

PRIORITY UPDATES FROM THE RESEARCH LITERATURE (PURLs)

Esketamine: A Possible Adjunctive Therapy for Treatment Resistant Depression

Annie Huang, DO, Jennifer L. Fernandez Vasquez, MD, and Catherine A. Yeager, PhD

If available in one's practice area, augmenting current medication therapy with esketamine results in greater rates of remission for treatment resistant depression as compared with quetiapine¹. (J Am Board Fam Med 2025;38:1120–1122.)

Keywords: Depression, Esketamine

Strength of Recommendation

B: Recommendation is based on a single randomized controlled trial with consistent quality.

Illustrative Case

A 37-year-old female with a history of major depressive disorder (MDD) presents for ongoing depressive symptoms despite psychotherapy and pharmaceutical treatments. She first tried fluoxetine for 6 months, then a switched to sertraline for over 6 months; both were titrated to maximum tolerable dose. She asks if there is something else that can help with her chronic depressive symptoms.

Clinical Context

Major depressive disorder is a condition that is defined by at least 2 weeks or more of mood and cognition changes with disturbances in sleep, appetite, and/or concentration, and loss of interest and pleasure. Depression is associated with several factors that decrease an individual's quality of life.²

Failure to respond to at least 2 or more trials of medication therapy with adequate dose and duration is considered treatment-resistant depression (TRD).³ Prevalence of TRD varies widely in medical literature (12 to 55%).²⁻⁵ Up to two-thirds of patients with MDD do not achieve remission with initial treatment. This lack of response is associated with negative outcomes such as medical comorbidities including anxiety and substance use disorders, incapacity for work, frequent hospitalizations, premature death, elevated risk of suicide and generally higher costs for health care systems.⁴⁻⁵ In 2010, it was estimated that MDD and TRD had a national economic burden of \$210.5 billion in the United States.⁶

Lack of response to pharmacologic treatment in depressed patients with suicide risk can be fatal.⁵ Traditional TRD treatments have included adjunctive therapies such as antipsychotics (eg, quetiapine), mood stabilizers such as lithium, and lamotrigine, or thyroid hormone (eg, T3 - triiodothyronine) in combination with antidepressants. However, these treatments can be limited in efficacy and often introduce challenging side effects.⁸ Clinical trials have shown that esketamine, administered as a nasal spray, is associated with greater remission rates compared with other adjunctive treatments.¹

Methods

This article was identified as a potential PURL through the standard systematic methodology.⁹

An additional literature search was conducted by searching [PubMed, Dynamed, UpToDate] with the terms [Treatment resistant depression, management, prevalence, treatment] to find additional

This article was externally peer reviewed.

Submitted 22 September 2025; accepted 3 October 2025.

From the DD Eisenhower Army Medical Center Family Medicine Residency, Augusta, GA (AH, JLFV, CAY).

Funding: None.

Conflict of interest: The authors declare no conflict of interest. The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

Deputy Editor: Carina Brown, MD, Cone Health Family Medicine Residency, Greensboro, NC, carina.brown@conehealth.com

Corresponding author: Catherine A. Yeager, PhD, DD Eisenhower Army Medical Center Family Medicine Residency, Augusta, GA (E-mail: catherine.a.yeager2.civ@health.mil).

Copyright © 2025 by Family Physicians Inquiries Network, Inc.

literature to place this research into the context of current clinical practice.

Study Summary

The ESCAPE-TRD trial, an open-label, rater-blinded, multi-country, randomized, active-controlled clinical trial, examined the efficacy and safety of esketamine nasal spray compared with extended-release quetiapine as augmentation therapy for TRD when used alongside a serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI). The study included 676 patients, ages 18 to 74 with TRD in a current episode lasting at least 4 to 6 weeks, who did not respond to a minimum of 2 antidepressant trials using at least 2 different medication classes. Baseline severity had to be ≥ 34 on the Inventory of Depressive Symptomatology–Clinician-Rated scale (range 0 to 84, higher scores indicate more severe depression). Those who had a history of substance use, severe suicide risk, recent electroconvulsive therapy (ECT) or ketamine use, concomitant psychotic disorders, noncompliance with previous regimens, significant cognitive impairment or were pregnant or lactating were excluded. Treatment intervention was esketamine nasal spray as an adjunct to antidepressant treatment with either selective SSRI or SNRIs with the control being quetiapine as an adjunct to SSRI or SNRI. Symptoms were assessed with the Montgomery-Asberg Depression Scale (MADRS), with scores ranging from 0 to 60 in which higher scores demonstrated greater severity of depression and scores below 12 demonstrated remission. Primary outcome was remission of depression at 8 weeks and key secondary outcome was prevention of relapse in treatment resistant depression at 32 weeks. Relapse was defined as a MADRS score increasing to greater than 18, which is the threshold indicative of moderate depression.

