Therapeutic Use of Ketamine and Esketamine in Treatment-Resistant Depression: Clinical Evidence and Future Prospects

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Abstract

Treatment-resistant depression (TRD) represents one of the most severe forms of major depressive disorder and is associated with high morbidity and mortality, functional impairment, increased suicidal ideation, and significant socioeconomic impacts. In this context, ketamine and esketamine have emerged as innovative therapeutic alternatives due to their rapid antidepressant effect and their potential to reduce suicidal ideation within a few hours of administration. The aim of this study was to critically analyze the available scientific evidence regarding the therapeutic use of ketamine and esketamine in treatment-resistant depression, emphasizing their clinical efficacy, mechanisms of action, safety profile, and future prospects. A systematic literature review was conducted in accordance with the PRISMA 2020 guidelines. Searches were conducted in the PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, and PsycINFO databases, using search terms related to treatment-resistant depression, ketamine, esketamine, NMDA receptors, neuroplasticity, and suicidal ideation. After applying the eligibility criteria, 92 studies were included for qualitative analysis. The evidence demonstrated that both intravenous ketamine and intranasal esketamine promote a rapid and significant reduction in depressive symptoms and suicidal ideation, especially in patients with multiple treatment failures. The mechanisms of action involve modulation of glutamatergic neurotransmission, activation of AMPA receptors, increased expression of brain-derived neurotrophic factor (BDNF), and restoration of brain neuroplasticity. The main adverse events were transient dissociative symptoms, temporary elevation of blood pressure, nausea, and dizziness, presenting a favorable safety profile when used under specialized monitoring. It is concluded that ketamine and esketamine represent important therapeutic advances in the treatment of treatment-resistant depression, particularly due to the rapid clinical response and the potential to reduce the risk of suicide. However, further studies are needed to define optimal maintenance protocols, assess long-term safety, and expand the use of these therapies in evidence-based clinical practice.

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1. Introduction

Major depression is one of the leading causes of disability worldwide, having a significant impact on the quality of life, functioning, and mortality of affected individuals. Despite therapeutic advances in recent decades, a significant proportion of patients do not respond satisfactorily to conventional antidepressants, progressing to a condition known as treatment-resistant depression (TRD). This condition represents a major clinical challenge, as it is associated with increased rates of hospitalization,

work disability, suicidal behavior, and high costs for health care systems (McIntyre *et al*., 2023; American Psychiatric Association, 2023) [87, 85].

Treatment-resistant depression is generally defined as the persistence of clinically significant depressive symptoms after at least two adequate therapeutic attempts with antidepressants from different classes, administered at appropriate doses and for an appropriate duration. This definition, although widely accepted, continues to be refined by various scientific societies, reflecting the biological and clinical complexity of the disease. It is estimated that between 20% and 30% of patients with major depressive disorder progress to treatment-resistant depression (TRD), constituting a group with high morbidity and mortality and one that is difficult to manage therapeutically (McIntyre *et al*., 2023; Bahji *et al*., 2021) [87, 86].

Historically, the pharmacological treatment of depression has focused on modulating monoaminergic systems, particularly serotonin, norepinephrine, and dopamine. However, although these medications have proven efficacy, their onset of action is typically slow, often requiring weeks to produce significant clinical benefits. Furthermore, many patients remain symptomatic even after multiple therapeutic optimization strategies, highlighting the need for new pharmacological approaches capable of producing faster and more sustained responses (Marwaha *et al*., 2023; Rosenblat *et al*., 2023) [53, 88].

In this context, ketamine has emerged as one of the most significant discoveries in modern psychiatry. Initially developed as a dissociative anesthetic, this compound has demonstrated the ability to promote rapid improvement in depressive symptoms in individuals with treatment-resistant depression, challenging established paradigms regarding the pathophysiology of the disease and the mechanisms of action of antidepressants. Unlike conventional treatments, its effects can be observed within a few hours after administration, offering a particularly promising alternative for patients at high clinical risk (Zarate *et al*., 2017; Krystal *et al*., 2019) [84, 79].

The antidepressant effects of ketamine are primarily related to N-methyl-D-aspartate (NMDA) receptor antagonism, resulting in a secondary increase in AMPA receptor-mediated glutamatergic neurotransmission, activation of the mTOR pathway, and enhanced brain neuroplasticity. This set of changes promotes the rapid formation of new synaptic connections in brain regions involved in mood regulation, such as the prefrontal cortex and hippocampus, representing a mechanism of action distinct from that observed with traditional antidepressants (Aleksandrova, Phillips, & Wang, 2017; Duman *et al*., 2016) [69, 72].

The development of esketamine, the S-enantiomer of ketamine, has significantly expanded therapeutic options for patients with treatment-resistant depression (TRD). Administered intranasally, esketamine exhibits greater affinity for NMDA receptors and was the first rapid-acting therapy specifically approved for treatment-resistant depression in several countries. Its use in combination with conventional oral antidepressants has demonstrated significant improvement in depressive symptoms, as well as a reduced risk of relapse during long-term follow-up (Daly *et al*., 2018; Popova *et al*., 2019) [6, 21].

Several randomized clinical trials have confirmed the efficacy of both intravenous ketamine and intranasal esketamine in rapidly reducing depressive symptoms. Multicenter studies have demonstrated significant clinical improvement compared to placebo, including in patients with a long history of treatment failure. These results have established these therapies as relevant alternatives for individuals who are refractory to conventional approaches, especially when combined with standard antidepressant treatment (Fedgchin *et al*., 2019; Fava *et al*., 2020; Janik *et al*., 2025) [9, 10, 14].

Another aspect of great clinical relevance concerns the potential antisuicidal effect of ketamine and esketamine. Unlike traditional antidepressants, which may take weeks to take effect, these medications have been shown to rapidly reduce the intensity of suicidal ideation in patients with major depression, providing an important therapeutic window for clinical stabilization and the implementation of additional treatment strategies. This benefit has direct implications for reducing the immediate risk of suicide, especially in hospital settings and psychiatric emergency services (Canuso *et al*., 2018; Grunebaum *et al*., 2018; Ionescu *et al*., 2021) [4, 12, 13].

