RESEARCH PAPER

Comprehensive Systematic Review of Esketamine Nasal Spray as a Standalone Rapid-Acting Treatment for Treatment-Resistant Depression: Integrating Clinical Trial Data and Emerging Real-World Evidence on Efficacy, Safety, And Relapse Prevention

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ABSTRACT
Major depressive disorder, or MDD, is a common cause of disability around the world. Treatment-resistant depression, or TRD, is a tough challenge. Many people do not respond well to treatment, which increases the risk of relapse and suicide. Esketamine is a new treatment that comes as a nasal spray. It works quickly and targets a specific brain receptor. This review looks at research from trials and real-world studies to see how well esketamine works, how safe it is, and if it helps prevent relapse when used alone.Research shows that esketamine reduces depressive symptoms more effectively than a placebo and other treatments like quetiapine. Many patients felt better within days, and some benefits lasted for weeks or even months after stopping treatment. Most side effects, like dizziness, nausea, and changes in blood pressure, were mild to moderate. These effects usually went away within two hours after taking the drug. There were no serious side effects or deaths reported. Also, gathering patient feedback during treatment helped doctors create better care plans.Some studies had small sample sizes, and there was not much information on long-term effects beyond 12 months. Still, the evidence suggests that esketamine is a fast-acting, effective, and mostly safe treatment for TRD. Ongoing phase 3 studies will help understand the best dosages and long-term results. Esketamine is an important step forward for patients who struggle with treatment-resistant depression.

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INTRODUCTION

Major depressive disorder (MDD) is linked to excessive morbidity and mortality and is the primary cause of disability globally in terms of the total number of years lost as a result of disability.[1]Approximately 30% of individuals with serious depression do not experience remission even after taking many antidepressants, and they are regarded as to experience depression that is resistant to therapy.[2] MDD treatment options are restricted by their poor response rates, early beginning of side effects, and delayed initiation of action. [3] Treatment-resistant depression (TRD) is the clinical term used to describe the subgroup of MDD patients who do not respond well to two or more antidepressants with appropriate dosage and duration.TRD is linked to an elevated risk of hospitalization, suicide, and future relapse.[4] Antidepressant-responsive individuals usually experience side effects over a period of weeks, during which they continue to research glutamatergic N-methyl-D-aspartate (NMDA) receptor modulators as a depression treatment. [2] Recently, esketamine, an N-methyl-d-aspartate receptor antagonist and the S-enantiomer of ketamine racemate, was authorized for use as a nasal spray to treat treatment-resistant depression (TRD).[5] It controls neurotrophic signaling by acting as a non-selective, non-competitive antagonist of the NMDA receptor, an ionotropic glutamate

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receptor. It may also restore synaptic function linked to mood and emotional behavior regulation.[6] This systematic review is important. Treatment-resistant depression (TRD) is a major problem. It affects about 30% of people with major depressive disorder. This type of depression costs a lot to treat and often leads to bad outcomes. We need to understand TRD better to help those who suffer from it.[7] Many people taking traditional antidepressants find that they do not work well. This shows that there is a strong need for new treatments. These new therapies should work quickly and help those who are struggling.[8] Esketamine nasal spray works differently than traditional antidepressants. It targets a specific receptor in the brain called the NMDA receptor. Clinical trials show that it can quickly help people feel better. Real-world evidence supports these findings as well. People using esketamine often experience a better response to treatment. They also have higher rates of remission and lower chances of relapse compared to those using standard treatments.[9] Even though it has been approved and is used more often, we still need to combine and carefully assess both clinical trial data and real-world evidence. This is important to fully understand how well it works, how safe it is, and what the long-term benefits are when used alone for treatment-resistant depression (TRD). This review will help fill that gap. It will give doctors and other important people useful, evidence-based information. This way, they can improve treatment strategies and help patients get better results.[7] This systematic review aims to comprehensively synthesize existing evidence on the efficacy, safety, and relapse prevention potential of esketamine nasal spray when used as a standalone, rapid-acting intervention for TRD. By integrating data from randomized controlled trials (RCTs) and real-world observational studies, this review seeks to evaluate the therapeutic promise of esketamine beyond adjunctive use, offering a nuanced perspective on its standalone viability in diverse clinical settings.

