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Esketamine Nasal Spray: Rapid Relief for TRD and Suicide Prevention—Mechanisms and Pharmacodynamics

Hui Song[1,*], Yang Luo[2,*], Lingzhi Fang[1]

[1]The Third Hospital of Mianyang, Sichuan Mental Health Center, Mianyang, Sichuan, People's Republic of China; [2]Jiang You Third People Hospital, Mianyang, Sichuan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hui Song, Email 182321767@qq.com

Abstract: Esketamine nasal spray has emerged as a promising rapid-relief therapy for treatment-resistant depression (TRD) and suicide prevention. This review examines the chemical structure and pharmacodynamics of esketamine, highlighting its primary action on NMDA receptors and additional effects on AMPA receptors, opioid receptors, monoaminergic receptors, and inflammatory pathways. Despite the synergistic mechanisms contributing to its clinical benefits not being fully understood, future studies are essential to refine our understanding and optimize clinical use. Clinical research indicates that esketamine effectively alleviates depressive symptoms and prevents suicidal behavior in TRD patients, demonstrating good safety and efficacy over extended periods. Specifically, multiple randomized controlled trials have shown that esketamine reduces depressive symptoms within hours and maintains these benefits over several weeks, with a favorable safety profile and minimal side effects observed in long-term use. The approval of esketamine for TRD has significant implications for healthcare practices and policies, offering a new therapeutic option that addresses the urgent needs of patients with severe depression.

Keywords: esketamine, treatment-resistant depression, TRD, NMDA receptors, pharmacodynamics, clinical benefits, safety and efficacy

Introduction

Esketamine nasal spray has emerged as a promising rapid-relief therapy for treatment-resistant depression (TRD) and suicide prevention. TRD is a significant clinical challenge, affecting a substantial proportion of patients with major depressive disorder (MDD). Despite the availability of various antidepressant medications and psychotherapies, a substantial number of patients do not respond adequately to conventional treatments. This review examines the chemical structure and pharmacodynamics of esketamine, highlighting its primary action on NMDA receptors and additional effects on AMPA receptors, opioid receptors, monoaminergic receptors, and inflammatory pathways. Although the synergistic mechanisms contributing to its clinical benefits are not fully understood, future studies are essential to refine our understanding and optimize clinical use.

With societal advancements and rapid economic growth, depression has become a prevalent mental health issue affecting over 300 million people worldwide.[1] Chronic relapsing symptoms are experienced by more than half of these patients,[2] underscoring the need for enhanced treatment strategies. Treatment-resistant depression (TRD), defined as persistent depression despite adequate trials with multiple antidepressants,[3] poses a significant challenge due to its unclear etiology and mechanisms. Clinical focus lies in symptom relief, while research endeavors aim to uncover new therapies and deepen understanding of TRD's complex nature.[4,5] This review integrates current knowledge on TRD, examining its diagnostic criteria, mechanisms, and potential therapeutic innovations, guiding future advancements in managing this debilitating condition.

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The treatment of treatment-resistant depression (TRD) remains a complex and multifaceted challenge, often requiring a multimodal approach that combines various therapeutic modalities, such as diverse antidepressant classes, augmented lithium therapy, electroconvulsive therapy, and psychotherapeutic interventions.[6,7] A pivotal turning point came on March 4, 2019, when the US FDA approved Esketamine, a novel nasal spray antidepressant, specifically for adults with TRD.[7,8] This groundbreaking development signaled a new frontier in TRD management, and the present review aims to synthesize the available evidence on esketamine's use, contributing to a refreshed understanding and potential advancements in the care of individuals struggling with this resilient form of depression.By examining the clinical trials, pharmacological mechanisms, and real-world experiences associated with esketamine, this comprehensive review offers insights into its therapeutic efficacy, safety profile, and implications for clinical practice. It also highlights the significance of personalized treatment plans and the need for continued research to optimize the integration of esketamine into the broader armamentarium of TRD treatments. Ultimately, this synthesis seeks to bridge the gap in current knowledge and inform future decision-making in the treatment of this highly debilitating condition.