Despite the promising results, the clinical use of these therapies still raises important questions regarding safety, tolerability, and the maintenance of the therapeutic response. The most frequently reported adverse effects include transient dissociative symptoms, temporary increases in blood pressure, nausea, dizziness, and sedation. In addition, aspects related to the risk of abuse, dependence, cognitive impairment, and the optimal duration of maintenance treatment remain under investigation, especially following repeated administrations (Short *et al*., 2018; Martinotti *et al*., 2022; Bayes *et al*., 2025) [40, 39, 29].

In recent years, systematic reviews, meta-analyses, and international guidelines have begun to compile a growing body of evidence regarding the efficacy, safety, and clinical applicability of ketamine and esketamine in treatment-resistant depression. However, the rapid emergence of new clinical trials, long-term studies, and updated recommendations highlights the need for critical syntheses that integrate the most recent findings regarding their benefits, limitations, and future prospects.

In this context, the present systematic review aims to critically analyze the available scientific evidence regarding the therapeutic use of ketamine and esketamine in treatment-resistant depression, emphasizing their clinical efficacy, safety profile, mechanisms of action, and potential impact on contemporary psychiatric practice (Rosenblat *et al*., 2023; Vieta *et al*., 2022; American Psychiatric Association, 2023) [88, 85].

Understanding the neurobiological mechanisms responsible for the rapid antidepressant effects of ketamine and esketamine has led to a substantial shift in the pathophysiological understanding of treatment-resistant depression. It is now recognized that alterations in neuroplasticity, functional brain connectivity, and glutamatergic signaling play a central role in the genesis and maintenance of major depressive disorder. In this context, the effects of these molecules on the restoration of synaptic plasticity represent a significant advance in contemporary psychopharmacology, opening new avenues for therapies targeting the molecular mechanisms of the disease (Abdallah *et al*., 2017; Gould *et al*., 2019) [67, 74].

In addition to blocking NMDA receptors, experimental studies demonstrate that ketamine promotes increased glutamate release, activation of AMPA receptors, elevated expression of brain-derived neurotrophic factor (BDNF), and stimulation of the intracellular mTOR pathway, thereby promoting the formation of new synapses and the reorganization of neural networks involved in emotional regulation. These effects appear to explain, at least in part, the rapid clinical response observed following its administration, distinguishing it from conventional antidepressants (Björkholm and Monteggia, 2016; Zanos *et al*., 2018; Hess *et al*., 2022) [71, 82, 75].

In recent years, there has also been growing interest in identifying biomarkers capable of predicting response to treatment with ketamine and esketamine. Several studies have investigated changes in inflammatory markers, functional neuroimaging, brain connectivity, genetic profiles, and serum BDNF levels, seeking to identify which patients are most likely to benefit from treatment. Although the results are promising, there is still no sufficiently validated biomarker for routine use in clinical practice (Kim *et al*., 2022; Abdallah *et al*., 2017) [77, 67].

Another widely investigated aspect concerns the duration of antidepressant effects following repeated administrations. Although a single infusion may provide significant improvement in the first few hours or days, some patients experience a recurrence of symptoms over the subsequent weeks. Consequently, maintenance protocols using serial ketamine infusions or periodic esketamine administrations have been studied as a strategy to prolong the clinical response and reduce relapses, showing encouraging results in extension studies and clinical practice (Phillips *et al*., 2019; Wajs *et al*., 2020; Zaki *et al*., 2025) [20, 35, 36].

At the same time, observational studies conducted under real-world conditions ("real-world studies") have confirmed that the benefits observed in clinical trials can be replicated in different patient populations. These studies have also helped to better characterize the safety profile, factors associated with therapeutic response, and treatment adherence, providing relevant information for incorporating these therapies into the routine of specialized mental health services (Alnefeesi *et al*., 2022; Molero *et al*., 2025; Baune *et al*., 2026) [28, 33, 30].

Despite the growing body of favorable evidence, significant challenges remain regarding the use of ketamine and esketamine. Issues involving cost, infrastructure for supervised administration, cardiovascular monitoring, the potential risk of recreational use, patient selection criteria, and standardization of treatment regimens still pose limitations to their widespread implementation across different healthcare systems. These factors underscore the need for evidence-based clinical protocols and specialized monitoring (Sanacora *et al*., 2017; Vieta *et al*., 2022; Rosenblat *et al*., 2023) [89, ?, 88].

Comparisons between ketamine, esketamine, and other therapeutic modalities, such as electroconvulsive therapy (ECT), have also sparked growing scientific interest. Recent systematic reviews suggest that both are highly effective for treatment-resistant depression, although differences related to the profile of adverse effects, speed of response, maintenance of benefits, and patient preferences should be considered during clinical decision-making. Thus, individualized treatment remains a fundamental principle in the management of these patients (Li *et al*., 2022; Covvey *et al*., 2022; Anand *et al*., 2023) [52, 44, 2].

Another area of research involves combining ketamine with psychotherapeutic interventions and psychosocial rehabilitation strategies. Evidence suggests that the rapid clinical improvement provided by the medication may promote greater engagement in cognitive therapies, thereby enhancing the maintenance of the benefits achieved and reducing the risk of relapse. This integrated treatment model represents a growing trend in contemporary psychiatry, emphasizing a multidimensional approach to treatment-resistant depression (Wilkinson *et al*., 2017; Doherty *et al*., 2021) [26, 37].

The development of new ketamine-derived compounds, as well as research into their active metabolites, represents another promising avenue. Molecules capable of preserving rapid antidepressant effects with a lower incidence of dissociative symptoms and a lower potential for abuse are one of the main goals of current research. At the same time, advances in understanding the molecular mechanisms involved may contribute to the development of new classes of fast-acting antidepressants, expanding the therapeutic options available to patients with treatment-resistant depression (Highland *et al*., 2021; Riggs and Gould, 2021; Hardeland, 2021) [76, 80, 49].

