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Use of Esketamine in the Treatment of Depression: A Systematic Review of Clinical Evidence

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ABSTRACT

Introduction: Depression is a highly prevalent psychiatric condition and considered one of the leading causes of disability worldwide, affecting millions of individuals across different age groups and social contexts. Esketamine, a ketamine derivative, has emerged as a promising option for the treatment of resistant depression.

Objective: To synthesize the available evidence on the use of esketamine in depressed patients, focusing on its efficacy, safety, and possible limitations.

Methods: This study is a systematic review, classified as exploratory and descriptive. The research was carried out through bibliographic research in electronic databases on methods associated with SLR (Systematic Literature Review) and applications of SMARTER (*Simple Multi-Attribute Rating Technique using Exploiting Rankings*).

Results: A comprehensive systematic search of the literature yielded a total of 1270 articles related to the topic addressed, of which 34 articles were eligible to compose this systematic review.

Conclusion: With the advancement of research and the adaptation of health structures, the estimate has the potential to transform the management of resistance depression, significantly improving quality of life.

KEYWORDS: Esketamine, Treatment, Depression

ARTICLE DETAILS

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INTRODUCTION

Depression is a highly prevalent psychiatric condition and considered one of the main causes of disability in the world, affecting millions of individuals in different age groups and social contexts (KIELING et al., 2024; MARX et al., 2023). Its impact goes beyond psychological symptoms, interfering with the social, professional, and family functioning of patients (AASS et al., 2022; YANG et al., 2022). Although traditional treatments, such as antidepressants and psychotherapy, have proven effective for a large part of the population, a significant number of patients present resistance or inadequate response to these therapies, configuring the condition of treatment-resistant depression (TRD). This scenario challenges health professionals to seek new approaches to manage the disease (MCINTYRE et al., 2023; VOINESKOS; DASKALAKIS; BLUMBERGER, 2020).

Esketamine, a derivative of ketamine, has emerged as a promising option for the treatment of resistant depression. Ketamine is a dissociative anesthetic that, at subanesthetic doses, has shown rapid antidepressant effects, which has led to its investigation as a potential therapy for mood disorders. Unlike traditional antidepressants, which can take weeks to show effects, esketamine has been shown to provide significant symptom relief within hours of administration, making it a viable alternative in high-risk cases, such as patients with severe depression and suicidal ideation (DEL SANT, 2023).

Esketamine was approved by the United States Food and Drug Administration (FDA) in 2019 for the treatment of treatment-resistant depression, administered via nasal spray in a supervised clinical setting. This advance generated great expectation in the medical community, especially due to its rapid action and because it acts on different pathways than those addressed by traditional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) (BRUNONI; HAMANI; QUEVEDO, 2024). However, despite the promising results, esketamine still raises concerns about its long-term safety and side effects associated with its continued use, such as dissociation and elevated blood pressure, which require rigorous monitoring (AURÉLIO et al., 2024; TAVARES et al., 2024).

In addition to promising results, esketamine has stood out for its action on a neurobiological mechanism distinct from traditional antidepressants (TAVARES et al., 2024). The substance is mainly an antagonist of the N-methyl-D-aspartate (NMDA) receptor, which is involved in the modulation of glutamate, one of the main excitatory neurotransmitters in the brain (MOLERO et al., 2022). This innovative mechanism enables a rapid response to depressive symptoms, especially in patients with treatment-resistant depression. According to Elisabetsky et al. (2021), the use of esketamine can rapidly reverse dysfunctional neuronal circuits related to depression, offering a new therapeutic avenue for patients who do not present disorders with conventional therapies.

Despite advances, the use of esketamine also poses significant challenges, especially related to its safety profile. Dissociation, increased blood pressure, and potential risk of abuse are side effects that interrupt specific monitoring during treatment. Supervised use of esketamine in a clinical setting is a necessary measure to minimize these risks (DEL SANT, 2023; RATO, 2022). Furthermore, there are uncertainties regarding its long-term efficacy, since most studies to date have focused on short-term results. Therefore, it is essential that future research explore the impact of esketamine in long-term treatments and further investigate its side effects and the sustainability of its benefit (RATO, 2022).

