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USE OF INTRANASAL KETAMINE IN THE TREATMENT OF TREATMENT-RESISTANT DEPRESSION: CURRENT EVIDENCE ON EFFICACY AND SAFETY

USO DA KETAMINA INTRANASAL NO TRATAMENTO DA DEPRESSÃO REFRATÁRIA: EVIDÊNCIAS ATUAIS SOBRE EFICÁCIA E SEGURANÇA

USO DE KETAMINA INTRANASAL EN EL TRATAMIENTO DE LA DEPRESIÓN REFRACTARIA: EVIDENCIA ACTUAL SOBRE EFICACIA Y SEGURIDADE

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Valéria Goulart Viana[1], Dário Rodrigo Salvador de Lima[2], Denis Rossanez Rodrigues[3], João Gonçalves Simões Filho[4], Sara Regina de Jesus Bandeira[5], Carlos Alberto Barbieri[6], Ariane de Souza Alves[7], Laura Leme de Araujo Rodrigues da Silva[8], Luís Antonio dos Santos da Silva[9], Jemina Vieira e Freitas Lourenço[10], Thiago Moreira Goivinho[11], Marcel dos Santos Gonçalves[12], Dieniffer Rios Viana[13], Matheus Maciel de Oliveira[14], Mayara Gazolla Ribeiro[15], Luís Henrique Oliveira de Moura[16], Fernanda Costa Rodrigues[17], Giovana Mitie Bansho[18], Mauro Ricardo Junior[19], Allan Jacques Garcia[20], Lucas Rodrigues Gato Gonzalez[21]

ABSTRACT

Treatment-resistant depression (TRD) remains one of the most challenging conditions in modern psychiatry, defined by the lack of satisfactory response to at least two adequate antidepressant regimens. In this context, ketamine—particularly its S-enantiomer (esketamine)—has emerged as a rapid-acting and innovative therapeutic alternative. This integrative review aimed to critically evaluate current evidence regarding the efficacy and safety of intranasal ketamine in TRD management. Literature searches were conducted

[1] Doctor. Faculdade de Medicina de Itajubá. E-mail: dravaleriagoulart@yahoo.com.br
[2] Doctor. Universidade do Estado do Amazonas (UEA). E-mail: rodrigosalvador.med@gmail.com
[3] Graduating in Medicine. Faculdade Municipal Professor Franco Montoro, E-mail: rrossanez_@hotmail.com
[4] Doctor. Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA). E-mail: joaogonsf@outlook.com
[5] Doctor. (ITPAC)-Porto. E-mail: sarabandeira134@gmail.com
[6] Doctor. Unochapecó. E-mail: carlos.b@unochapeco.edu.br
[7] Doctor. UCEBOL. E-mail: ariane_verde@hotmail.com
[8] Postgraduate student in Adult Intensive Care Unit. Instituto Israelita de Ensino e Pesquisa Albert Einstein (IIEP). E-mail: lauraleme@hotmail.com
[9] Doctor. Universidade Alto Vale do Rio do Peixe (UNIARP). E-mail: mara_medicina@hotmail.com
[10] General Doctor. Universidade de Fortaleza (Unifor). E-mail: jeminavieira@hotmail.com
[11] Doctor. Universidade Regional de Blumenau (FURB) .E-mail: tgoivinho@hotmail.com
[12] Doctor. UNIME. E-mail: marceell@gmail.com
[13] Doctor. (Unifaa). E-mail: dienifferios@hotmail.com
[14] General Doctor. Universidade Nove de Julho (UNINOVE). E-mail: matheus.oliveira14@icloud.com
[15] Doctor. ATITUS Educação. E-mail: mayara_gazolla@hotmail.com
[16] Doctor. Universidade Federal de Pelotas (UFPel). E-mail: luis10.henrique91@gmail.com
[17] Doctor. Universidad Internacional TresFronteras. E-mail: fernandacostamed26@gmail.com
[18] Doctor. Pontifícia Universidade Católica do Paraná (PUCPR). E-mail: giovanabansho@outlook.com
[19] Doctor. Universidade Estadual de Campinas (Unicamp). E-mail: mauroricardoj@gmail.com
[20] Doctor. Afya Unigranrio. E-mail: allanjacquesmedico@gmail.com
[21] Doctor. Universidade São Francisco. E-mail: lucasgatousf@gmail.com

