The Ketamine Paradox: Why the Weaker Enantiomer May Prove the Stronger Antidepressant

Zubeen H[1], Tushar S[2] & Rutuja S[3]

[1]Student of D.Y. Patil School of Pharmacy, Ambi, Talegaon Dabhade- 410507 Pune, India

[2]Student of D.Y. Patil School of Pharmacy, Ambi, Talegaon Dabhade- 410507 Pune, India

[3]Professor of D.Y. Patil School of Pharmacy, Ambi, Talegaon Dabhade- 410507 Pune, India

Corresponding author: zubeenhussain06@gmail.com
Doi: 10.5281/zenodo.20082423
Received: 11 April 2026
Accepted: 24 April 2026

Abstract

Ketamine — a dissociative anaesthetic and uncompetitive NMDA receptor antagonist — represents the most significant advance in depression pharmacology in half a century. As a racemic mixture of (S)-ketamine (esketamine) and (R)-ketamine (arketamine), it harbours a central paradox: the enantiomer with weaker NMDA binding appears, in preclinical models, to produce stronger and more durable antidepressant effects with fewer adverse effects. Esketamine has received FDA approval for treatment-resistant depression (TRD) and major depressive disorder with acute suicidal ideation, yet arketamine — despite being pharmacologically inferior on the receptor affinity metric used to justify esketamine — consistently outperforms it in animal models. This review examines the mechanistic, clinical, and critical dimensions of this paradox, arguing that NMDA affinity is an incomplete framework for predicting antidepressant potency and that the field has perhaps been measuring the wrong thing.

Keywords: Ketamine; Esketamine; Arketamine; Treatment-resistant depression; NMDA receptor antagonism; Sigma-1 receptor; (2R,6R)-hydroxynorketamine; Rapid-acting antidepressants; mTORC1 signalling; Synaptogenesis; Dissociative side effects; Stereochemistry; Enantiomers.

1. Introducton

For sixty years, antidepressant pharmacology meant monoamines. Tricyclics, MAOIs, SSRIs — each generation better tolerated, all operating through the same logic: adjust monoamine availability, then wait.[25] The waiting was the problem. A patient started on an SSRI might spend six to twelve weeks uncertain whether it was working or

deteriorating throughout. Treatment-resistant depression — failure to respond to two adequate trials — affects roughly 30% of patients, historically the most severely ill, for whom sequential monoaminergic adjustments offered diminishing returns.[22]

Ketamine, synthesised in 1962 and FDA-approved as an anaesthetic in 1970, entered the antidepressant picture almost accidentally. Berman and colleagues published the first controlled data in 2000: a single sub-anaesthetic infusion produced rapid, meaningful reductions in depressive symptoms.[1,21] Subsequent NIMH trials confirmed that — 0.5 mg/kg intravenously over 40 minutes lifted severe depression within hours, with no precedent in antidepressant pharmacology and no explanation fitting the prevailing monoamine framework. Its chiral structure — two enantiomers, esketamine and arketamine — offered a way in, and the investigation that followed uncovered a paradox that reshaped mechanistic assumptions about antidepressant action.

2. Chemical structure and stereochemistry

Ketamine (C13H16ClNO, MW 237.73 g/mol) belongs to the arylcyclohexylamine class. The chiral centre at carbon C2 of the cyclohexanone ring generates two non-superimposable mirror-image molecules: esketamine (S-configuration) and arketamine (R-configuration).[4,14] On paper, they are identical. In vivo, they are meaningfully different.

Esketamine binds NMDA receptors at a Ki of 0.30 µM. Arketamine manages only 1.40 µM — roughly four times weaker.[17] That gap explains esketamine's faster channel blockade, more pronounced dissociation, and the frontal cerebral hypermetabolism seen on PET imaging. Arketamine's weaker NMDA binding would, by traditional receptor pharmacology logic, predict inferior antidepressant potency. The preclinical literature says the opposite. The resolution of that contradiction requires looking beyond NMDA affinity.

