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# ESKETAMINE AND DEEP BRAIN STIMULATION IN TREATMENT-RESISTANT DEPRESSION: A LITERATURE REVIEW

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**ABSTRACT**

**Background:** Depression is a significant mental health condition affecting numerous individuals worldwide, leading to disability within society and posing a heightened risk of suicide, thereby diminishing overall quality of life. Depression, often a contributing factor in suicides, is associated with various prevalent medical conditions such as obesity, diabetes, stroke, Parkinson's disease, and multiple sclerosis. Treatment-resistant depression (TRD) affects approximately 30% of patients with major depressive disorder.
**Aim of the study:** This study aims to assess the efficacy of modern depression treatments such as intranasal esketamine administration and deep brain stimulation.
**Material and methods:** A review of literature was conducted using several scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. Only articles in English were included for further analysis. The keywords used were: “depression”, “esketamine”, “ketamine”, and “deep brain stimulation”. Ultimately, 30 articles were selected for analysis.
**Results:** Intranasal esketamine has shown promising results, including improved well-being and alleviation of symptoms, although caution is advised in patients with hypertension. While deep brain stimulation is traditionally used for movement disorders like Parkinson's disease, recent findings suggest its potential as a viable treatment for severe depression. Long-term studies indicate that both approaches effectively facilitate remission of depression.
**Conclusions:** Depression poses a significant threat to individuals' health and well-being, necessitating a comprehensive treatment approach. Tailored strategies encompassing pharmaceutical interventions, surgical procedures, and psychotherapy can collectively contribute to substantial improvements in daily functioning and reduce the risk of suicidal behaviors.

**KEYWORDS**

Depression, Esketamine, Ketamine, Deep Brain Stimulation

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## Introduction

Depression is a serious mental illness affecting many patients around the world. It is responsible for disability in society and is associated with a high risk of suicide, as well as reducing the quality of life [1,27]. Symptoms often recur, and there are periods of remission and aggravation of the disease [28,29]. Some of the more notable symptoms include a consistently depressed mood, recurrent thoughts of death and suicide, feelings of worthlessness, social isolation, and anhedonia, which lead to a significant reduction in overall quality of life [2,30]. Depression, a prominent factor in suicides, is linked to numerous prevalent medical conditions, including obesity, diabetes, stroke, Parkinson's disease, and multiple sclerosis. It also elevates the likelihood of Alzheimer's disease and sudden cardiac death [3]. TRD occurs in up to about 30% of patients with major depressive disorder. It can be diagnosed if at least 2 treatment attempts fail. Special attention should be paid to these patients, as each failed treatment attempt reduces the chance of achieving remission [4]. Patients with TRD are at special risk because suicide attempts are much more common in them than in those with treatment-responsive depression [5]. Resistance may appear in the form of lingering depressive symptoms post-treatment, along with diminishing efficacy during ongoing treatment. Options for managing escalating resistance are constrained and typically entail persisting with existing modalities such as combining, augmenting, or changing medications, introducing electroconvulsive therapy (ECT), or experimenting with alternative neurostimulation methods. However, these approaches carry the potential for complications, including heightened toxicity associated with increased medication doses or combination therapies [3].

## Aim of the study

The aim of this study was to systematically analyze contemporary therapeutic strategies for depression by reviewing current literature on the use of intranasal esketamine, ketamine, and deep brain stimulation. This review sought to assess their effectiveness, safety profiles, practical clinical value, and potential roles in treating patients with treatment-resistant depression.

## Methodology

This study was designed as a narrative literature review focusing on modern treatment methods for depression. A comprehensive search of the scientific literature was conducted across multiple electronic databases, including PubMed, Scopus, Web of Science, Google Scholar, and the Cochrane Library. The search covered publications available up to date. Only articles published in English and presenting original research, systematic reviews, meta-analyses, or clinically relevant case studies were considered for inclusion. A combination of medical subject headings (MeSH) and free-text terms was used to identify relevant publications. The primary keywords included: “depression”, “esketamine”, “ketamine”, and “deep brain stimulation”. Boolean operators such as AND and OR were applied to refine the search (e.g., “depression AND esketamine”, “treatment-resistant depression OR ketamine”). Titles and abstracts were screened for relevance, and full texts of potentially eligible studies were subsequently evaluated. Studies were included if they met the following criteria: (1) focused on pharmacological, neuromodulation, or device-based modern treatments for depression; (2) involved human participants; and (3) provided measurable clinical outcomes related to depressive symptom improvement or treatment safety. Exclusion criteria were: (1) articles not available in English, (2) animal or in vitro studies, (3) publications lacking sufficient methodological detail, and (4) conference abstracts without accessible full text. After applying these criteria, 30 articles were selected for final analysis. Data extracted from each study included sample characteristics, intervention type and dosage, study design, primary outcomes, and reported adverse effects. Findings were synthesized narratively, with emphasis on therapeutic efficacy, safety, and emerging clinical considerations.