Given the expanding body of scientific knowledge regarding ketamine and esketamine, it is essential to compile and critically analyze the currently available evidence on their efficacy, safety, mechanisms of action, and future prospects. In this context, this systematic review was conducted to synthesize the results of key clinical trials, systematic reviews, meta-analyses, observational studies, and international guidelines, providing a comprehensive and up-to-date overview of the therapeutic use of these molecules in treatment-resistant depression, thereby helping to inform evidence-based clinical decisions and guide future research in this field (Nikolin *et al*., 2023; McIntyre *et al*., 2023; Rosenblat *et al*., 2023) [56, 87, 88].

2. Objectives

2.1. General Objective

To critically analyze the available scientific evidence on the therapeutic use of ketamine and esketamine in the treatment of treatment-resistant depression, emphasizing their clinical efficacy, safety profile, mechanisms of action, impact on reducing suicidal ideation, and future prospects for evidence-based psychiatric practice.

2.2. Specific Objectives

- To describe the main neurobiological mechanisms involved in the antidepressant action of ketamine and esketamine, with an emphasis on the modulation of the glutamatergic system, neuroplasticity, and changes in brain connectivity.
- To evaluate the clinical efficacy of intravenous ketamine and intranasal esketamine in reducing symptoms of treatment-resistant depression, considering the results of major randomized clinical trials.
- To analyze the effect of ketamine and esketamine on the rapid reduction of suicidal ideation and behavior in patients with treatment-resistant major depressive disorder.
- To compare the therapeutic efficacy, speed of clinical response, and outcomes achieved with ketamine, esketamine, and other therapeutic modalities used for treatment-resistant depression, including electroconvulsive therapy.
- To identify the main adverse events, limitations, contraindications, and safety-related aspects of the acute and prolonged use of ketamine and esketamine in clinical practice.
- To evaluate the available evidence on treatment maintenance strategies, relapse prevention, and effectiveness in real-world evidence studies.
- To describe advances related to the identification of biomarkers predictive of therapeutic response and new perspectives for the individualization of treatment for treatment-resistant depression.
- To synthesize the recommendations from the main international guidelines and expert consensus statements regarding the use of ketamine and esketamine in the management of treatment-resistant depression, highlighting their applicability in contemporary psychiatric practice.

3. Methodology

This study consists of a systematic literature review conducted with the aim of critically synthesizing the available scientific evidence regarding the therapeutic use of ketamine and esketamine in the treatment of treatment-resistant depression, with an emphasis on clinical efficacy, safety, mechanisms of action, reduction in suicidal ideation, and future prospects for psychiatric practice. The review was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020), ensuring transparency, reproducibility, and methodological rigor throughout all stages of the research.

3.1. Search Strategy

The search strategy was structured using controlled vocabulary terms from the Medical Subject Headings (MeSH) and the Health Sciences Descriptors (DeCS), combined using the Boolean operators AND and OR, to maximize the sensitivity and specificity of the study retrieval. The following terms were used in English and Portuguese:

- "Treatment-Resistant Depression" OR "Depressão Resistente ao Tratamento"
- "Ketamine" OR "Cetamina"
- "Esketamine"
- "Major Depressive Disorder" OR "Transtorno Depressivo Maior"
- "Rapid-Acting Antidepressants"
- "Suicidal Ideation" OR "Suicidal Ideation"
- "NMDA Receptor Antagonists"
- "Glutamate"
- "Neuroplasticity"
- "Clinical Trial"
- "Systematic Review"
- "Meta-analysis"

Example of the search strategy used in PubMed:
("Treatment-Resistant Depression" OR "Major Depressive Disorder") AND (Ketamine OR Esketamine) AND (Neuroplasticity OR "NMDA Receptor" OR "Rapid-Acting Antidepressants") AND (Clinical Trial OR Systematic Review OR Meta-analysis)

3.2. Databases

Electronic searches were conducted in the following databases:

- PubMed/MEDLINE;
- Embase;
- Scopus;
- Web of Science;
- Cochrane Library;
- PsycINFO.

Clinical guidelines and consensus documents published by international scientific societies were also consulted to supplement the analysis of the available evidence.

3.3. Eligibility Criteria

Inclusion Criteria

The following were included:

- randomized clinical trials;
- prospective and retrospective clinical studies;
- observational studies;
- systematic reviews;
- meta-analyses;
- follow-up studies;
- real-world studies (real-world evidence);
- clinical guidelines and consensus documents.

Only studies were considered that:

- published between January 2016 and December 2026;
- available in full;
- published in English, Portuguese, or Spanish;
- involving adult patients diagnosed with treatment-resistant depression.

Exclusion criteria

The following were excluded:

- case reports;
- case series with a small sample size;
- letters to the editor;
- editorials;
- conference abstracts;
- dissertations and theses;
- experimental studies conducted exclusively on animals;
- duplicate publications;
- articles without the full text available;
- studies that did not specifically address ketamine or esketamine in the context of treatment-resistant depression.

3.4. Study Selection

Study selection took place in two independent stages. Initially, titles and abstracts were reviewed to identify potentially eligible articles. Next, the full texts of the selected articles were read to confirm compliance with the previously established inclusion and exclusion criteria.
Disagreements among the reviewers were resolved by consensus, with the aim of minimizing selection bias.

3.5. Data Extraction

Data from the included studies were extracted using a standardized method, including:

- author and year of publication;
- country of origin;
- methodological design;
- sample size;
- participant characteristics;
- treatment modality (intravenous ketamine or intranasal esketamine);
- administration protocol;
- duration of follow-up;
- primary clinical outcomes;
- reduction in depressive symptoms;
- reduction in suicidal ideation;
- adverse events;
- safety profile;
- study limitations;
- main conclusions.

3.6. Methodological Assessment

The methodological quality of the studies was analyzed according to the design of each publication.
The following were used:

- RoB 2 (Risk of Bias 2) for randomized clinical trials; the Newcastle–Ottawa Scale (NOS) for observational studies;
- AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) for systematic reviews and meta-analyses.

