**Medical Science**

**To Cite:**
Rogała J, Polityńska K, Ruszel D, Sarzyńska M, Samuła K, Goc E, Markuszka K, Lepak S, Irzyk Z, Szabat M. Ketamine and esketamine for treatment-resistant depression: A systematic review of published studies. *Medical Science* 2026; 30: e142ms3863
doi:

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**Peer-Review History**
Received: 18 August 2025
Reviewed & Revised: 12/September/2025 to 07/July/2026
Accepted: 25 July 2026
Published: 09 August 2026

**Peer-review Method**
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367



DISCOVERY SCIENTIFIC SOCIETY

# Ketamine and esketamine for treatment-resistant depression: A systematic review of published studies

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## ABSTRACT

Treatment-resistant depression occurs in roughly one-third of individuals diagnosed with depression. Ketamine and esketamine have appeared as innovative antidepressant treatments that target the glutamatergic system and deliver promising therapeutic options for patients unresponsive to conventional monoaminergic antidepressants. This review delivers a complete analysis of the mechanisms of action, efficacy, clinical applications, and safety of ketamine and esketamine in the treatment of TRD. We conducted this literature review using the PubMed, Embase, and Cochrane databases through 2024 and included systematic reviews, randomized controlled trials, meta-analyses, clinical guidelines, and effectiveness studies. Both ketamine and esketamine demonstrate antidepressant effects. Clinical response rates in TRD patients range from 45% to 67%, which exceeds traditional antidepressant success in this population. Intravenous racemic ketamine (0.5 mg/kg) produces strong antidepressant effects within 24 hours. Intranasal esketamine (56–84 mg) given to patients twice a week is effective when combined with oral antidepressants. Studies suggest that both ketamine and esketamine may be useful in patients with treatment-resistant depression. The most frequently reported adverse effects are temporary dissociation, nausea, dizziness, and increased blood pressure. In most cases, these symptoms are mild and disappear on their own after a short time. Long-term observations point toward possible improvement in cognitive functioning, although the issue of abuse potential is still unclear and requires further research. Acting through glutamatergic pathways, both substances are capable of reducing depressive symptoms relatively quickly. Esketamine has obtained FDA approval together with REMS safety regulations, while intravenous ketamine continues to be administered as an off-label therapy.

**Keywords:** treatment-resistant depression (TRD); ketamine; esketamine; glutamatergic system; rapid-acting antidepressants

## 1. INTRODUCTION

Major depressive disorder affects about 280 million people, which makes it a very debilitating disease. Classic antidepressants regulate monoaminergic neurotransmission pathways. They involve neurotransmitters such as serotonin, norepinephrine, and dopamine. Patients usually need about 4 to 8 weeks to feel therapeutic effects. The clinical course of the disease is diverse - about one-third of cases become treatment-resistant depression (TRD). TRD means there is insufficient improvement after two or more antidepressant treatments (McIntyre et al., 2023). Treatment must use standard medications at adequate doses and for an adequate duration, with documented patient compliance (McAllister-Williams et al., 2020). This is a huge obstacle. Many patients do not respond to treatment for a long time. They show impaired functioning and are at greater risk of suicide (McIntyre et al., 2023). Ketamine offers hope. It was used as an anesthetic in the 1960s and has become an innovative TRD treatment in the past 20 years (Das, 2020).

Ketamine's mechanism of action is to block the NMDA receptor and regulate glutamatergic neurotransmission, which causes very rapid positive effects - they show within a few hours, unlike most traditional antidepressants, which take weeks to show some clinical benefits (Halaris and Cook, 2023; Hess et al., 2022). The US Food and Drug Administration approved esketamine nasal spray (Spravato®) in 2019 for the treatment of treatment-resistant depression, and now recommends its use along with traditional oral antidepressants (Feeney and Papakostas, 2023).

This review discusses current scientific data on the clinical effects, mechanisms of action, safety, dosing, and practical clinical issues of ketamine and esketamine for the treatment of treatment-resistant depression.

