

Esketamine vs. Quetiapine: Which Augmentation Strategy for TRD?

Written by The Life Science Feed Editorial Team · Edited by Mara Voss

Treatment-resistant depression (TRD) remains a significant challenge in psychiatric practice, leaving many patients with persistent symptoms despite multiple therapeutic attempts. For clinicians, the choice of augmentation strategy after initial antidepressant failure is important, balancing rapid symptom relief with long-term tolerability and safety. The field has long sought clearer guidance on how newer, rapid-acting agents compare to established options.

KEY TAKEAWAYS

- **The Pivot:** Direct comparative data between esketamine and quetiapine augmentation for TRD provides a clearer picture of their respective roles.
- **The Data:** Both agents demonstrate efficacy in reducing depressive symptoms, but their onset of action and side effect profiles differ substantially.
- **The Action:** Clinicians should weigh the need for rapid response against tolerability, considering patient-specific factors and the potential for adverse events with each agent.

Major depressive disorder affects millions globally, and a substantial proportion of these individuals will not achieve remission with standard antidepressant monotherapy. When a patient fails to respond adequately to at least two different antidepressant treatments of adequate dose and duration, they are typically classified as having treatment-resistant depression. This clinical reality necessitates augmentation strategies, where an additional medication is added to the existing antidepressant regimen to enhance its therapeutic effect. The goal is not merely symptom reduction, but often full remission, which is associated with better long-term outcomes and reduced risk of relapse. The unmet need in TRD is profound, driving the development and investigation of novel agents and comparative effectiveness research.

Esketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, represents a newer class of antidepressant with a distinct mechanism of action, offering a rapid onset of effect. It is administered intranasally and requires supervised administration due to its dissociative properties and potential for abuse. Quetiapine, an atypical antipsychotic, has a well-established role as an augmentation agent in TRD, often used at lower doses than those for psychotic disorders. Its mechanism involves antagonism at dopamine D2 and serotonin 5-HT2A receptors, among others, contributing to its mood-stabilizing and antidepressant effects. The comparison of these two agents is particularly relevant given their differing pharmacological profiles, administration routes, and safety considerations. Understanding their head-to-head performance helps refine treatment algorithms for a complex patient population.

Comparing Mechanisms and Clinical Profiles

Esketamine's rapid antidepressant effects are thought to stem from its modulation of glutamatergic neurotransmission, particularly through NMDA receptor antagonism. This leads to a cascade of intracellular events, including increased synaptic plasticity and neurogenesis, which are believed to counteract the neurobiological deficits seen in depression. The drug's dissociative effects, including depersonalization and derealization, are transient but require careful monitoring during and immediately after administration. Its use is typically restricted to certified clinics, adding a logistical layer to its accessibility. Patients receiving esketamine must be monitored for at least two hours post-administration for these acute side effects, as well as for blood pressure elevations. This structured environment is a significant departure from typical outpatient psychiatric care.

Quetiapine, in contrast, exerts its antidepressant effects through a broader pharmacological profile. At lower doses, its potent antagonism of histamine H1 and alpha-1 adrenergic receptors contributes to sedation and anxiolysis, while its partial agonism at 5-HT1A receptors and antagonism at 5-HT2A and D2 receptors are thought to mediate its antidepressant and mood-stabilizing properties. It is available in immediate-release and extended-release formulations, offering flexibility in dosing. Unlike esketamine, quetiapine can be prescribed for at-home use, making it a more accessible option for many patients. But its use is associated with metabolic side effects, including weight gain, dyslipidemia, and hyperglycemia, which necessitate regular metabolic monitoring. These long-term safety concerns are a critical consideration for chronic use in a population already at risk for cardiometabolic disease.

Trial Design and Patient Selection

A head-to-head trial comparing esketamine and quetiapine augmentation would typically enroll adult patients diagnosed with major depressive disorder who have not responded to at least two prior antidepressant treatments. Such a trial would aim to reflect real-world clinical practice, including patients with varying degrees of illness severity and comorbidity, while excluding those with severe psychiatric comorbidities that might confound results or pose safety risks, such as active substance use disorder or psychotic features. Patients would continue their stable background antidepressant therapy throughout the study period. Randomization would assign patients to either intranasal esketamine plus their oral antidepressant or oral quetiapine extended-release plus their oral antidepressant. The primary endpoint would likely be a change from baseline in a standardized depression rating scale, such as the Montgomery-Åsberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale (HAM-D), at a predefined time point, often around 6 to 8 weeks. Secondary endpoints would include remission rates, response rates, functional improvement, and various safety and tolerability measures. The duration of such a trial would need to be sufficient to capture both acute efficacy and the emergence of adverse events, potentially extending to several months or longer for maintenance phases. For a deeper dive into the complexities of defining and managing treatment resistance, consider our article on why a shifting definition changes who gets care.

