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Efficacy, Effectiveness, and Safety of Psilocybin and Ketamine versus Conventional Treatments or Placebo in Adults with Treatment-Resistant Depression: A Systematic Review

Jhoan Utria Castro[1*], Camila Lopez Echeverri[2], Paula Andrea Lubo Brito[3], Sofia Torres Olaya[4], Maria Camila Martinez Negrete[5], Juan Pablo Alzate Granados[6]

[1*]Institutional Affiliation: Asociacion de Psiquiatras de Argentina, Email: utria624@hotmail.com
[2]Institutional Affiliation: Institución Universitaria Visión de las Americas, Email: camilalopeze99@gmail.com
[3]Institutional Affiliation: Universidad Metropolitana, Email: Paula.andrea1209@hotmail.com
[4]Institutional Affiliation: Fundación Universitaria Juan N. Corpas, Email: csto4444@gmail.com
[5]Institutional Affiliation: Fundación Universitaria Sanitas, Email: Camilamartneg@gmail.com
[6]Institutional Affiliation: Universidad Nacional de Colombia, Email: juanpabloalzategranados@gmail.com

Abstract:
Background: Treatment-resistant depression (TRD) is a severe form of major depressive disorder that does not respond to at least two adequate antidepressant trials. Emerging evidence suggests that psilocybin and ketamine may produce rapid, clinically meaningful antidepressant effects, but no prior systematic review has directly compared their efficacy, effectiveness, and safety in TRD.
Objective: To systematically assess the efficacy, real-world effectiveness, and safety of psilocybin and ketamine/esketamine compared with conventional pharmacologic treatments or placebo in adults with TRD.
Methods: Following PRISMA guidelines, we included randomized controlled trials (RCTs), open-label, and prospective observational studies in adults with TRD. Primary outcomes were changes in depressive symptoms (e.g., MADRS, QIDS-SR16), response/remission rates, and safety. Due to clinical heterogeneity, no meta-analysis was performed.
Results: Nine studies met inclusion criteria. Psilocybin (25 mg COMP360) reduced MADRS scores by 12.0 points at 3 weeks versus 5.4 with placebo (adjusted difference: −6.6; $p < 0.001$). In another RCT, remission rates were higher with psilocybin (57%) versus escitalopram (28%). Intravenous ketamine (0.5 mg/kg) produced ~8-point MADRS reductions at 24h, with 64% achieving response versus 28% with placebo. Intranasal esketamine showed 4–6 point greater MADRS reductions over 4 weeks compared to placebo. Adverse effects for both agents, including dissociation, nausea, and mild hypertension, were transient and manageable.
Conclusions: Both psilocybin and ketamine demonstrate rapid antidepressant effects with acceptable safety in TRD. Psilocybin may achieve sustained remission with minimal dosing, while ketamine/esketamine require ongoing administration. Further long-term, head-to-head trials are warranted to establish comparative effectiveness and durability of response.

Keywords: Depressive Disorder; Treatment-Resistant; Psilocybin; Ketamine; Antidepressive Agents; Randomized Controlled Trials as Topic

Introduction:

Major Depressive Disorder (MDD) is a chronic, recurrent psychiatric illness characterized by persistent low mood, anhedonia, cognitive impairments, and vegetative symptoms (1). Globally, MDD represents a leading cause of disability, with the World Health Organization estimating that over 280 million individuals are affected as of 2021, a figure that has continued to rise, especially in the aftermath of the COVID-19 pandemic. The burden of MDD is substantial, contributing significantly to years lived with disability (YLDs), healthcare utilization, and economic loss through reduced productivity (2).

Among individuals diagnosed with MDD, an estimated 20% to 30% develop Treatment-Resistant Depression (TRD), defined as failure to respond to at least two adequate trials of antidepressant therapies from different pharmacologic classes. Conventional treatments for MDD, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), have demonstrated efficacy in mild to moderate depression (3,4). However, in TRD populations, these agents often exhibit delayed onset, limited remission rates, and are frequently associated with side effects such as sexual dysfunction, weight gain, and emotional blunting—all of which negatively impact adherence and quality of life.

In this context, novel therapeutic strategies have garnered interest. Ketamine, originally used as an anesthetic, functions primarily as an NMDA receptor antagonist and has shown rapid and robust antidepressant effects in both intravenous and intranasal formulations (5). Similarly, psilocybin, a serotonergic psychedelic found in certain species of

mushrooms, exerts its effects through 5-HT2A receptor agonism and has been reported in recent trials to produce substantial reductions in depressive symptoms after only one or two administrations. Both agents have been studied for their potential to disrupt maladaptive neural circuits, enhance neuroplasticity, and induce enduring psychological shifts, offering promising mechanisms to overcome pharmacologic resistance (6).

Despite the growing body of evidence supporting the antidepressant properties of psilocybin and ketamine, significant gaps remain in our understanding of their comparative efficacy, durability of effects, and long-term safety profiles in TRD (7). While several randomized controlled trials (RCTs) have demonstrated statistically significant improvements in depressive symptoms following acute treatment with either agent, these studies are often limited by small sample sizes, short follow-up periods, and considerable heterogeneity in outcome measures. For example, psilocybin trials often include structured psychotherapeutic support, which may confound the attribution of outcomes solely to the pharmacological intervention (8).