What arketamine has that esketamine lacks is meaningful sigma-1 receptor activity.[19] Sigma-1 receptors are intracellular chaperone proteins concentrated in limbic structures — hippocampus and prefrontal cortex — modulating BDNF-TrkB activity, IP3-receptor calcium handling, and mitochondrial function. Their engagement produces antidepressant-like effects through pathways entirely independent of glutamate signalling. Arketamine runs two mechanisms simultaneously. Esketamine runs one.

Table 1. Stereochemical and Pharmacological Comparison of Ketamine Enantiomers

Property	Racemic Ketamine	Esketamine (S)	Arketamine (R)	Significance
Configuration	R, S Mixture	S(+)	R(-)	Determines receptor binding
NMDA Affinity Ki	0.53 µM	0.30 µM	1.40 µM	S ~4x stronger
Antidepressant Duration	~7 days	3–5 days	Longer (preclinical)	R-enantiomer advantage

Dissociative Effects	Moderate	Pronounced	Minimal	Key safety difference
Sigma-1 Binding	Partial	Negligible	Significant	Unique to arketamine
FDA Approval	Anaesthesia	TRD & MDSI (,)	Investigational	Regulatory status

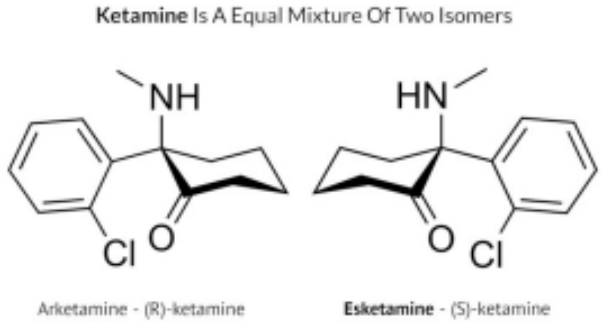

Figure 1: Schematic representation of racemic ketamine and its enantiomers. The chiral centre at C2 determines distinct pharmacological behaviour.

2.1 Pharmacodynamics and mechanism of action

Early mechanistic thinking on ketamine was clean: block NMDA receptors, trigger a glutamate surge, activate AMPA receptors, drive mTORC1-mediated synaptogenesis, restore prefrontal and hippocampal synaptic architecture damaged by chronic stress.[6,25] That account was not wrong — it just turned out to be incomplete in ways that matter considerably for understanding which enantiomer actually works better, and why.

2.2 NMDA blockade and downstream cascade

Ketamine acts as an open-channel blocker — entering the NMDA pore after opening, halting ion flux from inside. The presynaptic terminal compensates with excess glutamate, which activates AMPA receptors that feed mTORC1 via Akt and ERK, triggering synaptic protein synthesis within the first hour.[6,13] BDNF-TrkB amplifies upstream; new dendritic spines form. This is why ketamine works in hours where SSRIs need weeks.[25]

2.3 The HNK Metabolite: A Challenge to NMDA-Centrism

The metabolite (2R,6R)-hydroxynorketamine (HNK), generated via CYP3A4/CYP2B6 metabolism, produces antidepressant effects through direct AMPA potentiation independently of NMDA blockade.[4] This finding carries significant implications: animals with fully occupied NMDA receptors still responded to HNK. If NMDA blockade were the necessary first step, that should not happen. For arketamine specifically — weaker at NMDA yet superior in

effect — the HNK pathway alongside sigma-1 engagement offers the most mechanistically credible explanation for what it is actually doing.[12,19]

2.4 Lateral Habenula Inhibition

The lateral habenula, which suppresses dopaminergic and serotonergic output and fires pathologically in depression models, is inhibited by ketamine through habenular NMDA blockade within minutes.[13] This likely explains mood improvement occurring during infusion — before mTOR-driven synaptogenesis could account for anything. It is a rapid, brute-force mechanism, and esketamine's stronger NMDA affinity makes it faster here. That speed, as discussed below, is esketamine's key clinical advantage.