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Chemical Structure and Pharmacodynamics of Esketamine

Structure

Esketamine is the S (+) enantiomer of ketamine (Ki = 0.30 mmol/L), an arylcyclohexylamine derivative with the molecular formula C13H16CINO, molecular weight 238, dissociation constant (pKa) 7.5, and partition coefficient (log P) 2.9 (Figure 1).[9,10]

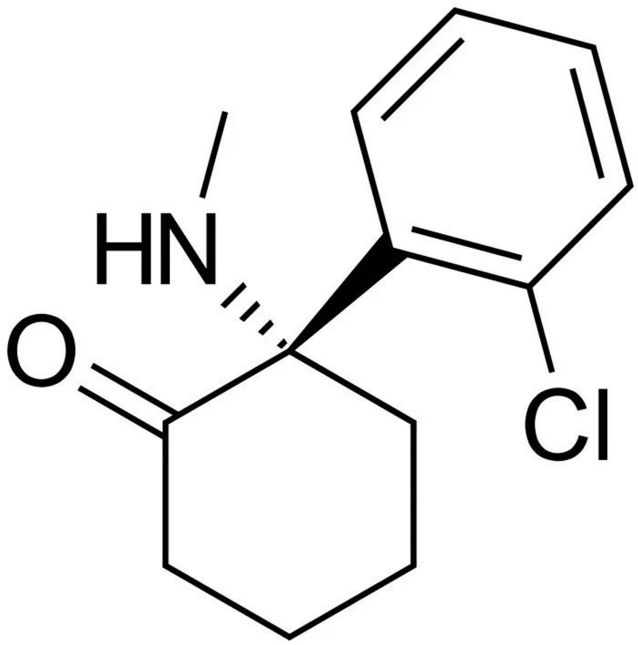

Figure 1 Structure of esketamine.

Pharmacodynamics

Esketamine, an antagonist at the NMDA (N-methyl-D-aspartate) receptor, has garnered attention for its distinct pharmacological profile compared to its enantiomer R-ketamine and the racemic mixture. With an affinity for NMDARs approximately three to four times higher, esketamine displays enhanced analgesic properties.[11,12] Notably, it exhibits a reduced potential for producing euphoria and unwanted side effects relative to ketamine, while also demonstrating neuroprotective qualities.[12–14] Recent research has underscored esketamine's ability to deliver rapid antidepressant effects, addressing the limitations of conventional TRD treatments, such as their slow onset and frequent side effects.[11,12]

Despite ongoing investigations, the exact molecular mechanisms underlying the antidepressant activity of both ketamine and esketamine at NMDAR binding sites remain a subject of debate.[12–14] The disinhibition hypothesis suggests that ketamine selectively targets NMDARs on GABAergic interneurons, releasing glutamate and disinhibiting pyramidal cells via AMPA receptor activation.[15,16] This glutamatergic surge is thought to play a crucial role in the rapid antidepressant response.[16,17] Alternatively, another theory proposes that baseline cortical activity engages extrasynaptic NMDARs, particularly those containing GluN2B subunits on pyramidal neurons, modulating extracellular glutamate levels and contributing to antidepressant effects.[18,19]

These theories, though not definitively resolved, provide valuable insights into the complex neurobiology of esketamine's antidepressant action and highlight the potential for targeted interventions in TRD treatment. Further studies are needed to clarify the precise mechanisms and optimize the therapeutic potential of esketamine in the context of depression treatment. The bioavailability of esketamine and ketamine varies depending on the route of administration, encompassing intravenous, oral, sublingual, intranasal, intramuscular, and rectal delivery. Among these, the intranasal route, via a nasal spray, is particularly efficient, with rapid absorption through the rich capillary network of the nasal mucosa, leading to peak plasma concentrations within 10 to 14 minutes.[20,21] This method minimizes taste disturbances commonly associated with oral administration and bypasses hepatic metabolism, thereby reducing the risk of liver toxicity.

Esketamine, when administered nasally, demonstrates a plasma protein binding rate of approximately 27%, enabling widespread distribution throughout various organs and tissues.[21,22] Following its peak systemic concentration, esketamine exhibits a biphasic decline in plasma levels, with an initial rapid decrease over 2 to 4 hours and a longer terminal half-life of 7 to 12 hours. As an NMDA receptor antagonist, esketamine rapidly initiates both acute and sustained antidepressant effects.[22–24] Intranasal administration is recognized for its clinical suitability, offering advantages over alternative routes. However, the precise mechanisms underlying its effectiveness and the differences in bioavailability across various administration methods are yet to be fully elucidated. Further research is necessary to consolidate our understanding.[22–24]

Efficacy and Safety of Esketamine Nasal Spray in TRD

Treatment-resistant depression (TRD) remains a significant clinical challenge, affecting a substantial proportion of patients who do not respond adequately to conventional antidepressants. Recent studies have highlighted the potential of esketamine nasal spray as a novel therapeutic option for TRD. This section summarizes key efficacy and safety studies of esketamine nasal spray in TRD, providing insights into its therapeutic benefits and potential limitations (Table 1).