Efficacy and Onset of Action

When comparing the efficacy of esketamine and quetiapine augmentation, the speed of symptom improvement is a key differentiator. Esketamine is known for its rapid antidepressant effects, with some patients experiencing significant symptom reduction within hours or days of the first dose. This rapid onset is particularly valuable for patients with severe, debilitating depression or those at acute risk. Quetiapine, while effective, typically exhibits a more gradual onset of action, with full therapeutic benefits often observed over several weeks. This difference in kinetics can influence

treatment decisions, especially when immediate relief is a priority. Both agents have demonstrated efficacy in reducing overall depressive symptom severity, but the magnitude of effect and the proportion of patients achieving remission can vary. Remission, defined as a near-complete absence of depressive symptoms, is the ultimate goal of treatment and is often more challenging to achieve in TRD. The trial would have meticulously tracked these rates, providing a direct comparison of how many patients in each arm moved from symptomatic to asymptomatic. The specific patient population, including prior treatment failures and duration of illness, would also influence the observed response and remission rates, highlighting the importance of careful patient selection in clinical practice. For a comprehensive overview of psychiatric conditions and their management, the Oxford Handbook of Psychiatry (4th ed) serves as an excellent resource.

Safety and Tolerability Profiles

The safety and tolerability profiles of esketamine and quetiapine are distinct and represent significant considerations for clinicians. Esketamine's acute side effects, including dissociation, sedation, and blood pressure elevation, necessitate its administration in a supervised setting. These effects are generally transient, resolving within two hours, but they can be distressing for some patients. Long-term safety concerns for esketamine include potential for urinary tract symptoms and cognitive effects, though data on these are still evolving. The potential for abuse, while low in the supervised clinical setting, is also a consideration. Quetiapine's side effect profile is characterized by metabolic disturbances, including weight gain, dyslipidemia, and increased risk of type 2 diabetes. Sedation is also common, particularly at the initiation of treatment, which can impact daily functioning. Other side effects include orthostatic hypotension and anticholinergic effects. The choice between these two agents often involves a careful risk-benefit assessment, balancing the immediate concerns with esketamine against the long-term metabolic risks associated with quetiapine. Patient preference and comorbidity burden, such as pre-existing metabolic syndrome, play a significant role in this decision-making process. The trial would have collected extensive data on adverse events, allowing for a direct comparison of their incidence and severity in each treatment arm. This granular data is essential for clinicians to counsel patients effectively and manage expectations regarding potential side effects. The specific rates of discontinuation due to adverse events in each group would also provide a practical measure of tolerability.

Limitations and Clinical Context

Any head-to-head trial, even a well-designed one, comes with inherent limitations. The open-label design is an obvious caveat for a study comparing two drugs with such distinct administration routes and acute effects. Blinding patients and clinicians to treatment assignment for esketamine versus oral quetiapine is practically impossible, which can introduce bias in subjective outcome measures. The duration of the trial might also be a limitation; while acute efficacy is important, TRD is a chronic condition, and long-term comparative data on sustained remission and relapse prevention are equally critical. The trial was not powered to detect differences in specific subgroups, such as those with comorbid anxiety disorders or a history of trauma, and that gap matters for personalized treatment. The generalizability of the findings to all TRD patients is also a consideration, as patients with severe medical comorbidities or active substance use might have been excluded, limiting the applicability to complex real-world cases. The cost-effectiveness of these treatments, particularly esketamine with its supervised administration requirements, is another practical consideration not always fully captured in efficacy trials. Understanding the full spectrum of treatment options, including newer approaches,

is vital for clinicians navigating this complex area; our previous coverage on esketamine vs. quetiapine augmentation provides additional context.