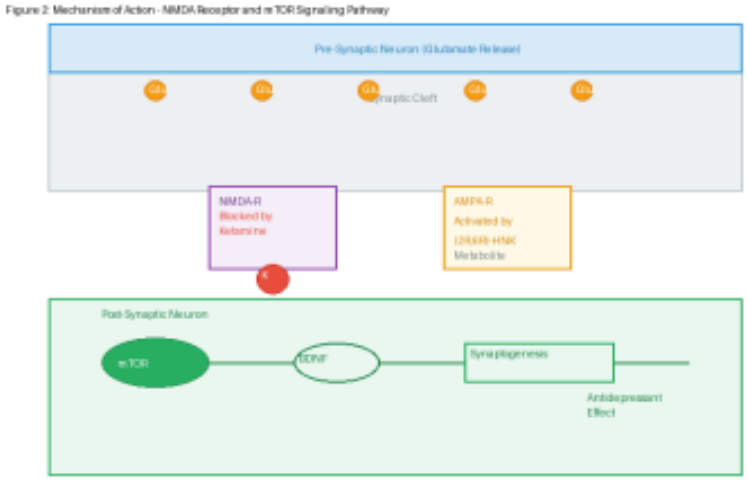

Figure 2: Simplified schematic of the ketamine mechanism. NMDA blockade triggers glutamate surge → AMPA activation → mTOR synaptogenesis. HNK provides additional AMPA stimulation independently of NMDA blockade.

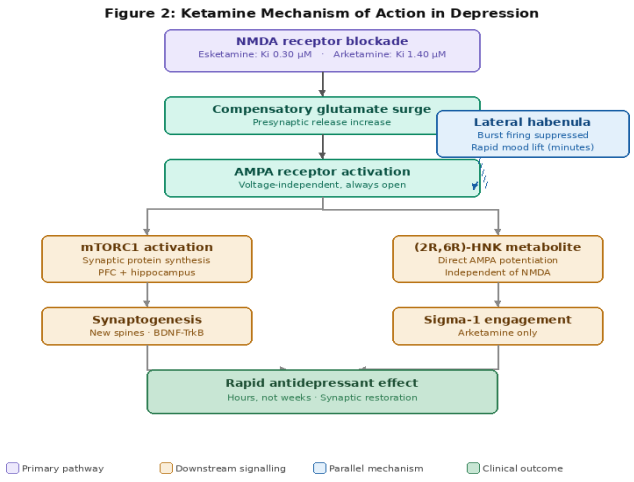

Figure 3: Mechanism of action of ketamine in depression.

2.5 Esketamine: clinical profile

Esketamine hydrochloride (Spravato) received FDA approval for TRD in March, and for major depressive disorder with acute suicidal ideation in August 2020 — the first antidepressant ever to demonstrate acute reduction of suicidality within hours of administration.[3,8] Dosing runs at 56 mg or 84 mg intranasally, twice weekly for induction.[3,5]

The TRANSFORM trials demonstrated statistically significant MADRS reductions versus placebo at 28 days.[7] The ASPIRE programme found a meaningful reduction in suicidal ideation at 24 hours — a timepoint where SSRIs are pharmacologically inert.[8] That single finding fills a gap psychiatry never had a pharmacological answer for, and it constitutes esketamine's most clinically irreplaceable contribution.

The limitations, however, are genuine and should not be minimised. Dissociation occurs in 25–40% of patients. The FDA's REMS mandate requires administration in certified facilities with at least two hours post-dose observation. Drug cost, monitoring requirements, and limited certified centre availability have produced a situation where access is demonstrably unequal — patients in well-resourced urban settings can access it; many cannot.[5] That inequity is part of any honest appraisal of esketamine's significance.

