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INTRANASAL ESKETAMINE IN TREATMENT-RESISTANT DEPRESSION: WHY DO REAL-WORLD CLINICAL PRACTICE OUTCOMES SURPASS THOSE OF CLINICAL TRIALS? A NARRATIVE REVIEW

ESKETAMINA INTRANASAL NO TRATAMENTO DA DEPRESSÃO RESISTENTE AO TRATAMENTO: POR QUE OS DESFECHOS DA PRÁTICA CLÍNICA DO MUNDO REAL SUPERAM OS DOS ENSAIOS CLÍNICOS? UMA REVISÃO NARRATIVA

ESKETAMINA INTRANASAL EN EL TRATAMIENTO DE LA DEPRESIÓN RESISTENTE AL TRATAMIENTO: ¿POR QUÉ LOS RESULTADOS DE LA PRÁCTICA CLÍNICA DEL MUNDO REAL SUPERAN LOS DE LOS ENSAYOS CLÍNICOS? UNA REVISIÓN NARRATIVA

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ABSTRACT

Intranasal esketamine was approved for the treatment of treatment-resistant depression on the basis of randomized clinical trials whose effects, when pooled in meta-analyses, were of modest magnitude. In contrast, observational studies conducted in routine clinical practice have reported substantial symptom reductions and increasing remission rates over follow-up. This review aimed to critically analyze the discrepancy between the efficacy observed in clinical trials and the effectiveness described in real-world studies, discussing the

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methodological, clinical and pharmacological factors that may explain it. This is a narrative literature review, with searches in the PubMed/MEDLINE, Scopus, Web of Science and Cochrane Library databases, covering publications from 2019 to 2026 and selecting twelve core references, including pivotal trials, meta-analyses, prospective cohorts and retrospective studies. The evidence shows that clinical trials yielded modest differences relative to the comparator, largely because the control group also received a new oral antidepressant and because placebo response in ketamine and esketamine studies is high. In real-world studies, the absence of a control group, therapeutic expectation, patient selection, dose flexibility and loss to follow-up tend to inflate effect sizes, although these settings also reveal progressive functional gains and benefits in populations excluded from trials. It is concluded that the apparent superiority of clinical practice outcomes should not be interpreted as evidence of greater efficacy, but rather as a reflection of different designs and questions. The critical integration of both sources, combined with controlled comparative studies and the monitoring of functional outcomes, is necessary to guide the rational use of esketamine in treatment-resistant depression.

Keywords: Esketamine. Treatment-resistant Depression. Real-world Evidence. Clinical Trials. Placebo Effect. Psychopharmacology.

RESUMO

A esketamina intranasal foi aprovada para o tratamento da depressão resistente ao tratamento com base em ensaios clínicos randomizados cujos efeitos, quando agrupados em metanálises, foram de magnitude modesta. Em contraste, estudos observacionais conduzidos na prática clínica de rotina relataram reduções substanciais de sintomas e taxas crescentes de remissão ao longo do seguimento. Esta revisão teve como objetivo analisar criticamente a discrepância entre a eficácia observada em ensaios clínicos e a efetividade descrita em estudos do mundo real, discutindo os fatores metodológicos, clínicos e farmacológicos que possam explicá-la. Trata-se de uma revisão narrativa da literatura, com buscas nas bases de dados PubMed/MEDLINE, Scopus, Web of Science e Cochrane Library, abrangendo publicações de 2019 a 2026 e selecionando doze referências principais, incluindo ensaios pivotais, metanálises, coortes prospectivas e estudos retrospectivos. A evidência mostra que os ensaios clínicos produziram diferenças modestas em relação ao comparador, largamente porque o grupo controle também recebeu um novo antidepressivo oral e porque a resposta ao placebo em estudos com cetamina e esketamina é alta. Em estudos do mundo real, a ausência de um grupo controle, a expectativa terapêutica, a seleção de pacientes, a flexibilidade de dose e a perda durante o seguimento tendem a inflar os tamanhos de efeito, embora esses contextos também revelem ganhos funcionais progressivos e benefícios em populações excluídas dos ensaios. Conclui-se que a aparente superioridade dos resultados da prática clínica não deve ser interpretada como evidência de maior eficácia, mas sim como reflexo de desenhos e questões diferentes. A integração crítica de ambas as fontes, combinada com estudos comparativos controlados e o monitoramento de desfechos funcionais, é necessária para orientar o uso racional da esketamina na depressão resistente ao tratamento.