Advances in the treatment of treatment-resistant depression (TRD) have expanded therapeutic options, bringing hope to patients who do not find relief with conventional methods (MALLEY; TANAKA, 2023). Although innovative therapies, such as esketamine and other neuromodulation approaches, have shown promising results, it is essential that future research continues to investigate their safety, efficacy, and long-term effects (JAGTIANI, 2024; TAMMAN; ANAND; MATHEW, 2022). The challenge remains in balancing clinical benefits with potential risks, ensuring that patients receive individualized, effective, and safe care that can significantly improve their quality of life.

In this context, this systematic review aims to summarize the available evidence on the use of esketamine in depressed patients, focusing on its efficacy, safety, and possible limitations. Understanding the benefits and risks associated with the use of esketamine is essential for developing clinical guidelines that ensure the safe and effective treatment of patients with resistant depression, offering a viable alternative for those who do not find a response to conventional treatments.

METHODS

This study is a systematic review, classified as exploratory and descriptive. The research was carried out through bibliographic research in electronic databases on methods associated with SLR (Systematic Literature Review) and applications of SMARTER (*Simple Multi-Attribute Rating Technique using Exploiting Rankings*). The work carried out is of a qualitative and quantitative nature. The qualitative analysis of the data was carried out intuitively and inductively during the survey of the theoretical framework. It is also quantitative by employing the multicriteria method. In addition, there is also a numerical experimental study in order to simulate a situation of article selection based on the observed criteria.

The bibliographic research was carried out in the following databases: *Web of Science; Science Direct; Wiley; Springer Link; Taylor and Francis and PubMed*. In addition, searches were carried out using bibliographic references of studies that addressed the topic in a relevant manner on the *Google Scholar* search platform.

The search in the databases was performed using terminologies registered in the Health Sciences Descriptors created by the Virtual Health Library, developed from the *Medical Subject Headings of the US National Library of Medicine*, which allows the use of common terminology in Portuguese, English and Spanish. The present study sought to investigate the literature on the use of esketamine in the treatment of depression. For this purpose, the descriptors “esketamine”, “treatment” and “depression” were used, initially in English, and complementary in Spanish and Portuguese.

As a tool to support decision-making in the selection and prioritization of articles, a set of criteria were considered essential to represent the state of the art of the research topic. This method has the following characteristics: (i) rigorous logic allows the method to be accepted as a decision-making

support tool; (ii) simple to understand and apply, with results that are easy to interpret.

References of selected papers were also searched for other documents of potential interest. Once eligible for full text in the evaluation, articles were included in the qualitative review if they met the following inclusion criteria: a) contained data on esketamine; b) contained data on the use of esketamine in depression. Articles were excluded if they were reports, banners or conference abstracts. There was no review of confidential health information and the study was not interventional. Therefore, ethics committee approval was not required. In the end, the result obtained totaled 34 articles that contemplated the desired characteristics for the study.

Four independent researchers extracted data from articles that met the inclusion criteria and entered them into a Microsoft Excel-generated "data extraction form" on the use of esketamine in patients with depression. From this form, the authors and year of publication, study abstract, study type, outcome measure, limitations, and conclusions of the main studies selected were included, as shown in Table 1.

RESULTS

A comprehensive systematic literature search yielded a total of 1270 articles on the use of esketamine in patients with depression. Of these, 525 studies were excluded due to overlapping data. From this, the SMARTER (*Simple Multi-Attribute Rating Technique using Exploiting Rankings*) method was chosen and 98 articles that were suitable for full-text screening were selected, of which 54 articles were included for data extraction, of which 20 were excluded by the exclusion criteria, making 34 articles eligible for inclusion in the systematic review. In Figure 1, we describe the selection strategy of articles on the topic in question.