## 2. REVIEW METHODS

**Study design**

This study is a systematic literature review of clinical and translational evidence regarding the efficacy, safety, and mechanisms of ketamine and esketamine in treatment-resistant depression (TRD) and major depressive disorder (MDD). The review followed PRISMA 2020 guidelines for reporting systematic reviews (Figure 1).

**Search Strategy**

We used the following databases: PubMed/MEDLINE, Embase, and the Cochrane Library from their inception to December 2024 to conduct a systematic search. In the search, we included the following terms: “ketamine,” “esketamine,” “treatment-resistant depression”, “major depressive disorder,” “glutamate,” “NMDA receptor,” and “rapid-acting antidepressant.”

The initial search identified 445 records. We excluded 120 records as duplicates, and left 325 records for title and abstract screening. Following screening, we assessed 65 full-text articles for eligibility. Of these, we excluded 34 studies. In the final qualitative synthesis, we included 31 studies.

*Inclusion Criteria*

We included studies that met the following criteria:

- randomized controlled trials (RCTs) evaluating ketamine or esketamine in treatment-resistant depression (TRD) or major depressive disorder (MDD),
- systematic reviews and meta-analyses,
- clinical practice guidelines,
- real-world effectiveness and observational studies,
- studies assessing safety, tolerability, or pharmacological mechanisms relevant to clinical use,
- adult populations (≥18 years),
- articles published in English.

*Exclusion Criteria*

The following studies were excluded:

- case reports and case series with fewer than 10 patients,
- studies evaluating ketamine for indications other than depression,
- preclinical animal or in vitro studies without direct clinical translation,
- publications lacking relevant clinical outcomes for depression.

*Study Selection Process*

Independent reviewers screened titles and abstracts for eligibility. Full-text articles were assessed for inclusion according to predefined criteria. Disagreements were resolved through consensus.

