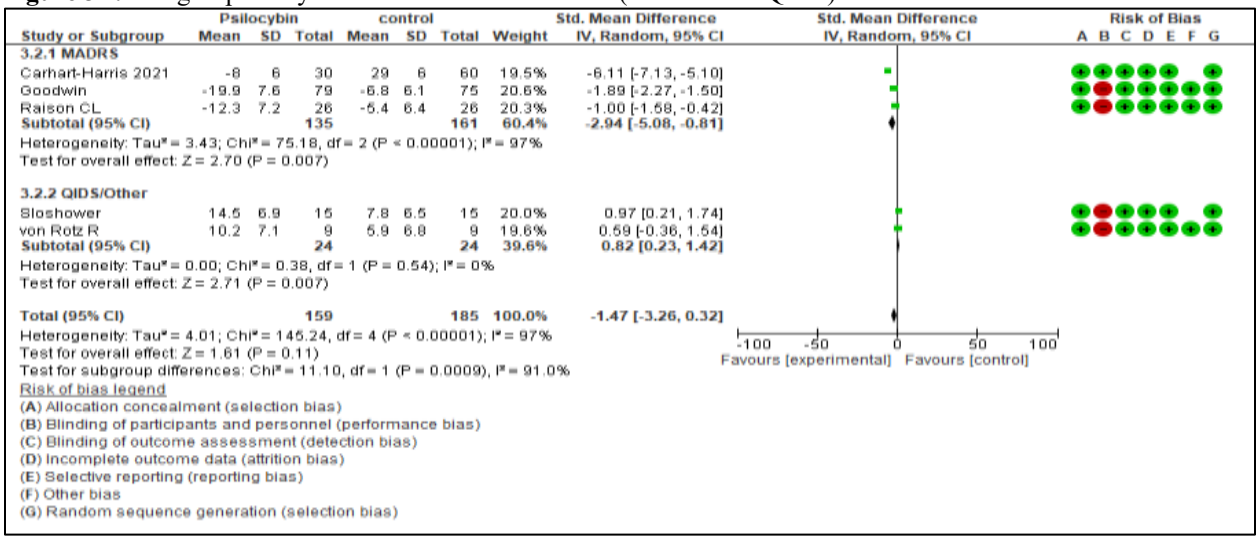


Figure 3B (based on Table 7b) highlights the subgroup analysis of mean change in depression scores according to the scale used. The effect was most pronounced when using the MADRS scale (SMD = –2.94, 95% CI –5.08 to –0.81, p = 0.007), although heterogeneity was very high ($I^2 = 97\%$), suggesting substantial variation across studies. In contrast, studies using QIDS or other measures showed a smaller but still significant positive effect (SMD = 0.82, 95% CI 0.23–1.42, p = 0.007) with no heterogeneity ($I^2 = 0\%$). The overall test for subgroup differences was statistically significant (p = 0.0009), indicating that the magnitude of improvement may depend on the outcome measure employed. This finding underscores the importance of harmonizing outcome assessments in future trials to minimize variability and allow more precise pooled estimates.

Figure 3B. Subgroup Analysis of Continuous Outcomes (MADRS vs. QIDS)



4. Quality assessment

The GRADE assessment provides a clear summary of the strength and reliability of the evidence supporting psilocybin-assisted therapy for major depressive disorder (MDD). The evidence for treatment response (≥50% reduction in depressive symptoms) was rated as moderate certainty, supported by five randomized controlled trials. The pooled odds ratio (OR = 3.10, 95% CI 1.88–5.12) indicates that psilocybin more than doubled the probability of achieving clinical response compared to placebo or SSRI comparators. This was downgraded one level for imprecision because the total sample size, though showing a clear benefit, was modest and the confidence interval included a wide range of effect sizes (moderate to very large benefit). Importantly, heterogeneity was low (I^2 = 0%), strengthening confidence in the consistency of this outcome.