Treatment-resistant depression (TRD) is defined as a lack of response to two or more consecutive treatments during the current depressive episode, leading to low remission rates and high relapse rates. The efficacy and safety of esketamine nasal spray compared to extended-release quetiapine augmentation therapy, both in combination with an SSRI or SNRI, remain unknown. A study conducted an open-label, single-blind (raters unaware of group assignments), multicenter, phase 3b, randomized, active-controlled trial comparing esketamine nasal spray with extended-release quetiapine in patients with TRD. Results showed that more patients in the esketamine group achieved remission at week 8 (27.1%) compared to the quetiapine group (17.6%), with a statistically significant difference (P = 0.003).[25] Esketamine nasal spray combined with an oral antidepressant significantly reduced the risk of relapse compared to placebo (log-rank P = 0.003, NNT = 6) in patients who achieved stable remission and by 51% (HR, 0.49; 95% CI,

Table 1 Efficacy and Safety Studies of Esketamine Nasal Spray in Treatment-Resistant Depression (TRD)

Author	Experimental Design	Research Function	Molecular Mechanism	Reference
(Andreas Reif, 2023)	Open-label, single-blind (raters unaware of group assignments), multicenter, Phase 3b, randomized, active-controlled trial	Evaluate the efficacy and safety of esketamine nasal spray vs extended-release quetiapine augmentation therapy in treatment-resistant depression	Analyze changes in gene expression and receptor binding patterns	[25]
(Ella J Daly, 2019)	Phase 3, multicenter, double-blind, randomized withdrawal study	Evaluate esketamine nasal spray efficacy for TRD	Not specified in the provided information	[26]
(Ewa Wajs, 2020)	Phase 3, open-label, multicenter, long-term (up to 1 year) study	Evaluate long-term safety and efficacy of esketamine nasal spray plus a new oral antidepressant in TRD patients	Not specified in the provided information	[27]
(Eva G Katz, 2021)	Post hoc analysis of esketamine nasal spray + oral antidepressant treatment	Assess benefit-risk profile in TRD patients	Not specified in the provided information	[9]
(Rachel Ochs-Ross, 2020)	Phase 3, double-blind, randomized controlled trial	Evaluate esketamine nasal spray efficacy in elderly patients with TRD	Not specified in the provided information	[2]
(Naim Zaki, 2023)	Phase 3, open-label, long-term extension study	Evaluate long-term efficacy and tolerability of esketamine in TRD patients	Not specified in the provided information	[28]
(Meredith Castro, 2023)	Subgroup analysis of a long-term, open-label extension study	Evaluate the efficacy and safety of a second induction and maintenance treatment with esketamine nasal spray in TRD patients who relapsed in SUSTAIN-1	Not specified in the provided information	[11]
(Ludovic Samalin, 2022)	Real-world data analysis of esketamine use in TRD patients through a French cohort Temporary Authorisation for Use (ATUc) programme	Evaluate the safety and efficacy of esketamine in real-world clinical practice for TRD patients	Not specified in the provided information	[11]
(Ludovic Samalin, 2022)	Real-world data analysis of esketamine use in TRD patients through a French cohort Temporary Authorisation for Use (ATUc) programme	Evaluate the safety and efficacy of esketamine in real-world clinical practice for TRD patients	Not specified in the provided information	[29]
(Giovanni Martinotti, 2022)	Observational, retrospective, multicentric study	Evaluate the effectiveness and safety of esketamine nasal spray in real-world clinical practice for TRD patients	Not specified in the provided information	[30]
(Kruti Joshi, 2024)	Retrospective observational cohort study	Identify factors associated with esketamine initiation and continuation in TRD patients	Not specified in the provided information	[31]
(Roger S McIntyre, 2024	Secondary analysis of a Phase IIIb randomized controlled trial	Explore the time course, burden, and consequences of treatment-emergent adverse events (TEAEs) in TRD patients treated with esketamine nasal spray versus quetiapine extended release	Not specified in the provided information	[32]

(*Continued*)

Table 1 (Continued).

