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EDITORIAL

Are ketamine and its enantiomers the answer to treatment-refractory depression?

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1. Introduction

Major depressive disorder (MDD) is a leading cause of global disability, affecting nearly 300 million people worldwide [1]. Despite the availability of traditional monoamine-based antidepressants, one-third of all patients encounter challenges in achieving full recovery [2]. Notably, remission rates in major depression are reportedly less than 15% among patients with two prior conventional treatment or augmentation failures, that is, with treatment-resistant depression (TRD) [3]. This underscores the urgent need for innovative treatment modalities to address the pervasive burden of depression. Advancements in understanding the neurobiological mechanisms of depression have led to the exploration of novel therapeutic pathways to overcome the limitations of conventional approaches.

Ketamine, an N-methyl-D-aspartate (NMDA) antagonist and dissociative anesthetic, has emerged as a potent treatment for TRD. Ketamine has demonstrated rapid and robust alleviation of symptoms in patients with TRD, with evidence supporting its efficacy in reducing suicidal ideation [4]. Initial studies revealed the rapid antidepressant effects of intravenous racemic ketamine, although sustainability posed a challenge [5]. Subsequent investigations explored repeated intravenous doses of racemic ketamine, showing effectiveness in maintaining short-term antidepressant effects [5].

Recognizing the limitations of intravenous administration, alternative delivery routes for ketamine were explored. A significant milestone was achieved with the approval of intranasal esketamine, alongside a conventional antidepressant, by the U.S. Food and Drug Administration (FDA) for TRD in March 2019. This editorial aims to critically appraise the evidence supporting the efficacy of ketamine and its enantiomers in treating treatment-resistant depression and to provide recommendations for clinicians.

2. Mechanisms of action

Ketamine's mechanism in treating TRD involves various neural pathways, with its antidepressant effects stemming from its ability to disinhibit NMDA receptors on inhibitory GABA interneurons. This disinhibition leads to enhanced glutamatergic activation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA), which initiate intracellular signaling cascades involving brain-derived neurotrophic factor-TrkB-ERK and PI3-AKT-mammalian target of rapamycin pathways [6]. Recent investigations also suggest that ketamine's impact may extend beyond the glutamate-GABA systems, potentially involving other low-affinity targets such as opioid receptors, including human-recombinant μ, κ, and δ opioid receptors [7]. Additionally, emerging evidence indicates the subgenual anterior cingulate cortex as a critical site of action for ketamine's antidepressant effects [7].

3. ketamine and its enantiomers

The exploration of various formulations and delivery routes of ketamine for TRD has been the focus of numerous studies. Intranasal esketamine combined with the initiation of a new antidepressant, or intravenous racemic ketamine administered either alone or in combination with an antidepressant, has demonstrated rapid and substantial effectiveness in adults with TRD in numerous randomized controlled trials [5,8].

The short-term effectiveness of intravenous racemic ketamine often necessitates repeated dosing to sustain therapeutic benefits [9]. Studies investigating a range of doses from 0.1–1.0 mg/kg suggest that higher doses (0.5–1.0 mg/kg) exhibit superior efficacy compared to lower doses (0.1–0.2 mg/kg) one day following administration [10]. Determining the optimal frequency of intravenous administration in patients with TRD remains a topic of investigation, with one multicenter double-blind study showing no discernible difference in acute antidepressant efficacy between twice-weekly and thrice-weekly intravenous administrations (0.5 mg/kg) [11].

Esketamine is a more potent NMDA receptor antagonist than its enantiomer R-ketamine [6]. Intranasal esketamine, evaluated in numerous registration trials prior to regulatory approval, was initiated concurrently with a conventional

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antidepressant and compared against a placebo co-administered with an antidepressant. Effective dosages were identified as 56 mg and 84 mg, administered twice weekly for 4 weeks, followed by weekly administration for an additional 4 weeks, and subsequently every 1–2 weeks thereafter [12]. A meta-analysis of intranasal esketamine augmentation in TRD revealed significant improvement of depressive symptoms, notwithstanding a notable placebo response [13]. Nevertheless, subgroup analysis suggested that differences compared to placebo were not statistically significant in certain subgroups (e.g. individuals with fewer than 3 previous antidepressant failures) [14]. Furthermore, a recent phase 3b, open-label, single-blind, multicenter trial compared intranasal esketamine with extended-release quetiapine alongside an SSRI or SNRI in 676 TRD patients. Results showed higher remission rates at week 8 in the esketamine group (27.1%) compared to the quetiapine group (17.6%), with fewer relapses in the esketamine group (21.7% vs. 14.1%). Esketamine also demonstrated better outcomes over 32 weeks, including higher remission and treatment response rates and greater reduction in MADRS scores from baseline [15].