2.6 Arketamine: emerging evidence

Arketamine sits in a peculiar position: pharmacologically weaker at the receptor most associated with ketamine's antidepressant mechanism, far less studied clinically, yet consistently superior in preclinical antidepressant models. Hashimoto's 2016 paper using social defeat stress and learned helplessness paradigms in mice was the inflection point.[2] Arketamine produced stronger antidepressant-like effects at equivalent doses, those effects lasted longer, and prepulse inhibition — an assay for psychotomimetic effects — was unaffected at antidepressant doses. The same doses of esketamine disrupted it. Greater efficacy and cleaner tolerability together redirected substantial research attention.[2,12]

Dendritic spine density studies in stressed animals show larger and more persistent structural improvements in the prefrontal cortex and hippocampus with arketamine versus esketamine at equivalent doses.[2,12] PET work found arketamine decreasing rather than increasing frontal glucose metabolism — corresponding to a calmer, less dysphoric experience, and suggesting fundamentally different prefrontal circuit engagement.[17] Arketamine also shows particularly robust effects on anhedonia and motivational deficits — domains that conventional antidepressants rarely touch and that represent a major unmet clinical need.[12]

Human evidence remains early. An open-label pilot by Leal et al. (2021) demonstrated intravenous arketamine producing antidepressant responses in TRD patients with a cleaner side-effect profile than racemic ketamine.[15] A placebo-controlled pilot from the same group (2023) provided the first controlled human data suggesting preclinical advantages may translate.[11] This is two small trials. The preclinical case is strong, but psychiatry has a long history of compelling rodent findings that failed human translation — that caveat must remain visible.

2.7 The paradox explained

The central question is straightforward: how does a molecule with four times weaker NMDA binding consistently outperform the stronger binder on antidepressant measures? The answer requires dismantling the assumption that NMDA affinity is the primary determinant of antidepressant potency.

Esketamine genuinely wins on speed. Stronger NMDA affinity means faster blockade, quicker glutamate surge, earlier AMPA activation, and measurable antidepressant effects within two to four hours.[1,21] In acute suicidal crisis, that speed is not a pharmacological footnote — it is the entire clinical rationale. The ASPIRE data is esketamine's most important evidence precisely because no other antidepressant can do what it does at 24 hours. Outside an acute crisis, however, speed becomes less decisive. For the broader TRD population — severely ill but not in immediate danger — duration and tolerability matter more. On those dimensions, arketamine wins substantially.[2,12]

The sigma-1 receptor is probably the key mechanism underlying arketamine's advantage. Running simultaneously with NMDA blockade — which is fast but short-lived — sigma-1 engagement drives neuroplastic changes that build more slowly and persist considerably longer.[12,19] Esketamine has no meaningful sigma-1 activity. That second arm is the most credible explanation for why arketamine's effects last weeks in animal models while esketamine's fade within days.

The PET imaging adds another dimension. Esketamine increases frontal glucose metabolism; the increase correlates directly with dissociation scores.[17] The metabolic activation and the psychotomimetic experience are the same event. Arketamine suppresses frontal metabolism and produces no dissociation — suggesting it achieves neuroplastic effects through prefrontal circuitry without the pharmacological turbulence esketamine creates. These are not just quantitative differences in the same mechanism; they suggest qualitatively different modes of action.

Why did esketamine get approved first, then? Timing and clinical need. By 2016, when Hashimoto's paper made the pharmacological case for arketamine, Janssen's esketamine programme was already years into large-scale trials.[22] Redirection was not realistic. More importantly, esketamine had something arketamine still lacks: human data for the most urgent clinical need. The two enantiomers are not competitors — they serve different purposes. Esketamine is an acute rescue agent for crisis presentations. Arketamine's profile — slower onset, longer duration, negligible dissociation, stronger structural effects — reads like a maintenance treatment. The population needing maintenance treatment is vastly larger.

2.8 Adverse effects and safety

Esketamine causes dissociation in 25–40% of patients — perceptual disturbance that most tolerate, but some do not, with meaningful dropout rates in practice.[17,20] Transient blood pressure rises of 10–20 mmHg systolic occur with both compounds via central sympathomimesis; pre-existing cardiovascular risk requires careful assessment.[13] Nausea, dizziness, and sedation are common enough that prophylactic antiemetics are routine at most centres.