Palavras-chave: Esketamina. Depressão Resistente ao Tratamento. Evidência do Mundo Real. Ensaios Clínicos. Efeito Placebo. Psicofarmacologia.

RESUMEN

La esketamina intranasal fue aprobada para el tratamiento de la depresión resistente al tratamiento sobre la base de ensayos clínicos aleatorizados cuyos efectos, cuando se agrupan en metaanálisis, fueron de magnitud modesta. En contraste, los estudios observacionales realizados en la práctica clínica de rutina han informado reducciones sustanciales de síntomas y tasas crecientes de remisión durante el seguimiento. Esta revisión tuvo como objetivo analizar críticamente la discrepancia entre la eficacia observada en ensayos clínicos y la efectividad descrita en estudios del mundo real, discutiendo los factores metodológicos, clínicos y farmacológicos que pueden explicarla. Se trata de una revisión narrativa de la literatura, con búsquedas en las bases de datos PubMed/MEDLINE, Scopus, Web of Science y Cochrane Library, cubriendo publicaciones de 2019 a 2026 y seleccionando doce referencias principales, incluyendo ensayos pivotales, metaanálisis, cohortes prospectivas y estudios retrospectivos. La evidencia muestra que los ensayos clínicos produjeron diferencias modestas respecto al comparador, en gran medida porque el grupo control también recibió un nuevo antidepresivo oral y porque la respuesta al placebo en estudios con ketamina y esketamina es alta. En estudios del mundo real, la ausencia de un grupo control, la expectativa terapéutica, la selección de pacientes, la flexibilidad de dosis y la pérdida durante el seguimiento tienden a inflar los tamaños de efecto, aunque estos contextos también revelan ganancias funcionales progresivas y beneficios en poblaciones excluidas de los ensayos. Se concluye que la aparente superioridad de los resultados de la práctica clínica no debe interpretarse como evidencia de mayor eficacia, sino como reflejo de diseños y cuestiones diferentes. La integración crítica de ambas fuentes, combinada con estudios comparativos controlados y el monitoreo de resultados funcionales, es necesaria para orientar el uso racional de esketamina en la depresión resistente al tratamiento.

Palabras clave: Esketamina. Depresión Resistente al Tratamiento. Evidencia del Mundo Real. Ensayos Clínicos. Efecto Placebo. Psicofarmaología.

1 INTRODUCTION

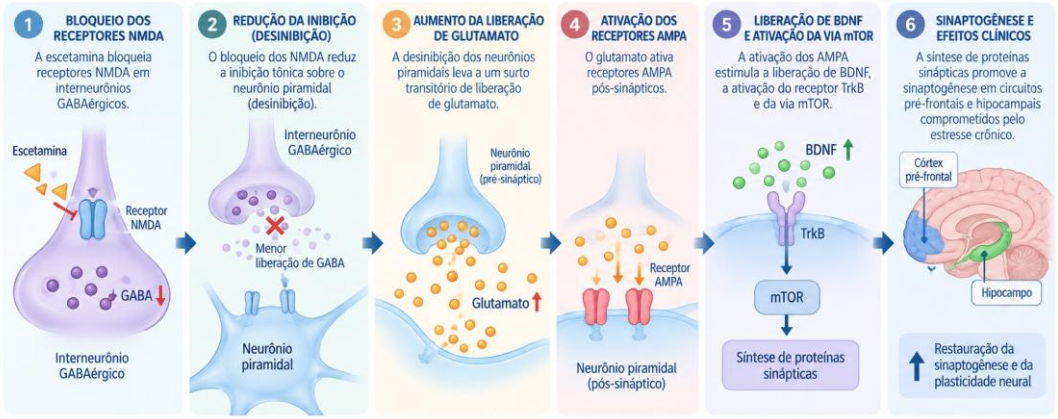
Treatment-resistant depression, most commonly defined as the lack of an adequate response to at least two antidepressants at adequate dose and duration in the current episode, is one of the most complex situations in clinical psychiatry. These patients accumulate prolonged suffering, functional impairment, greater use of health services and an increased risk of suicide, which makes the search for therapeutic strategies with mechanisms distinct from those of monoaminergic antidepressants a priority for both clinical care and research.