2 METHODS:

2.1 SEARCH STRATEGY

We carefully reviewed all the articles about managing chronic diseases and pharmacist intervention. We searched four databases: Web of Science, EMBASE, Scopus, and PubMed. We used specific phrases like "Pharmacist Intervention" and "Chronic Disease Management" to find relevant articles. On PubMed, we used Medical Subject Headings (MeSH) terms. For EMBASE, we used Emtree terms. We selected the studies based on the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). This process helped us find the most important research on this topic.

2.2 STUDY SELECTION:

2.2.1 INCLUSION CRITERIA:

- ✓ Patients with Treatment-Resistant Depression (TRD) are diagnosed using DSM-5 or ICD-10 criteria.
- ✓ Esketamine nasal spray is given as a standalone treatment.
- ✓ Different types of studies are used. These include Randomized Controlled Trials (RCTs), open-label trials, cohort studies, and real-world evidence studies. A systematic review combines results from these studies.
- ✓ Only studies published in English are considered.
- ✓ They must have been published within the last 10 years.

2.2.2 EXCLUSION CRITERIA

- ✓ We Excluded case reports, editorials, narrative reviews, and commentaries.
- ✓ We did not include studies that involved kids or teenagers under 18.
- ✓ We also excluded studies that used animals.
- ✓ If a study combined esketamine with an oral antidepressant, we left it out too.
- ✓ Finally, we only considered studies that were published in English.

2.3 DATA EXTRACTION

The authors gathered important information for the systematic review. They looked at the authors' names, the year the studies were published, and the characteristics of the populations involved. They also examined how effective esketamine nasal spray is as an antidepressant. They noted how quickly it works, its safety profile, and how well patients tolerate it. All relevant data was collected. Two authors, D.P. and A.G., reviewed the extracted data for any errors. If they found any discrepancies, they discussed them and reached an agreement.

2.4 DATA ANALYSIS

Each study included a description of its findings. When we had similar outcome data from two or more trials, we combined that data. We knew that differences in methods and clinical practices might affect the results. Because of this, we used a random effects model for the meta-analysis. We created a single comparison by combining similar studies that had multiple parts. For continuous outcomes, we reported the results as mean differences along with a 95% confidence interval.

2.6 STUDY PROTOCOL REGISTRATION

The study protocol was registered with PROSPERO CRD420251041128

RESULTS:

3.1 STUDY CHARACTERISTICS:

We found 46 papers in total. We looked at 30 of them more closely. We removed 23 papers based on our exclusion criteria. This left us with 7 publications to evaluate for relevance. Out of these, 2 had unclear methods and not enough data. Additionally, 1 article gave results that were not relevant. In the end, we had 4 articles that met our standards.(Figure.1)

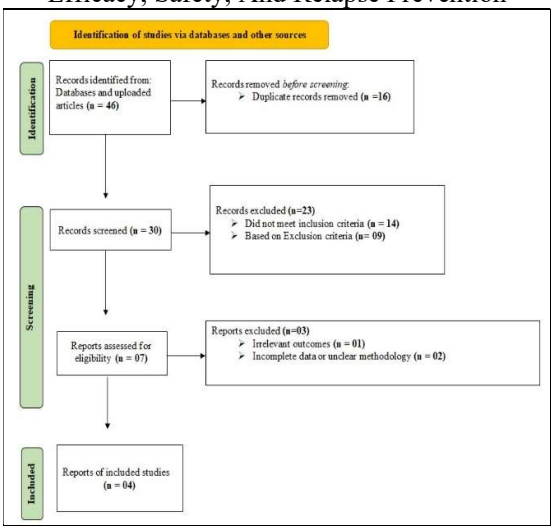

Figure.1 Prisma Flowchart

STUDY (YEAR)	TYPE OF STUDY	POPULATION CHARACTERISTICS	ANTIDEPRESSANT EFFECTS OF ESKETAMINE NASAL SPRAY	SAFETY PROFILE AND TOLERABILITY OF ESKETAMINE	OUTCOMES
Ella J et.al., (2017)	A Randomized Clinical Trial	Total 67 participants , 33 for placebo and 34 esketamine.	With faster, longer-lasting response and remission rates, particularly at higher doses, esketamine demonstrated bigger, dose-dependent reductions in MADRS scores than placebo. These gains persisted throughout the open-label and follow-up periods.	With no reports of psychosis or fatalities, individuals receiving esketamine had moderate, temporary dizziness, headache, dissociation, and blood pressure rises that peaked 30 to 40 minutes after the dosage and subsided within two hours.	Strong, long-lasting effectiveness in treating TRD was demonstrated by intranasal esketamine (28–84 mg); bigger trials are now being conducted to determine the best frequency and duration of dosage.
Madeline Brendle et.al., (2021)	retrospective cohort study	171 TRD patients	Treatment-resistant depression responds well to intranasal esketamine.	Esketamine demonstrated high tolerability; for 99% of patients, dissociation went away in two hours, resolving concerns regarding treatment time commitment in the clinic and validating REMS monitoring standards.	The substantial disease burden of TRD and the efficacy of esketamine treatment in reducing anxiety and depression symptoms without raising serious safety concerns are

