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Ketamine and Esketamine in Treatment-Resistant Depression: A New Era of Rapid-Acting Antidepressants

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Abstract: Depression is one of the most common mental disorders worldwide and remains a leading cause of disability. Despite the use of traditional monoaminergic antidepressants, nearly one-third of patients do not achieve sufficient benefit, leading to the development of treatment-resistant depression (TRD). In recent years, new drugs targeting the glutamate system have been developed, among which ketamine and its S-enantiomer, esketamine, have emerged as highly promising options. Clinical trials and meta-analyses have shown that ketamine can produce rapid antidepressant effects within just a few hours. Esketamine, approved in intranasal form, demonstrates a similar level of efficacy while generally having a more favorable side-effect profile. Both drugs have been shown to reduce suicidal thoughts, highlighting their important role in urgent clinical situations.

Short-term use appears to be relatively safe, though temporary side effects such as dissociation, dizziness, nausea, and elevated blood pressure may occur. Long-term studies suggest the potential for continued treatment, but emphasize the need for regular monitoring of cognitive function and caution regarding misuse or overuse. In Uzbekistan, there is growing interest in implementing glutamate-modulating agents in clinical practice, though strict pharmacovigilance is strongly emphasized.

Overall, ketamine and esketamine represent a new approach to managing TRD. Their rapid onset and clinically meaningful outcomes make them valuable treatment options. Responsible integration into clinical practice, inclusion in national treatment guidelines, and further long-term and region-specific studies could significantly improve treatment outcomes.

Key words: Ketamine; Esketamine; Treatment-resistant depression; Major depressive disorder; NMDA receptor antagonists; Rapid-acting antidepressants; Suicidal ideation; Intranasal administration; Uzbekistan; Clinical efficacy

1. Introduction

Depression is one of the most common psychiatric disorders worldwide and is among the leading causes of disability and reduced quality of life [1]. According to the World Health Organization, more than 280 million people globally suffer from depressive disorders, highlighting the condition as a major public health challenge [1]. Despite the availability of various antidepressants, about one-third of patients do not achieve full symptom relief. This group is classified as having treatment-resistant depression (TRD), which remains one of the most serious therapeutic challenges in psychiatry [3,4].

Conventional antidepressants primarily target monoaminergic systems—serotonin, norepinephrine, and dopamine pathways [2,4]. However, their limited effectiveness in TRD cases has prompted the search for new pharmacological strategies. Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, modulates the glutamate system and has been proposed as a promising agent with rapid antidepressant properties [5,13]. Clinical evidence indicates that even a single intravenous infusion of ketamine can reduce depressive symptoms within a few hours—markedly

different from the delayed onset seen with traditional antidepressants [5,14]. Initially developed and widely used in anesthesiology, ketamine later attracted psychiatric interest due to its rapid effects and unique pharmacodynamic profile [2,17]. Today, it is being actively investigated as a novel antidepressant option for TRD [5,7].

Esketamine, the S-enantiomer of ketamine, shows greater pharmacological potency and generally fewer adverse effects compared to the racemic mixture [6,8]. In 2019, the U.S. Food and Drug Administration (FDA) approved intranasal esketamine specifically for TRD patients, based on strong clinical evidence of its efficacy [6,7]. Subsequent randomized controlled trials and meta-analyses confirmed esketamine's effectiveness in rapidly alleviating depressive symptoms. Furthermore, its use during the maintenance phase has been shown to play an important role in preventing relapse [9,11,12]. Nevertheless, questions remain regarding its long-term safety, risk of dependence, and potential cognitive consequences, which continue to be explored in ongoing studies [12,13].

In addition to international findings, regional perspectives are also noteworthy. The Uzbek-language textbook Psychiatry (2019) highlights the clinical potential of glutamatergic modulators, including ketamine, for patients unresponsive to selective serotonin reuptake inhibitors [16]. Similarly, the 2020 textbook Pharmacology describes ketamine's unique mechanism of action and its possible integration into future clinical practice [17]. Internationally recognized sources, such as Stahl's Essential Psychopharmacology, also support the neurobiological rationale for ketamine and esketamine therapy [2].