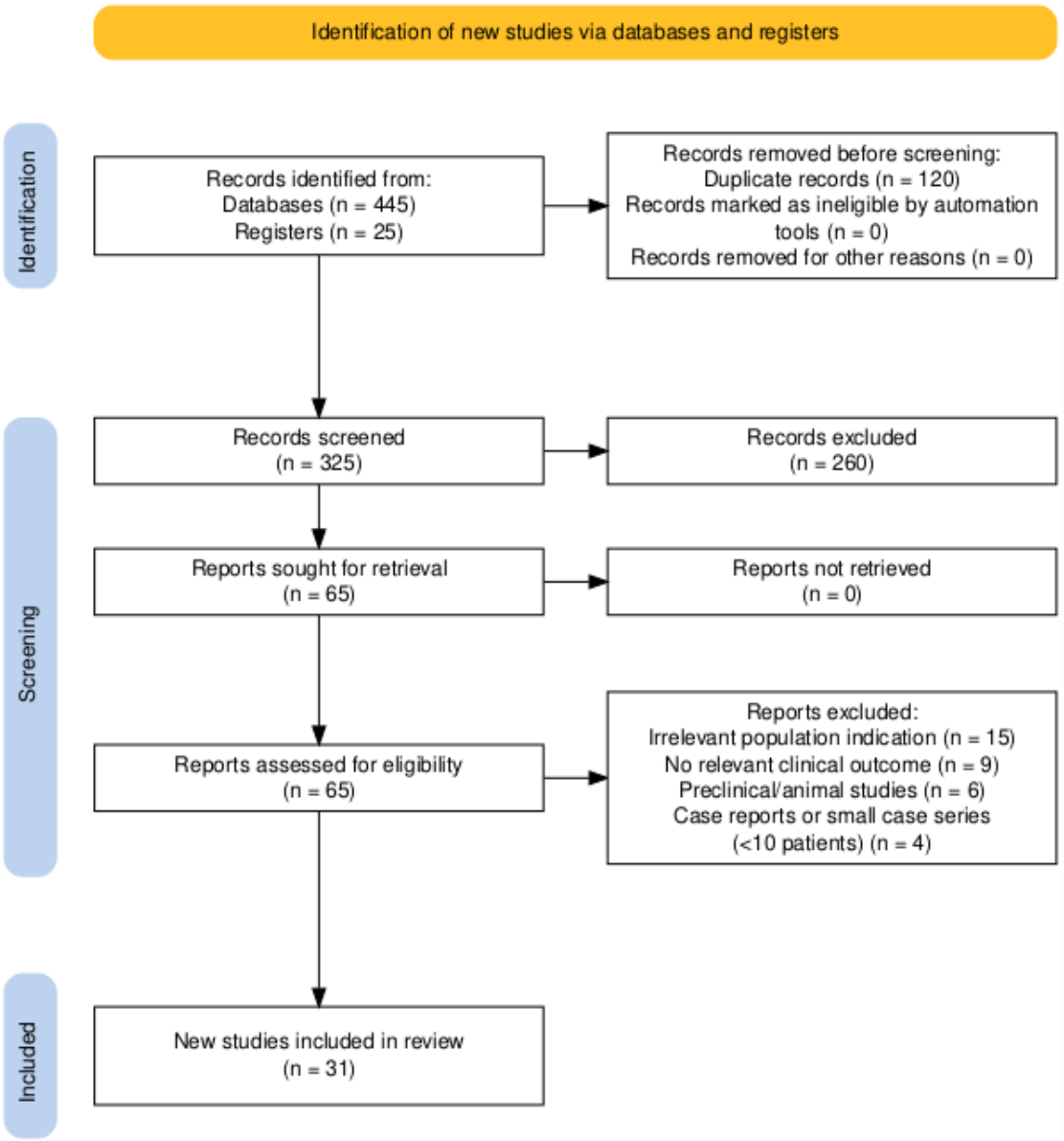


**Figure 1**. PRISMA 2020 flow diagram used to illustrate the study selection process.

## 3. RESULTS AND DISCUSSION

### Definition and Epidemiology of Treatment-Resistant Depression

The most common definition of treatment-resistant depression says that it has to be insufficient improvement in symptoms after two or more attempts at antidepressant treatment at an adequate dose, lasting for an adequate period of time (usually a minimum of 8 weeks) and with adherence to recommendations within a single depressive episode (McIntyre et al., 2023; McAllister-Williams et al., 2020). TRD occurs in about 30% patients with MDD, and its risk factors are chronic diseases, cardiovascular diseases, anxiety disorders, substance use, childhood trauma, and a higher number of previous depressive episodes. Treatment of TRD shows significantly worse outcomes compared to treatment-responsive depression, and it results in a higher financial pressure on healthcare. Patients with TRD usually experience greater functional impairment, have a greater risk of suicide, and also lower quality of life (McIntyre et al., 2023).

Mechanisms of Action

**Glutamatergic Neurotransmission**

Ketamine and esketamine are drugs that act as non-competitive NMDA receptor blockers. (Hess et al., 2022; Le et al., 2022). Blocking these receptors on GABAergic interneurons increases release of glutamate - the primary excitatory neurotransmitter in the central nervous system, which is known to be the most important transmitter in learning and memory processes. Increased glutamate secretion causes greater activation of AMPA receptors (Lewis et al., 2024; Hess et al., 2022). That activates other neurotransmission pathways, leading to increased secretion of brain-derived neurotrophic factor (BDNF), activation of the mTORC1 pathway, and also increased synaptic protein production (Hess et al., 2022; Le et al., 2024). All of these processes finally cause the restoration of synaptic connections, especially in the prefrontal cortex and hippocampus, which are brain regions most associated with depressive symptoms (Das, 2020; Le et al., 2024; Araújo-de-Freitas et al., 2021).

**Supplementary Mechanisms**

Among other mechanisms of action of ketamine and esketamine, we can mention: modulating opioid receptors (particularly μ and κ receptors), exerting anti-inflammatory effects by reducing pro-inflammatory cytokines, increasing monoaminergic neurotransmission, and exerting indirect effects through ketamine metabolites. All of these mechanisms may also provide antidepressant effects independent of NMDA receptor (Hess et al., 2022; Halaris and Cook, 2023).

