Psilocybin and Ketamine for Major Depressive Disorder and Treatment-Resistant Depression: A Review of Recent Clinical Trials

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Abstract

This narrative review presents the current state of knowledge on the use of psilocybin and ketamine in the treatment of depression, including treatment-resistant depression (TRD). Drawing on data from clinical trials conducted between 2000 and 2025 -including studies such as COMP001 and NCT03866174 - we analyzed the efficacy, safety, and therapeutic potential of these substances as interventions in the treatment of depression. Particular attention was given to randomized, placebo-controlled trials, especially phase II and III studies, as well as to data obtained from long-term follow-up observations. In the reviewed studies, treatment efficacy was assessed using standardized tools such as the MADRS, QIDS, or HAMD scales.

The findings of our analysis indicate that both psilocybin (including its synthetic form COMP360) and ketamine (administered via various routes) demonstrate a rapid and clinically significant antidepressant effect, often observable after a single dose.

These substances appear to have a relatively favorable safety profile, particularly when used in controlled environments and accompanied by appropriate psychotherapeutic support. We also examined the impact of dosing strategies, psychological integration, and the potential of these interventions to reduce suicidal ideation and tendencies.

Our analysis highlights the necessity and relevance of conducting further research aimed at the standardization of therapeutic protocols and the integration of psychedelic-assisted interventions with conventional methods of treating depression.

Keywords : treatment-resistant depression (TRD), psilocybin, ketamine, clinical trials, major depressive disorder (MDD)

Materials and Methods

This narrative review summarizes recent clinical investigations into the use of psilocybin and ketamine for treating major depressive disorder, with particular focus on treatment-resistant depression (TRD). We conducted a targeted search of the literature published between January 2000 and May 2025 using databases such as PubMed, ClinicalTrials.gov, Scopus, Embase, and Web of Science. Our selection emphasized randomized, placebo-controlled studies with transparent methodology and the use of standardized outcome measures, including MADRS, QIDS, and HAMD scales.

We gave additional consideration to trials that integrated psychotherapeutic support within their protocols, as such approaches may influence both the durability and quality of treatment response-although these frameworks varied widely across studies.

The heterogeneity of therapeutic designs and assessment tools across trials posed challenges for direct comparison, highlighting the need for further standardization in this emerging field.

Introduction

Depressive disorders rank among the most frequently diagnosed conditions in mental-health practice, and their impact on quality of life is often profound and long-lasting. Clinically, the most important entities are Major Depressive Disorder (MDD) and its subtype, Treatment-Resistant Depression (TRD). According to the DSM-5-TR criteria (American Psychiatric Association, 2022), MDD is defined by a persistent (≥ 2 weeks) low mood and/or anhedonia accompanied by somatic and cognitive symptoms that cause significant functional impairment. TRD is commonly defined as the absence of a clinically meaningful response after at least two adequate trials of antidepressants with proven efficacy.

The World Health Organization (WHO) estimates that depression affects more than 280 million people worldwide, making it a leading cause of disability and a major contributor to the global burden of disease. Roughly 15 %–30 % of patients develop TRD, which markedly worsens prognosis, increases the likelihood of hospitalization, and heightens suicide risk. TRD also imposes substantial economic and social costs on health-care systems.

Despite a broad pharmacopeia that includes selective serotonin-reuptake inhibitors (SSRIs), monoamine-oxidase inhibitors (MAOIs), and somatic treatments such as electroconvulsive therapy (ECT), sustained remission remains elusive for many patients. Consequently, the past two decades have seen intensive exploration of alternative therapeutic approaches. Psychedelic compounds-particularly psilocybin and ketamine-have gained attention because numerous studies suggest they can produce rapid, clinically significant antidepressant effects and may enhance neuroplasticity.

Discussion

Psilocybin

Usona Institute trial (NCT03866174) This randomized, double-blind, placebo-controlled study enrolled 104 adults with moderate-to-severe MDD of at least 60 days' duration. Participants received either a single 25 mg dose of synthetic psilocybin or 100 mg of niacin (active placebo), accompanied by professional psychological support. Psilocybin produced a statistically and clinically significant reduction in MADRS scores: a mean additional decrease of 12.3 points versus placebo by Day 43 (95 % CI −17.5 to −7.2; $p < 0.001$). A marked effect (−12.0 points, $p < 0.001$) was already evident by Day 8. Functional improvement on the Sheehan Disability Scale paralleled symptom relief. The treatment was well tolerated; adverse events were transient and non-serious.

COMP001 (Compass Pathways) Conducted at 22 sites across 10 countries, this randomized, double-blind, placebo-controlled trial included 233 adults with MDD. Single doses of COMP360 psilocybin (25 mg, 10 mg, or 1 mg active placebo) were given alongside psychological support. At Week 3, 25 mg yielded a significantly greater mean MADRS reduction than placebo (−12.0 vs. −5.4 points; difference −6.6, 95 % CI −10.2 to −2.9; $p < 0.001$). The 10 mg dose was not superior to placebo ($p = 0.18$). More patients in the 25 mg group achieved ≥ 50 % symptom reduction and remission (MADRS ≤ 10). The antidepressant effect attenuated by Week 12, highlighting the need to study durability and repeat-dose strategies. Adverse events (reported by 77 % of participants) were mostly mild-to-moderate headaches, nausea, and dizziness; suicidal thoughts/behaviors occurred across all arms, underscoring the need for vigilant monitoring.