Therefore, this article aims to present updated information on the clinical efficacy, safety, and long-term outcomes of ketamine and esketamine in the management of TRD, integrating both international evidence and regional scientific perspectives.

2. Methods

This review was conducted using a narrative review methodology. The main aim was to summarize the available evidence on the clinical efficacy, safety, and long-term outcomes of ketamine and esketamine in the treatment of treatment-resistant depression (TRD).

2.1 Literature Search Strategy

A comprehensive literature search was carried out in PubMed, Scopus, and Web of Science databases. The following keywords were used: *"ketamine," "esketamine," "treatment-resistant depression," "NMDA receptor antagonist," "clinical efficacy."* Only peer-reviewed studies published between 2000 and 2023 were included. In addition, landmark studies published before 2000 that first demonstrated the antidepressant potential of ketamine were also reviewed when necessary [5].

Priority was given to randomized controlled trials (RCTs), systematic reviews, meta-analyses, and large observational studies [6–12,15]. To ensure a complete overview of current clinical practice, clinical guidelines and expert consensus papers were also included [13]. Non-English studies were considered only if a full translation was available.

2.1.1 Textbooks and Local Sources

To strengthen the theoretical and educational perspective, authoritative sources in psychiatry and pharmacology were reviewed. *Stahl's Essential Psychopharmacology* was used as a neurobiological reference for explaining ketamine's mechanism of action [2]. Uzbek-language academic sources were also included, such as *Psychiatry* (UzMU, 2019) and *Pharmacology* (Tashkent Medical Academy, 2020), which present local perspectives on glutamatergic modulators [16,17].

Additionally, official documents and guidelines approved by the Ministry of Health of Uzbekistan—particularly the National Strategy for the Development of Psychiatric Services (2022–2026)—were analyzed [18]. Legal documents published on the **Lex.uz** portal were also reviewed to illustrate the process of integrating innovative therapies into the healthcare system [19].

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2.1.2 Data Synthesis

Findings from international studies and local publications were qualitatively synthesized. The data were organized into four key domains:

1. Clinical efficacy of ketamine and esketamine in TRD.
2. Safety and tolerability, including adverse effects and long-term risks.
3. Outcomes of long-term treatment and relapse prevention.
4. Local perspectives and future prospects for Uzbekistan and comparable healthcare systems.

This approach allowed for a balanced and context-sensitive analysis, combining global evidence with regional insights.

3. Results

3.1 Clinical efficacy of ketamine

The clinical efficacy of racemic ketamine in treatment-resistant depression (TRD) has been clearly demonstrated in numerous studies. Berman et al. (2000) were the first to report a significant reduction in depressive symptoms within a few hours of intravenous administration—much faster than the delayed effects of traditional monoaminergic antidepressants [5]. Later randomized controlled trials (RCTs) confirmed response rates of up to 70% in TRD patients, compared with 40–50% typically seen with standard treatments [13]. However, remission rates were lower (30–40%), and the antidepressant effect usually lasted less than one week [14]. These findings highlight ketamine as a rapid-acting treatment option, although maintaining long-term benefit remains a major challenge.

Meta-analyses further support this view, showing that ketamine is one of the few currently available drugs capable of producing such rapid antidepressant effects [16]. In addition to reducing depressive symptoms, some studies have also shown a significant decrease in suicidal thoughts within 24 hours, underscoring its therapeutic importance [10].

3.1.2 Esketamine in treatment-resistant depression

Esketamine, the S-enantiomer of ketamine, has gained particular attention due to its higher pharmacological selectivity and better tolerability. In pivotal phase III clinical trials, intranasal esketamine combined with oral antidepressants significantly reduced relapse risk compared with placebo plus antidepressant [6,7]. Singh et al. (2016) also reported that intravenous esketamine produced antidepressant effects comparable to racemic ketamine in TRD patients [8].