Due to the lack of a properly designed head-to-head trial, the comparative efficacies of intranasal esketamine and intravenous racemic ketamine remain uncertain [16]. Nonetheless, findings from a single study suggested that twice- or thrice-weekly intravenous racemic ketamine might exhibit superiority over intranasal esketamine [17]. A recent meta-analysis that compared intranasal and intravenous ketamine formulations failed to discern a significant difference between the two formulations or routes of administration in terms of efficacy at 24 hours, 7 days, and 28 days [12]. Another meta-analysis concluded that intravenous ketamine may offer superior efficacy and lower dropout rates [5]. However, drawing definitive conclusions from these analyses is challenging due to the heterogeneity observed across the studies.

Preliminary reports have also highlighted racemic ketamine's effectiveness in treating TRD through oral, intramuscular, and subcutaneous formulations. Among these, the oral formulation has been subject to relatively more studies in TRD, with evidence indicating efficacy after repeated dosing, although data on efficacy remains insufficient [18,19].

Importantly, although R-ketamine is a far less potent NMDA receptor antagonist than S-ketamine, increasing preclinical evidence suggests R-ketamine may have more potent and longer lasting antidepressant effects than S-ketamine, alongside fewer side effects [20–22]. As a matter of fact, a pilot trial of R-ketamine has demonstrated rapid-acting and sustained antidepressant effects in individuals with treatment-resistant depression [23]. However, head-to-head comparisons with S-ketamine and racemic ketamine are necessary. The precise molecular target for R-ketamine's effects is not definitively known, but evidence suggests the σ1 receptor is a strong candidate [24]. σ1 receptors are ligand-regulated transmembrane proteins expressed by neurons, microglia, astrocytes, and oligodendrocytes [25]. Agonists of σ1 receptors such as R-Ketamine can shift microglia polarization from pro-inflammatory to reparative [25]. Importantly, σ1 receptor stimulation is considered a valid target for novel antidepressants [26].

Finally, whilst ketamine may have antidepressant properties, its acute psychoactive effects complicate successful masking in placebo-controlled trials [27]. Importantly, in a recent study assessing the antidepressant efficacy of intravenous ketamine versus placebo a completing blinding of the participants was obtained with surgical anesthesia. Results showed no significant difference between ketamine and placebo [27].

4. Ketamine and ECT

Electroconvulsive therapy (ECT) remains widely recognized as the gold standard to treat TRD due to its high efficacy. However, concerns persist regarding its cognitive adverse effects and the challenges associated with administration. In a recent meta-analysis by Rhee et al., 2022, six clinical trials comprising 340 patients (162 for ECT and 178 for ketamine) were included. The overall pooled standardized mean difference for depression symptoms favored ECT over racemic ketamine (IV and IM), suggesting its superiority in improving depression severity [28]. Additionally, Anand et al., 2023 conducted an open-label, noninferiority trial involving 403 TRD patients without psychosis, randomized to receive either IV ketamine or ECT in a 1:1 ratio [29]. Results indicated that 55.4% of the ketamine group and 41.2% of the ECT group achieved treatment response, with ketamine deemed noninferior to ECT. However, it is noteworthy that response rates in certain ECT subgroups were unexpectedly low, which contradicts existing literature citing response rates as high as 80–90% [30].

5. Adverse events

Currently, studies on the safety of Esketamine for long-term and repeated treatment are relatively limited. In their recent research, Jiang et al., (2023) evaluated the U.S. Food and Drug Adverse Event Reporting System (FAERS) database [31]. Analysis of FAERS data indicates higher AE reports among females aged 18–65, with common issues including dissociation, sedation, nausea, vomiting, anxiety, elevated blood pressure, dizziness, and suicidal ideation. Serious risks such as increased hospitalization and death were also linked to Esketamine. Moreover, Esketamine's effects on mood and mental states, including euphoric mood, feeling of relaxation, and feeling drunk, could substantially increase the risk of misuse and addiction. Despite its use in treating suicidal patients, there is a notable incidence of suicidal ideation and attempts. Further, long-term administration of esketamine for has been associated with an increase in lower urinary tract symptoms (LUTS), including dysuria, pollakiuria, urgency, nephrolithiasis, hematuria, and incontinence [32]. There are also reports of ketamine-induced cystitis [33].