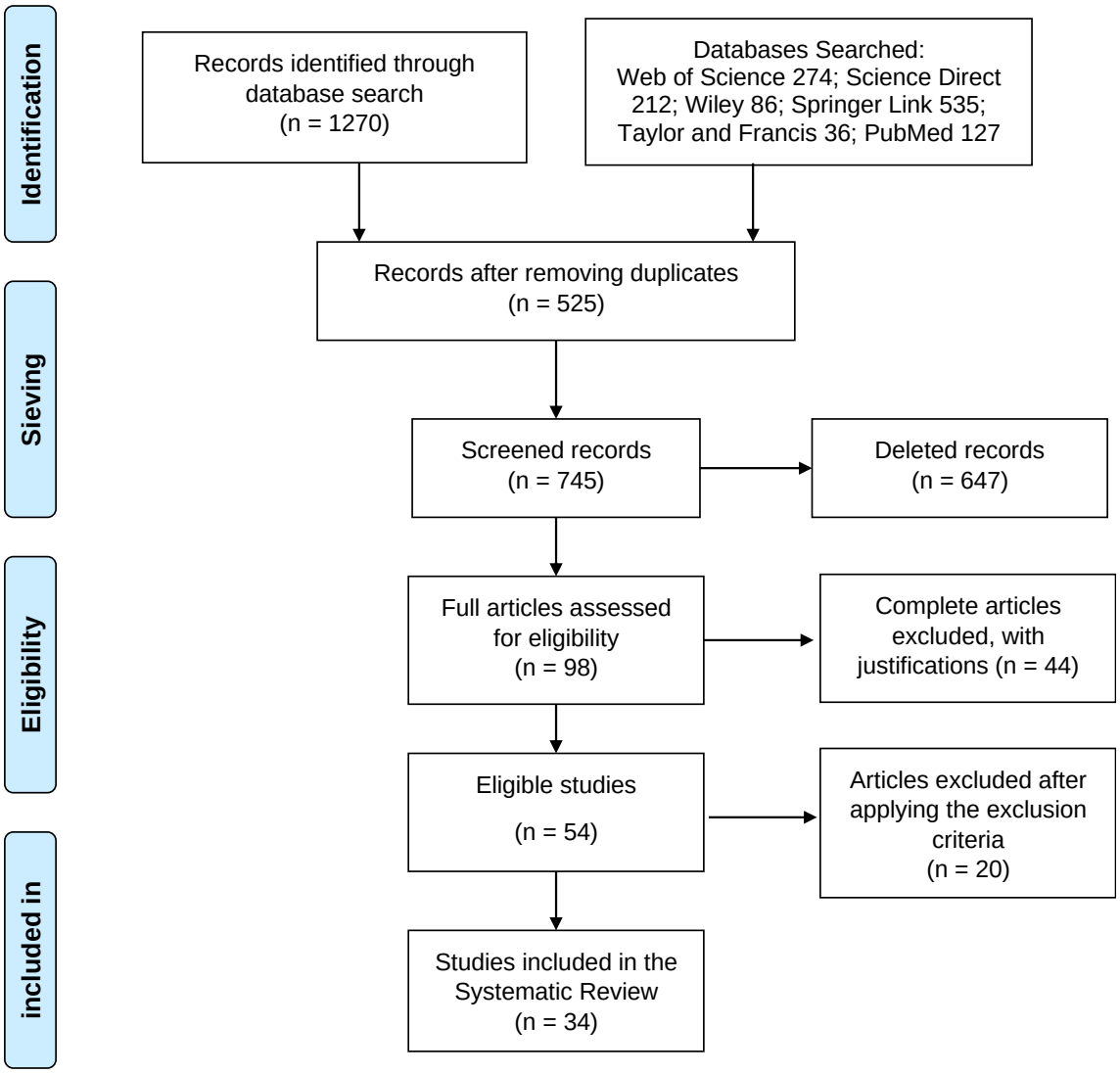

Figure 1. Article search strategy
Source: Authors (2024)