Additionally, the U.S. Food and Drug Administration (FDA) has granted both psilocybin (2019) and esketamine (2019) breakthrough therapy designation for treatment-resistant depression, reflecting preliminary evidence of substantial benefit over existing therapies. However, the field lacks a comprehensive, systematic comparison of these agents, both between each other and against standard treatments or placebo controls. There is also a need for rigorous synthesis of head-to-head data, assessment of adverse event profiles, and exploration of differential responses across clinical subgroups (6). To date, no published systematic review has concurrently examined the efficacy, effectiveness, and safety of both psilocybin and ketamine using standardized evaluation criteria in adult TRD populations.

The purpose of this systematic review is to evaluate and synthesize the current evidence on the efficacy, effectiveness, and safety of psilocybin and ketamine compared to conventional pharmacologic treatments or placebo in adult populations diagnosed with treatment-resistant depression. Specifically, this review aims to answer the following questions:

1. Do psilocybin and ketamine demonstrate superior efficacy in reducing depressive symptoms compared to standard treatments or placebo?
2. What are the observed short- and long-term safety profiles of these compounds in clinical trials involving TRD patients?
3. How does real-world effectiveness (including functional and quality of life outcomes) compare between these psychedelic compounds and traditional interventions?

We hypothesize that both psilocybin and ketamine will show greater short-term efficacy in reducing depressive symptom severity compared to placebo and potentially superior or non-inferior outcomes relative to conventional antidepressants in TRD. Furthermore, we anticipate that although both drugs may be associated with transient adverse effects (e.g., dissociation, nausea), their overall safety profiles will be acceptable within controlled clinical settings.

Methods:

1. Study Design

This work was conducted as a systematic review of the literature, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. No meta-analysis was performed due to heterogeneity in interventions, outcome measures, and follow-up durations across studies.

2. Eligibility Criteria

2.1 Types of Studies

We included randomized controlled trials (RCTs), open-label clinical studies, and observational prospective studies with clinical outcomes. Case reports, retrospective designs, narrative reviews, and non-peer-reviewed material were excluded.

2.2 Types of Participants

Eligible participants were adults (≥18 years) diagnosed with treatment-resistant depression (TRD), defined as failure to achieve clinical response after at least two adequate antidepressant trials from different pharmacological classes.

2.3 Types of Interventions

We included studies assessing psilocybin or ketamine (racemic IV ketamine or intranasal esketamine), administered alone or alongside psychological support. Interventions were compared against placebo, standard antidepressants (e.g., SSRIs), or other active comparators (e.g., ECT).

2.4 Types of Outcomes

2.4.1 **Primary Outcomes**

- Change in depressive symptom severity measured by validated instruments (e.g., MADRS, QIDS-SR16)
- Clinical response (≥50% reduction in baseline depressive score)
- Remission (score below a pre-specified threshold)

2.4.2 Secondary Outcomes

- Duration and sustainability of response/remission
- Functional and quality of life measures

- Adverse effects and safety profiles (including dissociative symptoms, cardiovascular changes, suicidal ideation)

3. Search Methods for Study Identification

3.1 Electronic Searches

We performed a comprehensive search of the following electronic databases from inception to March 2025:

- PubMed
- Embase
- PsycINFO
- Cochrane CENTRAL

The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to: "psilocybin", "ketamine", "esketamine", "depression", "treatment-resistant depression", and "clinical trial".

3.2 **Other Sources**

Additional references were identified through:

- Screening of reference lists of included studies and relevant reviews
- Clinical trial registries (e.g., ClinicalTrials.gov)
- Manual searches of high-impact journals in psychiatry and pharmacology

4. Data Collection and Analysis

4.1 Study Selection

Two reviewers independently screened titles and abstracts of all records. Full-texts of potentially eligible studies were assessed for inclusion. Disagreements were resolved through discussion or consultation with a third reviewer.

4.2 **Data Extraction and Management**

Data were independently extracted by two reviewers using a standardized extraction form. Extracted data included study design, participant characteristics, intervention details, outcome measures, and results. Discrepancies were resolved by consensus.

5. **Risk of Bias Assessment**

Each included study was assessed for risk of bias using appropriate tools based on the study design:

- Randomized trials were assessed using the Cochrane RoB 2.0 tool
- Non-randomized studies (e.g., open-label trials) were evaluated descriptively, considering selection and performance biases.

Domains evaluated included randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting. A summary risk of bias table was generated.

6. **Bias Control**

6.1 **Management of Missing Data**

Studies were included only if sufficient outcome data were available for the primary outcomes. We did not impute missing data; outcomes were analyzed as reported by the original authors.

6.2 **Assessment of Reporting Bias**

Due to the qualitative synthesis approach, no formal funnel plots or statistical tests for publication bias were performed. However, we qualitatively assessed selective reporting within studies and cross-checked outcomes with trial registries when available.

7. **Synthesis Plan**

Due to clinical and methodological heterogeneity (differences in doses, co-interventions, outcome measures, and follow-up duration), we did not perform a meta-analysis. Results were synthesized narratively, organized by intervention (psilocybin or ketamine/esketamine) and type of comparison (placebo or active control). Tables were used to summarize study characteristics and main findings.

Results:

Figure 1 shows the flow of study selection. A total of 476 records were identified through database searching. Seventy-one duplicate records were removed prior to screening, leaving 405 unique records for title and abstract review. Of these, 393 records were excluded, and the full texts of the remaining 12 articles were retrieved and assessed for eligibility. None of the reports were unavailable for retrieval. After full-text review, three studies were excluded on the basis of study design, yielding nine studies that met all inclusion criteria and were incorporated into the qualitative synthesis.