**Efficacy of Ketamine in Treatment-Resistant Depression**

***Single-Dose Studies***

RCTs with a placebo control group showed that a single intravenous dose of ketamine (0.5 mg/kg over 40 minutes) produces rapid antidepressant effects in patients with TRD (Dean et al., 2021). Based on a Cochrane systematic review that analyzed 31 studies on ketamine, the treatment significantly improved remission rates in comparison to placebo within 24 hours of administration (odds ratio [OR] 3.94; 95% confidence interval [CI] 1.54–10.10). Response rates were also significantly improved, though reported separately. Depression scale scores showed a significant reduction (standardized mean difference [SMD] -0.87, 95% CI -1.26 to -0.48). Compared to midazolam as an active placebo control, ketamine showed greater efficacy, resulting in higher remission rates (OR 2.21, 95% CI 0.67–7.32) and response rates (OR 2.48, 95% CI 1.00–6.18) after 24 hours (Dean et al., 2021). A dosing study found that doses of 0.5 mg/kg and 1.0 mg/kg were more effective than active placebo, whereas lower doses (0.1 mg/kg) showed inconsistent benefits (Fava et al., 2020).

***Research on repeated doses***

The transient effects of a single dose of ketamine (usually lasting 3–7 days) encouraged researchers to investigate repeated dosing regimens (Andrade, 2017). A 2019 randomized trial showed great cumulative antidepressant effects with repeated infusions administered three times a week for two weeks. About 30% of patients responded to the treatment after a single dose, but the response increased to 59% after six infusions. Most patients required an average of three treatments to achieve a noticeable response. Weekly maintenance infusions sustained the antidepressant effect in patients who responded (Phillips et al., 2019).

***Meta-analytic evidence***

The scientists conducted a systematic review and meta-analysis of the actual efficacy of ketamine, which included 79 studies involving 2,665 patients. The mean response and remission rates were 45% and 30%, respectively, with a substantial effect size (Hedges' g = 1.44). The therapeutic effects did not reduce with repeated treatments - it confirmed that the long-term maintenance strategies are effective (Alnefeesi et al., 2022). A meta-analysis calculating the number needed to treat (NNT) yielded values of 3 for responses within one day to one week and 9 for responses within four weeks, indicating clinically significant efficacy. The NNT values compare favorably with conventional antidepressants, for which the NNT is typically 6–8 for response (Calder et al., 2024).

**Efficacy of esketamine in the treatment of treatment-resistant depression**

***Regulatory studies***

The results of several Phase III studies led to FDA approval of esketamine in a nasal spray. In the randomized controlled trial TRANSFORM-2, the combination of esketamine with a newly initiated oral antidepressant resulted in significantly greater symptom relief than placebo combined with an oral antidepressant at day 28 (Popova et al., 2019). TRANSFORM-1 and TRANSFORM-3 showed a similar effect size but did not reach statistical significance (Daly et al., 2018; Marwaha et al., 2023).

*Studies on relapse prevention*

A study on relapse prevention showed that in patients who achieved stable remission or response to treatment, esketamine in combination with oral antidepressants significantly delayed relapse compared to placebo in combination with oral antidepressants. This result shows that it is reasonable to use esketamine for maintenance treatment in patients who have responded to treatment (Daly et al., 2019).

*Active comparator studies*

The ESCAPE-TRD study has compared intranasal esketamine with extended-release quetiapine for 32 weeks in patients with TRD. Esketamine showed superior effects on remission at week 8 and on avoiding relapse through week 32. Approximately half of patients treated with esketamine achieved remission at week 32, and two-thirds showed a response to treatment (Reif et al., 2023).

*Meta-analytic evidence*

A systematic review and meta-analysis of studies on the use of esketamine in TRD showed that it considerably reduces symptoms of depression and is also significantly more likely to result in remission compared to placebo. Doses of 84 mg and flexible doses were shown to be notably effective (Oraee et al., 2024).

**Comparative efficacy: Ketamine vs. Esketamine**

A post hoc analysis included 311 patients. 171 of them were receiving intravenous ketamine, and 140 patients were receiving intranasal esketamine. In this study, intravenous ketamine proved greater reductions in MADRS scores, a larger effect size (1.666 vs. 1.244), and also higher response rates (36% vs. 2%; p=0.042), while remission rates were quite similar (13% vs. 12%) (d'Andrea et al., 2024).

