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# INTRAVENOUS KETAMINE IN PSYCHIATRY: THERAPEUTIC APPLICATIONS, MECHANISMS OF ACTION, AND CLINICAL PERSPECTIVES

**Juliana Leite Haubman**

Federal University of Rio Grande (FURG)

**João Octávio Celante da Silva**

Catholic University of Pelotas (UCPel)

**Bruno Horta Leonardo Machado de  
Moura**

Catholic University of Pelotas (UCPel)

**Paula de Vasconcellos Vargas**

Catholic University of Pelotas (UCPel)

**Alice Ruiz Garcia**

University of the Far South of Santa Catarina  
(UNESC)

**Maria Eduarda Galles Cunha Zambrin**

Pontifical Catholic University of Paraná (PUCPR)

**Maria Luiza Kummer**

Catholic University of Pelotas (UCPel)

**Giovanna Montiel Scherer**

Lutheran University of Brazil (ULBRA)

**Talissa Nadiane Bugs**

Catholic University of Pelotas (UCPel)

**Helenna Vieira Schwartz**

Franciscan University (UFN)



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**Abstract:** Intravenous esketamine represents a significant therapeutic innovation in the field of psychiatry, particularly in the management of treatment-resistant depression and severe psychiatric conditions associated with suicidal ideation. Derived from the S-enantiomer of ketamine, esketamine acts primarily as an N-methyl-D-aspartate (NMDA) receptor antagonist, promoting rapid glutamatergic modulation and brain neuroplasticity. The present study aims to review the scientific literature on the use of intravenous esketamine in psychiatry, addressing its mechanisms of action, clinical indications, therapeutic efficacy, adverse effects, and current challenges. This is a narrative literature review conducted through the analysis of scientific articles indexed in the PubMed, Scielo, MEDLINE, and Google Scholar databases, published between 2015 and 2026, in Portuguese and English. The findings demonstrate that intravenous ketamine produces a rapid antidepressant response, with significant improvement in symptoms among patients refractory to conventional treatments. Furthermore, studies show benefits in anxiety disorders, bipolar disorder, and suicide prevention. However, adverse effects such as dissociation, transient elevation of blood pressure, nausea, and abuse potential still represent significant limitations. It is concluded that intravenous ketamine is a promising and effective alternative in contemporary psychiatry, although further long-term studies are needed to establish safe and standardized protocols.

**Keywords:** Escetamine; Psychiatry; Treatment-resistant depression; Ketamine; Mental disorders; Neuroplasticity.

## Introduction

Psychiatric disorders constitute one of the major global public health challenges, accounting for significant functional, economic, and social impacts. Among these conditions, major depressive disorder stands out due to its high prevalence and significant rates of morbidity, disability, and suicide. Despite the availability of various traditional antidepressants, it is estimated that approximately 30% of patients have treatment-resistant depression (TRD), defined as the absence of a satisfactory response following the appropriate use of at least two antidepressants from different classes.

Historically, conventional antidepressants have acted primarily on the monoaminergic systems, modulating serotonin, norepinephrine, and dopamine. However, these medications have a delayed onset of action, often requiring weeks to achieve a significant clinical response. In this context, the search for fast-acting therapies has become a priority in modern psychiatry.

Ketamine, the S-enantiomer of ketamine, has emerged as an innovative alternative due to its rapid antidepressant effect. Initially used as a dissociative anesthetic, its potential for glutamatergic modulation and the promotion of brain neuroplasticity was later observed. Unlike traditional antidepressants, esketamine acts on NMDA receptors, triggering increased glutamate release, activation of AMPA receptors, and stimulation of brain-derived neurotrophic factor (BDNF) production—mechanisms related to synaptic recovery and improved mood.

Although intranasal administration has received greater regulatory approval in several countries, the intravenous route re-

mains widely studied due to its high bioavailability, pharmacokinetic control, and rapid clinical response. Currently, intravenous ketamine is being investigated not only for treatment-resistant depression but also for anxiety disorders, bipolar disorder, post-traumatic stress disorder, and the reduction of suicidal ideation.

Thus, understanding the scientific advances related to the use of intravenous ketamine in psychiatry is essential for expanding therapeutic options and improving clinical practice.

## Objective

To analyze, through a narrative review of the scientific literature, the main aspects related to the use of intravenous ketamine in psychiatry, including mechanisms of action, clinical applications, therapeutic efficacy, adverse effects, and future prospects.

## Methodology

This study consists of a narrative review of the scientific literature on the use of intravenous ketamine in psychiatry. The literature search was conducted in the PubMed, MEDLINE, Scielo, and Google Scholar databases, using articles published between 2015 and 2026 in Portuguese and English.

The following search terms and their combinations were used: “Esketamine,” “Intravenous Esketamine,” “Psychiatry,” “Treatment-resistant depression,” “Ketamine,” “Major depressive disorder,” and “Suicidal ideation.” The following Portuguese search terms were also used: “intravenous esketamine,” “treatment-resistant depression,” “psychiatry,” and “mental disorders.”