Author	Experimental Design	Research Function	Molecular Mechanism	Reference
(Madeline Brendle, 2022)	Cost-effectiveness analysis using a Markov model	Estimate the cost-effectiveness of esketamine nasal spray relative to intravenous ketamine for patients with treatment-resistant depression (TRD) in the US	Not specified in the provided information	[33]
(Richard L Doty, 2021)	Multicenter, randomized, double-blind, Phase III studies	Assess the potential impact of long-term intermittent treatment with esketamine nasal spray on olfactory function and nasal tolerability in TRD patients	Not specified in the provided information	[34]

0.29–0.84) in those who achieved stable response.[26] In this phase 3, open-label study, esketamine nasal spray combined with an oral antidepressant showed long-term safety. Common adverse events included dizziness (32.9%), dissociation (27.6%), nausea (25.1%), and headache (24.9%). Most events were mild or moderate and resolved quickly. Cognitive performance generally improved or remained stable, and there were no cases of interstitial cystitis or respiratory depression.[27] This post hoc analysis supports a positive benefit-risk balance for esketamine nasal spray + oral antidepressant in both induction and maintenance treatment of patients with treatment-resistant depression, showing increased remission and response rates with minimal differences in serious AEs.[9] Elderly patients with major depression have a poorer prognosis, are less responsive to treatment, and show greater functional decline compared with younger patients, highlighting the need for effective treatment; in this phase 3 double-blind study, esketamine nasal spray combined with a new oral antidepressant showed a trend toward improved efficacy in patients aged 65–74 years ($p = 0.017$) but not in those aged ≥75 years ($p = 0.930$), with continued improvement observed in the long-term open-label study.[2] Patients with treatment-resistant depression (TRD) have higher relapse rates and decreased daily functioning, and in the phase 3, open-label, long-term extension study (SUSTAIN-3), esketamine nasal spray combined with an oral antidepressant showed sustained efficacy and tolerability over 31.5 months, with 35.6% and 46.1% of participants achieving remission at induction and optimization/maintenance endpoints, respectively.[11,28,29] Other studies also demonstrated the significant role of esketamine in treating treatment-resistant depression (TRD), showing improvements in remission rates and sustained efficacy over extended periods. These findings collectively highlight the potential of esketamine as an effective therapeutic option for patients with TRD, particularly in improving both short-term and long-term outcomes. Despite some common adverse events, such as dizziness and dissociation, the overall safety profile of esketamine remains favorable, supporting its use in clinical practice.[30–34]

Esketamine's Mode of Action for Treating Depression That is Resistant to Therapy

While the approval of esketamine for the treatment of treatment-resistant depression marks a significant milestone, the complete understanding of its underlying mechanisms remains an area of active research and exploration. It is believed that the therapeutic action of esketamine is multifaceted, engaging a constellation of molecular pathways that collectively contribute to its rapid antidepressant effects.[35,36] Key among these mechanisms is the modulation of NMDA receptors, with esketamine functioning as an antagonist, thereby dampening excessive glutamatergic signaling, which is implicated in the pathophysiology of depression. Additionally, esketamine's interaction with AMPA receptors plays a crucial role. By potentiating AMPA receptor function, it promotes neuronal plasticity and enhances the release of neurotransmitters, such as glutamate, which can rapidly improve mood.[37] Furthermore, the drug has been shown to interact with opioid receptors, potentially influencing reward and pain pathways, and modulating mood.[38] Esketamine also impacts monoaminergic systems, which include serotonin, norepinephrine, and dopamine receptors, all of which are known to be

involved in mood regulation.[39] By influencing these receptors, it can rebalance the brain's neurotransmitter levels, contributing to its antidepressant action.

Lastly, the drug has been implicated in inhibiting pro-inflammatory responses, suggesting a role in reducing neuroinflammation that may contribute to depressive symptoms.[39] By targeting these various mechanisms simultaneously, esketamine appears to exert a broad-spectrum effect on the brain's neural networks, providing relief to those who have not responded well to conventional treatments.

NMDA Receptor

However, the interplay between these mechanisms and how they synergistically contribute to the clinical benefits observed in patients with treatment-resistant depression is not yet fully elucidated. Future studies are essential to refine our comprehension of these complex processes and to optimize the use of esketamine in clinical practice.

NMDAR (N-methyl-d-aspartate receptor), the NMDA receptor, a tetrameric ion channel present in the cell membrane, is assembled from GluN1 subunits along with combinations of GluN2A and GluN2B subunits. Research has consistently implicated the involvement of NMDAR blockage in the antidepressant action of esketamine. This compound selectively targets postsynaptic neurons, GABAergic interneurons, and even extra-synaptic NMDARs on glial cells, ultimately leading to the suppression of GABAergic interneuron activity and disinhibition of glutamatergic transmission, particularly within the prefrontal cortex.[35,36]

It is widely accepted that the primary mechanism involves preferential inhibition of GABAergic interneurons. Studies have revealed that, in rats, intravenous anesthetic doses of ketamine decrease prefrontal glutamate levels, whereas subanesthetic doses elevate these levels, promoting disinhibition of pyramidal neurons and rapid antidepressant-like effects.[37,38] Researchers have further shown that manipulating NMDAR expression in mice can mimic depressive behaviors, highlighting the critical role of these receptors.[38]

Esketamine, with twice the affinity for NMDARs compared to ketamine, not only blocks postsynaptic NMDARs but also influences the release of eEF2 kinase, which in turn enhances the production of Brain-Derived Neurotrophic Factor (BDNF).[40] The augmentation of BDNF levels by esketamine is thought to be a key factor in eliciting its rapid antidepressant response. These findings shed light on the intricate cellular and molecular mechanisms underlying esketamine's unique therapeutic potential in treating resistant depression.