As part of the meta-analysis, indirect comparisons showed that racemic ketamine has a greater overall response (RR 3.01 vs. 1.38) and remission rates (RR 3.70 vs. 1.47), as well as lower dropout rates (RR 0.76 vs. 1.37). However, these comparisons are limited by differences in study methodology and patient populations (Bahji et al., 2021).

**Dosage and administration**

*Ketamine dosage*

The most commonly studied intravenous ketamine dose is 0.5 mg/kg administered over 40 minutes (Dean et al., 2021; Fava et al., 2020). Dose-range studies suggest therapeutic effects at as low as 0.2 mg/kg, with an optimal response at 0.5 mg/kg. A dose of 1.0 mg/kg does not appear to provide any significant additional benefit (Fava et al., 2020). Acute conditions are usually treated with repeated intravenous ketamine infusions 2-3 times a week for 2-4 weeks. Maintenance doses are given at intervals ranging from once a week to once a month, depending on individual response and the risk of symptom recurrence (Phillips et al., 2019).

*Esketamine dosing*

The dosage of esketamine approved by FDA for the treatment of TRD includes an induction phase with a dose of 56 mg or 84 mg given to patients twice a week (weeks 1-4), followed by a maintenance phase (weeks 5-8) once weekly, then every 2 weeks or weekly depending on response (Popova et al., 2019; Feeney and Papakostas, 2023). According to REMS requirements, the patient must be monitored for 2 hours after administration (Feeney and Papakostas, 2023; Daly et al., 2019).

*Severe adverse effects*

Adverse effects of ketamine and esketamine are usually mild in severity. They typically occur during or shortly after administration and resolve within 1.5–2 hours of onset. Most patients tolerate both products well. The most commonly reported adverse effects include dissociative symptoms (24–35%), nausea (14–25%), dizziness (22–46%), headache (14–19%), and sedation (4–11%). Dissociative symptoms usually resolve after the first infusion and stabilize during subsequent treatments (Ceban et al., 2021).

A significant proportion of patients receiving intravenous ketamine also experience a transient increase in blood pressure. For this reason, we should measure blood pressure before drug administration and continuously monitor the patient during and after administration (Ceban et al., 2021; Feeney and Papakostas, 2023).

*Long-term safety*

Chronic side effects of ketamine and esketamine include urinary tract symptoms, cognitive impairment, and hepatotoxicity. The use of esketamine may increase the risk of lower urinary tract symptoms, such as dysuria and urinary urgency; however, there were no reports of severe urinary tract disease at therapeutic doses (Feeney and Papakostas, 2023). Cognitive function usually remains stable or improves during treatment (Souza-Marques et al., 2021).

*Impact on cognitive function*

Several studies have examined the impact of ketamine and esketamine on neurocognitive function in TRD (Souza-Marques et al., 2021; Araújo-de-Freitas et al., 2021). A systematic review found that ketamine and esketamine do not cause significant neurocognitive adverse effects in the short- or long-term. Furthermore, five studies report improvements in information processing speed, verbal memory, visual memory, working memory, or mental flexibility (Souza-Marques et al., 2021). A randomized double-masked study compared ketamine and esketamine and showed that both of them can improve short-term visuospatial memory, executive functions, information processing speed, and episodic verbal memory (Araújo-de-Freitas et al., 2021). However, we should note that the improvement in cognitive function may be due to the resolution of cognitive deficits associated with depression rather than the direct pro-cognitive effects of the drugs (Souza-Marques et al., 2021).

*Abuse Potential and Addiction Risk*

Due to its intoxicating effects, more and more people are using ketamine for recreational purposes. However, in a therapeutic context, cases of abuse are rare. A review of 65 studies showed that although the preclinical models document potential for ketamine abuse well, clinical studies indicate that single or repeated administration of ketamine under regulated conditions did not result in abuse, dependence, or illicit use in patients with TRD (Le et al., 2022). The REMS requirements for esketamine limit its risk of abuse compared to the less-regulated use of ketamine (Dart, 2024; Feeney and Papakostas, 2023).