In this context, esketamine, the S-enantiomer of ketamine, was approved in an intranasal formulation for use in combination with an oral antidepressant in adults with treatment-resistant depression. Approval was based mainly on phase 3 trials, such as TRANSFORM-2, which evaluated the induction phase (Popova *et al.*, 2019), and SUSTAIN-1, which investigated relapse prevention (Daly *et al.*, 2019). Subsequently, the ESCAPE-TRD trial compared esketamine with extended-release quetiapine, both combined with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, providing an active comparator relevant to clinical practice (Reif *et al.*, 2023).

Unlike classic antidepressants, esketamine acts primarily as a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor. The most widely accepted model proposes that preferential blockade of these receptors on GABAergic interneurons reduces tonic inhibition of pyramidal neurons, producing a transient increase in glutamate release. This glutamate activates AMPA receptors, triggering the release of brain-derived neurotrophic factor (BDNF), activation of the mTOR pathway and synthesis of synaptic proteins, with restoration of synaptogenesis in prefrontal and hippocampal circuits impaired by chronic stress (Zanos; Gould, 2018). This mechanism helps explain the rapid antidepressant response observed in some patients, as shown in Figure 1.

Figure 1

Proposed mechanism of action for the antidepressant effect of esketamine



Source: prepared by the authors based on Zanos and Gould (2018).

Several years after approval, a considerable body of observational studies conducted in routine services in different countries has accumulated. These studies, often referred to as real-world evidence, describe broad symptom reductions and increasing remission rates over follow-up (Martinotti *et al.*, 2022; Lapa *et al.*, 2026). At the same time, a recent meta-analysis of clinical trials concluded that the benefit of esketamine as an adjunct is modest, comparable to augmentation strategies with atypical antipsychotics, and with no demonstrated effect on suicidality itself (Fountoulakis; Saitis; Schatzberg, 2025).

This apparent contradiction has practical implications. Clinicians and health managers need to decide whether esketamine should occupy an earlier place in the treatment algorithm, how to justify its cost and how to inform patients about realistic expectations of response. Accordingly, this narrative review aims to critically analyze the discrepancy between the efficacy observed in clinical trials and the effectiveness reported in real-world studies of intranasal esketamine in treatment-resistant depression, discussing the methodological, clinical and pharmacological factors that may explain it.

2 METHODOLOGY

This is a narrative literature review, designed to gather, analyze and critically interpret evidence on the use of intranasal esketamine in treatment-resistant depression, focusing on the comparison between the results of clinical trials and those of real-world observational

studies. The guiding question was structured according to the PICo strategy, with P (Population) being adults with treatment-resistant depression; I (Interest) the use of intranasal esketamine and its outcomes in terms of efficacy, effectiveness, functioning and safety; and Co (Context) controlled clinical trials and routine clinical practice. Based on these components, the following question was formulated: why do the results reported in real-world clinical practice with intranasal esketamine appear superior to those observed in clinical trials, and how should this difference be interpreted?

The search was conducted in the PubMed/MEDLINE, Scopus, Web of Science and Cochrane Library databases, using controlled descriptors and free-text terms related to esketamine, intranasal esketamine, treatment-resistant depression, real-world evidence, effectiveness, randomized controlled trial and placebo response, combined using the Boolean operators AND and OR and adapted to the specificities of each database. The strategy prioritized studies reporting symptomatic, functional or safety outcomes, as well as analyses discussing the external validity of trials and the role of placebo response.

The time frame covered the period from 2019, the year of the regulatory approval of intranasal esketamine, to 2026, so as to include the pivotal trials and the most recent real-world studies. Studies published in Portuguese, English and Spanish were considered. Earlier publications could be used only as conceptual background, when considered essential for understanding the mechanism of action or the representativeness of clinical trial samples.