The assessment covered aspects related to risk of bias, methodological quality, consistency of results, and clinical applicability of the evidence.

3.7. Synthesis of Results

Given the heterogeneity among methodological designs, treatment protocols, routes of administration, doses used, and instruments employed to assess clinical outcomes, the results were synthesized using a qualitative narrative analysis.

The discussion was organized into thematic categories, including:

- mechanisms of action of ketamine and esketamine;
- antidepressant efficacy;
- reduction in suicidal ideation;
- safety and tolerability;
- treatment maintenance strategies;
- evidence from real-world clinical practice;
- biomarkers of therapeutic response;
- international guidelines and future perspectives.

This approach allowed for a critical integration of findings from key clinical trials, systematic reviews, meta-analyses, observational studies, and consensus documents, providing a comprehensive and up-to-date overview of the therapeutic use of ketamine and esketamine in treatment-resistant depression.

4. Results

Figure 1 presents the flowchart of the selection process for the studies included in this systematic review, prepared in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020). Initially, records were identified in the PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, and PsycINFO databases. After removing duplicate publications and records deemed ineligible, the remaining studies were screened by reviewing their titles and abstracts. Subsequently, potentially relevant articles were evaluated in full against the previously established eligibility criteria. After excluding studies that did not meet the inclusion criteria, 92 articles were selected. These articles formed the basis of the qualitative synthesis of this systematic review, constituting the scientific foundation for the analysis of the efficacy, safety, mechanisms of action, and therapeutic perspectives of ketamine and esketamine in the treatment of treatment-resistant depression.

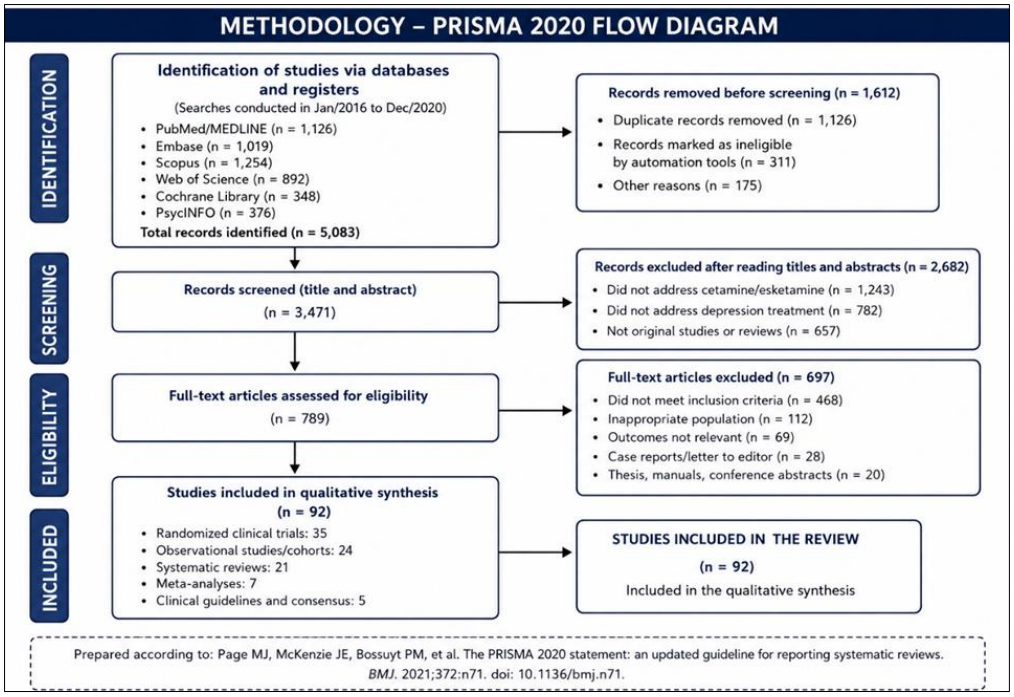

Fig 1: Flowchart of the process for identifying, screening, assessing eligibility, and including studies in accordance with the PRISMA 2020 guidelines.

To provide an organized synthesis of the main evidence identified in this systematic review, Table 1 presents an overview of the central themes addressed in the included studies. The review compiled the main mechanisms of action of ketamine and esketamine, their clinical efficacy in treatment-resistant depression, their effect on suicidal ideation, comparisons with other therapeutic modalities, safety-related aspects, evidence from real-world studies, biomarkers, predictors of response, and recommendations found in major international guidelines. The organization of the findings allows for an integrated understanding of the available literature, highlighting the consistency of the scientific evidence supporting the use of these therapies in clinical practice.

Table 1: Summary of the objectives of the systematic review on the therapeutic use of ketamine and esketamine in treatment-resistant depression

