REVIEW ARTICLE

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Rapid-acting interventions in treatment-resistant depression – a comparative review of esketamine and psilocybin

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Abstract

Introduction and Objective. Treatment-resistant depression (TRD) remains a major clinical challenge affecting patients who fail to respond to at least two adequate antidepressant trials. The development of rapid-acting interventions targeting non-monoaminergic pathways has introduced new therapeutic possibilities. The aim of the review is to critically examine intranasal esketamine and psilocybin-assisted psychotherapy in TRD, comparing their mechanisms of action, clinical efficacy, durability of response, and safety profiles.

Materials and Method. A narrative review method consisting of a literature review was conducted using PubMed and Google Scholar databases. Randomized controlled trials, phase II-IV clinical trials, systematic reviews, and meta-analyses published primarily within the last eight years were analyzed. Case reports and preclinical studies were excluded.

Brief description of the state of knowledge. Esketamine, an NMDA receptor antagonist, has demonstrated rapid antidepressant effects within hours and has received regulatory approval for TRD. While effect sizes are generally modest, relapse prevention has been shown in maintenance trials. Psilocybin, a 5-HT2A receptor agonist administered within a structured psychotherapeutic framework, has shown promising antidepressant effects in early-phase trials, including a large phase IIb study, with sustained improvement following limited dosing. However, its evidence base remains constrained by methodological challenges and limited long-term data.

Summary. Both agents converge on neuroplasticity-related mechanisms yet differ substantially in clinical implementation. Esketamine is an approved rapid-acting option for TRD, whereas psilocybin remains investigational. Further adequately powered trials and long-term safety data are required to define their roles within evolving treatment paradigms.

Key words

neuroplasticity, treatment-resistant depression, antidepressive agents, esketamine, psilocybin

INTRODUCTION

Major depressive disorder (MDD) is a psychiatric condition characterized by persistent depressed mood or loss of interest or pleasure, accompanied by cognitive, emotional, and somatic symptoms that must be present for at least two weeks and cause clinically significant functional impairment [1]. MDD remains one of the leading causes of disability worldwide and is associated with substantial functional impairment, increased suicide risk, and significant socio-economic burden [2, 3]. Despite the availability of multiple monoaminergic antidepressants, approximately 6% – 55% of patients fail to achieve remission after at least two adequate treatment trials. This condition, commonly defined as treatment-resistant depression (TRD), represents a major clinical challenge and is associated with markedly poorer outcomes compared to non-resistant MDD [4]. Conventional pharmacotherapies are further limited by delayed onset of action and frequent adverse effects that compromise adherence [5, 6].

The limitations of traditional antidepressants have stimulated the development of rapid-acting treatment strategies, designed to produce clinically meaningful symptom reduction within hours to days rather than weeks. These interventions target neurobiological systems beyond classical monoaminergic pathways and aim to address the substantial unmet needs of patients with TRD [7].

Intranasal esketamine was the first rapid-acting agent to receive regulatory approval specifically for TRD. Its

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introduction marked a significant development in psychiatric therapeutics by demonstrating that antidepressant effects could be achieved rapidly and through mechanisms distinct from traditional oral agents. Since its approval by regulatory agencies, esketamine has been incorporated into clinical practice as an adjunctive treatment option for individuals with resistant depression [8, 9].

In parallel with advances in glutamatergic modulation, renewed clinical research has investigated psilocybin-assisted psychotherapy as a potential treatment for TRD. Unlike continuous daily pharmacotherapy, psilocybin is administered episodically within a structured therapeutic framework [10, 11].

OBJECTIVE

The aim of this review is to critically examine emerging rapid-acting pharmacological interventions in treatment-resistant depression, with particular focus on intranasal esketamine and psilocybin-assisted psychotherapy. A further objective is to compare their mechanisms of action, clinical efficacy, durability of response, and safety profiles in order to evaluate their implications for current treatment paradigms in TRD. Additionally, the review highlights methodological challenges and current limitations of the available evidence.