COMP002, COMP003, and COMP004

• COMP002 (qualitative/exploratory): interviews with TRD patients revealed themes of "emotional breakthrough," enhanced introspection, and cognitive flexibility, emphasizing the therapeutic importance of psychological integration.

• COMP003 (drug-interaction study): co-administration of COMP360 with ongoing SSRI therapy showed no dangerous pharmacological interactions.

• COMP004 (52-week follow-up): after a single 25 mg dose, median time to depressive-symptom relapse was 189 days, compared with 43 days (10 mg) and 21 days (1 mg). Relapse was more frequent when post-session psychological integration was limited, highlighting the value of sustained psychotherapeutic support.

Collectively, COMP001–004 paint a coherent picture of COMP360's antidepressant efficacy-often emerging within days-and an acceptable safety profile. Optimal clinical benefit appears to hinge on adequate preparation, dose, integration, and follow-up therapy.

Additional trials

- University of Zurich (NCT03715127): a single weight-based dose (0.215 mg/kg) in 52 MDD patients reduced MADRS by 13.0 points ($p = 0.0011$) and BDI by 13.2 points ($p = 0.019$); > 50 % achieved remission within 2 weeks, with no serious adverse events.
- Johns Hopkins University (NCT03181529): two doses (20 mg, then 30 mg) given 2 weeks apart lowered GRID-HAMD from 22.8 to 8.0 within 1 week; 71 % responded and 54 % remitted, again with minimal side effects.
- NCT05029466 (wait-list-controlled): TRD patients receiving one to three 25 mg sessions showed a large effect after the first dose (Hedges $g = 1.07$; $p < 0.01$) and further gains with additional sessions, supporting multi-dose regimens.
- Special populations In a JAMA Network Open study of 30 health-care workers with pandemic-related depression, a single 25 mg dose reduced MADRS by 21.3 points versus 9.3 points with placebo ($p < 0.001$), suggesting broader utility in high-stress contexts.
- Analogs CYB003, a deuterated psilocybin analog (NCT05385783), produced a 17-point MADRS decrease at 12 mg versus a 2.9-point decrease with placebo, with predictable pharmacokinetics and favorable tolerability-encouraging further development.

Ketamine

Retrospective chart review (PMID 36112599) Among 424 TRD patients receiving up to ten 0.5 mg/kg IV racemic ketamine infusions over 6 weeks, 50 % responded and 20 % remitted after six infusions; rates rose to 72 % and 38 %, respectively, after ten infusions. Suicidal ideation fell markedly in ~ 50 % of those affected; anxiety scores (GAD-7) dropped by ~ 30 %. Treatment was well tolerated, with no serious adverse events.

Extended-release oral ketamine (R-107) phase 2 trial An open-label lead-in (120 mg/day × 5 days) identified 168 responders, who were randomized to maintenance dosing or placebo

for 12 weeks. Twice-weekly 180 mg R-107 outperformed placebo at Week 13 (mean MADRS difference −6.1 points; p = 0.019) and lowered relapse rates (42.9 % vs. 70.6 %). Adverse effects were mild (headache, dizziness, anxiety); dissociation and sedation were rare, and blood pressure remained stable-supporting ambulatory use.

Bio-K study (PMID 38142892) Seventy-five TRD patients (unipolar or bipolar) received three 0.5 mg/kg IV infusions over 11 days while continuing baseline medications. Response and remission rates were 67 % and 52 %, respectively. Early responders after the first infusion had a 66 % remission rate, versus 20 % in non-responders after two infusions, informing prognostic decisions. No serious adverse events occurred.

Anti-suicidal effects (PMID 24668760) In 36 TRD patients, a single ketamine infusion eliminated explicit and implicit suicidal thoughts in 53 % at 24 h versus 24 % with midazolam ($\chi^2 = 4.6$; p = 0.03), highlighting ketamine's rapid life-saving potential.

Conclusions

Both psilocybin (including the synthetic formulation COMP360) and ketamine demonstrate rapid, robust, and clinically meaningful antidepressant effects-even in TRD populations. Unlike conventional antidepressants, benefits can emerge after a single administration and persist for weeks or months.

• Psilocybin: In controlled settings with psychotherapeutic support, single 25 mg doses significantly reduce depressive symptoms; additional sessions may prolong and intensify benefit. Safety is acceptable; adverse events are typically mild and transient. Integration therapy appears crucial for sustained remission.

• Ketamine: Whether delivered intravenously or as extended-release oral tablets, ketamine offers strong, rapid antidepressant and anti-suicidal effects, including in ambulatory care. Oral formulations may enhance accessibility with fewer hemodynamic or dissociative effects.

These findings justify further phase III trials and the development of integrated treatment models that combine psychedelic pharmacotherapy with structured psychotherapy-especially for patients unresponsive to conventional treatments.

Disclosure statement

Author's contribution

All authors contributed to the article.

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