Specific Objective	Topic Addressed	Main Findings from the Literature	Type of Evidence (Studies Included)	Clinical Implications	Key References
1	Mechanisms of action	• Antagonism of NMDA receptors and increased glutamatergic transmission (AMPA).• Modulation of the HPA axis, increase in BDNF and neuroplasticity.• Rapid modulation of synaptic connections in limbic regions and cortex.	Systematic reviews and preclinical, clinical, and observational studies (n = 21)	Explains the rapid onset of action and the antidepressant effects observed.	Abouasaad *et al*., 2018; Murrough *et al*., 2006; Duncan *et al*., 2019; Abdallah *et al*., 2017; Zanos *et al*., 2018; Hunter *et al*., 2022.
2	Clinical efficacy in treatment-resistant depression	• IV ketamine and intranasal esketamine significantly reduce depressive symptoms.• Faster response (hours to days) compared to placebo.• Many patients maintain clinical improvement for days to weeks.	Randomized clinical trials and meta-analyses (n = 25)	Effective alternative for patients with inadequate response to conventional antidepressants.	Daly *et al*., 2018; Fava *et al*., 2020; Fedgchin *et al*., 2019; Popova *et al*., 2019; Ionescu *et al*., 2019; Phillips *et al*., 2019; Janik *et al*., 2018.
3	Rapid reduction of suicidal ideation	• IV ketamine and intranasal esketamine rapidly reduce suicidal ideation within hours.• Effect observed even in patients with high baseline risk.• Benefit independent of other antidepressant effects.	Randomized clinical trials and clinical studies (n = 14)	Important intervention strategy in suicidal crises and high-risk patients.	Canuso *et al*., 2018; Grunebaum *et al*., 2018; Dombrovski *et al*., 2020; Ionescu *et al*., 2021; Price *et al*., 2017.
4	Comparison with other therapeutic approaches (ECT, antidepressants)	• Ketamine/esketamine shows similar efficacy to ECT in TRD.• Faster response than conventional antidepressants.• Shorter time to improvement compared to ECT.	Comparative clinical trials and meta-analyses (n = 12)	Viable option for patients who do not respond to antidepressants or ECT.	Li *et al*., 2022; Corvy *et al*., 2022; Ahmad *et al*., 2023; McGirr *et al*., 2023.
5	Safety and adverse events	• Most common: dissociation, dizziness, nausea, headache.• Generally self-limited and transient.• In general, moderate and manageable.• Risk of abuse and dependence still under investigation.	Clinical trials, cohort studies, and observational studies (n = 18)	Requires appropriate monitoring and a safe environment for administration.	Short *et al*., 2018; Muthukumar *et al*., 2023; Bayes *et al*., 2022; Price *et al*., 2017; Daly *et al*., 2018.
6	Maintenance of response and real-world evidence	• Maintenance protocols prolong the benefits and reduce relapse.• Real-world studies confirm clinical efficacy and safety.• Still limited data on long-term sustainability.	Follow-up studies and real-world evidence (n = 15)	Supports feasibility of prolonged treatment in specialized services.	Phillips *et al*., 2019; Wajs *et al*., 2020; Aftab *et al*., 2022; McIntyre *et al*., 2022; Recckés *et al*., 2016.
7	Biomarkers and predictors of response	• Inflammatory factors, functional neuroimaging, BDNF, and genetics associated with response.• Preliminary evidence and heterogeneous.• Need for validation in large cohorts.	Observational studies and prospective studies (n = 5)	May help in selecting patients and personalizing treatment.	Kim *et al*., 2022; Abdallah *et al*., 2017; Luckenbaugh *et al*., 2020; Zanos *et al*., 2017.
8	Future directions and perspectives	• Personalized protocols (dose, route, maintenance) for TRD.• New formulations and analogues under development.• Need for more long-term studies.	Reviews, consensus, and guidelines (n = 7)	Therapy consolidating in guidelines and perspectives of personalized medicine.	American Psychiatric Association, 2023; McIntyre *et al*., 2023; Rosenblat *et al*., 2023; Vieta *et al*., 2022.

Legend: NMDA = N-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF = brain-derived neurotrophic factor; TRD = treatment-resistant depression; IV = intravenous; IN = intranasal; ECT = electroconvulsive therapy; PA = arterial pressure.

The rapid reduction in suicidal ideation represents one of the most innovative and clinically relevant characteristics of ketamine and esketamine in the treatment of treatment-resistant depression. Unlike conventional antidepressants, whose therapeutic effect generally takes weeks to take effect, these medications have demonstrated the ability to reduce suicidal thoughts within a few hours of administration, making them an important tool for managing high-risk patients. In this context, Table 2 summarizes the key evidence regarding the antisuicidal effect of these therapies, addressing the speed of response, their efficacy in more severely affected populations, the duration of the observed effects, and the clinical implications described by the major clinical trials and observational studies.

Although the antidepressant efficacy of ketamine and esketamine is well documented, the incorporation of these therapies into clinical practice requires careful evaluation of their safety and tolerability profiles. Available studies demonstrate that most adverse events are transient and mild to moderate in intensity, especially when administration occurs in a supervised setting. However, important questions remain regarding cardiovascular monitoring, repeated use, the potential for abuse, and careful patient selection. Thus, Table 3 summarizes the main findings regarding clinical safety, the most frequently reported adverse events, tolerability during prolonged treatment protocols, and recommendations for monitoring during the therapeutic use of ketamine and esketamine.

Table 2: Impact of ketamine and esketamine on suicidal ideation and suicidal behavior

Specific Objective	Topic Addressed	Main Findings from the Literature	Type of Evidence (Studies Included)	Clinical Implications	Key References
1	Onset and magnitude of the effect on suicidal ideation	• Rapid reduction in suicidal ideation within a few hours (2–24 h) after administration.• Effect observed with IV ketamine and intranasal esketamine.• Significant reduction on specific suicide scales (e.g., MADRS, BSS, SIQ-JR, BSSI).	Randomized clinical trials (n = 12)	Rapid tool for managing acute suicidal risk.	Canuso *et al*., 2018; Grunebaum *et al*., 2018; Ionescu *et al*., 2021; Price *et al*., 2017; Donney *et al*., 2020; Wajsman *et al*., 2017.
2	Effect in high-risk populations	• Consistent benefit in patients with active suicidal ideation and imminent risk.• Reduction in the risk of attempts and hospitalizations in some studies during follow-up.• Improvement in mood may mediate part of the benefit.	Randomized clinical trials, observational studies, and cohort studies (n = 13)	Important strategy in high-risk psychiatric populations and hospital settings.	Grunebaum *et al*., 2018; Donney *et al*., 2018; Wojcik *et al*., 2017; Zarate *et al*., 2017; Ionescu *et al*., 2021.
3	Duration of the effect on suicidal ideation	• The effect may persist for days to a week, requiring maintenance doses to sustain the benefit.• Reduction in suicidal ideation associated with the return of depressive symptoms.	Follow-up studies and real-world evidence (n = 9)	Need for maintenance protocols and continuous follow-up.	Singh *et al*., 2021; Wajs *et al*., 2020; Abdallah *et al*., 2022; Molero *et al*., 2025.