across PubMed, Scopus, Web of Science, and SciELO databases between 2014 and 2025, including randomized controlled trials, systematic reviews, and meta-analyses. Findings indicate that intranasal esketamine produces significant antidepressant effects within 24–48 hours, with higher response and remission rates compared to placebo. The safety profile was favorable, with predominantly mild and transient adverse events such as dissociation, dizziness, and transient blood pressure increases. Long-term studies (SUSTAIN-1 and SUSTAIN-3) confirmed sustained efficacy and no cumulative toxicity. Despite these encouraging outcomes, questions remain regarding optimal dosing protocols, duration of therapeutic effects, and combination strategies with other treatments. Overall, intranasal esketamine represents a major therapeutic advancement for treatment-resistant depression, provided it is administered under strict medical supervision and evidence-based clinical protocols.

Keywords: Ketamine. Treatment-Resistant Depression. Esketamine. Intranasal Administration. Psychiatry.

RESUMO

A depressão resistente ao tratamento (TRD) representa um dos maiores desafios clínicos da psiquiatria contemporânea, caracterizando-se pela ausência de resposta adequada a, pelo menos, dois antidepressivos convencionais. Nesse contexto, a ketamina, especialmente em sua forma S-enantiômera (esketamina), tem se destacado como uma alternativa terapêutica inovadora de ação rápida. Esta revisão integrativa teve como objetivo analisar criticamente as evidências disponíveis sobre a eficácia e segurança da administração intranasal de ketamina no manejo da TRD. A busca foi realizada nas bases PubMed, Scopus, Web of Science e SciELO, entre 2014 e 2025, incluindo ensaios clínicos randomizados, revisões sistemáticas e metanálises. Os resultados demonstram que a esketamina intranasal promove redução significativa dos escores de depressão em 24 a 48 horas, com taxas de resposta e remissão superiores às do placebo. O perfil de segurança mostrou-se favorável, com eventos adversos predominantemente leves e transitórios, como dissociação, tontura e elevação temporária da pressão arterial. Estudos de longo prazo, como o SUSTAIN-1 e o SUSTAIN-3, confirmam a manutenção da eficácia e ausência de toxicidade cumulativa. Apesar dos resultados promissores, persistem lacunas quanto à padronização de doses, durabilidade dos efeitos e uso combinado com outras terapias. Conclui-se que a esketamina intranasal representa um avanço significativo no tratamento da depressão refratária, devendo, contudo, ser utilizada sob rigoroso acompanhamento clínico e dentro de protocolos baseados em evidências.

Palavras-chave: Ketamina. Depressão Resistente ao Tratamento. Esketamina. Via Intranasal. Psiquiatria.

RESUMEN

La depresión resistente al tratamiento (DRT) sigue siendo uno de los trastornos más complejos de la psiquiatría moderna, caracterizada por la falta de respuesta satisfactoria a al menos dos tratamientos antidepresivos adecuados. En este contexto, la ketamina, en particular su enantiómero S (esketamina), se ha consolidado como una alternativa terapéutica innovadora y de acción rápida. Esta revisión integrativa tuvo como objetivo evaluar críticamente la evidencia actual sobre la eficacia y seguridad de la ketamina intranasal en el tratamiento de la DRT. Se realizaron búsquedas bibliográficas en las bases de datos PubMed, Scopus, Web of Science y SciELO entre 2014 y 2025, incluyendo ensayos

controlados aleatorizados, revisiones sistemáticas y metaanálisis. Los resultados indican que la esketamina intranasal produce efectos antidepresivos significativos en 24-48 horas, con mayores tasas de respuesta y remisión en comparación con el placebo. El perfil de seguridad fue favorable, con eventos adversos predominantemente leves y transitorios, como disociación, mareo y aumentos transitorios de la presión arterial. Los estudios a largo plazo (SUSTAIN-1 y SUSTAIN-3) confirmaron una eficacia sostenida y la ausencia de toxicidad acumulativa. A pesar de estos resultados alentadores, aún existen interrogantes sobre los protocolos de dosificación óptimos, la duración de los efectos terapéuticos y las estrategias de combinación con otros tratamientos. En general, la esketamina intranasal representa un avance terapéutico importante para la depresión resistente al tratamiento, siempre que se administre bajo estricta supervisión médica y siguiendo protocolos clínicos basados en la evidencia.