The Receptor for Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole-Propionic Acid (AMPAR)

AMPAR, or the AMPA receptor, is a heteromeric ion channel composed of four subunits, GluA1 through GluA4 or GRIA-D, which assemble into tetrameric receptors through dimerization. Serving as an ionotropic glutamate receptor, AMPAR is pivotal for the swift propagation of synaptic signals in the central nervous system. Recent research has emphasized the significance of AMPAR activation in the antidepressant effects of ketamine.[35,38] Preclinical studies have demonstrated that administering the AMPAR antagonist 2.3-dihydroxy-7-nitro-quinoline-6-sulfonamide (NBQX) negates ketamine's rapid intravenous antidepressant response. Similarly, treatment with the AMPAR agonist CX546 reduces immobility time in the forced swim test in rats, concurrent with increased BDNF and mTOR levels in the hippocampus and the medial prefrontal cortex.[37,38,40] The addition of NBQX counteracts the antidepressant effects of ketamine when CX546 is present, indicating a direct link between AMPAR activation and ketamine's therapeutic action.

Esketamine, though with a slightly lower affinity for AMPAR than ketamine, is also thought to engage this receptor as part of its antidepressant mechanism.[38,39,41] The activation of AMPARs seems to be a contributory factor in the rapid antidepressant response observed with both ketamine and esketamine, supporting the notion that AMPAR modulation plays a crucial role in their therapeutic efficacy.

Opioid Receptors

G protein-coupled receptors (GPCRs), particularly opioid receptors, play a vital role in modulating intracellular cyclic adenosine monophosphate (cAMP) levels through their influence on adenylate cyclase activity. These receptors are

widely expressed in both the central and peripheral nervous systems and are activated by endogenous peptides, including endorphins, enkephalins, and dynorphins, in response to pain signals.[23,42] They are crucial for pain modulation and emotional processing. Recent research has shed light on the potential role of esketamine in pain management, particularly in the context of depression in cervical cancer patients. Studies have shown that esketamine can effectively alleviate postoperative pain in these patients, outperforming racemic ketamine at equivalent doses.[43] Intravenous administration of esketamine has been documented to enhance analgesia, leading to reduced pain perception and decreased requirements for anesthetic agents.[35,44] Moreover, opioid receptors have been implicated in mood disorders, including depression. There is accumulating evidence from double-blind crossover trials that suggests a connection between ketamine and opioid receptor interactions in the treatment of treatment-resistant depression.[43–45] Administration of naloxone, an opioid receptor antagonist, orally at 50 mg prior to ketamine infusion has been found to dampen the antidepressant and anti-suicidal effects of ketamine, pointing towards the involvement of opioid receptors in its rapid therapeutic action.

Despite these findings, the exact regulatory mechanisms linking opioid receptors to ketamine's antidepressant effects remain to be fully elucidated. Further clinical trials and mechanistic studies are needed to deepen our understanding of this complex interplay and to optimize the use of esketamine in the treatment of treatment-resistant depression. These studies will help clarify the precise role of opioid receptors and their contribution to the broader pharmacological profile of esketamine.

Monoaminergic Receptors

The dopaminergic system encompasses five distinct receptor subtypes, while the serotonergic system includes seven receptor subclasses, all of which play critical roles in the brain and spinal cord. Ketamine functions as a partial agonist at the D2 dopamine receptor and interacts with serotonin receptors, significantly contributing to its antidepressant properties.[44,46] Research has demonstrated that co-administration of a serotonin receptor antagonist can mitigate ketamine's rapid antidepressant response, underscoring the importance of serotonin signaling in this process.[27,47]