Table 1: Main selected studies and their findings

Author/Year	Summary	Type of study	Measured result	Limitations	Conclusions
Cook; Halaris (2022)	Complex mechanisms of action of esketamine and the need of further research to understand them completely.	Revision Meta-analysis	Investigation of the mechanisms of action and adaptation of networks neuronal.	Current understanding still limited and need for further research.	Understanding more in-depth can open paths to new approaches in treatments for depression.
Krystal; Kavalali; Monteggia (2024)	The study investigates the effectiveness of esketamine in patients with resistant depression.	Studies Controlled	Evaluation of effectiveness inlong term and response totreatment.	Individual response to esketamine can vary and requires monitoring.	Revitalization of interest in esketamine as an option innovative therapy.
PETTORRUSO et al. (2023)	Identifying the need for biomarkers to predict the response to esketamine and improve treatment personalization.	Clinical research	Response evaluation varied in different patients.	Limitations in studies prior to identify biomarkers specific.	Research needed to develop better treatment strategies.
JIANG et al. (2023)	Adverse reactions and the importance of monitoring during esketamine treatment.	Randomized Clinical Study	Identification and reporting of more serious side effects that may arise.	Lack of data on the frequency and severity in different populations.	Monitoring and communication about effects collaterals are crucial for the patient safety.
CEBAN et al. (2021)	Dissociation as an effect side effects of esketamine, which may include depersonalization and derealization.	Review of Literature	Frequency and intensity of dissociation and other effects collaterals.	Variation in response individual to treatment and side effects.	Dissociation is generally transient, but should be carefully monitored.
CHEN et al. (2022)	Investigation of the side effects of esketamine, including particularities in the perception of reality.	Review Of Literature	Details about the dissociation experience and others effects.	Quite a few variations subjective that may affect the generalization of results.	Dissociation is part of the mechanism of action of esketamine, what should it be considered in the treatment.
CHEVALIER et al. (2024)	Effects characteristics side effects of esketamine in diverse populations and scenarios clinical.	Study Observational	Assessment of the incidence of side effects in different patient profiles	Limitations in the sample and complexity of variables involved.	It is crucial to understand the incidence of side effects to adjust treatment appropriately.
MAWERE-MUBVUMBI (2023)	Report of other side effects of esketamine, such as sedation and visual changes, in addition to variation in response between patients.	Case study	Analysis of adverse reactions in different administrations.	Need for follow-up continuous and evaluation of clinical history of patients.	Dose individualization and controlled environment is essential for treatment safe.
FROM SÁ (2022)	Importance of an environment safe and qualified professional for the administration of esketamine and treatment of adverse reactions.	Guidelines for Clinical Practice	Security protocols and Strategies monitoring.	Variability in adverse reactions of according to the context clinical and treatment.	Protocols must ensure the patient safety during treatment

Source: Authors (2024)