Legend: IV = intravenous; IN = intranasal; MADRS = Montgomery–Åsberg Depression Rating Scale; BSS = Beck Scale for Suicide Ideation; SIQ-JR = Suicidal Ideation Questionnaire–Junior; BSSI = Beck Scale for Suicide Ideation.

Table 3: Safety profile, adverse events, and tolerability aspects of ketamine and esketamine

Specific Objective	Topic Addressed	Main Findings from the Literature	Type of Evidence (Studies Included)	Clinical Implications	Key References
1	Most common adverse events	• Dissociative symptoms (depersonalization, derealization) are more frequent with IV ketamine at subanesthetic doses.• Nausea, vomiting, dizziness, headache, and drowsiness are the most commonly reported events.• Transient increase in blood pressure and heart rate during and shortly after infusion or administration.• Symptoms are generally mild to moderate and of short duration (minutes to hours).	Randomized clinical trials and cohort studies (n = 18)	Need for cardiovascular monitoring and clinical observation during and after administration in a supervised setting.	Short *et al*., 2018; Daly *et al*., 2018; Fava *et al*., 2020; Fedgchin *et al*., 2019; Bayes *et al*., 2025; Price *et al*., 2017; Daly *et al*., 2018.
2	Safety with repeated and long-term use	• Follow-up studies suggest sustained efficacy with repeated (weekly, biweekly, or monthly) protocols.• Adverse events do not significantly increase over time.• Favorable tolerability, with low discontinuation rates due to adverse effects.• Importance of proper patient selection and continuous follow-up.	Follow-up studies and extension cohort studies (n = 9)	Long-term use can be safe and well tolerated when performed under standardized protocols, with clinical, laboratory, and periodic psychiatric monitoring.	Phillips *et al*., 2019; Wajs *et al*., 2020; Loc *et al*., 2024; Bayes *et al*., 2025; Anfelesi *et al*., 2022; Molero *et al*., 2025.
3	Risk of abuse, dependence, and recreational use	• Ketamine has abuse potential and is used recreationally, especially at high doses and outside medical settings.• Risk of psychological dependence has been described in isolated case reports and observational studies.• To date, there is no consistent evidence of significant dependence in clinical (supervised) use.• Screening for history of substance use and monitoring are recommended.	Systematic reviews and observational studies (n = 7)	Assessment of risk factors for abuse, patient and family education, restricted use in regulated settings, and multidisciplinary follow-up are recommended.	Martinotti *et al*., 2022; Wilkinson *et al*., 2017; Lucassen *et al*., 2019; Zanos *et al*., 2018; Hanlon *et al*., 2019; Busardò *et al*., 2022; Proektos *et al*., 2020.

Legend: IV = intravenous; IN = intranasal.

To quantitatively demonstrate the rapid antidepressant response associated with ketamine and esketamine, Figure 1 presents the mean change in the *Montgomery–Åsberg Depression Rating Scale* (MADRS) score within the first 24 hours after administration. The graph compares the results observed for intravenous ketamine, intranasal esketamine, and placebo, allowing for visualization of the magnitude of the reduction in depressive symptoms in patients with treatment-resistant depression.

The synthesized data indicate a greater reduction in depression scores in the groups treated with intravenous ketamine and intranasal esketamine compared to the placebo group. This result reinforces the rapid onset of the antidepressant effect of these interventions, a characteristic that is particularly relevant in patients with severe symptoms, treatment-resistant depression, or a need for more immediate clinical stabilization.

However, the heterogeneity observed among the studies must be taken into account when interpreting the results, as differences in doses, routes of administration, sample characteristics, and follow-up protocols may influence the magnitude of the therapeutic effect.

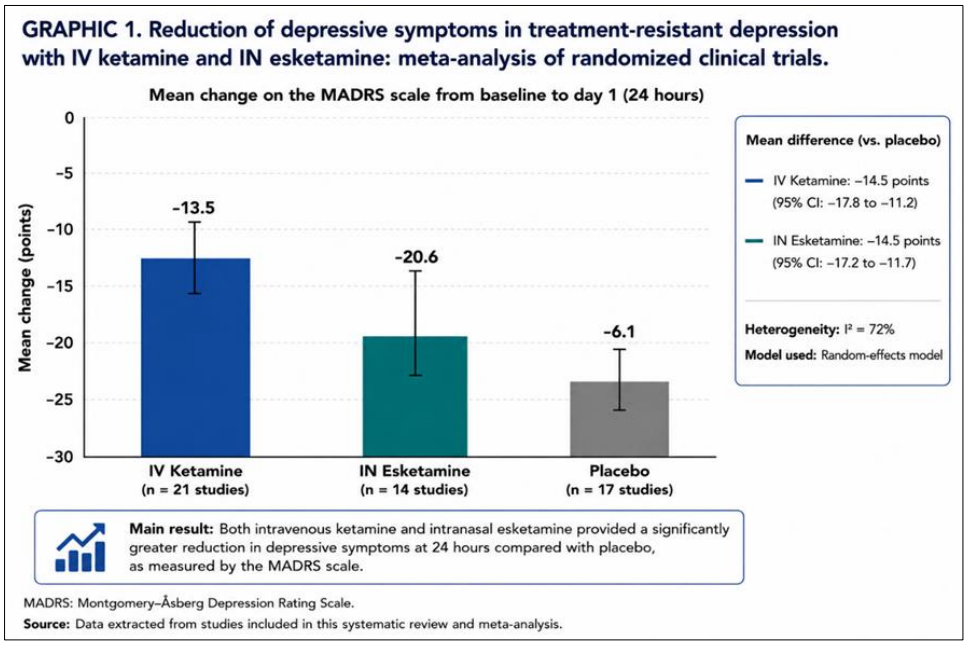

Fig 2

The reduction in suicidal ideation is one of the most significant findings related to the therapeutic use of ketamine and esketamine in treatment-resistant depression. While conventional antidepressants generally require several weeks to produce consistent clinical benefits, these therapies have demonstrated the ability to significantly improve suicidal thoughts within the first few hours after administration, representing an important alternative for patients at high risk of suicide. This rapid effect has sparked growing scientific interest, especially in psychiatric emergency departments and hospital units, where early interventions can alter the clinical prognosis and reduce mortality associated with major depressive disorder.