Esketamine nasal spray was found to be superior to extended-release quetiapine in achieving remission at week 8 (91/336 (27.1%) vs 60/340 (17.6%), respectively, adjusted $P = .003$; adjusted odds ratio (AOR), 1.74; 95% CI, 1.20-2.52) and preventing relapse through week 32 after remission at week 8 (21.7% vs 14.1%, respectively, AOR 1.72; 95% CI, 1.15 to 2.57). Based on the definition of remission compared with relapse, 2 to 3 points on the MADRS may be clinically meaningful. Patients in the esketamine group also showed a greater reduction in depressive symptoms over time compared with those in the quetiapine

group even though remission was not achieved in these cases, with least squares mean change from baseline in MADRS of -2.2 (95% CI, -3.6 to -0.8) at the 32 week follow up favoring esketamine. At week 32, a last-observation-carried-forward analysis showed that 75.5% of the esketamine group had treatment response compared with 55.5% of the quetiapine group (odds ratio 2.48; 95% CI, 1.78-3.46).

Adverse events were more common in the esketamine group at 91.9% vs 78% in the quetiapine group. These were transient and mild with the most common symptom being dizziness. Discontinuation rates were high in both groups, with the esketamine group at 23% and quetiapine group at 40%. Discontinuation due to adverse events or poor treatment response was less frequent in the esketamine group compared with the quetiapine group; 14 patients (4.2%) vs 37 patients (11%). Serious adverse events were low (5.7% vs 5.1%); however, there was 1 death in each arm of the trial, both unrelated to treatment.

What Is New

Findings from this study demonstrate a promising pharmacologic treatment for TRD that improves symptoms and increases chance of remission as compared with usual pharmacologic augmentation with the antipsychotic quetiapine. There are limited prior studies that demonstrate the effectiveness of this treatment compared with the current standard of care.

Caveats

While this was a large-scale study, it may have inherent bias since researchers have affiliations with Janssen Pharmaceuticals, the manufacturer of esketamine nasal spray. In addition, the trial was single-blind, so patients knew they were receiving esketamine. Authors used extensive exclusion criteria that eliminated comorbid behavioral health conditions. Comorbid conditions are commonly seen in TRD, which raises questions about the effectiveness of esketamine augmentation in the “typical” patient with TRD. In addition, the study population was primarily female (67%) and White (92%), which makes it difficult to generalize across other groups. It should also be noted that the discontinuation rate for both interventions was remarkably high because of adverse events or low efficacy.

Challenges to Implementation

Esketamine nasal spray would be difficult to implement in American primary care settings. Only physicians registered with the FDA's Risk Evaluation and Mitigation Strategy (REMS) program could prescribe and administer esketamine, so there is presently limited availability. Furthermore, patients need to be observed in office for at least 2 hours after administration of the drug, a requirement that may be difficult to implement in a busy primary care clinic. In addition, some health insurance formularies may not include esketamine at this time.

References

1. Reif A, Bitter I, Buyze J, ESCAPE-TRD Investigators, et al. Esketamine nasal spray versus quetiapine for treatment-resistant depression. *N Engl J Med* 2023; 389:1298–309.
2. World Health Organization. *Depression and other common mental disorders: global health estimates*. Geneva: World Health Organization; 2017. License: CC-BY-NC-SA 3.0 IGO.
3. Gaynes BN, Lux L, Gartlehner G, et al. Defining treatment-resistant depression. *Depress Anxiety* 2020;37:134–45.
4. Li CT. Overview of treatment-resistant depression. *Prog Brain Res* 2023;278:1–23.1.
5. Little A. Treatment-resistant depression. *Am Fam Physician* 2009;80:167–72.
6. Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry* 2015;76:155–62.
7. *Depression in adults: treatment and management*. London: National Institute for Health and Care Excellence (NICE); June 29, 2022.
8. Ruberto VL, Jha MK, Murrough JW. Pharmacological treatments for patients with treatment-resistant depression. *Pharmaceuticals (Basel)* 2020;13:116.
9. Smith P, Castelli G. The Priority Updates from the Research Literature (PURLs) Methodology. *J Am Board Fam Med* 2024;37:799–802.