					both demonstrated in this research.
Andreas Reif et.al., (2023)	Open-label, randomized, active-controlled trial	Esketamine was given to 336 individuals, whereas quetiapine was given to 340.	Using an intention-to-treat methodology, the trial evaluated recurrence through week 32 and MADRS-based remission at week 8. Alternative remission criteria were also employed for comparison with esketamine studies.	Esketamine and quetiapine groups had adverse events in 91.9% and 78.0% of cases, respectively; severe events occurred in 5.7% and 5.1% of cases, with two serious events linked to esketamine and none for quetiapine.	Compared to quetiapine, esketamine demonstrated higher rates of remission (27.1% vs. 17.6%) and relapse-free rates (21.7% vs. 14.1%), as well as safety profiles that were in line with established therapeutic effects and stronger MADRS improvement.
Maria Pepe et.al., (2023)	Not mentioned	25 TRD patients	Intranasal esketamine shows greater efficacy for treatment-resistant depression.	After receiving esketamine, patients had moderate, temporary nausea, elevated blood pressure, and dissociation. These symptoms peaked at 40 minutes and went away with observation, with the degree of dissociation diminishing over the course of consecutive sessions.	Overall, patient and clinician perceptions aligned after three months of ESK-NS therapy demonstrated successful in TRD patients; adding patient comments may improve clinical evaluations and personalised care.

DISCUSSION:

This review looked closely at how well intranasal esketamine works for people with treatment-resistant depression (TRD). The researchers included various types of studies, such as randomized controlled trials and real-world studies. They found that esketamine consistently helped reduce depression symptoms quickly and had manageable side effects.

All the studies showed that patients had significant improvements in their depression scores compared to those who received a placebo or other medications like quetiapine. Ella J. et al. (2017) found that higher doses of esketamine led to faster and lasting improvements, even after treatment stopped. Similarly, Andreas Reif et al. (2023) showed that esketamine had better rates of remission and fewer relapses compared to quetiapine, proving it works well in real-life situations.

The safety of esketamine was also a positive point. Most side effects, like dizziness, nausea, and temporary increases in blood pressure, were mild to moderate. They usually went away within two hours. Serious side effects were rare, and there were no reports of psychosis or deaths. Madeline Brendle et al. (2021) noted that 99% of patients felt their dissociative symptoms go away within two hours, which supports the monitoring requirements of the REMS program.

Studies, such as the one by Maria Pepe et al. (2023), also considered patient views. Both patients and doctors mostly agreed on the effectiveness of esketamine after three months. Listening to patient feedback can help tailor treatment plans, making sure that both symptom relief and side effects are considered in decisions about care.

Some studies show promising results for intranasal esketamine. However, there are some limitations to consider. Some studies had small sample sizes. Also, we lack long-term data beyond 8 to 12 months. Differences in how studies were designed, patient types, and dosing schedules can affect how we apply these findings to everyone.

Overall, the evidence suggests that intranasal esketamine works well as a quick and tolerable option for treating treatment-resistant depression (TRD). Future research is important. Ongoing phase 3 trials will help us find the best dosing schedules. They will also help us understand long-term effects and how to prevent relapse. This research will help us use esketamine effectively for different groups of patients.

CONCLUSION:

Intranasal esketamine is a new treatment for patients with depression that doesn't respond to other therapies. It works quickly and can keep symptoms from coming back. Many studies show that esketamine is more effective than a placebo or other treatments. Patients still feel the benefits even after stopping the treatment. Most side effects are mild and go away quickly, which makes it safe to use at home with proper monitoring. Listening to patients about their experiences can help doctors create better treatment plans. Although there is strong evidence supporting esketamine, more large studies are needed. These studies will help us understand how to use esketamine better and make sure its benefits last over time

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