Characteristics of the Included Studies

Follow-up duration in psilocybin studies was generally short (assessing acute response at 3–6 weeks post-dose), whereas ketamine studies included very early evaluations (e.g., 24 hours after a single infusion) as well as short-term follow-up (1–4 weeks, with repeated-dose regimens or maintenance with esketamine). Below are the efficacy/effectiveness and safety findings, organized by intervention.

Efficacy and Effectiveness of Psilocybin

Controlled Trials:

Controlled evidence suggests that psilocybin (combined with psychological support) may produce rapid and significant symptom reductions in patients with treatment-resistant depression (TRD), although results have not been uniform. In the largest phase IIb randomized clinical trial to date (233 TRD patients) (9), a single 25 mg dose of

psilocybin (COMP360 formulation) produced a mean reduction of 12.0 points on the Montgomery-Åsberg Depression Rating Scale (MADRS) at 3 weeks, compared to a 5.4-point reduction with the minimal 1 mg dose (psychedelic placebo) (9). The adjusted between-group difference was significant (~6.6 points, $p<0.001$) in favor of 25 mg psilocybin (9). Consequently, clinical response rates at 3 weeks (≥50% improvement) were higher with psilocybin (~37%) than with placebo (~18%), and remission (minimal depression) occurred in ~30% of patients with 25 mg vs <10% with 1 mg. However, with extended follow-up, the proportion with sustained response at 12 weeks declined (~20% in the 25 mg group), indicating that in many cases the improvement from a single dose was not maintained beyond 1–2 months.

Another RCT (Carhart-Harris et al., 2021) compared psilocybin (two 25 mg sessions) to a conventional SSRI antidepressant (daily escitalopram) over 6 weeks. In this study of 59 patients (some with prior treatments but not strictly TRD), psilocybin achieved higher response (70% vs 48%) and remission rates (57% vs 28%) than escitalopram, but the difference in average improvement on the depressive symptom scale (QIDS-SR-16) did not reach statistical significance in the primary analysis (10). That is, after 6 weeks both groups showed substantial improvement with no significant difference in mean symptom reduction (−8.0 points with psilocybin vs −6.0 with escitalopram, $p=0.17$) (10), although the remission rate was twice as high in the psilocybin arm. These results suggest at least non-inferiority of psilocybin compared to a standard antidepressant in the short term, with the potential for a greater proportion of remissions, but larger samples are needed to confirm this.

Effectiveness in Open-Label Studies:

In controlled settings without a placebo group, findings are consistent with controlled trials, showing marked improvements following psilocybin-assisted therapy. A pioneering open-label study (Carhart-Harris et al., 2016) administered psilocybin in two sessions (10 mg and then 25 mg, one week apart) to 12 TRD patients. A marked reduction in self-reported depressive symptoms was observed from the first week post-treatment (mean reduction on the QIDS scale of ~11.8 points), which largely persisted at 3 months (~9.2-point improvement from baseline, with effect size $g\approx2$) (11). All patients showed some improvement, and ~58% achieved clinical response at one week (11), although some partially relapsed over time.

More recently, an open-label trial in highly treatment-resistant depression (≥5 failed treatments, "severe TRD") evaluated a single 25 mg dose of psilocybin in 12 patients. At 3 weeks, MADRS score decreased by ~15.8 points (95% CI: −25.4 to −6.3) from baseline, and this improvement persisted at 12 weeks (change of −17.2 points, 95% CI: −25.2 to −9.1) (12). This study suggests that even in cases of extreme resistance, psilocybin may induce clinically significant and lasting improvements in some patients (12).

Associated Symptoms:

In addition to alleviating core depressive symptoms, psilocybin may positively affect comorbidities. In the included RCTs, a rapid reduction in concurrent anxiety was consistently reported in patients treated with psilocybin. In fact, 4 out of 5 reviewed RCTs found a significant anxiolytic effect of psilocybin compared to control. Regarding suicidal ideation, the evidence is less consistent: only one RCT showed a significant improvement in suicidal ideation with psilocybin, while other studies showed no clear differences or had too few suicidal events to analyze. It is important to note that in the COMP360 trial, events of suicidal ideation or behavior occurred in all groups, including placebo, during the follow-up period (9), reflecting the inherent risk in the treatment-resistant depression population rather than a clear pharmacological adverse effect.

Summary:

In summary, psilocybin in a controlled therapeutic setting showed short-term antidepressant efficacy in several studies (especially with ~25 mg doses), with some patients achieving remissions lasting weeks to months. However, larger and longer-duration trials are needed to confirm long-term effectiveness and comparisons with established treatments (9).

Efficacy and Effectiveness of Ketamine/ Esketamine

Controlled Trials (IV Ketamine vs Placebo):

Ketamine has been extensively investigated in treatment-resistant depression (TRD), primarily in its racemic intravenous formulation at subanesthetic doses (typically 0.5 mg/kg in a single 40-minute infusion). Controlled clinical trials, starting with pilot studies between 2006–2013, have consistently demonstrated a rapid and potent antidepressant effect of ketamine compared to placebo. In a multicenter RCT with 73 TRD patients (Murrough et al., 2013), a single ketamine infusion led to significantly greater improvement in MADRS scores at 24 hours compared to an active placebo (midazolam). The absolute difference was approximately 8 MADRS points in favor of ketamine (13). Clinically, 64% of patients treated with ketamine achieved response within 24 hours, compared to 28% in the midazolam group (13). This rapid efficacy—often visible as early as 2–4 hours

post-infusion—has been reproduced in numerous studies. A recent meta-analysis synthesizing ~30 trials found that ketamine (either racemic IV or esketamine) approximately doubles the likelihood of response by the end of treatment compared to placebo (RR ≈2.14) and increases remission rates (RR ≈1.64) (14). Likewise, the magnitude of the antidepressant effect in symptom reduction is estimated to be of moderate size in favor of ketamine (effect size d ≈ −0.63) (14).