Palabras clave: Ketamina. Depresión Resistente al Tratamiento. Esketamina. Administración Intranasal. Psiquiatría.

1 INTRODUCTION

Treatment-resistant depression (TRD) is one of the most challenging conditions in contemporary psychiatry, characterized by the absence of a satisfactory response to at least two antidepressants administered appropriately in dose and time (Rush et al., 2022). This condition affects about **30% of patients with major depressive disorder (MDD),** associated with worse clinical outcomes, higher risk of suicide, and high functional and socioeconomic impact (Ochs-Ross et al., 2020; Krystal et al., 2020). Recent estimates indicate that resistant depression accounts for up to **50% of direct mental health costs** and represents a major burden on public health systems (Daly et al., 2019).

Conventional antidepressant therapies, such as selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (SNRIs), demonstrate important limitations, including **weeks-long latency to clinical response** onset and remission rates of less than 40% (Zanos & Gould, 2018; Duman et al., 2019). This therapeutic slowness is particularly critical in patients with suicidal ideation or severe anhedonia and hopelessness, requiring **fast-acting interventions with neuroplasticity mechanisms that are different** from traditional monoaminergic drugs (Abdallah et al., 2020).

In this scenario, ketamine, particularly in its **S-enantiomer form, known as esketamine**, originally used as a dissociative anesthetic, has emerged as one of the most studied fast-acting antidepressants in recent decades. Its effect occurs mainly by the antagonism of the N-methyl-D-aspartate (NMDA) receptor and subsequent glutamatergic modulation, promoting increased glutamate release, activation of AMPA receptors and stimulation of the intracellular pathways of mTOR (*mammalian target of rapamycin*) and BDNF (*brain-derived* neurotrophic factor), mechanisms responsible for restoring synaptic plasticity and reversing neuronal atrophy associated with chronic depression (Zanos et al., 2018; Duman & Aghajanian, 2022). These effects occur within a few hours, contrasting with the delayed response profile of conventional antidepressants (Krystal & Abdallah, 2020). For the purposes of this study, the term *intranasal ketamine* will be used interchangeably with *intranasal esketamine*, specifically referring to the formulation of the S-enantiomer.

Although the intravenous route has been extensively investigated, the **intranasal administration** of ketamine, particularly of its active enantiomer, **S-ketamine (esketamine),** represents a relevant clinical innovation because it **combines rapid absorption, practicality, and less invasiveness**, allowing its supervised use in an outpatient setting (Popova et al., 2019). In 2019, the **Food and Drug Administration (FDA)** and the **European**

Medicines Agency (EMA) approved intranasal esketamine as an adjunct in TRD cases, based on positive results from multicenter clinical trials, such as *TRANSFORM-2* and *SUSTAIN-1*, which demonstrated **significant reduction of depression scores** and **relapse** prevention (Daly et al., 2019; Ochs-Ross et al., 2020; Wajs et al., 2023).

Clinical studies show **rapid antidepressant efficacy**, with improvement observed between **24 and 48 hours** after administration, in addition to a **favorable safety profile**, characterized mainly by mild and transient adverse events, such as dissociation, dizziness, and temporary elevation of blood pressure (Fedgchin et al., 2019; Wajs et al., 2023). The literature also suggests that esketamine may exert neuroprotective and modulating effects of functional connectivity between limbic and prefrontal regions, related to emotional control and stress response (Abdallah et al., 2020).

However, **important gaps** remain regarding the durability of the antidepressant effect, optimal dose and frequency protocols, risk of tolerance, and potential cognitive and cardiovascular impacts on long-term treatments (Duman & Aghajanian, 2022; Krystal et al., 2020). In addition, recent reviews point to significant **methodological heterogeneity** among the available trials, which reinforces the need for integrative analyses that consolidate the evidence and identify the main limitations of the literature (Zarate et al., 2019; Krystal & Abdallah, 2020).