Randomized clinical trials, systematic reviews with meta-analysis, prospective and retrospective cohort studies and reviews of the mechanism of action that addressed esketamine in treatment-resistant depression in adults and provided information relevant to at least one of the axes of the review were included. Editorials, letters to the editor, isolated case reports, exclusively preclinical studies with no application to the clinical argument and studies on other indications, such as postpartum or perioperative depression, were excluded. Selection was performed by reading titles and abstracts, followed by full-text analysis of potentially eligible studies. In the end, twelve references were selected as central to support the thematic axes of the review.

3 RESULTS

The pivotal trials established the efficacy of esketamine within a specific design: all participants started a new oral antidepressant, and the comparator group received this antidepressant combined with a placebo spray. In TRANSFORM-2, esketamine combined with the new antidepressant produced a significantly greater reduction on the Montgomery-Åsberg Depression Rating Scale (MADRS) after four weeks, but the mean difference relative to the comparator was approximately four points, with response rates of 69.3% versus 52.0% (Popova *et al.*, 2019). In SUSTAIN-1, maintenance esketamine meaningfully reduced the risk of relapse among patients in stable remission and among stable responders (Daly *et al.*, 2019). ESCAPE-TRD, in turn, demonstrated a higher remission rate at week eight with esketamine than with quetiapine, 27.1% versus 17.6%, in an open-label trial with blinded raters (Reif *et al.*, 2023).

When these and other trials were pooled in a systematic review with meta-analysis including 87 studies, effect sizes between weeks two and four ranged from 0.15 to 0.23, considered weak but significant, and similar to those obtained with atypical antipsychotic augmentation; no specific effect on suicidality was demonstrated (Fountoulakis; Saitis; Schatzberg, 2025). A meta-analysis focusing on placebo response in ketamine and esketamine trials showed that this component may account for up to 72% of the total response observed in the treated group, which narrows the difference between arms even when patients' absolute improvement is large (Matsingos *et al.*, 2024).

In the field of real-world clinical practice, the picture is different. The systematic review with meta-analysis of observational studies, with searches up to April 2025 and nine included studies, found a pooled effect size of Hedges' g = -1.98, with no significant influence of sex or of comorbidities such as anxiety, personality disorders and substance use; adverse events were frequent, with dissociation reported in about half of patients (Lapa *et al.*, 2026). The Italian multicenter REAL-ESK study had already described the effectiveness and good tolerability of esketamine in routine services, with a progressive reduction in depressive symptoms during the first months of treatment (Martinotti *et al.*, 2022).

Studies published after the window of that meta-analysis broaden the picture. The French prospective ELLIPSE cohort followed adults who started esketamine under real-world conditions for twelve months and described a median of three prior treatment lines, lower

than in earlier cohorts, suggesting progressively earlier use of the drug (Llorca *et al.*, 2026). A multicenter prospective study of 60 patients showed, at the end of six months, symptomatic remission rates of 46.7% and functional remission rates of 33.3%, the latter achieved more slowly and inversely associated with the number of prior antidepressant trials and with baseline functional disability (Guglielmo *et al.*, 2026). A retrospective cohort in a community clinic compared intranasal esketamine and intravenous ketamine, observing response rates of 64.9% and 69.2%, respectively, large within-group reductions and over 90% completion of the induction phase, with no significant difference between formulations (Bellanti *et al.*, 2026).

Taken together, the studies allow the evidence to be organized into five axes: the magnitude of effect in controlled trials, the role of placebo response and study design, symptomatic effectiveness in the real world, the trajectory of functional and long-term outcomes, and the safety and tolerability profile. To provide a systematized overview of the methodological characteristics and main contributions of each study, the selected studies are presented in Table 1, with authorship, objective, design, population and main findings.

