

Durability of Esketamine in Treatment Resistant Depression

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Treatment-resistant depression (TRD) is a chronic, recurrent condition. It is associated with substantial morbidity, impaired functioning, and high relapse rates. Around 30% of patients with major depressive disorder (MDD) fail to respond adequately after several treatment trials. This highlights a critical unmet need for effective, rapid-acting therapies ^[1]. Esketamine nasal spray (Spravato) is an N-methyl-D-aspartate (NMDA) receptor antagonist and the first antidepressant with a novel mechanism approved in decades ^[2]. Short-term efficacy is well established. However, questions remain about its long-term effectiveness and its role in relapse prevention. This review examines evidence from key randomized controlled trials, long-term extension studies, and regulatory data to evaluate the durability of antidepressant response and the prevention of relapse with esketamine. Available evidence shows that continued esketamine treatment significantly delays relapse in patients who reach remission or a stable response. However, long-term outcomes beyond one year are still not fully defined.

Introduction

Major depressive disorder (MDD) is a leading cause of disability worldwide. It affects around 300 million people and contributes to the global burden of disease ^[3]. Despite many pharmacologic and psychotherapeutic interventions, a significant proportion of patients do not achieve adequate response. Treatment-resistant depression (TRD) is most commonly defined as failure to respond to at least two adequate antidepressant trials. It affects about 30% of people with MDD and is linked to higher relapse, chronicity, comorbidity, and suicide ^[1]. The economic burden is substantial. TRD accounts for disproportionate healthcare costs and lost productivity. Conventional antidepressants mainly target monoaminergic neurotransmission. They

have a delayed onset—usually 4–6 weeks—and incomplete efficacy in TRD, leaving a critical unmet need for rapid-acting and effective therapies ^[4].

The discovery of ketamine's rapid antidepressant effects in the early 2000s marked a major shift in depression therapeutics. Relief could occur within hours, not weeks ^[5]. Esketamine, the S-enantiomer of racemic ketamine, was developed to exploit its rapid onset while potentially improving safety and tolerability. It was approved by the United States Food and Drug Administration in March 2019 for the treatment of TRD in combination with an oral antidepressant. It was also approved for MDD with acute suicidal ideation. Esketamine thus represented the first new antidepressant mechanism in decades ^[2]. Its non-competitive antagonism of NMDA receptors triggers downstream glutamatergic signaling. This action differs from monoaminergic approaches. It offers rapid symptom relief and a theoretical basis for lasting benefit through synaptic plasticity and network reorganization ^[6].

The value of esketamine extends beyond its rapid onset to its long-term effects. TRD is recurring by nature. Residual symptoms cause a high relapse risk, even after an initial response ^[7]. Maintenance pharmacotherapy is often needed for high-risk patients. The best duration and method for esketamine use are not yet clear. Short-term efficacy is shown in randomized controlled trials. But questions remain about its effect in relapse prevention, its response durability with continued use, and its position compared to other therapies for TRD. This review brings together evidence from pivotal trials, long-term extension studies, real-world data, and comparative research to assess the durability of esketamine's effects and role in relapse prevention in TRD.

Mechanism of Action and Rationale for Maintenance Treatment

The pharmacologic rationale for esketamine centers on glutamatergic modulation. This is different from typical monoaminergic antidepressants. Esketamine, as the S-enantiomer of ketamine, non-competitively antagonizes NMDA receptors. It then triggers activation of AMPA receptors and the mTOR and BDNF–TrkB pathways [6]. These cascades promote synaptic plasticity, dendritic remodeling, and network changes in brain regions involved in mood, impulse control, and the stress response. This mechanism may explain the rapid antidepressant effects seen within 24 hours. It also supports the idea of maintenance treatment to stabilize mood regulation circuits [8].

Short-Term Efficacy as a Basis for Long-Term Outcomes

Multiple randomized controlled trials show short-term efficacy, though effect sizes are modest and results vary. In the TRANSFORM program, esketamine plus an oral antidepressant reduced MADRS scores compared with placebo plus an oral antidepressant at day 28. Mean differences ranged from about 3 to 9 points [9, 10]. Not all phase III trials met primary endpoints. TRANSFORM-1 showed a non-significant trend for the fixed 84 mg dose. TRANSFORM-3 in older adults yielded mixed results, with better responses in the 65–74 age group than in those 75 and older [11]. Meta-analyses indicate a statistically significant but small effect. Mean differences are around 2.9–4.0 MADRS points at 4 weeks. The clinical relevance is debated, as worthwhile differences may range from 3 to 9 points [12, 13]. Rapid symptom improvement—often within 24–72 hours—is an advantage over traditional therapies [14, 15]. Real-world studies, such as the French ESKALE cohort, show progressive symptom improvement and higher remission rates

within 3 months. Functional gains are seen in workplace productivity and psychosocial functioning [16, 17].

