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- Durability of Esketamine in Treatment Resistant Depression
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Viewpoint Article

Durability of Esketamine in Treatment Resistant Depression

Iryna Salapenka, MD and Tyler Kjorvestad, MD

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

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

effectiveness within the expanding therapeutic landscape for TRD.

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Editorial

Psilocybin-Associated Transient Multidomain Functional Recovery in Advanced Alzheimer's Disease: Lessons from a Landmark Case Report and the Wider Evidence Landscape

Tyler Kjorvestad, MD

The popular press has highlighted a striking case report published in *Frontiers in Neuroscience* describing transient but multidomain functional improvement in an octogenarian woman with advanced Alzheimer's disease following high-dose psilocybin-containing mushroom administration [1]. The New York Post coverage brought the findings to a wide audience, describing an 80-year-old patient with a 10-year history of Alzheimer's (including five years of marked hypofunction, monosyllabic speech, chronic urinary incontinence, executive dysfunction, dysphagia, dependent mobility, and flat affect) who, after receiving 5 g of psilocybin-containing mushrooms (Enigma strain), experienced spontaneous autobiographical speech approximately 19 hours post-administration, followed by progressive improvements in continence, ambulation, autonomous dressing, emotional responsiveness, eye contact, social interaction, contextual memory recollection, and engagement in conversation [1]. A second 3 g session one month later further enhanced verbal expressivity, humor, and gait agility, with continence persisting [1].

As a clinician whose work has consistently examined the therapeutic potential and limitations of psychedelic compounds across psychiatric and emerging neurologic indications, I approach this report with the same measured, evidence-based framework that has characterized my prior analyses. The case is both compelling and humbling. It does not demonstrate disease reversal, as the authors explicitly note, but it does raise the hypothesis that residual functional capacity in late-stage neurodegeneration may persist and become transiently accessible under specific neuromodulatory conditions [1]. This editorial integrates the NY Post coverage and full case details with the comprehensive evidence review provided, examines mechanistic plausibility, safety, and ethical aspects, and delivers practical recommendations for the field.

Case Report

The patient's baseline state reflected profound, longstanding deficits consistent with advanced Alzheimer's disease [1]. The intervention was observational and exploratory, with no established dosing framework for dementia. The acute phase included autonomic activation, suspected hyperthermia, profuse sweating, and a prolonged, deep-sleep-like state [1]. The subsequent improvements were objective and spanned autonomic, motor, executive, memory, affective, and social domains [1]. Particularly notable was the restoration of urinary continence after more than five years of chronic incontinence, a function that relies on integrated interoceptive awareness, executive inhibition, and fronto-insular networks [1]. One-month follow-up confirmed sustained continence and a positive subjective experience ("It is pleasant to come here") [1].

This single-case observation is consistent with the larger trend seen in my earlier editorials on ketamine in psychotic disorders and psilocybin versus SSRIs: dramatic, sometimes unexpected functional shifts in refractory conditions can occur under psychedelic influence, yet they must be interpreted with extreme caution in the absence of controlled data [2, 3]. The authors correctly emphasize that causality cannot be established and spon-

taneous fluctuations cannot be excluded [1]. Nevertheless, the report functions as a powerful signal for hypothesis generation.

Mechanistic Plausibility: Converging Pathways Supported by Preclinical Data

The case gains substantial weight when situated within the extensive mechanistic literature. Classical serotonergic psychedelics act primarily as 5-HT_2A receptor agonists, a receptor highly expressed in cortical regions critical for cognition and dysregulated across the Alzheimer's continuum [4, 5]. Beyond acute receptor agonism, these compounds engage downstream signaling cascades, including BDNF/TrkB, mTOR, and sigma-1 receptor (Sig-1R) pathways, which converge on processes impaired in Alzheimer's disease: synaptic plasticity, neuroinflammation, mitochondrial function, and network connectivity [6–9].

Landmark preclinical work has shown that psychedelics promote structural neuroplasticity ("psychoplastogenesis") through intracellular 5-HT_2A receptor activation localized to the Golgi apparatus [10]. A single dose of psilocybin can produce approximately a 10% increase in dendritic spine size and density that persists for a month [11]. LSD and psilocin bind TrkB (the BDNF receptor) with affinities roughly 1,000-fold higher than conventional antidepressants, and plasticity/antidepressant-like effects in preclinical models depend on TrkB but are independent of 5-HT_2A for the behavioral component [12]. A systematic review of 20 studies confirmed rapid changes in plasticity-related genes and proteins, with effects outlasting acute drug action [13].