It is important to note that ketamine's improvement is transient unless doses are repeated: typically, the effect peaks within 24–48 hours post-infusion and then gradually wanes, so that by day 7 many patients have lost much of the initial benefit. However, strategies involving multiple infusions (e.g., several doses over two weeks) can prolong the duration of response and achieve higher rates of sustained remission. Some trials have explored induction regimens (repeated infusions) followed by maintenance (spaced dosing); although results vary, in general around 50–70% of TRD patients can achieve a response after a short series of ketamine infusions, and a smaller proportion maintain remission with weekly or biweekly maintenance doses.

Compared to conventional rescue treatments for TRD, ketamine has also shown efficacy. For instance, in patients with acute suicidal risk, intravenous ketamine has outperformed midazolam in rapidly reducing suicidal ideation, and in indirect comparison to antipsychotics or benzodiazepines (sometimes used for acute suicidal ideation), it is more effective at alleviating suicidal thoughts within hours.

Intranasal Esketamine (Controlled Trials):

Esketamine (S-enantiomer of ketamine), administered intranasally, has been approved as a treatment for TRD in combination with an oral antidepressant. Phase III controlled clinical trials (with ~200–300 patients per study) evaluated intranasal esketamine (flexible doses ~56–84 mg, twice weekly) added to a new antidepressant versus antidepressant + placebo spray. Results showed significantly greater improvement in depression at 4 weeks in the esketamine group. In one of these studies, the mean MADRS reduction was ~21–23 points with esketamine + antidepressant vs ~17 points with antidepressant alone (difference of ~4–6 points; $p<0.05$) (15). One-month response rates with esketamine were around 55–60%, significantly higher than the ~40% observed with antidepressant + placebo (15). Consistently, approximately 50% of patients treated with esketamine achieved clinical response within the first month, and ~25–30% reached remission, surpassing the rates with added placebo.

Although in one specific study (TRANSFORM-1) the primary outcome did not reach significance for the higher dose (15), the totality of Phase III evidence supported esketamine's efficacy, particularly in combination with SSRIs/SNRIs. Additionally, withdrawal and maintenance studies (e.g., SUSTAIN-1) showed that continuing esketamine biweekly or monthly after acute response reduces relapse risk compared to discontinuation, supporting its effectiveness as maintenance therapy in TRD.

Ketamine vs Conventional Treatments:

Beyond placebo comparators, ketamine protocols have been compared to rescue alternatives in TRD such as electroconvulsive therapy (ECT). In general, ECT remains the most effective treatment for severe TRD, although ketamine may approach its efficacy and has practical advantages. A systematic review (6 studies, n=340) directly compared ketamine vs ECT and found ECT to be slightly superior in acutely reducing depressive severity (16). For example, in the largest trial included, 1-month remission was ~63% with ECT versus 46% with a course of IV ketamine. However, ketamine showed a faster antidepressant response (days vs weeks for ECT), and in some studies with longer follow-up the differences narrowed.

No significant differences in serious adverse effects were found between ECT and ketamine (16), although ECT may involve more cognitive effects (e.g., memory loss), whereas ketamine may be associated with acute psychiatric effects (e.g., dissociation). For patients who cannot or do not wish to undergo ECT, IV ketamine may be a viable alternative, although where feasible, ECT still yielded slightly higher average remission rates.

Summary:

In summary, ketamine's efficacy in TRD is well established in the short term: it produces rapid and clinically meaningful improvements in a substantial proportion of refractory patients, especially with repeated administration. Long-term effectiveness requires maintenance strategies (periodic ketamine/esketamine dosing or transition to other therapies), as its effect tends to diminish over time.

Safety and Tolerability

Psilocybin Safety Profile:

In controlled settings with psychological support, psilocybin has been well tolerated by most patients, with no significant organic toxicities or addictive potential observed to date. No serious adverse events (SAEs) directly attributable to psilocybin have been reported in clinical trials (e.g., no cardiac arrhythmias, seizures, serotonin syndrome, etc.). The most common adverse effects (AEs) associated with psilocybin are transient symptoms during or shortly after the session: headache (frequently

reported in both psilocybin and comparator groups), nausea, dizziness/vertigo, and transient elevation of blood pressure. In the COMP360 trial, 77% of participants receiving 25 mg psilocybin experienced some AE (vs ~66% in the 1 mg group) (9), with the most common being headache, nausea, and dizziness (9). These symptoms typically appear on the day of administration or the following day and resolve spontaneously.

During the psychedelic experience itself, nearly all patients report some degree of acute anxiety or transient disorientation (10), especially during the onset phase (first 1–2 hours). In open-label studies, all patients experienced brief episodes of anxiety or fear during the psilocybin ascent (11), and some exhibited transient confusion or disorganized thinking; however, with the presence of trained therapeutic staff, these effects were managed without lasting complications. No cases of persistent psychosis or manic switching have been reported in psilocybin depression trials—participants are usually carefully screened to exclude histories of psychotic or bipolar disorders, reducing this risk. Patterns of compulsive use were also not observed; since psilocybin is administered in a few controlled sessions, its addictive potential is low (it lacks significant dopaminergic reinforcement mechanisms).