MATERIALS AND METHOD

A narrative review method consisting of a literature review was conducted using the PubMed and Google Scholar databases. Search terms included: 'treatment-resistant depression', 'esketamine', 'intranasal esketamine', 'psilocybin', 'psychedelics', and 'rapid-acting antidepressants', as well as related variations of these terms. The review focused on randomized controlled trials, phase II-IV clinical trials, systematic reviews, and meta-analyses. To ensure up-to-date evaluation of current evidence, priority was given to studies published within the last 8 years. Case reports and non-clinical animal studies were excluded.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Esketamine – mechanism of action. Esketamine, the S-enantiomer of racemic ketamine, represents a significant departure from traditional monoaminergic antidepressants by directly targeting the glutamatergic system [12]. It functions as a nonselective, noncompetitive antagonist at the N-methyl-D-aspartate (NMDA) receptor, possessing a three to four times higher affinity for these receptors compared to the (R)-enantiomer [13]. The primary mechanism involves the antagonism of NMDA receptors on GABAergic inhibitory interneurons in the prefrontal cortex, which leads to a 'disinhibition' of excitatory signalling and a subsequent surge in glutamate release. This glutamatergic modulation triggers downstream activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and stimulates neuroplasticity pathways, including the secretion of brain-derived neurotrophic factor (BDNF) and activation of the mammalian target of rapamycin (mTOR) pathway. Clinically, these molecular cascades facilitate rapid synaptogenesis, potentially reversing the synaptic deficits associated with chronic depressive states [12].

Acute antidepressant efficacy. The clinical hallmark of esketamine is its rapid onset of action. The meta-analysis by Wang et al. of double-blind randomized controlled trials (DB-RCTs) demonstrates that significant improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) scores can be observed as early as 2–4 hours after the first administration. Meta-analyses focusing specifically on patients with treatment-resistant depression demonstrate a clear time-dependent pattern of antidepressant efficacy following intranasal esketamine administration. The largest effect size is observed in the early post-dose period, with a standardized mean difference (SMD) of -0.67 within 2–4 hours. However, this estimate is derived from a single study and should therefore be interpreted with caution. At 24 hours, the antidepressant effect remains significant (SMD -0.48), although substantial heterogeneity has been reported (I^2 = 73%), necessitating the use of a random-effects model. Subsequently, effect sizes attenuate but remain statistically significant at one week (SMD -0.27) and at weeks 3–4 (SMD -0.23), with lower heterogeneity across studies. This trajectory suggests a rapid onset of antidepressant action followed by a gradual reduction in effect magnitude over time [14].

In a randomized, placebo-controlled phase 4 clinical trial, Janik et al. evaluated intranasal esketamine as monotherapy in adults with treatment-resistant depression. By day 28, treatment was associated with significant improvements in MADRS scores, with least-square mean differences versus placebo of -5.1 for the 56 mg dose and -6.8 for the 84 mg dose [15]. However, in a PRISMA-compliant systematic review and meta-analysis, Fountoulakis et al. characterized the overall efficacy of esketamine as modest, reporting pooled effect sizes ranging from 0.15–0.23 at weeks 2–4. The authors noted that the initial superiority over placebo tended to diminish over time, partly due to progressive improvement in the treatment-as-usual (TAU) comparator groups [16].

Maintenance of response and relapse prevention. Maintaining the initial antidepressant benefit remains a clinical challenge. In randomized withdrawal designs, such as the SUSTAIN-1 trial, continuing esketamine treatment after 16 weeks of induction/optimization, significantly delayed relapse compared to switching to a placebo nasal spray. The risk of relapse was reduced by 51% in stable remitters and 70% in stable responders [17]. Long-term extension data from the SUSTAIN-3 study suggest that these benefits can persist for up to 6.5 years in patients who remain on maintenance treatment [9].

Comparative efficacy. Esketamine has demonstrated competitive efficacy when compared to conventional augmentation strategies. In the ESCAPE-TRD trial, esketamine nasal spray was found to be superior to quetiapine XR augmentation in achieving remission at week 8 (27.1% vs. 17.6%) and maintaining a relapse-free state through week 32 [18]. Network meta-analysis conducted by Vázquez et al. generally ranks esketamine and lithium as having lower numbers-needed-to-treat (NNT) for response (NNT = 7 and 5, respectively), compared to atypical antipsychotics like aripiprazole or brexpiprazole (NNT = 9–16) [19].

Anti-suicidal effects. Esketamine has been investigated in patients with major depressive disorder and acute suicidal ideation, primarily for its potential to induce rapid reductions in clinician-assessed suicide risk. In a double-blind, randomized, placebo-controlled trial conducted by Canuso et al., patients at imminent risk for suicide received intranasal esketamine in addition to standard-of-care treatment. In a *post hoc* analysis of this study, a higher proportion of patients receiving intranasal esketamine achieved resolution of suicide risk (defined as clinician global judgment scores of 0–1) compared with placebo at 4 hours (21.2% vs. 9.7%) and 24 hours (40.0% vs. 6.5%) following the first dose [20]. However, these findings are based on a single *post hoc* analysis and should be interpreted cautiously. Consistent with this, the meta-analysis by Fountoulakis et al. did not confirm a sustained anti-suicidal effect at 4 weeks, and there is currently no robust evidence supporting the use of esketamine for long-term suicide prevention [16].