Comparative studies suggest that esketamine causes fewer dissociative symptoms (about 25%) compared with racemic ketamine (up to 40%) [9]. In 2019, the U.S. Food and Drug Administration (FDA) approved intranasal esketamine for TRD, making it the first NMDA receptor antagonist officially approved for this indication [20].

3.1.3 Safety and tolerability

Short-term clinical trials indicate that ketamine and esketamine are generally well tolerated. The most common side effects include nausea, dizziness, headache, and temporary increases in blood pressure [7,8]. Dissociation is also frequent but usually resolves within 1–2 hours and is considered manageable [10].

Although long-term safety data remain limited, encouraging results have been reported. In a one-year open-label study, esketamine maintained good tolerability without new safety concerns [11]. Nevertheless, ongoing monitoring is essential due to the potential for cognitive side effects and the risk of misuse [12].

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3.1.4 Long-term outcomes

The duration of antidepressant effects remains a key question. In a study by Kryst et al. (2020), many patients experienced relapse within weeks after stopping esketamine, emphasizing the need for maintenance treatment [12]. Strategies such as flexible dosing and combining therapy with psychotherapy have been suggested to prolong remission [18]. Most reviews agree that structured maintenance protocols are required for sustained benefit, as single or short-term treatment tends to provide only temporary relief [16].

Data summary for tables and figures

Table 1. Clinical response and remission rates in TRD

Treatment	Response rate (%)	Remission rate (%)	Duration of effect
Racemic ketamine (IV)	60–70	30–40	3–7 days
Esketamine (IV)	55–65	25–35	3–7 days
Esketamine (IN)	50–60	20–30	Up to 2 weeks
Conventional antidepressants	40–50	15–20	4–8 weeks

Table 1. Clinical response and remission rates in treatment-resistant depression (TRD). Summary of short-term response rates, remission rates, and duration of effect for intravenous racemic ketamine, intravenous esketamine, intranasal esketamine, and conventional antidepressants. Data compiled from randomized controlled trials and meta-analyses [5–9,13–16].

Figure 1. Antidepressant effect at 24h (MADRS reduction)

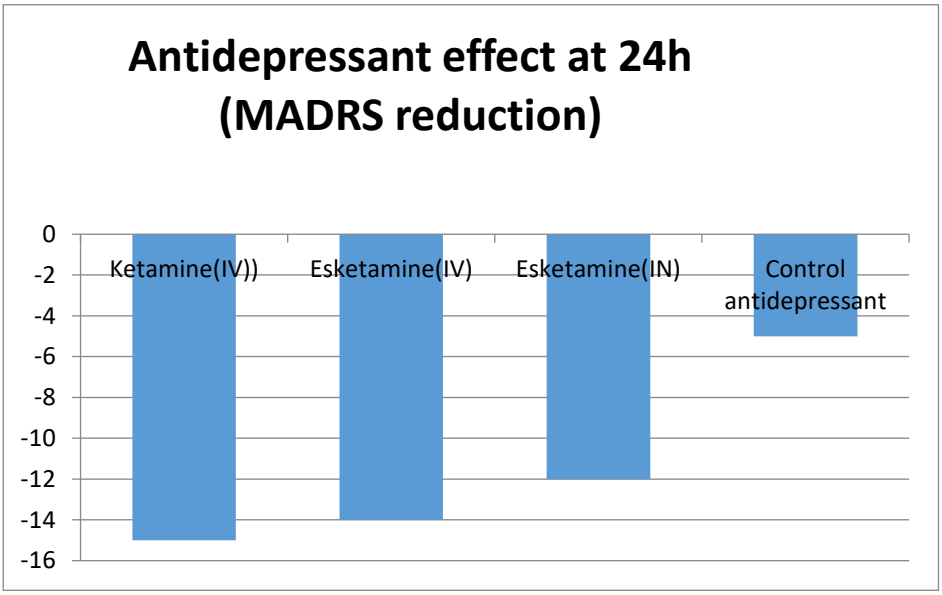

Figure 1. Antidepressant effect at 24 hours (MADRS reduction).