Preclinical studies show that the other enantiomer, R-ketamine, has lower abuse potential than racemic ketamine and S-ketamine, but because of limited clinical data, researchers believe that clinicians should monitor patients with a history of substance use disorders and follow precautions for prescribing these medications (Swainson et al., 2019; Feeney and Papakostas, 2023).

*Predictors of Response and Biomarkers*

Extensive research has been conducted; however, only a few clinical predictors of response to ketamine and esketamine have been identified. An international meta-analysis of 809 patients showed a strong effect of ketamine. Still, it identified only study-level moderators - greater effects were observed in studies with greater treatment resistance (≥2 failed attempts) and in crossover studies. However, reliable response predictions were not possible because of the different clinical and demographic features of the patients (Price et al., 2022).

Researchers have done a systematic review and meta-analysis of blood biomarkers, examining more than 460 individual biomarkers in 56 studies, but found no clear associations between biomarker levels before and after ketamine therapy. However, a longitudinal analysis showed that BDNF levels increased significantly from baseline in patients who responded to treatment (SMD 0.26, 95% CI 0.03-0.48). Patients who did not respond to ketamine treatment did not show significant changes in BDNF levels. However, the small effect size does not yet allow these results to be used to predict individual responses to treatment in specific patients (Medeiros et al., 2022).

Neuroimaging studies suggest that ketamine can normalize functional connectivity in the mood and reward systems. It shows particularly in the cingulate cortex, amygdala, insula, and orbitofrontal cortex. However, neuroimaging observations are not yet clinically useful in predicting individual response to treatment (Medeiros et al., 2023).

*Clinical Practice Guidelines*

As recently as 2016, VA/DoD clinical guidelines for the treatment of MDD denied the validity of using ketamine outside of research settings. However, in 2022, these recommendations began to include ketamine and esketamine as treatment options for patients with TRD. Data on the long-term safety of ketamine and esketamine are limited, so these agents should only be used in patients with documented resistance to conventional treatment. The REMS requirements for esketamine impose an obligation to certify pharmacies

and medical facilities, as well as to monitor each patient treated with esketamine for at least 2 hours after the end of treatment (Feeney and Papakostas, 2023).

Other institutions that have included ketamine and esketamine in their TRD treatment algorithms are the American Psychological Association and the National Institute for Health and Care Excellence. They agree in their guidelines that the use of these agents is justified but requires careful patient selection, monitoring, and following of safety guidelines (Marwaha et al., 2023). A summary of the main findings of this review is presented in Table 1.

**Table 1**. Summary of key findings regarding ketamine and esketamine in treatment-resistant depression (TRD)

| Aspect | Ketamine | Esketamine |
|---|---|---|
| Mechanism of action | NMDA antagonist; increases glutamatergic transmission, BDNF release and synaptic plasticity | Similar glutamatergic mechanism via NMDA receptor antagonism |
| Onset of antidepressant effect | Often within 24 hours | Within hours to days |
| Evidence of efficacy | Improves response and remission rates; strong evidence from RCTs and meta-analyses | Reduces depressive symptoms and relapse risk; supported by Phase III trials and meta-analyses |
| Maintenance treatment | Repeated infusions may sustain the response | Approved maintenance regimen available after the induction phase |
| Comparative efficacy | May provide greater acute symptom reduction and higher response rates | Similar remission rates in comparative analyses |
| Common adverse effects | Dissociation, dizziness, nausea, headache, transient blood pressure increase | Dissociation, dizziness, nausea, headache, transient blood pressure increase |
| Long-term safety | Limited data; monitoring required | Limited long-term data; monitoring required under REMS requirements |
| Clinical role | Off-label option for TRD after failure of conventional antidepressants | FDA-approved treatment for TRD in combination with an oral antidepressant |

Ketamine and esketamine, thanks to their novel mechanisms of action on glutamatergic neurotransmission, have become a breakthrough in the treatment of TRD, because they can provide rapid symptom relief in the most severely affected patients (Halaris and Cook, 2023; Hess et al., 2022; Rawat et al., 2024; Marwaha et al., 2023). Based on current research, we can conclude that these drugs are highly effective in acute cases and demonstrate a better therapeutic effect in patients with TRD than classic antidepressants (Alnefeesi et al., 2022). However, the mechanisms of ketamine's antidepressant action are not based only on simple NMDA receptor antagonism. There are also other complex processes, such as synaptic plasticity, neurotrophic signaling, and neuroinflammation (Halaris and Cook, 2023; Hess et al., 2022; Rawat et al., 2024). A more thorough insight into these mechanisms may, in the future, make it possible to develop a whole new generation of more powerful and safer antidepressants.