Long-Term Efficacy and Relapse Prevention (Randomized Evidence of Maintenance Effect)

The key question for practice is whether esketamine's benefits persist over time. In the SUSTAIN-1 trial, patients achieving stable remission or response after 16 weeks of open-label esketamine were randomized to continued treatment or placebo withdrawal. Continuing esketamine significantly delayed relapse. Hazard ratios were 0.49 for remitters and 0.30 for responders, with absolute risk reductions of around 19% and 32%, respectively [18]. However, the randomized withdrawal design has key limitations. Only responders were included, potentially inflating the benefit. The control group also underwent active withdrawal, which could trigger relapse [12, 19]. A meta-analysis of 7 randomized trials confirmed a reduced risk of relapse with continued esketamine (hazard ratio 0.38). However, FDA concerns about one center's data could not be fully addressed due to privacy restrictions [12].

Open-Label Long-Term Data

Open-label extension studies provide greater insight into long-term outcomes but face significant methodological limitations. SUSTAIN-2 and SUSTAIN-3 followed patients for up to one year and 6.5 years, respectively. They showed sustained symptom improvement and stable remission among those who continued treatment [20, 21]. Cognitive performance stayed stable or improved from baseline, and no new safety signals appeared [21]. But there were no comparator groups, high rates of participant attrition, and industry sponsorship, all of which limit causal inference. Data beyond 1 year are scarce, so there is uncertainty about the lasting benefit and

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the optimal duration of maintenance therapy [22, 23].

Comparison with Other (IV) Ketamine Interventions

Comparative effectiveness data help put esketamine's role in context. In the ESCAPE-TRD trial, esketamine plus an SSRI or SNRI showed higher remission at 8 weeks than quetiapine extended-release (27.1% versus 17.6%). Relapse rates were lower through 32 weeks [24]. Network meta-analyses suggest esketamine's effect sizes are similar to those of other augmentation strategies, including second-generation antipsychotics and lithium [25]. Observational reports compare intranasal esketamine with IV racemic ketamine and show similar response and remission rates. IV ketamine may work faster and allow longer intervals between treatments [26, 27]. Efficacy also appears similar to repetitive transcranial magnetic stimulation (rTMS). This stresses the need for head-to-head comparative trials [28].

Safety and Tolerability

Safety and tolerability considerations are paramount in long-term use. Common adverse effects include dissociation, dizziness, sedation, nausea, dysgeusia, and transient increases in blood pressure, typically resolving within hours of administration [29, 30]. Longitudinal analyses show dissociative symptoms decline over repeated administrations [30]. The number needed to harm is less than 10 for several adverse effects, including dissociation and dizziness [31]. Serious adverse events are not significantly increased, though long-term concerns regarding cognitive effects, abuse liability, and urologic toxicity remain theoretical given limited long-term data [32, 33]. The requirement for supervised administration under a Risk Evaluation and Mitigation Strategy (REMS) program reflects these considerations and creates practical barriers

to access [34, 35]. Notably, reporting of harms in published trials has been found to be incomplete compared to regulatory data, suggesting the importance of consulting multiple data sources [33].

Limitations

Several limitations characterize the current evidence base. Pivotal trials enrolled relatively low-stage TRD patients with fewer failed antidepressant trials than typically seen in clinical practice, potentially overestimating effectiveness [12, 36]. Effect sizes, while statistically significant, are modest, and the clinical significance of delayed relapse versus absolute prevention of recurrence remains debated. No clear predictors of response have been identified, though younger age, employment, and fewer prior failed treatments may be associated with better outcomes [37]. The heterogeneity of TRD definitions and the absence of consensus on what constitutes meaningful treatment resistance complicate interpretation and generalizability [1].

Conclusion

In conclusion, esketamine represents a meaningful but modestly effective advancement in TRD treatment, offering rapid symptom relief and a mechanism-based rationale for maintenance therapy. Evidence supports its use for acute treatment and relapse delay when continued as maintenance therapy, though the magnitude of benefit appears smaller than initially hoped, and long-term outcomes beyond one year remain insufficiently defined. Its best-established role is as augmentation for patients with inadequate response to two or more oral antidepressants who require rapid symptom improvement or who have relapsed following initial response. Future research should focus on identifying patient subgroups most likely to benefit, optimizing maintenance dosing strategies, and clarifying long-term safety and comparative

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effectiveness within the expanding therapeutic landscape for TRD.

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