Comparison of mean reduction in Montgomery–Åsberg Depression Rating Scale (MADRS) scores at 24 hours following treatment with intravenous ketamine, intravenous esketamine, intranasal esketamine, and conventional antidepressants. Data synthesized from published clinical trials [5–9,13,14]. Figure created by authors based on reported outcomes.

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Figure 2. Frequency of common adverse effects

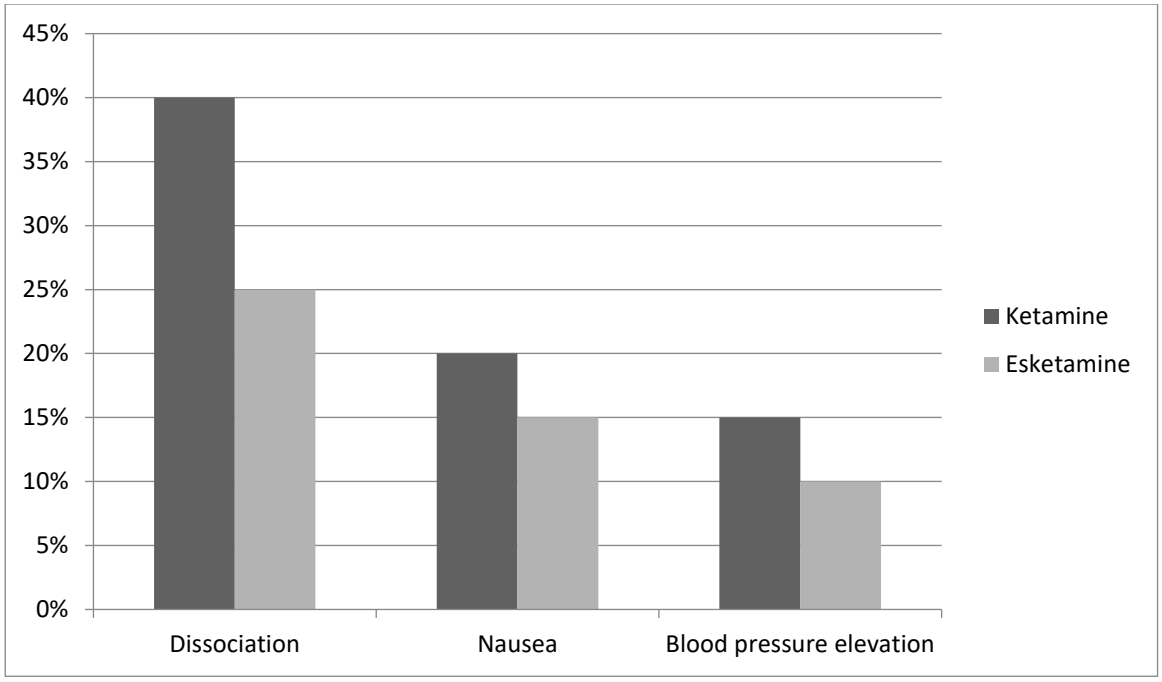

Figure 2. Frequency of common adverse effects.

Rates of dissociation, nausea, and transient blood pressure elevation observed in patients treated with ketamine or esketamine. Data extracted from clinical trials [7–12]. Figure created by authors based on extracted data.

4. Discussion

The findings of this review confirm ketamine and esketamine as significant advances in the management of treatment-resistant depression (TRD). Unlike traditional antidepressants, which often require several weeks for full therapeutic effect, ketamine and esketamine can rapidly reduce depressive symptoms within hours [5,13]. This rapid onset is especially critical in severe suicidal crises where urgent intervention is required [10].

The mechanism of ketamine differentiates it from monoaminergic antidepressants. By blocking NMDA receptors, ketamine enhances glutamatergic signaling, promotes synaptic plasticity, and increases the release of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF) [2,5]. This mechanistic innovation has positioned glutamatergic modulation as a promising direction for drug development [16]. However, while short-term efficacy is consistently demonstrated, the transient nature of its effects necessitates repeated dosing or adjunctive strategies [14].