Table 1

Summary of the studies included in the narrative review on intranasal esketamine in treatment-resistant depression

Author(s) / Year	Objective	Design	Population / Setting	Main findings and contributions
Zimmerman; Mattia; Posternak, 2002	To determine whether participants in pharmacological trials for depression are representative of patients in routine clinical practice.	Outpatient observational study	Outpatients with major depression assessed according to typical trial criteria	A large proportion of patients seen in routine care would be excluded from trials due to comorbidities, severity or other criteria, limiting the external validity of controlled results.
Zanos; Gould, 2018	To review the mechanisms of the antidepressant action of ketamine and its enantiomers.	Mechanistic review	Preclinical and clinical evidence	Described the pyramidal neuron disinhibition hypothesis, with a glutamate surge, AMPA receptor activation, BDNF release, mTOR activation and synaptogenesis.
Popova *et al.*, 2019	To evaluate the efficacy and safety of flexibly dosed esketamine combined with a new oral antidepressant (TRANSFORM-2).	Randomized, double-blind, controlled clinical trial	Adults with treatment-resistant depression	Esketamine superior to comparator at four weeks, with a mean difference of about four points on the MADRS; comparator with a high response rate.
Daly *et al.*, 2019	To evaluate esketamine for relapse prevention (SUSTAIN-1).	Randomized withdrawal clinical trial	Adults in stable remission or response after induction	Maintenance esketamine meaningfully reduced the risk of relapse in stable remitters and responders.
Martinotti *et al.*, 2022	To describe the effectiveness and safety of esketamine in routine services (REAL-ESK).	Multicenter observational study	Patients with treatment-resistant depression in Italy	Progressive symptom reduction in the first months and good tolerability, with predominantly transient adverse effects.
Reif *et al.*, 2023	To compare esketamine with extended-release quetiapine (ESCAPE-TRD).	Randomized, open-label clinical trial with blinded raters	Adults with treatment-resistant depression	Higher remission at week eight with esketamine (27.1% versus 17.6%) and more patients relapse-free through week 32.

Author(s) / Year	Objective	Design	Population / Setting	Main findings and contributions
Matsingos *et al.*, 2024	To quantify placebo response in ketamine and esketamine trials.	Systematic review with meta-analysis	Double-blind trials in major depression	High placebo response, possibly accounting for up to 72% of the total response, which compresses the difference between arms.
Fountoulakis; Saitis; Schatzberg, 2025	To synthesize the efficacy, effect on suicidality and adverse effects of esketamine.	Systematic review with meta-analysis (PRISMA)	87 studies included	Weak but significant effect (0.15 to 0.23), similar to that of atypical antipsychotics; no demonstrated effect on suicidality.
Lapa *et al.*, 2026	To synthesize real-world evidence on intranasal esketamine.	Systematic review with meta-analysis of observational studies	Nine studies of adults with treatment-resistant depression	High pooled effect size (g = -1.98), increasing remission over follow-up, dissociation in about half of patients; caution due to the absence of controls.
Llorca *et al.*, 2026	To describe the profile, patterns of use and outcomes at twelve months (ELLIPSE).	Multicenter prospective cohort	Adults with unipolar major depression in France	Earlier use in the treatment sequence (median of three prior lines) and effectiveness and safety data at twelve months.
Guglielmo *et al.*, 2026	To describe symptomatic and functional trajectories over six months.	Multicenter prospective cohort	60 patients with treatment-resistant depression	Symptomatic remission of 46.7% and functional remission of 33.3% at six months; functional remission slower and lower in patients with more prior trials.
Bellanti *et al.*, 2026	To compare induction outcomes with intranasal esketamine and intravenous ketamine.	Retrospective cohort in a community clinic	63 adults with treatment-resistant depression	Response rates of 64.9% and 69.2%, large within-group reductions and high induction completion, with no significant difference between formulations.

Source: prepared by the authors based on the studies included in the review.

4 DISCUSSION

The main question raised by this review is not whether esketamine works, but why the magnitude of benefit appears so different depending on the type of study. The most consistent answer is that controlled trials and real-world studies answer different questions. A trial

measures the incremental effect of the drug relative to a comparator, whereas an observational study measures the patient's total change over time, adding together the effect of the medication, regression to the mean, the natural history of the episode, therapeutic expectation and the effect of the care that accompanies treatment.

The design of the pivotal trials contributed to narrowing the difference between arms. Because all participants started a new oral antidepressant and received structured follow-up, the comparator group also improved substantially (Popova *et al.*, 2019). Added to this is the high placebo response documented in ketamine and esketamine studies (Matsingos *et al.*, 2024). An additional aspect is imperfect functional blinding: transient dissociative effects make it easier for patients and raters to identify allocation, which may both inflate and distort estimates. The result is a modest incremental effect that does not necessarily reflect individual clinical experience (Fountoulakis; Saitis; Schatzberg, 2025).