Safety and tolerability. Esketamine is generally well-tolerated under controlled conditions, with a distinct profile of transient adverse events. The most frequent effects observed in a long-term extension study conducted by Zaki et al. include headache (36.9%), dizziness (33.9%), nausea (33.6%), dissociation (25.5%), nasopharyngitis (23.8%), somnolence (23.1%), dysgeusia (20.2%), back pain (20.0%), anxiety (18.6%) and vertigo (18.6%). Among adverse events reported on esketamine dosing days, the vast majority resolved within the same day (97%) [9]. Dissociative and perceptual symptoms typically peaked shortly after administration and generally resolved within approximately 120 minutes post-dose. Moreover, evidence suggests that both the frequency and intensity of dissociative symptoms decrease with repeated intranasal esketamine administrations [21, 22]. Transient increases in blood pressure have also been consistently reported; however, these haemodynamic changes were generally asymptomatic and not associated with serious cardiovascular complications [23].

Importantly, discontinuation rates due to adverse events are relatively low (6.4%) [9]. While concerns regarding abuse potential exist, real-world data have not yet shown evidence of widespread misuse [9, 24].

Critical perspective and translational relevance. Esketamine illustrates the clinical feasibility of glutamatergic modulation as a rapid-acting antidepressant strategy. By demonstrating that targeting the glutamate system is clinically viable, it has paved the way for a new generation of antidepressant research.

However, a balanced clinical view must acknowledge limitations. Recent independent meta-analyses suggest that the effect sizes are small-to-moderate, and that the quality of evidence is often limited by industry sponsorship and the potential for functional unblinding due to dissociative side effects [16, 17]. Unresolved questions remain regarding the optimal duration of maintenance treatment, the existence of a withdrawal syndrome, and the long-term impact on neurocognition in elderly populations. These considerations emphasize the importance of continued independent evaluation and long-term outcome data.

Psilocybin – mechanism of action. Psilocybin is a naturally occurring serotonergic psychedelic tryptamine that acts as a prodrug and is rapidly converted to its active metabolite, psilocin, which primarily exerts its effects through agonism of the serotonin 5-HT2A receptor [25]. Activation of cortical 5-HT2A receptors, particularly on layer V pyramidal neurons in the prefrontal cortex, initiates glutamatergic modulation and engages intracellular signalling pathways associated with synaptic plasticity, including BDNF- and mTOR-related processes [26, 27]. A schematic overview of the proposed molecular and synaptic cascade is presented in Figure 1. These mechanisms may partly explain the sustained antidepressant effects reported after one or a limited number of psilocybin administrations.

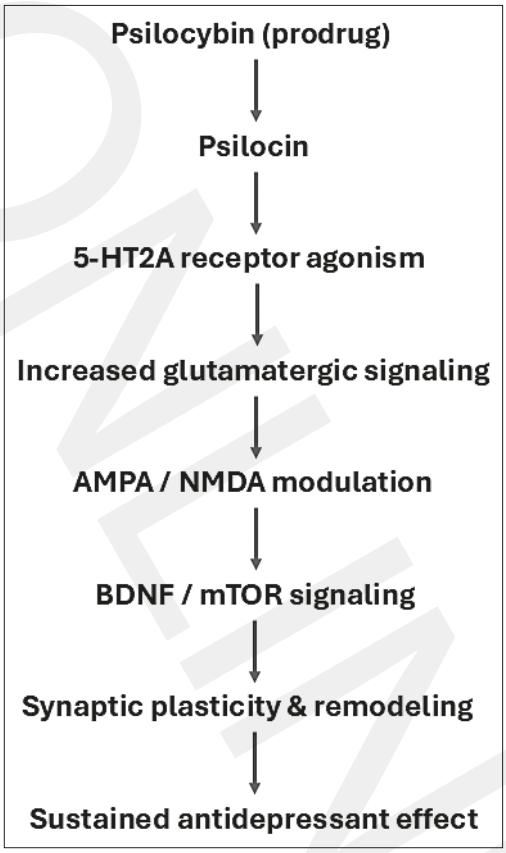

Figure 1. Conceptual schematic of the proposed mechanism of action of psilocybin in treatment-resistant depression [25–27]

In addition to molecular and synaptic mechanisms, psilocybin has been shown to induce changes in large-scale brain networks implicated in affective and self-referential processing. Neuroimaging studies in patients with treatment-resistant depression have reported post-treatment alterations in resting-state functional connectivity, including modulation of networks involving the medial prefrontal cortex and limbic regions [28]. These alterations frequently involve the default mode network (DMN), a system implicated in self-referential processing and rumination, which has been reported to show post-treatment normalization of functional connectivity following psilocybin administration [29]. Importantly, these network-level changes appear to persist beyond the acute subjective effects of psilocybin, and have been correlated with clinical improvement [28, 29]. Nevertheless, the causal relationship between serotonergic signalling, network reorganization, and antidepressant response remains incompletely understood, and current evidence is largely derived from small samples and correlational analyses.