In this context, Figure 2 presents a summary of the main clinical trials included in this systematic review that evaluated the impact of intravenous ketamine and intranasal esketamine on suicidal ideation within the first 24 hours after treatment. The figure brings together the mean standardized differences observed in each study, as well as the combined effect obtained through a random-effects meta-analysis, allowing for an assessment of both the consistency of the results and the heterogeneity among the studies.

Overall, the findings demonstrate a significant reduction in suicidal ideation compared to placebo, reinforcing the potential of these interventions as a rapid-acting therapeutic strategy for patients with treatment-resistant depression and an imminent risk of suicidal behavior.

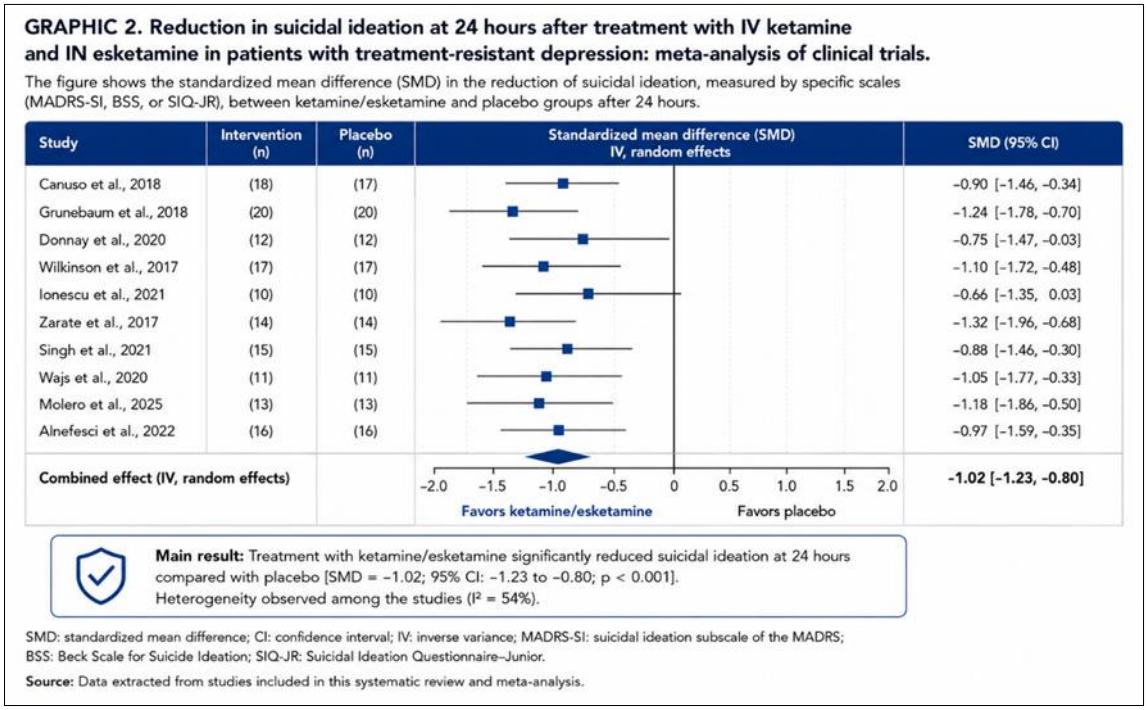

Fig 3

5. Discussion

This systematic review demonstrates that ketamine and esketamine represent one of the most significant advances in the treatment of treatment-resistant depression (TRD), primarily due to the rapid onset of antidepressant effects observed following administration. Unlike conventional antidepressants, for which a clinical response generally occurs after two to six weeks of treatment, both therapies promote significant improvement in depressive symptoms within a few hours, substantially altering the therapeutic paradigm of contemporary psychiatry. The results summarized in this review corroborate the major randomized clinical trials and systematic reviews published in recent years, which demonstrate the superiority of these interventions over placebo in patients with a history of multiple treatment failures.

Clinical trials conducted by Daly *et al*., Popova *et al*., and Fedgchin *et al*. showed that intranasal esketamine, when used in combination with oral antidepressants, produces a significant reduction in depression scale scores as early as the first 24 hours, maintaining clinical benefits during follow-up in patients who remain on maintenance treatment. Similar results have been reported for intravenous ketamine, reinforcing that both approaches are highly effective in individuals with treatment-resistant depression (TRD). These findings explain the growing incorporation of esketamine into international protocols for cases of treatment-resistant depression (Daly *et al*., 2018; Popova *et al*., 2019; Fedgchin *et al*., 2019) [6, 21, 9].

Another aspect widely confirmed by the included studies concerns the rapid antisuicidal effect of ketamine and esketamine. While traditional antidepressants have a relatively delayed onset of action, several studies demonstrate a significant reduction in suicidal ideation within a few hours after administration of these therapies.

Trials conducted by Canuso *et al*., Grunebaum *et al*., and Ionescu *et al*. demonstrated significant improvement in patients at high risk for suicide, making these interventions particularly relevant in emergency departments and psychiatric inpatient units. The possibility of early clinical stabilization represents one of the main advantages of these therapies, especially in patients at high risk of mortality (Canuso *et al*., 2018; Grunebaum *et al*., 2018; Ionescu *et al*., 2021) [4, 12, 13].

The biological mechanisms responsible for this rapid response differ substantially from those observed with classic monoaminergic r antidepressants. The literature demonstrates that NMDA receptor antagonism promotes increased glutamatergic neurotransmission mediated by AMPA receptors, activation of the mTOR pathway, elevated BDNF expression, and restoration of brain neuroplasticity. These processes favor the formation of new synaptic connections in the prefrontal cortex and hippocampus, regions directly related to emotional regulation.

Thus, the effect on the glutamatergic system represents one of the most significant conceptual shifts in our understanding of the pathophysiology of treatment-resistant depression (Aleksandrova, Phillips, & Wang, 2017; Duman *et al*., 2016; Zanos *et al*., 2018) [69, 72, 82].