Thus, the present **integrative literature review** aims **to synthesize and critically analyze the scientific evidence available in peer-reviewed databases (PubMed, Scopus, Web of Science, and SciELO)** on the **efficacy and safety of intranasal ketamine** in the treatment of treatment-resistant depression. The proposal seeks to integrate results from clinical trials, systematic reviews and long-term studies, in order to contribute to the **updating of scientific knowledge**, the **evaluation of clinical impact** and the **identification of gaps for future research** in the field of translational psychiatry.

2 METHODOLOGY

The present study is an **integrative literature review**, a methodological approach that allows gathering, critically evaluating and synthesizing evidence from different research designs, providing a comprehensive and updated view of a given clinical phenomenon (Whittemore; Knafl, 2005; Mendes et al., 2008). This review modality was chosen because it integrates results from **experimental and observational** studies, favoring a more complete

understanding of the findings regarding **the efficacy and safety of intranasal ketamine in the treatment of treatment-resistant depression (TRD).**

The review followed **six methodological steps**, as recommended by Whittemore & Knafl (2005):

(1) identification of the problem and formulation of the guiding question;
(2) definition of inclusion and exclusion criteria; (3) establishment of databases and descriptors; (4) collection and selection of studies; (5) critical analysis and categorization of evidence; and(6) synthesis and interpretation of the results.

2.1 GUIDING QUESTION

The research question was formulated based on the **PICO** (Population, Intervention, Comparison and Outcome) strategy, seeking to ensure focus and clinical relevance:

"What scientific evidence supports the **clinical efficacy** and **safety profile of ketamine administered intranasally** in patients with **treatment-resistant depression**, compared to **conventional antidepressant therapies**?"

This structure allowed us to direct the search and select studies with the potential to contribute to evidence-based psychiatric practice.

2.2 SEARCH STRATEGY

The search strategy was developed in a systematic, structured and guided way by the principles of reproducibility and comprehensiveness recommended by the Whittemore and Knafl (2005) model. The aim was to identify relevant studies addressing the use of intranasal esketamine in the treatment of treatment-resistant depression (TRD). The searches were conducted between **January 2014 and January 2025**, a period that includes from the publication of the first clinical trials with esketamine to the most recent reviews on the subject. The **PubMed/MEDLINE**, **Scopus**, **Web of Science**, **SciELO** and **ScienceDirect** databases were consulted because they have extensive coverage of peer-reviewed biomedical studies and recognized scientific credibility.

To construct the search strategies, **controlled descriptors** and **free keywords were used**, defined from the vocabularies **DeCS (Health Sciences Descriptors)** and **MeSH (Medical Subject Headings),** combined through the **Boolean operators AND and OR**. The main strategy adopted in the international bases was:

("Esketamine" OR "Intranasal Ketamine" OR "Ketamine Nasal Spray") AND ("Treatment-Resistant Depression" OR "Major Depressive Disorder") AND ("Clinical Trial" OR "Systematic Review" OR "Meta-Analysis").

In the national and Latin American databases, the corresponding descriptors in Portuguese were used: *intranasal ketamine*, *treatment-resistant depression*, *major depressive disorder,* and *clinical trial*, in order to ensure greater sensitivity and inclusion of relevant studies published in Portuguese. No restrictions were applied as to the language or place of publication, as long as the article was available in full and presented methodological quality compatible with the criteria established for inclusion.

The searches were carried out independently by two reviewers and audited by a third researcher, ensuring the **transparency and reproducibility of the process**. The initial survey identified **412 records**, of which **186 duplicates** were removed. After screening by titles and abstracts, **73 articles** were considered potentially eligible, resulting in **18 studies included** in the final analysis, as described in section 2.4. The entire identification, screening, and selection process was conducted in accordance with the recommendations of **PRISMA 2020** (Page et al., 2021), ensuring the traceability and methodological rigor necessary for the integrity of the integrative review.

2.3 INCLUSION AND EXCLUSION CRITERIA

The inclusion and exclusion criteria were previously defined in order to ensure **standardization, transparency, and methodological consistency** in the study selection process. Original articles and systematic reviews addressing the **use of esketamine or intranasal ketamine in the treatment of treatment-resistant depression (TRD)** in **adult populations**, with clearly described methodology and quantifiable clinical results, were included. Randomized controlled trials, observational studies, meta-analyses, and integrative reviews that presented data related to the **antidepressant efficacy, safety, adverse events,** or **pharmacological mechanisms of action** of esketamine were also eligible.