6. Expert opinion

Ketamine has been extensively studied for its efficacy in treating TRD, with various formulations and delivery routes investigated. Studies have shown that intranasal esketamine or intravenous racemic ketamine, rapidly and substantially alleviate symptoms in adults with TRD. The effectiveness of

intravenous racemic ketamine often requires repeated dosing, with higher doses (0.5–1.0 mg/kg) showing superior efficacy compared to lower doses (0.1–0.2 mg/kg). While the optimal dosing frequency remains under investigation, studies have demonstrated acute antidepressant efficacy with both twice-weekly and thrice-weekly intravenous administrations. Intranasal esketamine, evaluated in numerous trials, has shown significant improvement in TRD, with effective dosages identified as 56 mg and 84 mg. Esketamine provides TRD patients an option that has been FDA approved and eliminates the logistical challenges associated with racemic ketamine. Esketamine may be an alternative or even provide greater efficacy than currently available adjunctive medications such as quetiapine. However, the comparative efficacy between intranasal esketamine and intravenous racemic ketamine remains uncertain due to the lack of properly designed head-to-head trials. Finally, clinicians should monitor for common esketamine side effects, and be aware of serious adverse events like increased risk of suicide, misuse and addiction. For long term use, the screening of LUTS is essential.

ECT remains the gold standard treatment for TRD but is associated with cognitive adverse effects and logistical challenges. A recent meta-analysis suggest that ECT may be superior to racemic ketamine in addressing depression severity in the acute phase. However, in a recent study racemic ketamine has been deemed noninferior to ECT in achieving treatment response. Nonetheless, in this study response rates in certain ECT subgroups were unexpectedly low, contradicting previous literature. However, the cognitive side effects and stigma associated with ECT treatments lead to patient preference for esketamine as an alternative. While there's ample evidence indicating that high doses of ketamine can cause long-term cognitive deficits, clinical trials with esketamine have shown that cognition generally remains stable or even improves with time, suggesting that when used correctly, there's no added risk of cognitive impairment (Nikayin et al., 2022).

In conclusion, ketamine and its enantiomer, esketamine, present promising avenues for the treatment of TRD. Research has demonstrated their rapid and substantial alleviation of symptoms in adults with TRD, offering hope to those who have not responded to traditional antidepressant therapies. While uncertainties remain regarding the comparative efficacy between different formulations and delivery routes, the growing body of evidence supporting the efficacy of ketamine and esketamine trials provides hope for individuals struggling with TRD.

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Declaration of interest

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Herrman H, Kieling C, McGorry P, et al. Reducing the global burden of depression: a lancet–world psychiatric association commission. The Lancet. 2019;393(10189):e42–e43. doi: 10.1016/S0140-6736(18)32408-5
2. Corriger A, Pickering G. Ketamine and depression: a narrative review. Drug Des Devel Ther. 2019;13:3051–3067. doi: 10.2147/DDDT.S221437
3. McAllister-Williams RH, Arango C, Blier P, et al. The identification, assessment, and management of difficult-to-treat depression: an international consensus statement. J Affect Disord. 2020;267:264–282. doi: 10.1016/j.jad.2020.02.023
4. Grunebaum MF, Galfalvy HC, Choo T-H, et al. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. Am J Psychiatry. 2018;175(4):327–335. doi: 10.1176/appi.ajp.2017.17060647
5. Bahji A, Vazquez GH, Zarate CA Jr. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord. 2021;278:542–555. doi: 10.1016/j.jad.2020.09.071
6. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. Mol Psychiatry. 2018;23(4):801–811. doi: 10.1038/mp.2017.255
7. Abdallah CG, Sanacora G, Duman RS, et al. Ketamine and rapid-acting antidepressants: a window into a new neurobiology for mood disorder therapeutics. Annu Rev Med. 2015;66:509–523. doi: 10.1146/annurev-med-053013-062946
8. 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
9. Jelen LA, Young AH, Stone JM. Ketamine: a tale of two enantiomers. J Psychopharmacol. 2021;35(2):109–123. doi: 10.1177/0269881120959644
10. Fava M, Freeman MP, Flynn M, et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Mol Psychiatry. 2020;25:1592–1603. doi: 10.1038/s41380-018-0256-5

•• **Important Double-blind placebo controlled trial investigating the efficacy of intravenous ketamine for TRD.**

11. Zhang Jc, Li Sx, Hashimoto K. R(−)-ketamine shows greater potency and longer lasting antidepressant effects than S(+)-ketamine. Pharmacol Biochem Behav. 2014;116:137–141. doi: 10.1016/j.pbb.2013.11.033
12. McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. Am J Psychiatry. 2021;178(5):383–399. doi: 10.1176/appi.ajp.2020.20081251
13. Papakostas GI, Salloum NC, Hock RS, et al. Efficacy of esketamine augmentation in major depressive disorder: a meta-analysis. J Clin Psychiatry. 2020;81(4):19r12889. doi: 10.4088/JCP.19r12889
14. Popova V, Ej D, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized

double-blind active-controlled study. Am J Psychiatry. 2019;176 (6):428–438. doi: 10.1176/appi.ajp.2019.19020172

•• **Important RCT on the efficacy of esketamine combined with an antidepressant in TRD.**