Anti-neuroinflammatory effects have been demonstrated in 29 of 36 preclinical studies measuring cytokines, with suppression of TNF-α and other markers in activated microglia via multiple serotonergic and TrkB pathways [14, 15]. The strongest direct evidence for disease-relevant pathology modification comes from DMT, which, when chronically administered in triple-transgenic AD mice, markedly alleviated cognitive impairment, reduced amyloid-β accumulation, restored sigma-1 receptor levels, and preserved ER-mitochondria contacts and calcium dynamics [16]. Sigma-1 receptor agonism attenuates amyloid toxicity, rescues LTP, improves memory in Aβ models, and synergizes with donepezil [17–19]. Default mode network modulation and increased global integration provide additional theoretical support for compensating AD-related network dysfunction [20, 21].

Despite the mechanistic promise, human data specific to Alzheimer's remain essentially absent [22]. No completed randomized controlled trials exist. Geriatric representation in the broader psychedelic literature is minimal; of approximately 1,400 patients across 36 trials, only 19 were aged 65 or older, with detailed safety data for just 10 [23]. A phase 1 low-dose LSD study in healthy older adults demonstrated excellent tolerability with no cognitive impairment [24]. The Parkinson's disease open-label psilocybin pilot (n=12) showed sustained improvements in depression, anxiety, and non-motor symptoms [25]. Indirect support comes from psychedelic therapy for end-of-life distress, where reductions in anxiety, depression, and demoralization have been observed [26]. A registered phase 2 trial of psilocybin for depression in early-stage Alzheimer's (NCT04123314) has not yet reported results [27].

Microdosing, often proposed as a safer approach for dementia, lacks supportive controlled evidence and may weaken cognitive control [28–30].

Safety, Ethical, and Practical Challenges in the Dementia Context

Cardiovascular effects are well documented, including increased blood pressure and heart rate across dose ranges [31, 32]. Chronic microdosing raises concerns regarding 5-HT_2B-mediated cardiac fibrosis [33]. In patients with dementia, the altered sensorium risks compounding disorientation and precipitating delirium-like states [34]. A systematic review noted serious adverse events in approximately 4% of participants with preexisting neuropsychiatric conditions [35].

Informed consent and decisional capacity present fundamental barriers. Moderate-to-severe dementia typically precludes the understanding required for a consciousness-altering intervention [36, 37]. The psychotherapeutic framework central to psychedelic protocols may be difficult or impossible for many patients to engage [38]. Drug interactions with cholinesterase inhibitors remain unstudied, and serotonin syndrome risk with concurrent serotonergic agents is a pharmacodynamic concern [39].

These realities reinforce the consistent position across my work: medicalization with rigorous supervision, appropriate screening, trained facilitators, and ethical supervision is mandatory [40, 41].

Areas of Future Research

An unresolved tension exists regarding mTOR: psychedelics activate this pathway for plasticity, yet mTOR hyperactivation in Alzheimer's suppresses autophagy and promotes pathology [42, 43]. This paradox, along with uncertainties about stage-specific 5-HT_2A receptor dysregulation, optimal dosing, long-term safety in elderly populations with impaired cognition, and whether effects are disease-modifying versus transiently symptomatic, defines the current frontier [44]. Emerging directions include non-hallucinogenic psychoplastogens that retain TrkB-mediated plasticity without acute subjective effects, potentially bypassing consent and safety barriers [45]. Serotonergic psychedelics as epigenetic modulators represent another nascent but promising angle [46].

Summary and Recommendations

The Lago et al. case report [1] and the broader evidence reviewed here illustrate both the intriguing potential and the considerable translational challenges of applying classical psychedelics to Alzheimer's disease. Preclinical mechanisms are robust and convergent, particularly DMT/Sig-1R effects on amyloid and mitochondria, neuroplasticity promotion, and anti-inflammatory actions. Human data, however, remain limited to one case report, a small safety study in healthy older adults, a Parkinson's pilot, and indirect end-of-life findings.

The most promising near-term application is likely psilocybin for neuropsychiatric symptoms (depression, anxiety, existential distress) in early-stage Alzheimer's, where patients retain capacity for informed consent and psychotherapeutic engagement—a hypothesis currently under investigation. Larger, controlled trials with biomarker confirmation, standardized outcomes, detailed safety monitoring, and capacity protocols are urgently needed. Development of non-hallucinogenic analogs needs to be prioritized. Until robust data accrue, responsible practice demands restraint, multidisciplinary collaboration, and observance of the highest ethical and evidence-based standards.

The field stands at an inflection point. Disciplined investigation may clarify whether these compounds can offer meaningful relief to patients and families confronting one of medicine's most devastating conditions.

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