Discontinuations due to adverse effects were infrequent and similar to placebo (e.g., 2–13% with psilocybin vs 4–21% with control across studies, with no significant difference) (11), suggesting acceptable tolerability. Nonetheless, psilocybin should be administered in controlled environments: rare episodes of reckless behavior or intense psychological distress during the session have been reported in non-controlled settings. In the trials, some events of suicidal ideation or self-harm occurred in the weeks following treatment, but these appeared in all groups (including placebo) and are attributed more to the severity of underlying depression than to the treatment itself (9). Even so, these findings underscore the need for close follow-up after administration, especially in severe TRD cases.

In sum, psilocybin appears to be safe and well tolerated under strict clinical protocols, with transient adverse effects mostly limited to the acute experience (e.g., anxiety, perceptual changes) and post-session headaches. Long-term safety data are limited; additional long-term follow-up studies are needed to confirm the absence of delayed neurocognitive or psychiatric effects.

Ketamine/Esketamine Safety Profile:

Ketamine, having been used for decades as an anesthetic, has a well-known physical safety profile, though its repeated use for depression presents specific considerations. In TRD studies, short-term safety of ketamine (one or a few doses) has generally been good, with some acute adverse effects consistent with its pharmacology. Common AEs during or immediately after a ketamine infusion include: dissociation (sense of unreality, disconnection, or perceptual hallucinations), dizziness, elevated blood pressure and heart rate, blurred vision, nausea/vomiting, drowsiness or sedation, and occasionally euphoria or anxiety.

A recent meta-analysis confirmed that, compared to placebo, ketamine (racemic or esketamine) is significantly associated with AEs such as dizziness/vertigo (OR ~3.85), transient hypertension (OR ~2.5), nausea (OR ~3.1), and vomiting (OR ~3.18) (14). Dissociation is one of the hallmark effects, with an odds ratio ~8 times higher than placebo (14), typically occurring rapidly (during IV infusion or minutes after esketamine inhalation) and resolving within 30–60 minutes. Although these effects can be uncomfortable, they rarely result in serious complications under controlled clinical conditions. In fact, rates of serious AEs or treatment discontinuation are not significantly different between ketamine and placebo in trials (RR ≈1.0 for all-cause discontinuations; RR ~1.56, p=0.05 for discontinuations due to AEs, marginally significant) (14), indicating that while more patients experience AEs with ketamine, they are generally manageable without the need to stop treatment. In studies comparing to ECT, no differences in serious AEs were observed between ketamine and electroconvulsive therapy.

Regarding long-term safety, the main concerns with repeated ketamine use include the potential for urological and neurocognitive toxicity, as well as the risk of dependence. Chronic recreational ketamine use has been associated with ulcerative cystitis (bladder irritation with urinary urgency and pain) and cognitive or memory deficits. In clinical protocols, exposure is much more controlled; nonetheless, some cases of mild urinary symptoms have been reported with repeated intranasal esketamine, prompting recommendations for monitoring if treatment extends over months.

Psychological tolerance and dependence on ketamine are possible—given its indirect activation of reward pathways—but in supervised clinical settings (infrequent administration, in-clinic under observation), the risk of misuse is low. In fact, guidelines emphasize that intranasal esketamine should only be administered in certified centers with two hours of post-dose observation to control for acute effects and prevent misuse.

Ketamine can cause significant blood pressure elevations during administration; it is therefore contraindicated in patients with uncontrolled

hypertension or unstable cardiovascular disease. Blood pressure was monitored during dosing in the trials (occasionally requiring antihypertensive medication if levels rose too high). No liver or other organ toxicity has been observed with sporadic psychiatric dosing. Some patients reported taste disturbances (dysgeusia) with intranasal esketamine, as well as numbness or mild irritation in the nasal mucosa.

Overall, intranasal esketamine showed an AE profile similar to IV ketamine: the most common effects were dissociation, dizziness, nausea, elevated blood pressure, and a sense of drunkenness; these effects peak around 40 minutes post-dose and then subside, usually allowing for patient discharge after 2 hours. The combination of oral antidepressant with esketamine did not appear to increase other adverse effects beyond those mentioned.

A relevant safety aspect is suicide/self-harm: since many TRD patients experience suicidal ideation, several trials monitored these events. IV ketamine studies often observed a rapid reduction in suicidal ideation following infusion (acute anti-suicidal effect). However, in longer follow-up periods, some patients still experienced suicide attempts as underlying depression persisted or relapsed—highlighting that ketamine does not eliminate the inherent risk in this population and ongoing follow-up is necessary. There is no evidence that ketamine worsens suicidal tendencies; rather, it tends to reduce them transiently. As a precaution, esketamine protocols excluded patients with recent active suicidal ideation, except in specific trials targeting acute ideation, where its reduction was demonstrated.

Risk of bias of included articles:

In evaluating the randomization process, Aaronson et al. (2024) and Carhart-Harris et al. (2016) were judged to be at high risk of bias, whereas Carhart-Harris et al. (2021), Goodwin et al. (2022), Murrough et al. (2013) and Fedgchin et al. (2019) were all deemed low risk. Deviations from the intended interventions again raised high risk in Aaronson et al. and Carhart-Harris et al. (2016), with the four remaining trials generating some concerns. Issues of adherence followed a similar pattern: high risk in Aaronson et al. and Carhart-Harris et al. (2016), low risk in Murrough et al., and some concerns in the others. Missing outcome data produced some concerns in five of the six studies, though Murrough et al. was rated low risk in this domain. Measurement of the outcome was vulnerable to bias in Aaronson et al. and Carhart-Harris et al. (2016), but low risk across the four later trials. Every study exhibited some concerns in the selection of reported results. Taken together, Aaronson et al. (2024) and Carhart-Harris et al. (2016) carry a high overall risk of bias, while Carhart-Harris et al. (2021), Goodwin et al. (2022), Murrough et al. (2013) and Fedgchin et al. (2019) are classified as having some concerns (table 3).