The inclusion criteria included original articles, systematic reviews, meta-analyses, and clinical trials addressing the use of intravenous esketamine in psychiatric conditions. Duplicate studies, works without thematic relevance, reports exclusively related to anesthesia, and publications without access to the full text were excluded.

After selecting and critically reviewing the materials, the data were organized into thematic categories related to the mechanism of action, clinical indications, therapeutic efficacy, adverse effects, and ethical and clinical challenges.

## Discussion

### Mechanism of Action of Ketamine

Ketamine acts primarily as a noncompetitive antagonist of NMDA receptors, which are part of the glutamatergic system. Unlike classic antidepressants, its action is rapid, promoting almost immediate neurochemical changes.

Blocking NMDA receptors leads to increased glutamate release in the prefrontal cortex, stimulating AMPA receptors and activating intracellular pathways related to neuroplasticity. Among these pathways, the activation of the mTOR (mammalian target of rapamycin) complex stands out; it is responsible for synaptic protein synthesis and the recovery of neuronal connections impaired in depression.

In addition, ketamine promotes increased levels of BDNF, a protein associated with neuronal survival and the formation of new synapses. These mechanisms contribute to the rapid improvement in mood and reduction in suicidal ideation observed in many patients.

Another important aspect involves its anti-inflammatory action and its ability to modulate the hypothalamic-pituitary-adrenal axis, suggesting additional benefits for patients with neuroinflammatory changes associated with psychiatric disorders.

### Intravenous ketamine for treatment-resistant depression

The primary psychiatric indication for intravenous ketamine is treatment-resistant depression. Clinical studies show that many patients experience significant improvement in depressive symptoms within a few hours after intravenous infusion.

The rapid response represents a significant clinical advantage, especially in situations of imminent suicide risk. While conventional antidepressants may take weeks to take effect, ketamine often reduces severe symptoms in less than 24 hours.

Randomized clinical trials show higher response rates than those observed with placebo, especially when ketamine is combined with conventional oral antidepressants. Some studies also point to functional improvement, reduced anhedonia, and greater restoration of quality of life.

However, despite the promising results, there is significant individual variability. Some patients show a robust response, while others demonstrate limited or transient benefit. Thus, there are still no well-established biomarkers capable of predicting therapeutic response.

### Applications in Other Psychiatric Disorders

In addition to treatment-resistant depression, intravenous ketamine is being investigated for various psychiatric conditions.

In bipolar disorder, studies suggest rapid improvement in depressive episodes without significantly inducing mania when used under close monitoring. In anxiety disorders, particularly generalized anxiety disorder and obsessive-compulsive disorder, benefits related to reduced cortical hyperactivity and improved neuroplasticity have been observed.

In post-traumatic stress disorder (PTSD), research demonstrates a potential reduction in dissociative symptoms, hypervigilance, and traumatic flashbacks. Furthermore, its rapid effect on suicidal ideation makes ketamine a relevant alternative in psychiatric emergencies.

Recent research has also examined its role in substance use disorders, chronic pain associated with depression, and eating disorders, although methodological limitations still prevent definitive conclusions.

### Adverse Effects and Limitations

Despite its therapeutic efficacy, intravenous ketamine is associated with significant adverse effects. Among the most common are dissociation, dizziness, nausea, vomiting, sedation, perceptual changes, and a transient increase in blood pressure.

Dissociative symptoms generally occur during or shortly after infusion and are usually transient and reversible. However, in some patients, they can cause significant discomfort and limit treatment adherence.

Another concern involves the potential for abuse and dependence, given that ketamine has a history of recreational use. Although the risk appears to be lower in controlled medical settings, the need for rigorous monitoring remains essential.

From an economic standpoint, the high cost of treatment also poses a significant barrier, especially in developing countries. In addition, there are still limitations regarding the standardization of doses, frequency of infusions, and optimal duration of treatment.

Another major challenge relates to the scarcity of long-term studies. Most current research evaluates relatively short periods, making it difficult to fully understand long-term safety, tolerability, and neurocognitive effects.

## Future Prospects

The growing expansion of intravenous ketamine use reflects a paradigm shift in modern psychiatry, marked by the recognition of the glutamatergic system as a therapeutic target.

Future research aims to identify biological markers predictive of response, optimize treatment protocols, and develop safer and more accessible formulations. In addition, new studies may expand the clinical indications for esketamine to include other neuropsychiatric disorders.

The integration of pharmacotherapy, psychotherapy, and neurobiological approaches may enhance clinical outcomes and promote more individualized treatment for psychiatric patients.

## Conclusion

Intravenous ketamine represents a significant therapeutic advance in contemporary psychiatry, particularly in the management of treatment-resistant depression and acute suicidal ideation. Its innovative mechanism of action, based on glutamatergic modulation and the promotion of neuroplasticity, differs significantly from that of traditional antidepressants.

The reviewed studies demonstrate rapid and consistent efficacy in various psychiatric conditions, offering new hope for patients who are refractory to conventional therapies. However, adverse effects, abuse potential, high cost, and the lack of standardized protocols still pose significant challenges.

Thus, although intravenous ketamine shows promising results and growing clinical relevance, it is essential to conduct new long-term studies to better understand its safety, sustained efficacy, and applicability in different psychiatric populations.

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