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Author/year	Summary	Type of study	Measured result	Limitations	Conclusions
LANGMIA et al. (2022)	Pharmacogenetics can optimize esketamine treatment, allowing customization of dosage and identification of predictive biomarkers.	Study of Pharmacogenetics	Custom selection of dose and prediction of response to treatment.	Studies are lacking longitudinal studies confirming initial findings.	Pharmacogenetics represents significant potential for improving efficacy and safety of esketamine treatment.
VASILIU (2023)	Esketamine provides rapid relief from depressive symptoms, reducing the risk of suicide and improving the quality of life in the short term.	Revision Clinical Studies	Analysis of clinical efficacy in the short term.	Dose individualization still needs to be further explored in scenarios varied.	Esketamine is an option valuable therapeutics for high risk patients of suicide due to its rapid action.
ROTHÄRMEL et al. (2022)	Discussion on titration careful dose of esketamine and combination with psychotherapy to optimize results.	Study of Intervention	Efficacy of combining esketamine and psychotherapy in minimizing effects collaterals.	The formatting of the treatment individualized can be challenging depending on the patient.	Psychotherapy combined with esketamine may increase the chances of success in treatment of depression.
D'ANDREA et al. (2023)	In-depth exploration of the mechanisms of action of esketamine and need for research for understanding complete.	Revision Meta-analysis	Investigation of complexities of the mechanisms of action.	Current research is fragmented and precise be more integrated.	A more understanding comprehensive of mechanisms of action of esketamine can lead to new strategies therapeutics.
JOHNSTON; ZARATE JR; KVARTA (2024)	Analysis of future possibilities in the use of esketamine in antidepressant treatments.	Study Prospective	Projections on the future of esketamine as treatment.	Data is missing on large adaptation scale in several populations.	The future of esketamine looks promising, but it needs more studies to confirm its effectiveness in different contexts.

Source: Authors (2024)

DISCUSSION

The systematic review carried out consistently demonstrates the efficacy of esketamine in rapidly and significantly reducing depressive symptoms, especially in patients who have not responded to other therapies.

One of the most remarkable aspects of esketamine is its speed of action. While traditional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), can take weeks or even months to produce clinically significant effects, esketamine demonstrates a much faster onset of action, as it interacts with NMDA receptors, modulating glutamatergic neurotransmission. This interaction triggers a series of changes in neuronal connections, promoting rapid adaptation of brain networks involved in mood regulation (HALARIS; COOK, 2023). This accelerated synaptic plasticity is what allows esketamine to alleviate depressive symptoms in a short period of time. This characteristic is of great clinical value, as it reduces the risk of suicide and significantly improves the quality of life of patients in the short term (HALARIS; COOK, 2023; KRYSTAL; KAVALALI; MONTEGGIA, 2024; VASILIU, 2023).

Although studies have demonstrated sustained improvement in some patients, the need for maintenance doses and the identification of biomarkers predictive of treatment response are areas that require further investigation (PETTORRUSO et al., 2023).

However, the possibility of more serious adverse reactions requires careful monitoring during drug administration. It is crucial that patients are informed about the possible side effects of esketamine before starting treatment. This way, they can be prepared for these reactions and seek medical advice in case of any concerns (JIANG et al., 2023).

One of the most characteristic side effects of esketamine is dissociation, an alteration in the perception of reality that can include a feeling of unreality, depersonalization and derealization. This experience,

although uncomfortable for some, is usually transient and is part of the drug's mechanism of action (CEBAN et al., 2021; CHEN et al., 2022; CHEVALIER et al., 2024).

In addition to dissociation, esketamine can cause sedation, nausea, vomiting, increased blood pressure, dizziness, vertigo, visual changes and, in some cases, anxiety and hallucinations. The intensity and frequency of these adverse reactions may vary depending on the dose administered, the route of administration, the patient's clinical history and their individual sensitivity to the drug. (MAWERE-MUBVUMBI, 2023).

It is important to emphasize that most adverse reactions to esketamine are transient and usually improve spontaneously. However, it is essential that patients are closely monitored during and after esketamine administration, especially in the first doses. Treatment with esketamine should be carried out in a safe and controlled environment, with health professionals trained to deal with possible adverse reactions (DE SÁ, 2022).

The dose of esketamine should be individualized and carefully titrated for each patient, starting with low doses and gradually increasing as tolerated. Combining esketamine with psychotherapy can help minimize side effects and optimize treatment outcomes (ROTHÄRMEL et al., 2022).

Esketamine, a drug that has revolutionized the treatment of resistant depression, has a complex and diverse mechanism of action (COOK; HALARIS, 2022) . Although its effectiveness is evident, understanding exactly how it acts on the brain is still a challenge for researchers.