Esketamine, the S-enantiomer of ketamine, was developed to improve tolerability while retaining antidepressant efficacy. Clinical trials support its use as both an acute and long-term treatment option for TRD, with evidence showing reduced relapse rates compared to standard antidepressant therapy [6,7,11]. Importantly, esketamine is associated with a lower incidence of dissociative side effects than racemic ketamine [9], making it a preferred choice in some patients. The FDA approval of intranasal esketamine in 2019 represented a landmark step in antidepressant pharmacotherapy [20].

Nevertheless, several limitations must be acknowledged. First, most clinical trials of ketamine and esketamine are short-term, making it difficult to fully assess long-term safety and cognitive outcomes [12]. Some studies report mild impairments in functions such as attention and working memory, though findings remain inconsistent [11]. Second, given ketamine's history as a recreational drug, the risk of misuse remains a pressing concern [12]. Although intranasal esketamine administered under clinical supervision reduces this risk, vigilance is still required.

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Another challenge is the heterogeneity of existing studies. Variations in dosing regimens, administration routes, patient populations, and outcome measures complicate direct comparisons and hinder the development of standardized protocols [18]. For example, intravenous ketamine has demonstrated the most consistent efficacy, yet its invasiveness and monitoring requirements limit use outside specialized centers [14]. In contrast, intranasal esketamine is more practical but may yield lower response rates [7,9].

The question of long-term outcomes also remains unresolved. Evidence suggests that ongoing esketamine treatment reduces relapse risk, but discontinuation often leads to rapid symptom recurrence [12]. This highlights the need to approach TRD with long-term management strategies similar to those used in other chronic psychiatric disorders [16]. Optimal protocols, including dosing frequency and integration with psychotherapeutic interventions, are yet to be clearly defined.

From a broader perspective, ketamine and esketamine have validated glutamatergic modulation as an effective therapeutic target, shifting the paradigm in psychiatry. This has stimulated the investigation of other NMDA receptor antagonists and glutamate modulators, such as rapastinel and AV-101 [18]. Future research may expand the treatment landscape further, offering safer or longer-lasting alternatives.

In conclusion, ketamine and esketamine represent major breakthroughs in TRD treatment. They provide rapid symptom relief, particularly in patients unresponsive to conventional antidepressants, yet questions regarding long-term safety, durability of effect, and abuse potential remain unresolved. Continued research is essential to refine treatment protocols, optimize maintenance strategies, and develop novel agents inspired by their mechanisms. Integrating these findings into evidence-based clinical guidelines will maximize patient benefit while minimizing associated risks.

5. Conclusion

Ketamine and its S-enantiomer esketamine represent a major breakthrough in the pharmacological management of treatment-resistant depression (TRD). Unlike conventional monoaminergic antidepressants, they target glutamatergic neurotransmission and can rapidly alleviate symptoms within hours of administration [5,13]. Such a rapid effect is particularly valuable in patients with high suicidal risk, where immediate intervention may be life-saving [10].

Clinical evidence consistently confirms the short-term efficacy of ketamine and esketamine, with higher response rates compared to standard treatments [6–9]. The FDA approval of esketamine in 2019 marked an important milestone, as its intranasal formulation offers greater practicality in routine clinical practice and is associated with lower rates of dissociative side effects [7,9,20].

At the same time, several challenges remain. The transient nature of their effects necessitates maintenance protocols, while concerns about cognitive function and misuse risk highlight the need for careful long-term monitoring [11,12]. Furthermore, heterogeneity in study designs continues to complicate the development of standardized clinical guidelines [16,18].

Despite these limitations, ketamine and esketamine have validated glutamatergic modulation as a novel therapeutic avenue, introducing a paradigm shift in the treatment of depression. Their success has stimulated research into other NMDA receptor antagonists and related agents, paving the way for safer and longer-acting antidepressant strategies [18].

In summary, ketamine and esketamine offer rapid and effective relief for patients with TRD, but further evidence is required to ensure their safe integration into long-term clinical practice. Ongoing research, refinement of clinical guidelines, and careful patient selection will be essential to maximize their potential while minimizing risks.

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