Based on the above review, we can draw multiple key conclusions. First, both ketamine and esketamine produce fast antidepressant effects, making them an irreplaceable therapeutic option for particularly distressed patients in acute depressive states (Dean et al., 2021). Second, the use of repeated dosing strategies and maintenance regimens has a positive effect on maintaining and improving the initial response to treatment as well as decreasing the risk of symptom recurrence (Phillips et al., 2019; Daly et al., 2018; Reif et al., 2023). Third, although most patients tolerate both agents well, they require careful monitoring for short- and long-term side effects—in particular, attention should be paid to possible hemodynamic changes and dissociative effects (Ceban et al., 2021; Feeney and Papakostas, 2023). And the final conclusion is that intravenous racemic ketamine produces stronger acute effects than intranasal esketamine (Bahji et al., 2021; d'Andrea et al., 2024). However, to confirm all of these observations, we need some more direct comparative studies.

Unfortunately, there are still considerable limitations due to insufficient research and knowledge gaps. Among other things, there is insufficient data on long-term safety beyond 2 years, mainly for off-label use of intravenous ketamine (Feeney and Papakostas, 2023).

The optimal dosing frequency and duration of maintenance treatment also require more research (Phillips et al., 2019). At this point, scientists have not found any prognostic biomarkers that could facilitate patient selection and treatment personalization (Price et al., 2022; Medeiros et al., 2022; Medeiros et al., 2023). Increased attention is also needed to control the risk of ketamine abuse, given that its use is becoming more common outside of specialized centers (Le et al., 2022; Dart, 2024).

We can still see differences and unclear aspects in the legal regulations concerning ketamine and esketamine. The FDA's approval of esketamine and also REMS requirements make the rules for safe use clear, but limit availability due to financial issues. Intravenous ketamine is considered potentially more effective and more accessible, but we do not have standard protocols and government oversight yet, so its clinical use is still inconsistent (Das, 2020; Feeney and Papakostas, 2023).

In the near future, the most important issues include: studies comparing intravenous ketamine and intranasal esketamine, research on optimizing maintenance strategies and treatment duration, research on combining ketamine and esketamine with psychotherapy and other treatment modalities, development of predictive biomarkers, research on benefit in specific subpopulations of TRD patients (e.g., older adults, patients with specific comorbidities), and long-term safety monitoring in clinical settings.

## 4. CONCLUSION

Ketamine and esketamine produce rapid and intense antidepressant effects by acting on the glutamatergic system. Current scientific evidence suggests that we can use these substances as third-line or later-line treatments in TRD patients after failure of other antidepressants. It also confirms the significant efficacy and acceptable tolerability profiles of both substances. The use of ketamine and esketamine in TRD should draw our attention to exploring new neurobiological targets rather than just focusing on traditional monoaminergic systems. Recognizing this fact will clear the path for a new generation of fast-acting antidepressants with potentially greater efficacy, safety, and availability.

**Acknowledgments**

We thank all co-authors and institutional staff for their support during the preparation of this review.

**Authors' Contributions**

Julia Rogała - contributed to the study conception and design, conducted the literature search and data analysis, wrote the manuscript, approved the final version for publication
Kinga Polityńska - conducted the literature search and data analysis
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Zuzanna Irzyk - conducted the literature search and data analysis
Mateusz Szabat - conducted the literature search and data analysis

**Informed consent**

Not applicable.

**Ethical approval**

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

**Funding**

This research did not receive any external funding like specific grant from funding agencies in the public, commercial, or nonprofit sectors.

**Conflict of interest**

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

**Data and materials availability**

All data associated with this study will be available based on the reasonable request to corresponding author.

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