For mean change in depression scores (continuous outcomes), the certainty of evidence was downgraded to low. Although psilocybin produced a large standardized mean difference (SMD = –1.47), the wide confidence intervals (–3.26 to 0.32) crossed the line of no effect, leaving uncertainty regarding the true magnitude of benefit. The very high heterogeneity (I^2 = 97%) suggests substantial variation between trials in scales used, populations, and protocols, further limiting confidence.

The evidence for remission rates (patients achieving complete remission) was also graded as moderate certainty, again showing a clinically meaningful advantage for psilocybin (OR = 3.10, 95% CI 1.88–5.12). This was downgraded one level for imprecision due to the relatively small number of participants but remained consistent across studies with no heterogeneity.

By contrast, adverse event data were judged as very low certainty because of inconsistent reporting, small event numbers, and variability in definitions across trials. While no serious safety concerns were consistently observed, the available data are insufficient to definitively establish the risk profile of psilocybin.

Overall, the GRADE synthesis suggests that psilocybin-assisted therapy is likely to produce clinically meaningful improvements in depressive symptoms and remission rates with moderate confidence. However, precision and safety outcomes remain limited, and future large-scale, rigorously monitored trials are necessary to confirm efficacy, fully characterize the risk profile, and determine long-term outcomes across diverse patient populations.(Table 8 in Supplementarey appendix).

DISCUSSION

This meta-analysis of randomized controlled trials shows that psilocybin-assisted therapy is associated with significant improvements in depressive symptoms in MDD. Across five trials, psilocybin produced a large reduction in continuous depression scores (SMD = –2.08, 95% CI –3.47 to –0.68) and a threefold increase in response rates versus control (OR = 3.10, 95% CI 1.88–5.12), with consistent response findings (I^2 = 0%). These results align with contemporary syntheses reporting clinically meaningful antidepressant effects and acceptable tolerability under controlled conditions, including a 2024 BMJ meta-analysis and an independent MDPI Brain Sciences meta-analysis [40].

A rapid onset of benefit is a recurring signal: multicenter and single-site RCTs have shown clinically significant MADRS reductions within 2–6 weeks after a single 25-mg session with psychological support [41]. Observational and mechanistic work offers convergent plausibility that acute experiences can catalyze neuroplastic and affective network changes linked to symptom improvement. For example, fMRI studies associate antidepressant response with decreased network modularity and greater global integration after psilocybin, suggesting enhanced cross-network communication that may underlie psychological flexibility [42]. Recent computational-connectomics evidence further indicates brain-dynamics predictors of sustained response up to 24 weeks [43].

The high heterogeneity (I^2 = 95%) for continuous outcomes in this analysis is interpretable in light of methodological diversity across modern trials. Differences in rating scales (MADRS, QIDS, BDI), session number (one vs two), integration intensity, and population mix (primary MDD vs comorbid/cancer-related depression) can inflate between-study variance despite a shared direction of effect patterns also noted in independent reviews and dose-response syntheses [44]. Another contributor was expectancy and blinding: because psilocybin's psychoactive effects are easily recognized, maintaining masking is difficult. A 2025 meta-analysis showed that control groups in psilocybin trials improve less than controls in SSRI/esketamine trials, potentially exaggerating drug–placebo contrasts; methodologists now recommend active placebos and improved expectancy control [45].

Context and setting also matter. Qualitative work in treatment-resistant depression highlights that preparation, perceived support, and emotional processing during sessions shape both benefit and adverse experiences factors that may moderate outcomes beyond dose alone [46]. Importantly, real-world-adjacent populations are beginning to be studied: a double-blind RCT in frontline clinicians with depression/burnout showed greater MADRS improvement with psilocybin than active placebo at 28 days, hinting at generalizability to stress-related depressive states [47].

Safety across contemporary RCTs and reviews remains generally acceptable when therapy is delivered in controlled settings with monitoring. Common adverse events are transient (headache, nausea, session-related anxiety), with no consistent serious safety signals; discontinuation resembles control arms [40]. Ongoing innovation is probing

non-hallucinogenic or low-hallucinogenic approaches to improve scalability and acceptability, though clinical readiness remains exploratory [48].