Clinical efficacy of psilocybin in treatment-resistant depression. Clinical evaluation of psilocybin suggests antidepressant efficacy in treatment-resistant depression, although outcomes vary depending on study design and population characteristics. The first investigation specifically targeting TRD was a single-arm, open-label feasibility study conducted by Carhart-Harris et al., which enrolled 12 patients with failure to respond to at least 2 prior antidepressant treatments. Depressive symptoms were assessed using the 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR16), demonstrating marked symptom reduction as early as one week following psilocybin administration (mean QIDS difference -11.8; 95% CI -9.15 to -14.35; p=0.002; Hedges' g=3.1), with substantial effects maintained at 3 months (-9.2; 95% CI -5.69 to -12.71; p=0.003; Hedges' g=2) [30]. Given the small sample size, open-label design, and absence of a control condition, these findings were interpreted as proof-of-principle rather than confirmatory evidence of efficacy.

A subsequent follow-up study expanding this cohort to 20 participants reported sustained reductions in depressive symptoms, with large effect sizes observed at 3 months (Cohen's d = 1.5; $p < 0.001$) and 6 months (Cohen's d = 1.4; $p < 0.001$) [31]. While these results suggest durability of response in a subset of patients, interpretation remains limited by the uncontrolled design and potential confounding effects of ongoing psychological support.

More rigorous evaluation was provided by a multicentre, double-blind Phase IIb randomized clinical trial conducted across 10 countries, enrolling 233 adults with TRD. Participants were randomized to receive a single dose of psilocybin at 25 mg, 10 mg, or an active control dose of 1 mg. Changes in depressive severity were assessed using the Montgomery-Åsberg Depression Rating Scale total scores from baseline to week 3. The 25 mg dose, but not the 10 mg dose, resulted in a significantly greater reduction in MADRS scores compared with the 1 mg control (least-squares mean change -12.0 vs. -5.4; 95% CI -10.2 to -2.9; $p < 0.001$), with a response rate of 37% [32]. Although the trial employed a double-blind design, the integrity of blinding in psychedelic studies may be challenged by the intensity of acute subjective effects. Nevertheless, the large sample size and multinational design strengthen the generalizability of these findings within a highly refractory TRD population, in which response rates are typically lower than those reported in non-resistant major depressive disorder [33].

Additional exploratory evidence comes from a smaller open-label study evaluating psilocybin administered adjunctively to ongoing selective serotonin reuptake inhibitor (SSRI) treatment in patients with TRD. In this cohort (n = 19), a single 25 mg dose was associated with a mean reduction in MADRS scores of -14.9 at week 3 (95% CI -20.7 to -9.2) [34]. Although limited by sample size and lack of a control group, this study provides preliminary evidence that discontinuation of SSRIs may not be a prerequisite for psilocybin's antidepressant effects.

Durability and therapeutic context of psilocybin in treatment-resistant depression. An important distinguishing feature of psilocybin compared with conventional antidepressant treatments is the durability of its observed antidepressant effects following limited administration. Available clinical data in treatment-resistant depression indicate that 1 or 2 supervised doses may be associated with sustained symptom improvement lasting weeks to months, rather than requiring continuous daily dosing. While the biological mechanisms underlying this persistence remain incompletely understood, current evidence suggests that psilocybin engages neuroplastic processes that may support longer-term changes in affective processing beyond the acute pharmacological effects [35, 36].

Crucially, psilocybin in clinical trials is administered within a structured therapeutic framework that integrates pharmacological intervention with psychological support. Treatment protocols typically include preparatory sessions aimed at establishing therapeutic rapport and setting expectations, a supervised dosing session conducted in a controlled environment with non-directive psychological support, and post-session integration designed to contextualize and consolidate the experience. Within this framework, the intensity and qualitative features of the acute subjective experience, including altered self-referential processing, have been reported to be associated with longer-term clinical outcomes. However, these associations should be interpreted cautiously, as they are derived largely from open-label or partially blinded studies, and do not establish a causal relationship between subjective experience and antidepressant efficacy [10, 35].