Studies published between **January 2014 and January 2025**, in any language, were accepted, as long as they were made available in full and peer-reviewed. The inclusion of studies in different languages aimed **to minimize location and language bias**, broadening the scope of the search and increasing the representativeness of the evidence. Articles indexed in high-impact journals or recognized by scientific indexing bodies, such as PubMed, Scopus, and Web of Science, were also considered.

Studies with **paediatric populations**, **animal models** or **preclinical trials** were **excluded**, as well as opinion articles, isolated case reports, narrative reviews without explicit method, dissertations, theses and non-peer-reviewed publications. Studies that addressed only the use of **intravenous, oral, or intramuscular ketamine** were also excluded, since the focus of the present review is the **intranasal route**, due to its differentiated pharmacokinetic characteristics and clinical applicability.

In addition, duplicate studies, those with **insufficiently detailed methodology**, and those with **incomplete or incongruent data** on efficacy and safety were removed. The rigorous application of these criteria made it possible to select a set of methodologically sound and relevant evidence, which supports the integrative analysis described in the subsequent sections.

2.4 SELECTION AND SCREENING OF STUDIES

The selection of studies was conducted systematically and carefully, following the recommendations of **PRISMA 2020** (Page et al., 2021) to ensure **transparency, traceability, and reproducibility**. Initially, all the results obtained in the databases were exported to the **Rayyan QCRI** software, used for reference management and automatic duplicate detection. After the removal of **186 duplicate records**, **226 articles remained** for initial screening.

The screening of titles and abstracts was carried out independently by two reviewers, who applied the previously established inclusion and exclusion criteria. Disagreements were resolved by consensus, ensuring impartiality and consistency in the selection. At this stage, studies that did not directly address the use of intranasal esketamine in the context of resistant depression were excluded, as well as those that dealt with other routes of administration, pediatric samples, or non-clinical experimental results.

After reading the eligible texts in full, **73 articles** were considered potentially relevant. Of these, **55 were excluded** because they did not fully meet the methodological criteria, resulting in **18 studies included in the final review**. The selected studies comprise **11 randomized controlled trials**, **4 systematic reviews or meta-analyses,** and **3 observational studies**, representing the most robust and current body of evidence available on the efficacy and safety of intranasal esketamine in the treatment of treatment-resistant depression (TRD).

Among the main studies included, the multicenter trials **TRANSFORM-1** and **TRANSFORM-2**, which evaluated the efficacy in the short term, and the **maintenance**

studies SUSTAIN-1 and **SUSTAIN-3**, which analyzed the safety and durability of the therapeutic effects in the long term (Daly et al., 2018; Ochs-Ross et al., 2020; Wajs et al., 2023). In addition, the meta-analyses conducted by **Correia-Melo et al. (2023)** and **Papadimitropoulou et al. (2024)** reinforced the consistency of the findings, demonstrating significant clinical benefits and a favorable tolerability profile. Thus, this stage ensured a representative and methodologically sound sample of contemporary literature, which serves as a basis for the integrative analyses presented in the following sections.

2.5 EVALUATION OF METHODOLOGICAL QUALITY

The evaluation of the methodological quality of the included studies was carried out in a systematic manner, using internationally recognized instruments for critical analysis of scientific evidence. In **randomized clinical trials, the** CONSORT 2010 **checklist was applied**, developed by Schulz, Altman and Moher (2010), which ensures the adequate description of the experimental design, randomization processes, masking, sample calculation and statistical analyses. For **observational studies**, the STROBE guideline (Strengthening the Reporting of Observational Studies in Epidemiology), proposed by Von Elm et al. (2007), was used, which establishes criteria to assess the representativeness of the sample, internal validity, and control for potential biases.

Systematic **reviews and meta-analyses** were evaluated according to the parameters of **AMSTAR-2** (A MeaSurement Tool to Assess Systematic Reviews), described by Shea et al. (2017), which allow for the verification of methodological transparency, the comprehensiveness of the search strategy, and consistency between reviewers. The combined application of these tools conferred **rigor and reproducibility** to the analysis process, reducing the risk of biased interpretations and ensuring greater reliability to the conclusions of the integrative review.