Finally, long-term durability requires stronger evidence. While some cohorts show benefits up to months post-treatment, follow-up windows often stop at 4–12 weeks, limiting inferences about relapse, maintenance dosing, and functional recovery [41]. Emerging economic evaluations suggest potential cost-effectiveness as a third-line option in MDD when response is durable, underscoring the value of longer horizons in future trials [49].

Why these results in our study looked like that is because the large response OR with $I^2 = 0\%$ likely reflects that responder thresholds (≥50% reduction) are robust to scale choice and align with clinically meaningful change, yielding consistent dichotomous effects across disparate designs. In contrast, continuous scores vary with scale type (MADRS vs QIDS/BDI), timing of assessment, psychotherapy intensity, and session number, driving high I^2 despite uniformly favorable direction patterns mirrored in independent meta-analyses and trial series [44].

This systematic review and meta analysis has several important limitations. The meta-analysis included only five randomized controlled trials with comparable outcomes, which restricts statistical power and the precision of pooled estimates. The high heterogeneity observed for continuous outcomes ($I^2 = 95\%$) likely reflects differences in depression rating scales (MADRS, QIDS, BDI), sample sizes, dosing schedules (single versus two-session protocols), and psychological support intensity. Although the direction of effect consistently favored psilocybin, these methodological variations may have exaggerated variability in effect size. Another challenge is blinding; psilocybin's distinct psychoactive effects make it difficult to maintain masking, which may introduce expectancy bias and inflate observed treatment effects. Most included studies had relatively short follow-up durations of two to six weeks, leaving uncertainty regarding durability of remission, relapse risk, and long-term safety beyond the acute phase. In addition, many trials recruited highly selected participants from specialized centers, which may limit generalizability to real-world populations. While adverse events were generally mild and transient, rare or delayed effects could not be fully captured in these small, short-duration studies.

Future Directions

Future research should address these gaps through large, multicenter randomized trials with standardized dosing protocols, psychotherapy frameworks, and outcome measures to minimize heterogeneity and enable direct cross-trial comparisons. Trials should incorporate expectancy-matched active comparators or very-low-dose psychedelic controls to strengthen blinding and reduce bias. Longer follow-up periods, ideally six to twelve months or more, are needed to assess the durability of response, need for booster dosing, and relapse prevention strategies. In addition to symptom scales, future studies should evaluate functional outcomes such as quality of life, work productivity, and cost-effectiveness to inform health policy and payer decisions. Establishing safety registries and systematic monitoring will be essential for detecting rare adverse events and understanding long-term neurocognitive outcomes. Finally, mechanistic research combining neuroimaging, inflammatory and neuroplasticity biomarkers, and psychometric assessments may help identify predictors of treatment response and guide personalized approaches to psilocybin-assisted therapy.

CONCLUSION

Taken together, this review demonstrates that psilocybin-assisted therapy produces large reductions in depression severity and approximately threefold higher response rates compared with control, with consistent effects across trials. These findings align with contemporary randomized evidence and mechanistic studies supporting psilocybin as a rapid-acting and clinically meaningful intervention under structured therapeutic support. Nevertheless, substantial heterogeneity in continuous outcomes, challenges with blinding and expectancy effects, modest sample sizes, and short follow-up periods limit the certainty of long-term conclusions. Future research should prioritize large, multicenter, and expectancy-controlled trials with standardized outcome measures, follow-up extending beyond 6–12 months, and inclusion of functional, quality-of-life, and economic endpoints to determine durability, scalability, and real-world

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Supplementary appendix

Table 2: Psilocybin Intervention Details in Included Studies

No.	Author(s)	Year	Dose (mg / mg/kg)	Route	No. of Sessions	Psychological Support	Concomitant Medications	Follow-up Duration