Discussion:

This systematic review synthesized evidence from nine clinical studies examining the efficacy, effectiveness, and safety of psilocybin and ketamine in adults with treatment-resistant depression (TRD). Both agents demonstrated rapid-onset antidepressant effects, with psilocybin showing clinically meaningful symptom reductions following one or two administrations, and ketamine producing immediate benefits, especially within 24–48 hours post-infusion. While psilocybin's benefits often required psychological support and were generally transient, ketamine's effects were similarly short-lived unless maintained via repeated dosing. Esketamine, the intranasal formulation of ketamine, showed moderate superiority over placebo in randomized trials, particularly when combined with oral antidepressants.

Psilocybin

The antidepressant efficacy of psilocybin has been substantiated through several rigorous clinical trials. In a Phase 2, double-blind, randomized controlled trial, Goodwin et al. (2022) administered a single 25 mg dose of psilocybin to adults with treatment-resistant depression (TRD), resulting in a statistically significant reduction in depressive symptoms compared to placebo. Specifically, the mean change in the Montgomery–Åsberg Depression Rating Scale (MADRS) score at week 3 was −12.0 in the 25 mg group versus −5.4 in the 1 mg group, yielding a between-group difference of −6.6 points (95% CI, −10.2 to −3.0; $p < 0.001$). Approximately 29% of participants in the 25 mg group achieved remission at week 3, compared to 8% in the 1 mg group (17,18).

Further evidence comes from a head-to-head trial comparing psilocybin with escitalopram, a selective serotonin reuptake inhibitor (SSRI). Carhart-Harris et al. (2021) conducted a six-week, double-blind, randomized controlled trial involving 59 patients with moderate-to-severe major depressive disorder. Participants received either two doses of 25 mg psilocybin three weeks apart plus daily placebo or daily escitalopram (10–20 mg) plus two doses of 1 mg psilocybin. The primary outcome, change in the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16) score, did not differ significantly between groups (−8.0 for psilocybin vs. −6.0 for escitalopram; between-group difference, −2.0; 95% CI, −5.0 to 0.9; $p = 0.17$). However, secondary outcomes generally favored psilocybin over escitalopram, including higher response rates

(70% vs. 48%) and remission rates (57% vs. 28%) (17,18).

Earlier open-label studies have also demonstrated psilocybin's potential. In a feasibility study by Carhart-Harris et al. (2016), 12 patients with TRD received two doses of psilocybin (10 mg and 25 mg) seven days apart, accompanied by psychological support. All participants showed some reduction in depressive symptoms at one week, with 67% achieving remission at one week and 58% maintaining remission at three months (11).

Ketamine and Esketamine

Ketamine's rapid antidepressant effects have been corroborated by multiple studies. In a randomized, double-blind, placebo-controlled trial, Murrough et al. (2013) administered a single intravenous infusion of ketamine (0.5 mg/kg) to patients with TRD. At 24 hours post-infusion, the ketamine group exhibited a significant reduction in MADRS scores compared to the midazolam (placebo) group, with a mean difference of 7.95 points (95% CI, 3.20–12.71; $p < 0.001$). The response rate at 24 hours was 64% for ketamine versus 28% for midazolam (19).

Meta-analyses have reinforced these findings. Bahji et al. (2022) conducted a systematic review and meta-analysis, reporting that ketamine significantly outperformed placebo in reducing depressive symptoms, with a standardized mean difference (SMD) of −0.63 (95% CI, −0.81 to −0.44). The pooled response rate was 45% (95% CI, 35%–55%), and the remission rate was 30% (95% CI, 21%–39%) (20).

Regarding esketamine, a stereoisomer of ketamine administered intranasally, several studies have demonstrated its efficacy. In a Phase 3, randomized, double-blind, placebo-controlled study, Fedgchin et al. (2019) evaluated fixed doses of intranasal esketamine (56 mg or 84 mg) combined with a newly initiated oral antidepressant in adults with TRD. At day 28, the esketamine groups showed greater reductions in MADRS scores compared to the placebo group, with least squares mean differences of −4.0 for 56 mg and −4.1 for 84 mg doses (both $p < 0.001$). Response rates were 69% for 56 mg, 77% for 84 mg, and 59% for placebo (21).

Comparative studies between ketamine and electroconvulsive therapy (ECT) have also been informative. In a multicenter, randomized controlled trial, Ekstrand et al. (2022) compared intravenous ketamine infusions with ECT in patients with unipolar depression. Remission rates at four weeks were 62.6% for ECT and 46.3% for ketamine ($p = 0.03$). While ECT was more effective in achieving remission, ketamine was associated with fewer cognitive side effects and improved neurocognitive functioning, particularly in attention and executive functions (21).

Collectively, these studies underscore the rapid and significant antidepressant effects of both psilocybin and ketamine in individuals with TRD. While psilocybin may offer sustained benefits with minimal dosing, ketamine and esketamine provide rapid symptom relief, albeit often requiring repeated administrations to maintain efficacy.