In real-world studies, these mechanisms act in the opposite direction. The absence of a control group prevents the pharmacological effect from being separated from nonspecific components, and pre-post treatment effect sizes tend to be large by construction (Lapa *et al.*, 2026). Esketamine is administered in a supervised setting, with frequent sessions, regular contact with the care team and high expectations because it is a new therapy with restricted access. Patients who discontinue treatment due to lack of efficacy or intolerance usually drop out of the analyses, which favors the retention of responders, and flexibility in dose, frequency and duration allows adjustments that the fixed protocols of trials do not accommodate (Martinotti *et al.*, 2022).

It would be a mistake, however, to reduce real-world findings to a methodological artifact. The populations treated in routine care differ from those included in trials, with more comorbidities, polypharmacy and chronicity, and a substantial proportion of these patients would never be eligible for a controlled trial (Zimmerman; Mattia; Posternak, 2002). The fact that effectiveness was not moderated by anxiety comorbidities, personality disorders or substance use (Lapa *et al.*, 2026) suggests that the benefit may extend to groups underrepresented in the pivotal studies. In addition, observational studies follow patients for longer periods and reveal trajectories that four-week trials do not capture, such as late remission and progressive functional recovery (Guglielmo *et al.*, 2026; Llorca *et al.*, 2026).

The functional dimension deserves emphasis. The partial dissociation between symptomatic improvement and functional recovery, observed over six months of follow-up, indicates that symptom scales alone may overestimate or underestimate the benefit perceived by patients in their daily lives (Guglielmo *et al.*, 2026). The association between a greater number of prior antidepressant trials and a lower likelihood of functional remission is also consistent with the trend toward earlier use of esketamine described in the French cohort (Llorca *et al.*, 2026), reinforcing the hypothesis that the timing of treatment initiation influences the outcome. This hypothesis, however, still requires confirmation in comparative studies.

Comparisons with other strategies help calibrate expectations. By comparing esketamine with quetiapine, ESCAPE-TRD offered a contrast closer to real clinical decision-making than placebo-controlled trials (Reif *et al.*, 2023). The community cohort that compared intranasal esketamine and intravenous ketamine suggested similar results between formulations, but the small sample size and differences between protocols preclude any conclusion of equivalence (Bellanti *et al.*, 2026). Regarding safety, the high frequency of dissociation and other adverse events in the real world (Lapa *et al.*, 2026), although generally transient, reinforces the need for structured monitoring, especially during prolonged use.

Some limitations should be considered. As this is a narrative review, study selection did not follow a systematic protocol and may reflect the authors' choices. A substantial proportion of real-world studies are open-label, lack a control group and may involve conflicts of interest related to the manufacturer, and definitions of response, remission and resistance vary across publications. Pragmatic randomized trials, target trial emulations using clinical databases and prospective registries with standardized functional outcomes are promising ways to bring the two sources of evidence closer together.

5 CONCLUSIONS

Intranasal esketamine shows statistically proven but modest efficacy in clinical trials, and substantial effectiveness in real-world clinical practice studies. This difference stems mainly from the fact that the two types of study measure different quantities: on the one hand, the incremental effect of the drug relative to an active comparator or to a placebo with a high response; on the other, the total clinical change under conditions of intensive and supervised care.

Real-world results should not be read as proof of superior efficacy, but neither should they be dismissed. They expand knowledge about populations excluded from trials, about the medium-term functional trajectory and about real patterns of use and safety. For clinicians, the most useful message is that esketamine may benefit a relevant proportion of patients with treatment-resistant depression, provided there is careful selection, realistic expectations, monitoring of symptoms and functioning, and attention to adverse effects.

Gaps remain regarding the optimal timing of initiation, predictors of response, direct comparison with other third-line strategies and the effects of prolonged use. Controlled comparative studies, pragmatic designs and prospective registries with standardized functional outcomes are needed to turn the apparent contradiction between trials and clinical practice into an integrated evidence base that is useful for decision-making.

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