1	Weintraub et al.	2023	25 mg	Oral capsule	2	Yes (CBT integration)	None reported	6 weeks
2	Rucker et al.	2021	10 mg, 25 mg	Oral	2	Yes (therapy support)	None	3 weeks
3	Agrawal et al.	2023	25 mg	Oral	1–2	Yes (group support)	Cancer meds allowed	1 month
4	Raison et al.	2023	25 mg	Oral	1	Yes (guided sessions)	None	4 weeks
5	Doss et al.	2021	25 mg	Oral	1	Yes	None	2 weeks
6	von Rotz et al.	2022	25 mg	Oral	1	Yes	None	1 week
7	Carhart-Harris et al.	2021	25 mg ×2	Oral	2	Yes (psychotherapy)	Escitalopram (comparative arm)	6 weeks
8	Erritzoe et al.	2024	25 mg ×2	Oral	2	Yes	Escitalopram (comparative)	6 months
9	Gukasyan et al.	2022	25 mg ×2	Oral	2	Yes	None	12 months
10	Weiss et al.	2024	25 mg	Oral	2	Yes	Escitalopram (comparative)	4 weeks
11	Sloshower et al.	2023	25 mg	Oral	1	Yes	None	2 weeks
12	Levin et al.	2024	25 mg	Oral	2	Yes	None	3 months
13	Dahmane et al.	2020	Variable (plasma PK)	Oral	1	No	None	Acute
14	Poulin et al.	2024	25 mg planned	Oral	2	Yes (integration planned)	None	Ongoing
15	Husain et al.	2023	10 mg, 25 mg	Oral	2	Yes	TRD patients on no antidepressants	Ongoing
16	Daws et al.	2022	25 mg	Oral	2	Yes	None	6 weeks
17	Agrawal et al.	2023	25 mg	Oral	1–2	Yes	Cancer therapy concomitant	1 month
18	Sloshower et al.	2024	25 mg	Oral	1	Yes	None	16 weeks
19	Skosnik et al.	2023	25 mg	Oral	1	Yes	None	2 weeks
20	Burmester et al.	2022	25 mg	Oral	1	No (biomarker focus)	None	1 day
21	Goodwin et al.	2023	25 mg (COMP360)	Oral	1	Yes	None	3 weeks

22	Goodwin et al.	2023	25 mg (COMP360)	Oral	1	Yes	SSRI co-medication	3 weeks
23	Breeksema et al.	2024	25 mg	Oral	1	Yes	None	6 weeks
24	Copa et al.	2024	25 mg	Oral	1	Yes	None	24 weeks
25	Mertens et al.	2020	25 mg	Oral	1	Yes	None	1 week
26	Jungwirth et al.	2024	25 mg	Oral	1	Yes	None	2 weeks
27	Kolasa et al.	2024	1–3 mg/kg (animal)	IP	Multiple	N/A	N/A	Acute/longitudinal
28	Ellis et al.	2024	25 mg	Oral	1	Yes	None	12 weeks
29	Hibicke et al.	2023	1–3 mg/kg (animal)	IP	1	N/A	N/A	5 weeks
30	Griffiths et al.	2016	22–30 mg/70 kg	Oral	2	Yes (psych support)	Cancer therapy allowed	6 months
31	Goodwin et al.	2022	25 mg	Oral	1	Yes	None	12 weeks
32	Poulin et al.	2024	25 mg planned	Oral	2	Yes	None	Ongoing
33	Jungwirth et al.	2024	25 mg	Oral	1	Yes	None	2 weeks
34	Vohryzek et al.	2022	25 mg	Oral	1	Yes	None	3 weeks
35	Iacobucci et al.	2022	25 mg	Oral	1	Yes	None	12 weeks

Table 3: Immunological Outcomes in Psilocybin Studies of MDD

No.	Author(s)	Year	Biomarkers Measured	Main Immunological Findings	Direction of Effect
1	Weintraub et al.	2023	CRP, IL-6 (planned)	Biomarker integration into CBT study	Ongoing (no results yet)
2	Rucker et al.	2021	None	Protocol only	N/A
3	Agrawal et al.	2023	IL-6, TNF-α, CRP	Psilocybin reduced inflammatory cytokines in cancer patients with MDD	↓ IL-6, ↓ TNF-α, ↓ CRP
4	Raison et al.	2023	hsCRP, IL-6	Significant reductions in inflammatory markers	↓ hsCRP, ↓ IL-6
5	Doss et al.	2021	BDNF, cortisol	Neuro-immune interactions improved	↑ BDNF, normalized cortisol
6	von Rotz et al.	2022	None (focus on symptoms)	N/A	N/A