Bladder toxicity has emerged in patients on prolonged therapeutic courses — urinary frequency, dysuria, haematuria, and potentially irreversible fibrosis.[8,10] Rates are lower than in recreational users but not zero; urinary symptom

monitoring at every visit is mandatory on maintenance treatment. Hepatotoxicity is documented in extended courses.[15,20] Whether repeated therapeutic dosing produces cumulative cognitive deficits remains unanswered — a genuine problem given that TRD requires long-term management.

2.9 Critical analysis and research gaps

The ketamine literature has grown fast, but the evidence base has not always matched the enthusiasm. Several gaps require honest acknowledgment.

Most trials follow patients for weeks to months, yet TRD requires potentially years of treatment, and what repeated dosing does to the bladder, liver, cardiovascular system, and cognition over several years remains unknown.[5,10] Long-term safety registries are largely absent. There is no reliable way to predict which patients will respond — a substantial proportion complete the full course, experience side effects, bear the cost, and do not improve. Identifying predictive biomarkers would transform clinical decision-making; nothing actionable exists yet.[13,25]

Esketamine and arketamine have never been directly compared in a properly powered RCT in humans.[11,16] Every comparative claim in the literature rests on preclinical data or indirect cross-study comparisons. This is a fundamental evidential limitation. The entire narrative around arketamine's superiority — compelling as the mechanistic case is — cannot be confirmed or refuted without a head-to-head human trial. The field speaks with more confidence than its evidence warrants on this point.

The mechanistic picture carries its own uncertainties. Whether NMDA antagonism is even strictly necessary — given HNK's NMDA-independent activity and arketamine's sigma-1 engagement — challenges the foundational framework the field has built on.[13,25] If the mechanism assumed to justify esketamine's approval is not the primary mechanism, the implications for how we evaluate future compounds are considerable. Mechanistic uncertainty is not a footnote; it matters for understanding non-response and for the rational design of next-generation treatments.

Cost and access inequity remain unresolved structural problems. REMS requirements, certified facility mandates, and drug cost make esketamine inaccessible to many patients who clinically qualify.[5] IV racemic ketamine is cheaper but lacks formal regulatory approval for depression, creating medicolegal ambiguity and inconsistent insurance coverage. Neither situation serves patients adequately, and the clinical literature has been insufficiently critical of this.

3. Future perspective

Arketamine needs properly powered randomised controlled trials in humans — that is the immediate clinical priority, and those trials are running.[11,15] The preclinical consistency across multiple independent laboratories is substantial enough that the question is no longer whether to investigate seriously, but whether human data will hold. If efficacy signals survive larger-scale trials, regulatory applications could follow within a few years.

The metabolite (2R,6R)-HNK warrants attention as an independent drug candidate. Producing antidepressant effects through AMPA potentiation without NMDA blockade means — in principle — delivering ketamine's downstream benefits without the dissociation that currently limits clinical uptake.[4,13] If HNK can be developed into a stable, bioavailable compound, it represents a conceptually cleaner approach than either enantiomer.

CYP3A4 and CYP2B6 variation affects ketamine metabolism and HNK generation, likely influencing both efficacy and tolerability — pharmacogenomics-informed enantiomer selection is a realistic near-term goal.[4,20] Using the post-infusion neuroplasticity window to consolidate psychotherapeutic work is a rational, underexplored combination strategy deserving controlled trials.[6,13]

4. Conclusion

The ketamine paradox is not really a paradox — it is a signal that the field was measuring the wrong thing. NMDA affinity alone does not predict antidepressant potency. Sigma-1 engagement, metabolite pharmacology, lateral habenula dynamics, and prefrontal circuit mode all contribute. That mechanistic complexity is the map for where the next generation of treatments comes from.