In contrast, esketamine has been found to augment serotonin release in a dose-dependent manner, particularly within the prefrontal cortex of the brain.[27,47] Additionally, studies suggest that the activation of dopamine D1 receptors in the medial prefrontal cortex could be another key factor underlying the antidepressant effects of esketamine.[47] Investigation have revealed that both ketamine and its enantiomer, esketamine, positively impact patient mood by modulating the midbrain dopamine system, particularly the D2 and D3 receptors, as well as monoamine transporters.[48,49] The acute antidepressant effect of esketamine appears to be closely tied to the activation of monoaminergic receptors, which in turn facilitates the enhanced release of monoamine neurotransmitters, such as dopamine and serotonin, contributing to improved mood and symptom relief. These findings emphasize the intricate interplay between different neurotransmitter systems and the potential therapeutic targets for novel antidepressant treatments. Further research is needed to fully understand the specific mechanisms by which ketamine and esketamine exert their rapid antidepressant effects and to develop more targeted and efficacious therapies for mood disorders.

Inflammatory Pathway

Extensive rodent research has established a strong correlation between depression and increased concentrations of pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β), particularly in brain areas like the hippocampus, anterior frontal gyrus, amygdala, and prefrontal cortex. Rodents subjected to nerve injury display behavioral patterns akin to depression, highlighting the role of inflammation in mood disorders.[20,21] Clinical studies parallel these findings, as depressed humans exhibit significantly higher serum levels of inflammatory markers like IL-6, TNF-α, and interferon-gamma (IFN-γ) compared to non-depressed individuals.[24,39]

Ketamine, known for its anti-inflammatory properties, has been shown to reduce TNF-α, C-reactive protein, and IL-6 levels, with IL-6 being particularly associated with post-surgical complications.[24,39] Similarly, esketamine, as an enantiomer of ketamine, exhibits similar actions by suppressing the synthesis of IL-6, TNF-α, and contributing to neuroprotection by reducing neuronal death and neuroinflammation.[37,38,42] In individuals with treatment-resistant depression, ketamine has demonstrated its anti-inflammatory capacity, and in rodent models of depression, it has led to a decrease in IL-6 and IL-1β expression within the prefrontal cortex and hippocampus.[37,38,42] Clinically, a significant

decline in IL-6 and IL-1β levels has been observed just 4 hours after intravenous ketamine administration in patients with treatment-resistant depression.[40,45] This indicates that ketamine's antidepressant effects might be, at least partially, mediated by its ability to suppress pro-inflammatory mediator production.

Given the similarities between ketamine and esketamine, it is plausible that esketamine's effectiveness in treating refractory depression could also involve the inhibition of pro-inflammatory factors. However, the literature on this topic is still limited, and more preclinical studies are needed to substantiate this hypothesis and explore the underlying molecular mechanisms.[26,27,46] The potential role of inflammation in the pathophysiology of depression and the subsequent targeting of inflammatory pathways using compounds like ketamine and esketamine offer promising avenues for future therapeutic strategies.

Neural Substrates Affected by Esketamine

Esketamine, as an NMDA receptor antagonist, exerts its rapid antidepressant effects through complex interactions with multiple neural substrates. Specifically, the prefrontal cortex (PFC), amygdala, and hippocampus play crucial roles in mood regulation, and their modulation by esketamine influences neural plasticity and synaptic connectivity.

The prefrontal cortex is a critical region involved in executive functions, emotional processing, and mood regulation. Esketamine's primary mechanism of action involves blocking NMDA receptors, which leads to increased glutamate release. This increase in glutamate activates AMPA receptors, promoting synaptic plasticity and neurogenesis. Specifically, the activation of AMPA receptors leads to downstream effects, such as the upregulation of brain-derived neurotrophic factor (BDNF) and the activation of the mammalian target of rapamycin (mTOR) pathway. These processes contribute to enhanced synaptic strength and stability, which are essential for the rapid antidepressant effects observed with esketamine.

The amygdala is a key structure involved in the processing of emotions, particularly fear and anxiety. Dysregulation of the amygdala is often implicated in mood disorders, including depression. Esketamine's modulation of NMDA receptors in the amygdala can lead to reduced hyperactivity and improved emotional regulation. The increased glutamate levels resulting from NMDA receptor blockade activate AMPA receptors, leading to enhanced synaptic plasticity and reduced anxiety-like behaviors. This modulation helps to normalize amygdala function and alleviate symptoms associated with depression.

The hippocampus plays a vital role in learning, memory, and mood regulation. Chronic stress and depression are associated with decreased hippocampal volume and impaired neurogenesis. Esketamine's ability to modulate NMDA and AMPA receptors in the hippocampus promotes neurogenesis and synaptic plasticity. Increased BDNF levels, mediated by AMPA receptor activation, enhance neurogenesis and promote the survival of new neurons. This process contributes to the restoration of hippocampal function and improves mood-related behaviors.