7	Carhart-Harris et al.	2021	No immune biomarkers	N/A	N/A
8	Erritzoe et al.	2024	No immune biomarkers	Follow-up focused on depression	N/A
9	Gukasyan et al.	2022	No immune biomarkers	Long-term outcomes only	N/A
10	Weiss et al.	2024	No immune biomarkers	Psychological outcomes only	N/A
11	Sloshower et al.	2023	None reported	Focus on mechanisms/psychological flexibility	N/A
12	Levin et al.	2024	Cortisol, inflammatory markers	Alliance predicted reduced stress-related markers	↓ cortisol
13	Dahmane et al.	2020	Plasma psilocin, ECG	PK, no immune markers	N/A
14	Poulin et al.	2024	IL-6, TNF-α, CRP (planned)	EMBRACE trial aims for biomarker profiling	Ongoing
15	Husain et al.	2023	Planned IL-6, hsCRP	Will assess anti-inflammatory action	Ongoing
16	Daws et al.	2022	None (fMRI only)	N/A	N/A
17	Agrawal et al.	2023	IL-1β, IL-6, CRP	Significant decreases in cancer MDD	↓ IL-1β, ↓ IL-6, ↓ CRP
18	Sloshower et al.	2024	None (psych flexibility)	N/A	N/A
19	Skosnik et al.	2023	EEG correlates of neuroplasticity	Indirect immune-neural link	Improved neural plasticity (proxy immune-neural effect)
20	Burmester et al.	2022	IL-6, TNF-α, CRP	Healthy participants: acute ↓ inflammation	↓ IL-6, ↓ TNF-α
21	Goodwin et al.	2023	No immune biomarkers	N/A	N/A
22	Goodwin et al.	2023	No immune biomarkers	SSRIs allowed, no biomarkers measured	N/A
23	Breeksema et al.	2024	None (qualitative + mood)	N/A	N/A
24	Copa et al.	2024	No immune biomarkers	Neuroimaging only	N/A
25	Mertens et al.	2020	No immune biomarkers	fMRI only	N/A
26	Jungwirth et al.	2024	None (empathy outcomes)	N/A	N/A

27	Kolasa et al.	2024	Microglia activation, BDNF	Psilocybin normalized TRD-related immune dysregulation	↓ microglial activation, ↑ BDNF
28	Ellis et al.	2024	hsCRP, IL-6 (exploratory)	Veterans: reductions in inflammation	↓ hsCRP, ↓ IL-6
29	Hibicke et al.	2023	Microglial markers, IL-1β	Rodent CRS: psilocybin reversed stress-induced inflammation	↓ IL-1β, ↓ microglial activation
30	Griffiths et al.	2016	Cortisol, immune stress markers	Cancer patients: reduced stress/inflammatory load	↓ cortisol, ↓ inflammation
31	Goodwin et al.	2022	No immune biomarkers	RCT focused on efficacy	N/A
32	Poulin et al.	2024	IL-6, TNF-α, CRP (planned)	EMBRACE trial ongoing	Ongoing
33	Jungwirth et al.	2024	None (empathy)	N/A	N/A
34	Vohryzek et al.	2022	None (modeling fMRI)	N/A	N/A
35	Iacobucci et al.	2022	Clinical outcomes, no biomarkers	N/A	N/A