The choice between esketamine and quetiapine augmentation for TRD is not straightforward. Both offer distinct advantages and disadvantages. Esketamine provides rapid relief, which can be life-saving for some patients, but requires a significant logistical commitment and carries acute side effect risks. Quetiapine offers a more traditional oral administration but comes with metabolic concerns and a slower onset of action. The decision must be individualized, taking into account patient preferences, comorbidities, prior treatment history, and the specific clinical context. For instance, a patient with severe, acute suicidality might benefit more from esketamine's rapid action, while a patient with metabolic syndrome might find quetiapine's side effect profile less appealing. The availability of resources for supervised esketamine administration also plays a role in accessibility. These considerations the need for a thorough clinical assessment and shared decision-making process with patients. The next trials need to show not just efficacy, but also how these agents perform in diverse, real-world populations over extended periods, and how they impact functional recovery and quality of life beyond just symptom scores. Comparative effectiveness research that includes other augmentation strategies, such as lithium or thyroid hormone, would further enrich the evidence base for TRD management. The ongoing evolution of treatment options for TRD highlights the persistent challenge of this condition and the continuous effort to improve patient outcomes. The long-term impact on cognitive function and overall quality of life, beyond depressive symptom reduction, remains an area requiring further investigation for both agents.

CLINICAL IMPLICATIONS

The direct comparison of esketamine and quetiapine augmentation for TRD provides clinicians with much-needed clarity, but it does not simplify the decision. The rapid onset of esketamine is a compelling advantage for patients in acute distress, offering a potential lifeline where traditional antidepressants have failed. But the logistical burden of supervised administration and the acute dissociative effects mean it is not a universally accessible or preferred option.

Quetiapine, with its established track record and oral formulation, remains a viable and often more practical choice for many. Its metabolic side effect profile, however, demands vigilance and proactive monitoring, particularly in a patient population already vulnerable to cardiometabolic disease. The trade-off between rapid, supervised intervention and slower, home-based treatment with metabolic risks is a complex one that requires careful patient counseling.

For the industry, these findings underscore the continued need for novel TRD treatments that combine rapid efficacy with a more favorable tolerability and administration profile. The current options, while effective for some, each carry significant caveats that limit their widespread applicability. Future developments should focus on agents that can bridge this gap, offering both speed and safety without the current logistical hurdles. The choice hinges on individual patient circumstances, including their tolerance for side effects, their ability to access specialized care, and the urgency of symptom relief. Clinicians must integrate this comparative data with a holistic understanding of their patient's needs and preferences, recognizing that no single augmentation strategy will be optimal for everyone with TRD.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. Nuñez NA, Joseph B, Pahwa M, et al. Augmentation strategies for treatment resistant major depression: A systematic review and network meta-analysis. *J Affect Disord.* 2022;302:385-400. doi:10.1016/j.jad.2021.12.134
2. Alnefeesi Y, Chen-Li D, Krane E, et al. Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis. *J Psychiatr Res.* 2022;151:693-709. doi:10.1016/j.jpsychires.2022.04.037
3. Subramanian S, Oughli HA, Gebara MA, Palanca BJA, Lenze EJ. Treatment-Resistant Late-Life Depression: A Review of Clinical Features, Neuropsychology, Neurobiology, and Treatment. *Psychiatr Clin North Am.* 2023;46(2):371-389. doi:10.1016/j.psc.2023.02.008
4. Kajumba MM, Kakooza-Mwesige A, Nakasujja N, Koltai D, Canli T. Treatment-resistant depression: molecular mechanisms and management. *Mol Biomed.* 2024;5(1):43. doi:10.1186/s43556-024-00205-y
5. Kverno KS, Mangano E. Treatment-Resistant Depression: Approaches to Treatment. *J Psychosoc Nurs Ment Health Serv.* 2021;59(9):7-11. doi:10.3928/02793695-20210816-01
6. Fountoulakis KN, Saitis A, Schatzberg AF. Esketamine Treatment for Depression in Adults: A PRISMA Systematic Review and Meta-Analysis. *Am J Psychiatry.* 2025;182(3):259-275. doi:10.1176/appi.ajp.20240515

LICENCE & RIGHTS

© 2026 The Life Science Feed. All rights reserved. This content is produced for medical education purposes. It may not be reproduced, distributed, or transmitted without prior written permission from The Life Science Feed.

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com