Several limitations temper these findings. First, the heterogeneity in trial designs (e.g., dosing schedules, outcome measures, inclusion criteria) precluded meta-analysis, reducing the capacity to generalize effect sizes across populations. Second, many studies had small samples and short follow-up durations—most psilocybin studies assessed outcomes at 3–6 weeks, limiting conclusions about long-term efficacy. Furthermore, risk of bias was rated as high in early psilocybin trials (Aaronson et al., 2024; Carhart-Harris et al., 2016), particularly due to deviations from protocols and missing data. Strengths include the focus on randomized controlled trials, the rigorous application of PRISMA guidelines, and comprehensive data on adverse events and safety, including across real-world and placebo-controlled settings.

The clinical implications are substantial. Psilocybin and ketamine provide promising alternatives for individuals with TRD, especially when rapid relief is critical or conventional antidepressants have failed. However, their transient effects necessitate clear protocols for maintenance and integration with psychological or pharmacological strategies. The low rates of serious adverse effects in clinical settings support their use under supervision, but real-world risks (e.g., misuse, psychiatric destabilization) require vigilance. Future research should prioritize head-to-head comparisons, long-term effectiveness, and biomarkers for predicting individual responses. Furthermore, trials should explore combined approaches (e.g., psilocybin plus SSRIs or ketamine plus cognitive therapy) to enhance durability.

Conclusions

Both psilocybin and ketamine demonstrate substantial short-term efficacy in reducing depressive symptoms among TRD patients, with acceptable safety profiles in clinical settings. Psilocybin may yield higher remission rates in certain patients, while ketamine offers ultra-rapid onset and greater evidence across clinical subgroups. Nevertheless, the short-lived effects, heterogeneity in study designs, and limited long-term data highlight the need for cautious interpretation and further investigation. These agents represent important, though not definitive, steps forward in the management of TRD.

Tables and figures:

Figure 1. PRISMA flow diagram

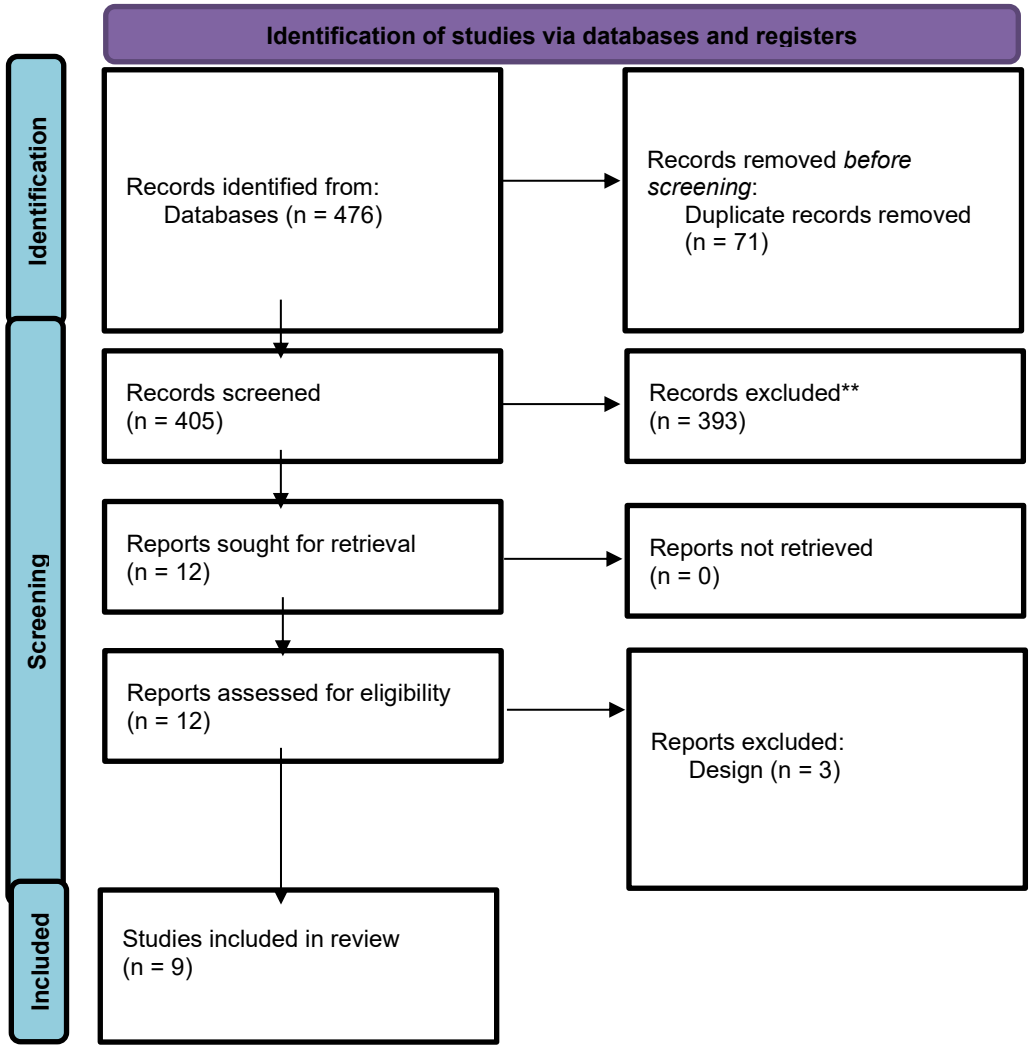

Table 1. Efficacy Trials (Psilocybin vs Conventional Treatments or Placebo)