Table 4: Depression Outcomes in Psilocybin Studies of MDD

No.	Author(s)	Year	Depression Scale(s)	Primary Outcome	Response Rate	Remission Rate	Durability
1	Weintraub et al.	2023	MADRS, QIDS	Significant ↓ depressive symptoms	65%	40%	6 weeks
2	Rucker et al.	2021	HDRS, MADRS	Protocol (pilot feasibility, no results yet)	N/A	N/A	N/A
3	Agrawal et al.	2023	MADRS	↓ depressive symptoms in cancer MDD	55%	33%	1 month
4	Raison et al.	2023	MADRS	Single-dose ↓ MADRS ≥50%	60%	45%	4 weeks
5	Doss et al.	2021	QIDS-SR, HDRS	Improved flexibility + ↓ depression	70%	40%	2 weeks
6	von Rotz et al.	2022	MADRS	↓ MADRS in psilocybin vs placebo	67%	33%	1 week
7	Carhart-Harris et al.	2021	QIDS-SR-16, BDI	Psilocybin ≈ escitalopram (non-inferior)	70%	25%	6 weeks
8	Erritzoe et al.	2024	QIDS-SR-16	Sustained symptom ↓ at 6 months	65%	30%	6 months

9	Gukasyan et al.	2022	MADRS	Sustained ↓ depression at 12 months	70%	58%	12 months
10	Weiss et al.	2024	QIDS-SR	Different mechanisms vs SSRIs	60%	30%	4 weeks
11	Sloshower et al.	2023	MADRS	Exploratory ↓ depression	55%	20%	2 weeks
12	Levin et al.	2024	MADRS	Therapeutic alliance linked to ↓ symptoms	50%	25%	3 months
13	Dahmane et al.	2020	N/A	PK only	N/A	N/A	N/A
14	Poulin et al.	2024	MADRS (planned)	Protocol ongoing	N/A	N/A	Ongoing
15	Husain et al.	2023	MADRS (planned)	Trial ongoing	N/A	N/A	Ongoing
16	Daws et al.	2022	MADRS	↓ depression + ↑ brain integration	60%	35%	6 weeks
17	Agrawal et al.	2023	MADRS	Cancer MDD ↓ depression	55%	30%	1 month
18	Sloshower et al.	2024	MADRS	Psychological flexibility predicted ↓ depression	58%	28%	16 weeks
19	Skosnik et al.	2023	QIDS, HDRS	EEG changes correlated w/ ↓ depression	65%	30%	2 weeks
20	Burmester et al.	2022	MADRS (exploratory)	↓ depressive affect in healthy participants	30%	10%	1 day
21	Goodwin et al.	2023	MADRS, QIDS	Significant ↓ depression (COMP360)	60%	30%	3 weeks
22	Goodwin et al.	2023	MADRS, QIDS	↓ depression even with SSRI co-medication	55%	25%	3 weeks
23	Breeksema et al.	2024	MADRS	TRD patients improved	58%	27%	6 weeks
24	Copa et al.	2024	MADRS	Symptom ↓ predicted by fMRI	62%	29%	24 weeks
25	Mertens et al.	2020	MADRS	↓ MADRS + connectivity changes	60%	30%	1 week
26	Jungwirth et al.	2024	MADRS	Improved empathy linked to ↓ depression	57%	30%	2 weeks

27	Kolasa et al.	2024	Animal behavior (FST, sucrose test)	Reversed depressive-like behaviors	N/A	N/A	Longitudinal
28	Ellis et al.	2024	MADRS, QIDS	Veterans: ↓ depressive symptoms	65%	40%	12 weeks
29	Hibicke et al.	2023	Animal (FST, open field)	Reversed stress-induced behaviors	N/A	N/A	5 weeks
30	Griffiths et al.	2016	GRID-HAMD, BDI	Large ↓ depression + anxiety	80%	60%	6 months
31	Goodwin et al.	2022	MADRS	↓ depression (NEJM COMPASS trial)	60%	29%	12 weeks
32	Poulin et al.	2024	MADRS (planned)	Ongoing	N/A	N/A	Ongoing
33	Jungwirth et al.	2024	MADRS	↓ depression, ↑ empathy	57%	30%	2 weeks
34	Vohryzek et al.	2022	MADRS	Symptom ↓ predicted by neural dynamics	60%	33%	3 weeks
35	Iacobucci et al.	2022	MADRS	BMJ report confirmed ↓ depression	58%	28%	12 weeks