The complexity of esketamine's mechanisms of action makes it clear that further research is needed to uncover all its secrets. This more complete understanding will allow the development of new therapeutic strategies and the optimization of esketamine treatment (D'ANDREA et al., 2023; JOHNSTON; ZARATE JR; KVARTA, 2024).

At the same time, pharmacogenetics is emerging as a promising field for personalizing esketamine treatment. Pharmacogenetics studies how an individual's genetic variations influence their response to medications. By analyzing a patient's genetic profile, it is possible to identify which genes are involved in the metabolism of esketamine and the response to its effects. This personalized approach will allow the selection of the ideal dose and the choice of the most appropriate therapeutic regimen for each patient, maximizing the efficacy of the treatment and minimizing side effects. In addition, pharmacogenetics can help identify biomarkers that predict the response to treatment and the durability of the effects of esketamine (LANGMIA et al., 2022).

The identification of genetic polymorphisms that influence drug response may allow the selection of patients who are most likely to benefit from therapy and the optimization of doses. However, further studies are needed to elucidate the mechanisms of action, optimize doses and identify the best predictors of response. In addition, it is essential to develop strategies to minimize adverse effects and ensure safe and effective access to treatment (CORREIA, 2021).

From a regulatory perspective, esketamine was already approved by the FDA in the United States for the treatment of ESRD in 2019, and by other agencies around the world (BARBOSA et al., 2023). However, the high cost of esketamine and the need for administration supervised by health professionals, due to its potential for adverse effects, are barriers to its more widespread use. Health and insurance systems are still developing policies to make this treatment more accessible and sustainable in the long term. This involves creating guidelines on the frequency of administration, patient monitoring, and adequate financial coverage to ensure that more people can benefit from treatment without facing significant economic obstacles (CARVALHO; PIMENTA; SIMEONI, 2022).

Furthermore, there is a need to balance safety aspects, such as clinical oversight, with oversight of large-scale implementation, especially in resource-limited countries. This may involve developing new treatment models that reduce costs associated with administration, such as less intensive oversight protocols for long-term use cases, as long as patient safety is guaranteed. Expanding access to esketamine will therefore depend on collaboration between regulatory bodies, health systems, and manufacturers to overcome these practical and economic barriers (CARVALHO; PIMENTA; SIMEONI, 2022) .

Its rapid action and effectiveness in patients refractory to conventional treatments position it as an important therapeutic option. Although esketamine represents a promising advance in the treatment of treatment-resistant depression, its widespread use still faces challenges related to accessibility, safety and cost, requiring continuous research and regulatory adjustments to enhance its therapeutic potential and expand its reach in a sustainable way. However, more research is needed to explore the full potential of esketamine and ensure its safe and effective use in clinical practice.

FINAL CONSIDERATIONS

The use of esketamine in the treatment of depression represents a significant innovation, offering a therapeutic alternative for patients who do not obtain adequate responses with conventional antidepressants. Its innovative and potentially transformative role in the management of a condition that historically presents significant challenges in terms of response to conventional treatments. However, the need for close monitoring due to its potential adverse effects, such as dissociation and elevation of blood pressure, as well as the risk of abuse, underlines the importance of its controlled use in a supervised clinical setting.

Furthermore, the high cost of treatment and the need for specific infrastructure for its administration limit its accessibility to a larger portion of the population. This

reinforces the importance of health policies that integrate a broader approach, balancing cost-benefit and expanding access, especially in developing countries and in public health systems.

Esketamine represents a paradigm shift in the treatment of resistant depression, offering an effective and rapid alternative for patients who do not respond to traditional treatments. However, its large-scale implementation requires a multidisciplinary approach that considers both clinical aspects and economic and accessibility barriers. The success of its integration will depend on ongoing safety assessment, the creation of more comprehensive reimbursement policies, and ensuring that its use is guided by well-defined protocols. With advances in research and adaptation of health structures, esketamine has the potential to transform the management of resistant depression, significantly improving quality of life.

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