Esketamine fills an acute gap that genuinely needed filling — its speed, and particularly its anti-suicidal data, represent capabilities psychiatry never had before 2019.[3,8] The dissociation, cost, and access barriers are real and cannot be minimised. Arketamine, if the trial data holds, offers a profile better suited to long-term management: longer duration, cleaner tolerability, stronger structural effects. Two small pilot studies support but do not confirm that promise.[11,15]

These enantiomers serve different clinical needs. Esketamine is an acute rescue agent for crisis presentations; arketamine may prove the more important maintenance option for a far larger population. The pharmacological case is now sufficiently clear. What remains is the clinical evidence.

5. References

1. Berman RM, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000;47(4):351-354.

2. Hashimoto K. R-Ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. Transl Psychiatry. 2016;6(9):e881.

3. Singh JB, et al. Approval of esketamine for treatment-resistant depression. Lancet Psychiatry. 2020;7(3):232-235.

4. Zanos P, et al. Ketamine and Ketamine Metabolite Pharmacology. Pharmacol Rev. 2018;70(3):621-660.

5. Vasiliu O. Esketamine for treatment-resistant depression: A review of clinical evidence. Exp Ther Med. 2023;25(3):111.

6. Li N, et al. mTOR-Dependent Synapse Formation Underlies the Rapid Antidepressant Effects of NMDA Antagonists. Science. 2010;329(5994):959-964.

7. Popova V, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray. Am J Psychiatry, 176(6):428-438.

8. Canuso CM, et al. Efficacy and Safety of Intranasal Esketamine for Symptoms of Depression and Suicidality. Am J Psychiatry, 175(7):620-630.

9. Seshadri A, et al. Efficacy of intravenous ketamine and intranasal esketamine for major depression. J Affect Disord. 2024;356:379-384.

10. Rodolico A, et al. Efficacy and safety of ketamine and esketamine for unipolar and bipolar depression. Front Psychiatry. 2024;15:1325399.

11. Leal GC, et al. Arketamine as adjunctive therapy for treatment-resistant depression: placebo-controlled pilot study. J Affect Disord. 2023;330:7-15.

12. Hashimoto K. Molecular mechanisms underlying the antidepressant actions of arketamine. Mol Psychiatry. 2021;26:606-617.

13. Krystal JH, et al. Ketamine and rapid antidepressant action. Neuropsychopharmacology. 2024;49:41-50.

14. Wei Y, et al. A historical review of antidepressant effects of ketamine and its enantiomers. Pharmacol Biochem Behav. 2020;190:172870.

15. Leal GC, et al. Intravenous arketamine for treatment-resistant depression: Open-label pilot study. Eur Arch Psychiatry Clin Neurosci. 2021;271:577-582.

16. Singh B, et al. Comparative effectiveness of intravenous ketamine and intranasal esketamine. J Clin Psychiatry. 2023;84(3):22m14742.

17. Vollenweider FX, et al. Differential psychopathology and cerebral glucose utilization produced by S- and R-ketamine. Eur Neuropsychopharmacol. 1997;7:25-38.

18. Mion G, Villevieille T. Ketamine pharmacology: an update. CNS Neurosci Ther. 2013;19(6):370-380.

19. Kalkman HO. Activation of sigma1-Receptors by R-Ketamine. Biomedicines. 2023;11:2664.

20. Feeney A, Papakostas GI. Pharmacotherapy: Ketamine and Esketamine. Psychiatr Clin N Am. 2023;46:277-290.

21. Berman RM, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000;47(4):351-354.

22. Zarate CA Jr, et al. A randomized trial of an NMDA antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006;63(8):856-864.

23. Murrough JW, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression. Am J Psychiatry. 2013;170(10):1134-1142.

24. Zorumski CF, et al. Ketamine: NMDA receptors and beyond. J Neurosci. 2016;36(44):11158-11164.

25. Duman RS, et al. Synaptic plasticity and depression: New insights from stress and rapid-acting antidepressants. Nat Med. 2016;22(3):238-249.