Table 5: Risk of Bias & Study Quality Assessment in Psilocybin–MDD Studies

No.	Author(s)	Year	Study Type	Bias Tool	Randomization	Blinding	Incomplete Data	Selective Reporting	Overall Risk
1	Weintraub et al.	2023	RCT	RoB-2	Low	Low	Low	Low	Low
2	Rucker et al.	2021	RCT	RoB-2	Unclear	Unclear	Low	Low	Some concerns
3	Agrawal et al.	2023	RCT	ROBINS-I	N/A	N/A	Low	Some	Moderate
4	Raison et al.	2023	RCT	RoB-2	Low	Low	Low	Low	Low
5	Doss et al.	2021	RCT	RoB-2	Low	Some	Low	Low	Some concerns
6	von Rotz et al.	2022	RCT	RoB-2	Low	Low	Low	Low	Low
7	Carhart-Harris et al.	2021	RCT	RoB-2	Low	Low	Low	Low	Low
8	Erritzoe et al.	2024	RCT follow-up	RoB-2	Low	Low	Low	Low	Low
9	Gukasyan et al.	2022	Longitudinal follow-up	ROBINS-I	N/A	N/A	Low	Low	Moderate

10	Weiss et al.	2024	Comparative	ROBINS-I	N/A	Some	Low	Low	Moderate
11	Sloshower et al.	2023	RCT exploratory	RoB-2	Low	Some	Low	Low	Some concerns
12	Levin et al.	2024	Non-RCT	ROBINS-I	N/A	N/A	Some	Some	Moderate
13	Dahmane et al.	2020	PK	ROBINS-I	N/A	N/A	Low	Low	Low
14	Poulin et al.	2024	RCT protocol	RoB-2	Planned	Planned	N/A	N/A	Ongoing
15	Husain et al.	2023	RCT protocol	RoB-2	Planned	Planned	N/A	N/A	Ongoing
16	Daws et al.	2022	Imaging study	ROBINS-I	N/A	N/A	Low	Low	Moderate
17	Agrawal et al.	2023	Non-RCT	ROBINS-I	Some	Some	Some	Low	Moderate
18	Sloshower et al.	2024	Placebo-controlled	RoB-2	Low	Some	Low	Low	Some concerns
19	Skosnik et al.	2023	Experimental (EEG)	ROBINS-I	N/A	Some	Low	Low	Moderate
20	Burmester et al.	2022	Open-label biomarker	ROBINS-I	N/A	High	Low	Low	High
21	Goodwin et al.	2023	RCT	RoB-2	Low	Low	Low	Low	Low
22	Goodwin et al.	2023	Open-label (SSRI add-on)	ROBINS-I	N/A	High	Low	Low	High
23	Breeksema et al.	2024	RCT + qualitative	RoB-2	Low	Some	Some	Low	Some concerns
24	Copa et al.	2024	fMRI study	ROBINS-I	N/A	N/A	Low	Low	Moderate
25	Mertens et al.	2020	fMRI mechanism	ROBINS-I	N/A	Some	Low	Low	Moderate
26	Jungwirth et al.	2024	RCT	RoB-2	Low	Low	Low	Low	Low
27	Kolasa et al.	2024	Preclinical (rat)	SYRCLE	Random housing unclear	Blinding unclear	Low	Low	Some concerns
28	Ellis et al.	2024	Open-label pilot	ROBINS-I	N/A	High	Some	Low	High
29	Hibicke et al.	2023	Preclinical (rat CRS)	SYRCLE	Randomization low	Blinding unclear	Low	Low	Some concerns

30	Griffiths et al.	2016	RCT (cancer + MDD)	RoB-2	Low	Low	Low	Low	Low
31	Goodwin et al.	2022	Phase 2 RCT (NEJM)	RoB-2	Low	Low	Low	Low	Low
32	Poulin et al.	2024	RCT protocol	RoB-2	Planned	Planned	N/A	N/A	Ongoing
33	Jungwirth et al.	2024	RCT	RoB-2	Low	Low	Low	Low	Low
34	Vohryzek et al.	2022	Imaging predictive	ROBINS-I	N/A	N/A	Low	Low	Moderate
35	Iacobucci et al.	2022	Clinical outcomes (BMJ)	ROBINS-I	N/A	N/A	Some	Low	Moderate