The interplay between the PFC, amygdala, and hippocampus is crucial for effective mood regulation. Esketamine's modulation of NMDA and AMPA receptors in these regions enhances synaptic plasticity and connectivity, leading to improved emotional regulation and cognitive function. Specifically, the enhanced BDNF signaling and mTOR pathway activation in the PFC, amygdala, and hippocampus contribute to the rapid antidepressant effects observed with esketamine.

In summary, esketamine's modulation of NMDA and AMPA receptors influences neural plasticity and synaptic connectivity in the prefrontal cortex, amygdala, and hippocampus. This integrated effect on multiple neural substrates underlies the rapid and sustained antidepressant effects of esketamine, making it a promising therapeutic option for treatment-resistant depression (TRD).

Esketamine Clinical Research as a Therapy for Refractory Depression

Currently, intravenous (IV) infusions and nasal mucosa sprays represent the primary pharmaceutical approaches for managing treatment-resistant depression (TRD). Research has highlighted the remarkable speed at which IV-administered esketamine produces antidepressant effects, with patients experiencing noticeable benefits within just two hours, while demonstrating acceptable tolerability with a single injection.[48] A specific investigation found that a single

0.25 mg/kg intravenous dose of esketamine led to a 59.3% efficacy rate and a 40.7% remission rate after 24 hours, indicating its potent therapeutic impact.[27,46,48]

Despite the rapid antidepressant action and favorable tolerability profile of IV esketamine, the need for administration in an outpatient or surgical setting can pose challenges to patient adherence due to the inconvenience and potential anxiety associated with such procedures. This highlights the potential superiority of nasal mucosa spray delivery in terms of practicality and patient acceptance.[40,42,50] Nasal sprays offer a more convenient and less intrusive method of administering esketamine, thus improving treatment compliance and potentially enhancing the overall treatment experience.

Effect of Esketamine on Treatment-Resistant Depression

Empirical evidence supports the notion that esketamine administered via nasal mucosa spray demonstrates robust antidepressant properties, particularly in individuals with treatment-resistant depression (TRD). In a meticulously designed, double-blind, randomized controlled trial involving 227 adult participants with TRD, two doses of esketamine (56mg and 84mg, flexible dosing) were compared with a placebo, all alongside oral antidepressants. The primary outcome measures clearly indicated that those receiving esketamine nasal mucosa spray exhibited marked alleviation of depressive symptoms compared to the placebo group.[38,51,52] By day 28, the response and remission rates stood at 52.0% and 31.0% for placebo recipients, while for the esketamine cohort, they reached 69.3% and 52.5%, respectively,[43] underlining the superior performance of the treatment. However, a separate randomized, double-blind study, focusing on an elderly population (aged 65 years and above) with TRD, administered oral antidepressants in conjunction with esketamine nasal mucosa spray (28mg, 56mg, or 84mg, flexible dosing) or placebo. Despite this, no appreciable difference was observed between the treatment and placebo arms in the primary efficacy assessment.[33,40] Intriguingly, post-hoc subgroup analyses revealed a statistically and clinically significant advantage for the esketamine group among patients aged 65 to 74, while those aged 75 and older did not exhibit such disparities.[44,50,53] These findings suggest that the efficacy of the nasal spray might be influenced by the age of the patient, with younger seniors potentially benefiting more from the rapid antidepressant action of esketamine.

The contrasting outcomes across different age groups emphasize the importance of considering individual patient characteristics when designing treatment plans for TRD. The nasal mucosa spray's rapid onset of action underscores its potential value in acute situations, yet the variable response among older adults calls for further investigation into age-related pharmacokinetics and pharmacodynamics of the drug. Future research should delve deeper into understanding these variations to optimize treatment strategies and improve outcomes for all TRD patients. A groundbreaking study examining the impact of esketamine nasal mucosa spray on reducing suicidal tendencies in high-risk individuals found compelling results. In this trial, 68 TRD patients, along with their standard treatment regimen, were administered twice-weekly 84 mg doses of esketamine nasal sprays for a duration of four weeks. The Montgomery-Åsberg Depression Rating Scale (MADRS) revealed a substantial and rapid decrease in suicidal ideation scores in the esketamine group, clearly distinguishing it from the placebo group as early as 4 hours post-administration.[27,46,51] Moreover, the MADRS demonstrated an immediate antidepressant effect, reflecting a decline in the overall score, which was evident at 4, 24, and 72 hours following the initial dose, with a statistically significant separation from the placebo.