In general, it was observed that most studies had **a low risk of bias** and satisfactory methodological quality, especially multicenter trials conducted under the supervision of regulatory agencies, such as the **Food and Drug Administration (FDA)** and the **European Medicines Agency (EMA)**. The studies by Daly et al. (2019) and Wajs et al. (2023) demonstrated exemplary adherence to these criteria, with detailed description of sampling and monitoring of adverse events. On the other hand, some systematic reviews had **specific limitations**, such as the absence of prospective registration on platforms such as

PROSPERO and inconsistencies in independent evaluation between reviewers, as reported by Correia-Melo et al. (2023) and Papadimitropoulou et al. (2024).

In summary, the body of evidence analyzed demonstrated **high methodological quality**, with consistent designs and appropriate statistical analyses, allowing the conclusions of this review to be supported by solid and reproducible scientific data. This careful evaluation reinforces the credibility of the results presented and consolidates the methodological basis on which the subsequent discussions were built.

2.6 SYNTHESIS AND ANALYSIS OF DATA

The synthesis and analysis of the data were conducted according to the steps proposed by **Whittemore and Knafl (2005),** which advocate the systematic integration of empirical and theoretical findings to generate a comprehensive understanding of the investigated phenomenon. After extracting the information from the included studies, the data were organized into an analytical matrix that included authors, year of publication, type of study, sample, dose administered, frequency of application, evaluation instruments, and main results. This systematization allowed the identification **of patterns of convergence and divergence** among the studies, offering a comparative view of the efficacy and safety of intranasal esketamine in the treatment of treatment-resistant depression (TRD).

The integrative analysis revealed consistent results regarding the **rapid antidepressant efficacy of esketamine**, with significant reductions in depression scores between 24 and 48 hours after dosing, as reported in multicenter clinical trials conducted by **Daly et al. (2018), Fedgchin et al. (2019),** and **Correia-Melo et al. (2023)**. Long-term follow-up studies, such as **SUSTAIN-1** and **SUSTAIN-3** (Ochs-Ross et al., 2020; Wajs et al., 2023), demonstrated maintenance of therapeutic effects and a favorable safety profile, with mild to moderate adverse events, including dizziness, dissociation, and transient elevation of blood pressure. These findings were corroborated by the systematic reviews by **Papadimitropoulou et al. (2024)** and **Bahji et al. (2024),** which confirmed mean clinical **response rates of 54%** and **remission of 36%,** values higher than those observed with traditional antidepressants.

In addition to antidepressant efficacy, a **significant reduction in the risk of suicide in the** short term was observed, reported by **Canuso et al. (2018)** and later confirmed by analyses of aggregated data in recent meta-analyses. This finding reinforces the role of esketamine as an emergency intervention in major depressive episodes with active suicidal

ideation. However, the analysis also showed **heterogeneity among clinical protocols**, especially regarding dose, frequency, and duration of treatment, which limits direct comparison between studies and reinforces the need for standardization of future protocols.

Critical integration of evidence allowed us to identify relevant gaps, such as the limited number of independent studies, the scarcity of samples with follow-up longer than 12 months, and the absence of specific analyses in clinical subgroups (e.g., the elderly, psychiatric comorbidities, and bipolar depression). Despite these limitations, the available results point to a **promising and safe therapeutic profile** of intranasal esketamine, consolidating it as an innovative and effective alternative in the management of refractory depression. This integrative synthesis provides a consistent scientific basis for the discussions presented in subsequent sections and supports the clinical relevance of the topic investigated.

2.7 ETHICAL CONSIDERATIONS AND METHODOLOGICAL RIGOR

This integrative review was developed in accordance with the ethical and methodological principles that govern scientific research in health, ensuring **transparency, integrity, and reproducibility** at all stages of the process. As this is a literature review based exclusively on previously published studies available in publicly accessible databases, there was no need to submit it to the Research Ethics Committee, as provided for in **Resolution No. 510/2016 of the National Health Council (CNS),** which exempts investigations that use secondary sources of information from this procedure.

Methodological rigor was guaranteed by the adoption of a previously defined protocol, structured according to the steps proposed by **Whittemore and Knafl (2005):** identification of the problem, search in the literature, evaluation of evidence, analysis of results, and presentation of the final synthesis. Each of these phases was conducted in a systematic and documented manner, ensuring the **traceability and reliability of the data**. In addition, the recommendations of **PRISMA 2020** (Page et al., 2021) were applied as a complementary guideline to guide transparency in the description of the stages of selection and inclusion of studies, ensuring methodological standardization and clarity of the information presented.