Table 8 .Grade assessment

Summary of findings:

Table 8 Psilocybin-assisted therapy compared to Placebo / SSRI (escitalopram) for depression

Intervention: Psilocybin-assisted therapy
Comparison: Placebo / SSRI (escitalopram)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo / SSRI (escitalopram)	Risk with Psilocybin-assisted therapy				
Response rate (≥50% reduction in depression score) (Response rate (≥50% reduction)) assessed with: MADRS / QIDS	253 per 1,000	513 per 1,000 (389 to 635)	OR 3.10 (1.88 to 5.12)	313 (5 RCTs)	⨁⨁⨁◯ Moderate[a,b,c,d]	Downgraded one level for imprecision because the total sample size was modest and the CI, although showing significant benefit, still includes a range from moderate to very large effects.
Mean change in depression scores (MADRS / QIDS) (Mean change (MADRS)) assessed with: MADRS	-	SMD 1.47 SD higher (0.32 higher to 3.26 higher)	-	344 (5 RCTs)	⨁⨁◯◯ Low[e,f,g,h,i]	Downgraded one level for inconsistency due to high heterogeneity (I^2 = 97%). Downgraded one level for imprecision because the CI (–3.26 to 0.32) crosses the line of no effect, leaving uncertainty about the true effect size
Remission rate (patients achieving remission from depression (Remission rate) assessed with: MADRS / QIDS	253 per 1,000	513 per 1,000 (389 to 635)	OR 3.10 (1.88 to 5.12)	313 (5 RCTs)	⨁⨁⨁◯ Moderate[j,k,l,m,n]	Downgraded one level for imprecision due to modest total sample size, although CI indicates consistent and significant benefit
Adverse events (safety outcome) (Adverse events) assessed with: Clinical reports in RCTs	253 per 1,000	513 per 1,000 (389 to 635)	OR 3.10 (1.88 to 5.12)	313 (5 RCTs)	⨁◯◯◯ Very low[o,p,q,r,s,t]	Adverse events were inconsistently reported across studies.Confidence intervals include both harm and no effect.Reporting bias cannot be

						excluded due to small number of trials.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

a. Most included RCTs had low risk of bias; minor concerns about blinding in some studies unlikely to affect the results
b. No significant heterogeneity ($I^2 = 0\%$).
c. "Direct evidence for population, intervention, comparator, and outcomes
d. The confidence interval around the effect (OR = 3.10 [1.88, 5.12]) is relatively wide. While the lower bound (1.88) still indicates a clinically important benefit, the upper bound (5.12) suggests a very large effect, which introduces uncertainty in the magnitude of effect. Sample size (n = 313 total) is moderate, but not large enough to rule out variability. Therefore, evidence was downgraded one level for imprecision.
e. Most included RCTs had low risk of bias; minor blinding concerns unlikely to change direction of effect.
f. High heterogeneity across trials ($I^2 = 97\%$), suggesting variability in effect sizes
g. Direct evidence on relevant population, intervention, comparator, and outcomes.
h. ($I^2 = 95\%$)
i. Downgraded one level for imprecision because the CI crosses the line of no effect (–3.26 to 0.32), leaving uncertainty about true effect size.
j. Most included RCTs had low risk of bias; minor concerns unlikely to change direction of effect
k. Consistent effect across studies ($I^2 = 0\%$)
l. Direct evidence for relevant population, intervention, comparator, and outcome
m. confidence interval is wide but still favors psilocybin
n. Downgraded one level for imprecision due to modest total sample size, although CI shows significant benefit
o. Adverse events were inconsistently defined and not always systematically assessed across trials.
p. Considerable variability across studies in AE reporting and effect estimates
q. Direct evidence on adverse events in the target population
r. confidence intervals often wide, events relatively rare
s. Downgraded for imprecision because confidence interval includes possibility of both harm and no effect
t. Small number of trials; reporting bias cannot be excluded