Esketamine's nasal mucosa spray has emerged as a potentially life-saving intervention for TRD patients, as it swiftly alleviates suicidal thoughts and decreases the likelihood of fatal outcomes.[40,42,43] Although limited, research exploring its role in recurrence prevention has shown promising results. One analysis suggested a 51% reduced risk of recurrence with the use of the nasal spray, with a clinically and statistically meaningful difference in the time to recurrence between the treatment and control groups.[48,50] Notably, the antidepressant effects of esketamine have been documented to persist for several weeks to even beyond two months after discontinuing repeated administrations.[26,48]

These findings propose that the combination of oral antidepressants and esketamine nasal mucosa spray could effectively minimize the recurrence of depressive episodes in TRD patients, offering a beneficial long-term therapeutic strategy. The synergistic effect of these treatments underscores the potential for improved patient outcomes and enhanced

mental health stability. Further studies are needed to solidify these observations and explore the most optimal dosing regimens and treatment durations for lasting benefits.

Esketamine's Safety in Treating Depressive Disorder That is Resistant to Therapy

In addition to rapid anti-depression, esketamine has a series of adverse reactions in both short - and long-term clinical studies, the most common include: schizophrenia, nausea, hypesthesia, anxiousness, lethargy, drowsiness, vertigo, increased blood pressure, and "drunkenness", etc., but clinical studies have found that most adverse events are mild and self-limiting.[28,52] Some transient adverse reactions such as elevated blood pressure, sedation, and separation symptoms are associated blood esketamine levels and typically persist for four to six hours. The psychotropic side effects, misuse, and existing limitations on the therapeutic application of esketamine may addiction tendencies.[46–48]

Long-term ketamine usage has been linked to ulcerative cystitis, a condition marked by painful and frequent urination, according to studies. In a similar vein, it has been demonstrated that ketamine use over time damages the liver.[47,50,51,53] During 52 weeks of esketamine treatment, no occurrences of ulcerative cystitis were reported by some researchers, and in an acute phase III clinical trial, there was no substantial liver damage observed in the esketamine group when compared to the placebo group.[54–56] Ketamine usage over an extended period can result in neurological damage and substance misuse. In healthy individuals, ketamine use can cause brief cognitive deficits linked to schizophrenia, such as reductions in memory, focus, and abstract reasoning. Esketamine nose mucosal sprays was also linked to a brief reduction in cognitive performance in healthy individuals but only within 40 minutes of administration compared with placebo, and this difference gradually disappeared over time.[53,55] Esketamine causes less cognitive impairment, reduced attention, and memory loss than ketamine, so esketamine is safer and better tolerated than ketamine.[53,54]

Summary and Prospect

In summary, esketamine has demonstrated rapid and significant anti-depression and anti-suicide effects in adult treatment-resistant depression (TRD) patients. When used over an extended period, it is safe, effective, and has low side effects, offering a novel option for the management of TRD in the future. However, it is undeniable that esketamine still poses risks of mental adverse reactions and potential abuse and misuse. Therefore, its clinical use must be strictly controlled and managed in a reasonable and standardized manner. To address these limitations, future research should further explore the mechanisms by which esketamine functions in treating TRD patients. Despite its obvious advantages in caring for adult TRD patients, there is a lack of extensive studies on the application of esketamine in elderly and adolescent populations. Therefore, prospective, large-sample, and multi-center randomized controlled studies should be conducted to accumulate more clinical experience in the field of TRD prevention and treatment in different populations. By addressing these limitations and conducting further research, we can better understand the full potential and appropriate use of esketamine in the treatment of TRD.

Data Sharing Statement

The data used to support this study are available from the corresponding author upon request.

In summary, esketamine has demonstrated rapid and significant anti-depression and anti-suicide effects in adult treatment-resistant depression (TRD) patients. When used over an extended period, it is safe, effective, and has low side effects, offering a novel option for the management of TRD in the future. However, it is undeniable that esketamine still poses risks of mental adverse reactions and potential abuse and misuse. Therefore, its clinical use must be strictly controlled and managed in a reasonable and standardized manner. To address these limitations, future research should further explore the mechanisms by which esketamine functions in treating TRD patients. Despite its obvious advantages in caring for adult TRD patients, there is a lack of extensive studies on the application of esketamine in elderly and adolescent populations. Therefore, prospective, large-sample, and multi-center randomized controlled studies should be conducted to accumulate more clinical experience in the field of TRD prevention and treatment in different populations. By addressing these limitations and conducting further research, we can better understand the full potential and appropriate use of esketamine in the treatment of TRD.

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Disclosure

The authors declare that they have no conflicts of interest.

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