Study (Design)	Population (Criteria)	Intervention (Comparator)	Primary Efficacy Outcome	Key Efficacy Findings
Goodwin et al. 2022 (9) (Phase IIb Randomized)	233 adults with TRD (≈3 failed antidepressants)	Single dose of psilocybin 25 mg (vs placebo 1 mg)	MADRS change at 3 weeks	Psilocybin 25 mg led to greater depression reduction than placebo (Δ = −6.6 MADRS points). 37% responded to psilocybin vs ~18% with placebo; ~30% achieved remission with 25 mg. No sustained response at 12 weeks in most cases.
Carhart-Harris 2021 (10) (Phase II Randomized, Double-Blind)	59 adults with moderate-to-severe major depression (not all strictly TRD)	Psilocybin 25 mg ×2 sessions + daily placebo (vs Escitalopram 10–20 mg daily + psilocybin 1 mg ×2)	QIDS-SR16 change at 6 weeks	No significant difference in mean symptom reduction (psilocybin = escitalopram, p=0.17). Higher remission rate with psilocybin (57% vs 28%) and trend toward higher response (70% vs 48%).
Carhart-Harris 2016 (11) (Open-Label Study)	12 patients with TRD (resistant to multiple drugs)	Psilocybin 10 mg + 25 mg (1 week apart) (no control)	QIDS change (baseline vs 1 week	Rapid and sustained improvement after psilocybin: −11.8 QIDS points at 1 week (g=3.1); improvement maintained at 3 months (−9.2 points). All patients improved to some extent;

Study (Design)	Population (Criteria)	Intervention (Comparator)	Primary Efficacy Outcome	Key Efficacy Findings
			vs 3 months)	67% had initial response, 42% remained in response at 3 months.
Aaronson et al. 2023 (12) (Open-Label, Observational)	12 patients with severe TRD (≥5 failed treatments)	Single dose of psilocybin 25 mg (no control)	MADRS change at 3 and 12 weeks	Clinically significant reduction in depression: −15.8 MADRS points at 3 weeks (95% CI −25.4 to −6.3); effect maintained at 12 weeks (−17.2 points). Suggests efficacy even in highly resistant cases.

Table 2. Key Efficacy Trials (Ketamine/Esketamine vs Conventional Treatments or Placebo)

Study / Design	Population (Criteria)	Intervention (Comparator)	Primary Outcome	Key Efficacy Findings
Murrough et al. 2013 (13) (Double-Blind RCT)	73 adults with TRD	IV Ketamine 0.5 mg/kg ×1 (vs Midazolam placebo)	MADRS change at 24 h	Ketamine superior to placebo at 24 h: ~8-point difference in MADRS. 64% responded to ketamine vs 28% to midazolam. Rapid effect within <1 day, but limited duration (many relapsed ~7 days).
2023 Meta-analysis (Bahji et al.) (14) (27 RCTs, multiple routes)	~1000 adults with depression (incl. TRD)	Ketamine (IV racemic, IM, IN) or IN Esketamine (vs placebo)	Final Response & Remission	Overall efficacy confirmed: ketamine increased response (RR ~2.14) and remission (RR ~1.64) vs placebo. Moderate effect size for symptom reduction (d = −0.63). Benefit observed for both IV ketamine and IN esketamine.
Fedgchin et al. 2019 (15) (TRANSFORM-2) (Phase III RCT)	223 adults with TRD (≥2 failures)	IN Esketamine 56/84 mg twice weekly + new SSRI (vs placebo spray + SSRI)	MADRS change at 28 days	Greater improvement with esketamine: MADRS reduction −21.4 vs −17 pts (Δ = 4.4, p=0.02). Response in ~53–70% (dose-dependent) vs 41% with placebo; Remission ~52% vs 31% with placebo at day 28. Results support esketamine efficacy in combination with AD.
Greg et al. 2022 (16) (Meta-analysis of 6 RCTs)	340 patients with TRD	IV Ketamine (varied courses) (vs ECT – Electroconvulsive Therapy)	Remission at end of treatment	ECT slightly superior to ketamine in acute antidepressant efficacy. Cumulative remission ~63% with ECT vs 43% with ketamine at ~1 month in the largest study. Ketamine showed faster onset; ECT had an advantage in depth of response.

Note: Typical IV ketamine doses are 0.5 mg/kg over 40 minutes; intranasal esketamine 56–84 mg. MADRS: Montgomery-Åsberg Depression Rating Scale; QIDS: Quick Inventory of Depressive Symptomatology; TRD: Treatment-Resistant Depression; RCT: Randomized Clinical Trial; IN: Intranasal; IM: Intramuscular; SSRI: Selective Serotonin Reuptake Inhibitor; ECT: Electroconvulsive Therapy.

Table 3. Clinical trial risk-of-bias assessment (RoB2)

Domain	Aaronson (2024)	Carhart-Harris (2021)	Goodwin (2022)	Murrough (2013)	Carhart-Harris (2016)	Fedgchin (2019)
Randomization process	High	Low	Low	Low	High	Low
Deviations from intended interventions	High	Some concerns	Some concerns	Some concerns	High	Some concerns
Adherence	High	Some concerns	Some concerns	Low	High	Some concerns
Missing outcome data	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Measurement of the outcome	High	Low	Low	Low	High	Low
Selection of reported result	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Overall Risk of Bias	High	Some concerns	Some concerns	Some concerns	High	Some concerns

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