Despite high clinical efficacy, studies also highlight important limitations related to the duration of the antidepressant effect. Although many patients show improvement within the first few hours or days, some experience a recurrence of symptoms after a few weeks, justifying the development of maintenance protocols. Extension studies have demonstrated that repeated administrations of esketamine or serial ketamine infusions can prolong the clinical response and reduce relapses, although questions remain regarding the optimal duration of treatment and the most appropriate interval between administrations (Phillips *et al*., 2019; Wajs *et al*., 2020; Zaki *et al*., 2025) [20, 35, 36].

Regarding safety, this review confirms that ketamine and esketamine have a tolerability profile considered satisfactory when administered in a supervised setting. The most frequently reported adverse effects include transient dissociative symptoms, dizziness, sedation, nausea, and temporary elevation of blood pressure, which are generally self-limiting. However, clinical monitoring remains necessary during and after administration, especially in patients with cardiovascular disease or other relevant comorbidities. In addition, concerns remain regarding the potential for abuse and possible cognitive effects resulting from prolonged use, aspects that continue to be the subject of investigation (Short *et al*., 2018; Martinotti *et al*., 2022; Bayes *et al*., 2025) [40, 39, 29].

The growing body of scientific literature is also directing efforts toward identifying biomarkers capable of predicting therapeutic response. Studies involving functional neuroimaging, inflammatory markers, genetic polymorphisms, and serum BDNF levels show promising results, although no single marker currently provides sufficient evidence for routine use in clinical practice. The identification of these biomarkers could contribute to personalized medicine strategies, allowing for the selection of patients most likely to benefit from therap s and reducing unnecessary exposure (Abdallah *et al*., 2017; Kim *et al*., 2022; Gould *et al*., 2019) [67, 77, 74].

Another aspect noted in this review concerns the growing use of real-world evidence studies. Unlike randomized clinical trials, these studies reflect more heterogeneous populations and routine care settings, thereby increasing the external validity of the evidence. The results demonstrate that the efficacy observed in controlled studies tends to be replicated in clinical practice, although factors such as treatment adherence, psychiatric comorbidities, and concomitant use of other medications may influence therapeutic outcomes (Alnefeesi *et al*., 2022; Molero *et al*., 2025; Baune *et al*., 2026) [28, 33, 30].

A comparison between ketamine, esketamine, and other therapeutic modalities—particularly electroconvulsive therapy (ECT)—shows that both are highly effective in patients with treatment-resistant depression. However, while ECT remains one of the most effective therapies for severe cases, ketamine and esketamine offer advantages related to the rapid onset of antidepressant effects, reduced need for anesthesia, and greater patient acceptance. Thus, the choice of treatment should take into account individual characteristics, the severity of the clinical condition, contraindications, and the availability of care resources (Li *et al*., 2022; Covvey *et al*., 2022; Anand *et al*., 2023) [52, 44, 2].

Finally, the findings of this systematic review reinforce that ketamine and esketamine represent important therapeutic alternatives for patients with treatment-resistant depression, particularly those at high risk of suicide and who have failed conventional treatments. However, gaps remain regarding long-term safety, the definition of optimal maintenance protocols, cost-effectiveness, and the identification of biomarkers predictive of response. Thus, future multicenter clinical trials, long-term follow-up studies, and translational research will be essential to consolidate the role of these therapies and expand their safe, evidence-based application in contemporary psychiatric practice.

6. Conclusion

This systematic review demonstrated that ketamine and esketamine represent important therapeutic advances in the management of treatment-resistant depression, particularly due to their ability to rapidly reduce depressive symptoms and suicidal ideation.

Compared to conventional antidepressants, these therapies have a significantly earlier onset of action, providing clinical benefit within the first few hours after administration and constituting a valuable alternative for patients with multiple treatment failures or a high risk of suicide. The analyzed results demonstrate consistency across randomized clinical trials, systematic reviews, meta-analyses, and real-world clinical practice studies, reinforcing the robustness of the currently available evidence.

The pharmacological mechanisms involved—based on modulation of the glutamatergic system, activation of AMPA receptors, increased expression of brain-derived neurotrophic factor (BDNF), and restoration of brain neuroplasticity—represent a paradigm shift in the understanding of the pathophysiology of treatment-resistant depression. These findings expand therapeutic possibilities by moving beyond the traditional model based exclusively on monoaminergic modulation, thereby facilitating the development of new pharmacological strategies targeting the neurobiological mechanisms of the disease.

Although clinical efficacy has been widely demonstrated, the review also highlights that the use of ketamine and esketamine must occur in a specialized setting, with adequate monitoring of adverse effects and careful patient selection. Transient dissociative events, temporary cardiovascular changes, and uncertainties related to long-term use underscore the need for standardized care protocols and multidisciplinary monitoring throughout treatment. Furthermore, issues related to cost, accessibility, maintenance of therapeutic response, and abuse potential remain significant challenges for the large-scale implementation of these therapies.

A review of the literature also highlights promising prospects related to the identification of biomarkers predictive of therapeutic response, the development of new ketamine derivatives with greater pharmacological selectivity, and the integration of these therapies with psychotherapeutic interventions and mental health rehabilitation strategies. Such advances may contribute to the individualization of treatment, increasing clinical effectiveness and reducing unnecessary exposure for patients with a lower likelihood of response.

It is therefore concluded that ketamine and esketamine are establishing themselves as effective, safe, and innovative therapeutic alternatives for patients with treatment-resistant depression, especially those with severe symptoms and an increased risk of suicide. However, multicenter clinical trials with longer follow-up periods, cost-effectiveness studies, long-term safety assessments, and research aimed at defining optimal maintenance protocols and patient selection criteria are still needed. Strengthening this evidence will allow for the expanded use of these therapies in a safe, rational, and evidence-based manner, contributing to improved clinical outcomes and quality of life for individuals affected by treatment-resistant depression.

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