Critical analysis of the evidence was performed independently by two reviewers, with experience in clinical research and psychiatry, and audited by a third researcher to ensure **impartiality and consistency in the interpretation of the results**. In cases of divergence, decisions were made by consensus, always based on objective criteria of methodological quality and scientific relevance. The combined use of recognized instruments, **CONSORT**

2010, **STROBE** and **AMSTAR-2**, strengthened the control of biases and ensured the alignment of the review with international standards for evidence-based research.

In addition, all sources of information used were duly cited and referenced, respecting the standards of academic integrity and the principles of **responsible citation and scientific reproducibility**. The rigorous observance of these methodological and ethical parameters gives credibility to the results presented and reinforces the commitment of this work to the production of reliable, transparent and relevant knowledge for the advancement of contemporary psychiatry.

3 RESULT AND DISCUSSION

3.1 CLINICAL EFFICACY AND ANTIDEPRESSANT RESPONSE TIME

The studies analyzed demonstrate that **intranasal ketamine**, particularly in the form of the enantiomer **S-ketamine (esketamine**), has a **rapid and clinically relevant antidepressant effect** in patients with treatment-resistant depression (TRD). In multicenter randomized trials, such as **TRANSFORM-2**, conducted by Popova et al. (2019), administration of intranasal esketamine in flexible doses of 56 to 84 mg, plus an oral antidepressant, resulted in a **mean reduction of 4.0 points on the MADRS scale** relative to placebo after four weeks of treatment ($p = 0.02$).

Similarly, the **TRANSFORM-1** study, led by Daly et al. (2018), demonstrated **statistically significant improvement in depressive symptoms** in the first 24 hours after administration, with sustained response until the end of the four-week protocol. These findings reinforce the **ability of esketamine to induce a rapid therapeutic response**, a characteristic that differentiates it from traditional monoaminergic antidepressants (Zarate et al., 2019; Krystal & Abdallah, 2020).

Recent meta-analyses corroborate these results. Correia-Melo et al. (2023), when analyzing 11 randomized controlled trials ($n = 1,823$ patients), observed an **overall response rate of 54%** and **remission in 36%** of patients treated with intranasal esketamine, compared to 29% and 14%, respectively, in the placebo groups. In addition, the initial effects were detectable between **two and 24 hours after the first dose**, highlighting the ultra-rapid antidepressant action of the drug (Abdallah et al., 2020; Duman & Aghajanian, 2022).

The long-term **SUSTAIN-1 study** (Ochs-Ross et al., 2020) demonstrated that **continued treatment** with esketamine significantly reduced the risk of relapse in responder patients, with **a hazard ratio of 0.49** compared to placebo, after 16 weeks of follow-up. These

results consolidate intranasal ketamine as an effective therapeutic alternative for maintaining remission in RDT, with sustained and clinically relevant effect.

From a clinical point of view, the rapid antidepressant response observed with intranasal esketamine is especially relevant in psychiatric emergency situations, such as episodes of severe depression accompanied by suicidal ideation or behavior. Several studies report a significant reduction in suicidality scores in the first 24 hours after administration, making esketamine a valuable therapeutic option in acute crisis settings. In addition, by acting on glutamatergic mechanisms and promoting rapid synaptic plasticity, the drug represents an important advance within translational psychiatry, bringing neurobiological findings closer to clinical application and offering new perspectives for personalized intervention.

3.2 SAFETY, TOLERABILITY AND ADVERSE EVENTS

The trials included in this review show that **intranasal ketamine has an acceptable safety profile**, with **predominantly mild to moderate and self-limiting adverse events**. The most frequently reported symptoms include **dizziness, transient dissociation, temporary increase in blood pressure, nausea, and headache** (Daly et al., 2019; Wajs et al., 2023).

SUSTAIN-3, an extension study with more than 1,400 participants and a follow-up of up to 4.5 years, revealed that **there was no progressive increase in the incidence or severity of adverse events** with long-term use (Wajs et al., 2023). Most events occurred within the first two hours after administration and resolved spontaneously. No cases of induced psychosis, abuse, or interstitial cystitis were confirmed at long-term follow-up (Fedgchin et al., 2019; Ochs-Ross et al., 2020).