15. Reif A, Bitter I, Buyze J, et al. ESCAPE-TRD Investigators. Esketamine nasal spray versus quetiapine for treatment-resistant depression. N Engl J Med. 2023;389(14):1298–1309. doi: 10.1056/NEJMoa2304145
16. Loo CK, Gálvez V, O'Keefe E, et al. Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular, and subcutaneous routes for ketamine in depression. Acta Psychiatr Scand. 2016;134(1):48–56. doi: 10.1111/acps.12572
17. Singh JB, Fedgchin M, Daly EJ, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am J Psychiatry. 2016;173(8):816–826. doi: 10.1176/appi.ajp.2016.16010037
18. Rosenblat JD, Carvalho AF, Li M, et al. Oral ketamine for depression: a systematic review. J Clin Psychiatry. 2019;80(3):18r12475. doi: 10.4088/JCP.18r12475
19. Meshkat S, Haikazian S, Di Vincenzo JD, et al. Oral ketamine for depression: An updated systematic review. World J Biol Psychiatry. 2023;24(7):545–557. doi: 10.1080/15622975.2023.2169349
20. Chang L, Zhang K, Pu Y, et al. Comparison of antidepressant and side effects in mice after intranasal administration of (R, S)-ketamine, (R)-ketamine, and (S)-ketamine. Pharmacol Biochem Behav. 2019;181:53–59. doi: 10.1016/j.pbb.2019.04.008
21. Yang C, Shirayama Y, Zhang J, et al. R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. Transl Psychiatry. 2015;5(9):e632. doi: 10.1038/tp.2015.136
22. Zhang JC, Li SX, Hashimoto KR. R(−)-ketamine shows greater potency and longer lasting antidepressant effects than S(+)-ketamine. Pharmacol Biochem Behav. 2014;116:137–41. doi: 10.1016/j.pbb.2013.11.033
23. Leal GC, Bandeira ID, Correia-Melo FS, et al. Intravenous arketamine for treatment-resistant depression: open-label pilot study. Eur Arch Psychiatry Clin Neurosci. 2020;271(3):577–582. doi: 10.1007/s00406-020-01110-5
24. Bonaventura J, Lam S, Carlton M, et al. Pharmacological and behavioral divergence of ketamine enantiomers: Implications for abuse liability. Mol Psychiatry. 2021;26(11):6704–6722. doi: 10.1038/s41380-021-01093-2
25. Nguyen L, Lucke-Wold BP, Mookerjee SA, et al. Role of sigma-1 receptors in neurodegenerative diseases. J Pharmacol Sci. 2015;127 (1):17–29. doi: 10.1016/j.jphs.2014.12.005
26. Salaciak K, Pytka K. Revisiting the sigma-1 receptor as a biological target to treat affective and cognitive disorders. Neurosci Biobehav Rev. 2022;132:1114–1136. doi: 10.1016/j.neubiorev.2021.10.037
27. Lii Tr, Smith Ae, Flohr JR, et al. Randomized trial of ketamine masked by surgical anesthesia in patients with depression. Nat Ment Health. 2023;1(11):876–886. doi: 10.1038/s44220-023-00140-x

•• **First Randomized Clinical Trial using surgical anesthesia as a masking method to assess the efficacy of ketamine compared to placebo.**

28. Rhee TG, Shim SR, Forester BP, et al. Efficacy and safety of ketamine vs electroconvulsive therapy among patients with major depressive episode: a systematic review and meta-analysis. JAMA Psychiatry. 2022;79(12):1162–1172. doi: 10.1001/jamapsychiatry.2022.3352

• **Imporant meta-analyis comparing ketamine and ECT**

29. Anand A, Mathew SJ, Sanacora G, et al. Ketamine versus ECT for nonpsychotic treatment-resistant major depression. N Engl J Med. 2023;388(25):2315–2325. doi: 10.1056/NEJMoa2302399
30. UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. The Lancet. 2003;361(9360):799–808. doi: 10.1016/S0140-6736(03)12705-5
31. Jiang Y, Du Z, Shen Y, et al. The correlation of Esketamine with specific adverse events: a deep dive into the FAERS database. Eur Arch Psychiatry Clin Neurosci. 2023. doi: 10.1007/s00406-023-01732-5

•• **Important analyis of the FAERS database concerning the adverse events of long term esketamine use.**

32. Zaki N, Chen LN, Lane R, et al. Long-term safety and maintenance of response with esketamine nasal spray in participants with treatment-resistant depression: interim results of the SUSTAIN-3 study. Neuropsychopharmacol. 2023 Jul;48(8):1225–1233. doi: 10.1038/s41386-023-01577-5
33. Chang M, Juruena MF, Young AH. Ketamine cystitis following ketamine therapy for treatment-resistant depression - case report. BMC Psychiatry. 2024 Jan 2;24(1):9. doi: 10.1186/s12888-023-05468-3