Safety and methodological considerations of psilocybin in treatment-resistant depression. From the safety perspective, psilocybin-assisted psychotherapy has generally been well tolerated in controlled clinical settings, with most adverse events being transient and occurring during or shortly after dosing sessions. Commonly reported effects include anxiety, nausea, headache, transient increases in blood pressure, and acute psychological distress, which are typically managed through structured psychological support and supervised administration. Importantly, available data in treatment-resistant depression indicate that serious adverse events are uncommon. However, transient worsening of suicidal ideation and instances of self-injurious behaviour have been reported, underscoring the necessity of rigorous patient screening, close monitoring, and integrated psychological care, particularly in highly complex and vulnerable populations [10].

Interpretation of efficacy and safety data is further complicated by several methodological challenges inherent to psychedelic research. Despite the use of formal double-blind designs, the intensity of acute subjective effects frequently results in functional unblinding, which may inflate observed treatment effects through expectancy and placebo mechanisms. In addition, most studies have been limited by small sample sizes, restricted ethnic and clinical diversity, and the exclusion of individuals with psychotic or bipolar spectrum disorders, thereby constraining the generalizability of findings to broader psychiatric populations. Variability in psychotherapeutic frameworks, dosing strategies, and follow-up duration further complicates cross-study comparisons. Collectively, these limitations highlight that psilocybin should currently be regarded as an investigational intervention in TRD, with its safety and clinical utility requiring confirmation in larger, adequately powered trials with longer-term follow-up and standardized therapeutic protocols [10, 35]. A comparative overview of the mechanisms, clinical evidence, and therapeutic characteristics of esketamine and psilocybin is presented in Table 1.

Table 1. Comparative overview of esketamine and psilocybin in treatment-resistant depression [8–12, 14, 26, 27]

Domain	Esketamine	Psilocybin
Regulatory status	FDA/EMA approved for TRD	Investigational; phase IIb completed
Primary pharmacological target	NMDA receptor antagonism	5-HT2A receptor agonism
Core neurobiological mechanism	Glutamatergic disinhibition leading to AMPA activation and engagement of BDNF/mTOR pathways	5-HT2A-mediated glutamatergic modulation engaging plasticity-related signalling pathways
Onset of antidepressant effect	Within hours	Within days to one week
Durability of response	Maintained with continued dosing; relapse prevention demonstrated in maintenance trials	Sustained improvement reported after 1 or 2 supervised sessions
Mode of administration	Repeated intranasal dosing, typically adjunctive to oral antidepressants	Episodic supervised dosing within structured psychological support

SUMMARY

The emergence of rapid-acting antidepressant interventions represents a significant development in the management of treatment-resistant depression. Intranasal esketamine has established a clinically validated model of glutamatergic modulation capable of producing rapid symptomatic improvement, supported by multiple randomized controlled trials and real-world data. Its efficacy, while generally modest in magnitude, is reproducible and has led to regulatory approval, positioning esketamine as an important addition to current therapeutic strategies for TRD.

Psilocybin-assisted psychotherapy, by contrast, remains investigational but introduces a conceptually distinct treatment paradigm. Rather than continuous pharmacological modulation, psilocybin is administered episodically within a structured psychotherapeutic framework, with evidence suggesting the possibility of sustained symptom reduction following limited dosing. However, the current evidence base is constrained by smaller sample sizes, challenges related to blinding, and limited long-term data. As such, psilocybin cannot yet be considered a standard clinical intervention in TRD, despite encouraging early findings.

Despite apparent convergence on glutamatergic plasticity-related pathways, the clinical models of implementation of esketamine and psilocybin differ substantially. Together, these approaches reflect a broader shift away from traditional monoaminergic models toward rapid-acting and neuroplasticity-oriented strategies. Ongoing research into additional glutamatergic modulators and investigational psychedelic compounds further suggests that this therapeutic direction may extend beyond the 2 agents discussed here. Whether this transition constitutes a true paradigm shift or an evolutionary expansion of existing treatment frameworks remains to be determined. Future research should prioritize adequately powered phase III trials, longer-term safety monitoring, and direct comparative studies to clarify patient selection, durability of response, and integration into clinical practice.

In conclusion, rapid-acting interventions, such as esketamine and psilocybin, signal a transformative period in the treatment landscape of TRD. While esketamine has already altered clinical practice, psilocybin represents a promising but still developing frontier. Continued rigorous investigation will determine the extent to which these therapies redefine the standards of care for patients with treatment-resistant depression.

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