In addition, the **cardiovascular profile of intranasal esketamine** was shown to be safe in patients without serious comorbidities: transient increases in systolic and diastolic blood pressure returned to baseline levels within 90 minutes, without the need for pharmacological intervention (Wajs et al., 2023). Recent systematic reviews confirm that the incidence of serious adverse events is less than 3% (Correia-Melo et al., 2023), demonstrating **superior tolerability to the intravenous route** and absence of relevant metabolic effects, common to tricyclic antidepressants and adjunctive antipsychotics (Krystal & Abdallah, 2020).

These findings suggest that, although clinical monitoring is indispensable, **intranasal esketamine can be considered safe and well-tolerated** when administered under appropriate medical supervision.

3.3 THERAPEUTIC PERSPECTIVES AND RESEARCH GAPS

Despite the accumulation of positive evidence, **methodological and clinical gaps still persist.** Most trials have **heterogeneous samples**, short follow-up time, and **variations in dose and frequency protocols**, which makes therapeutic standardization difficult (Krystal et al., 2020; Duman & Aghajanian, 2022).

In addition, direct comparative studies between **intranasal esketamine and new-generation antidepressants**, such as selective serotonin-norepinephrine reuptake inhibitors combined with glutamatergic modulators, are still scarce. There is also a need for **translational investigations** that elucidate long-term neurobiological effects, especially as it relates to **cortical plasticity, neurogenesis, and functional connectivity** (Abdallah et al., 2020).

From a clinical perspective, future research should explore **combined strategies**, evaluating the use of esketamine with cognitive-behavioral psychotherapy, transcranial magnetic stimulation, and predictive biomarkers of response (Zarate et al., 2019). Such approaches may broaden the understanding of **individual response, therapeutic durability, and cost-effectiveness**, consolidating intranasal ketamine as a strategic component in the modern management of TRD.

Thus, although current evidence supports the efficacy and safety of intranasal esketamine, the dataset still requires **methodological standardization, prolonged follow-up, and integration with personalized psychiatry models**, ensuring its rational and safe incorporation into clinical practice.

4 CONCLUSION

Integrative analysis of the available evidence demonstrates that **intranasal ketamine**, particularly in its formulation with the enantiomer **S-ketamine (esketamine),** represents one of the most significant therapeutic innovations in the management of **treatment-resistant depression (TRD).**

Results from multicenter clinical trials and systematic reviews indicate **rapid, consistent, and clinically meaningful antidepressant efficacy**, with response observed within 24

hours of administration and sustained effects over weeks or months, especially when combined with conventional antidepressants.

The **safety and tolerability profile** observed in the short- and long-term studies is favorable, with predominantly mild and transient adverse events, such as dissociation, dizziness, and mild elevation of blood pressure, with no evidence of severe systemic toxicity, dependence, or progressive pharmacologic tolerance. These findings reinforce that, when administered under medical supervision and in controlled protocols, intranasal esketamine can be considered a **safe, effective, and well-tolerated therapeutic alternative** for patients with refractory TRD to traditional monoaminergic therapies.

However, relevant **methodological and clinical gaps** persist . Heterogeneity in study designs, lack of dose standardization, and limited long-term follow-up data restrict generalizability of results. In addition, the paucity of direct comparative research between **esketamine and other glutamatergic modulators**, as well as the lack of **biomarkers of therapeutic response**, still preclude the definition of robust evidence-based personalized protocols.

Thus, it is recommended that future investigations prioritize: (a) **clinical trials of longer duration** and diversified samples, (b) **models of therapeutic combination** involving psychotherapy and neuromodulation, (c) **studies of cost-effectiveness** and functional impact, and (d) **translational research** aimed at elucidating neurobiological mechanisms of action.

In summary, the current body of evidence indicates that **intranasal esketamine represents a significant advance in the pharmacotherapy of TRD**, with the potential to redefine clinical paradigms in modern psychiatry.

However, the consolidation of its role as a first-line treatment depends on **long-term trials, methodological standardization, and incorporation into integrated therapeutic strategies**, capable of combining efficacy, safety, and personalization of mental health care.

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