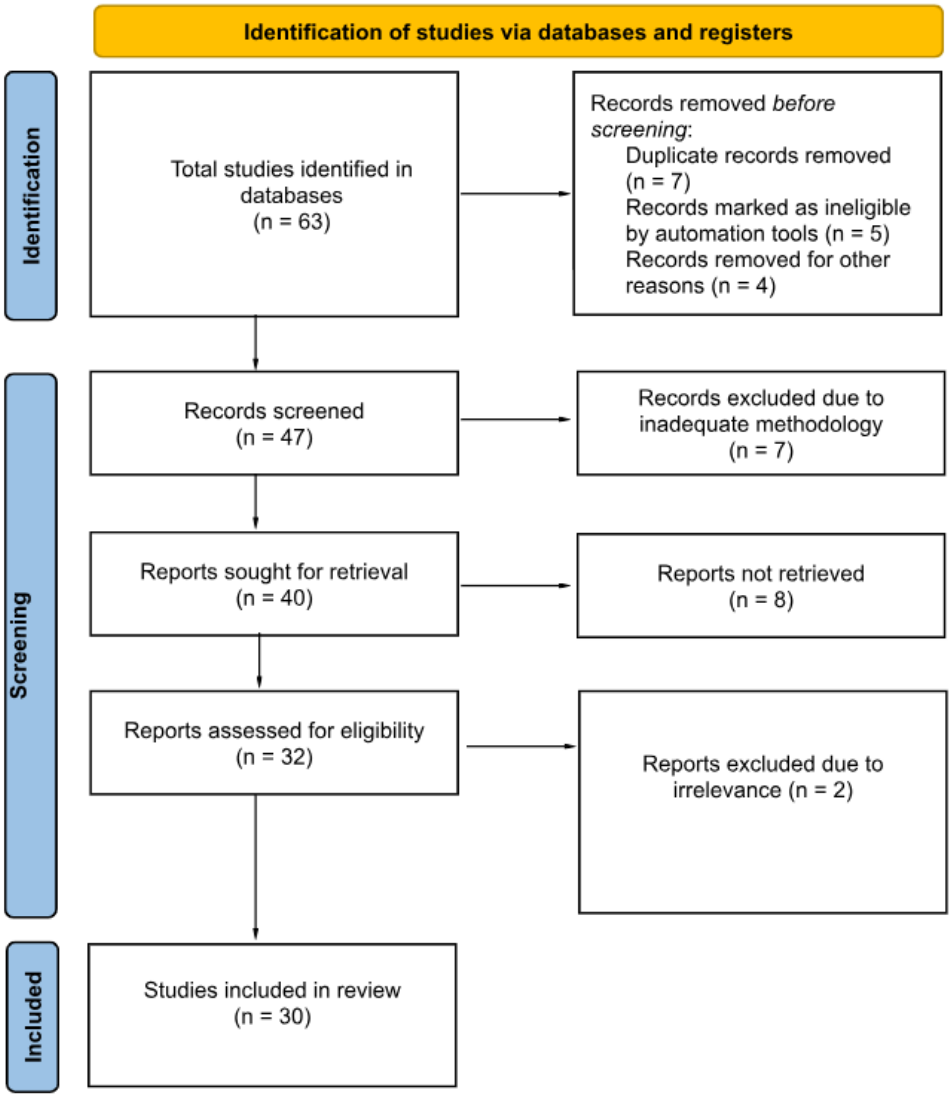


**Fig. 1.** PRISMA flowchart for conducting the literature search.

**Results**

ESKETAMINE/KETAMINE

Esketamine is the S-enantiomer of the racemate ketamine and an N-methyl-d-aspartate receptor antagonist that was recently approved as a drug for administration as a nasal spray for the treatment of TRD [6,7,8,9]. Esketamine administered intravenously and intranasally, along with oral antidepressant therapy, yielded rapid and robust reductions in TRD symptoms along with controllable tolerance. These were short-term studies, so long-term safety has not been established. Potential risks associated with long-term use of esketamine include cognitive deficits, bladder toxicity with interstitial/ ulcerative cystitis, hepatotoxicity, and substance dependence. A study conducted by Wajs E, Aluisio L, Holder R, et al. [10] was designed to evaluate the safety, tolerability, and efficacy of esketamine nasal spray and a new oral antidepressant to empirically validate its long-term use in patients with TRD. A total of 1,161 patients were studied, and 802 of them were included in the study. At the end of the study, 364 patients had been dosed for 6 months and 136 for 12 months. The average age at the start of the study was 52.2 years, 62.6% of the patients were female, and 85.5% were Caucasian. A baseline dose of 28mg was given to patients for 4 weeks. Then, after evaluating efficacy, the next dosage was redetermined. The most commonly reported side effects were dizziness, dissociation, nausea, and headache. Symptoms were mild and usually resolved within a day of drug administration. No cases of drug-seeking, overdose, or abuse of esketamine were observed, and patients did not ask for an increase in the frequency of dosing intervals (other than those specified in the protocol) or an increase in the dose of esketamine. One patient had his dose reduced because of moderate-intensity tachycardia, which was assessed as possibly esketamine-related and which resolved within 5 days. Urinary symptoms were judged to be

unrelated to esketamine intake. Acute hypertension occurred in 4% of patients, which was more common in those with a history of hypertension. Due to low blood pressure, the dose was reduced or temporarily inhaled in six patients. Four patients were withdrawn from the study due to hypertension. Patients showed no significant laboratory changes, ECG changes, or respiratory depression. Cognitive functions were not altered. The most commonly reported "withdrawal" symptoms in Week 1 were fatigue, lethargy, and lack of energy, with insomnia at the endpoint. G. Katz et al. [11], using data from five phase III trials, attempted to determine the benefit-risk ratio of using esketamine with oral antidepressants in the treatment of TRD. Benefits were to include improved quality of life in relation to remission or response to treatment, while risks were related to death, suicidal thoughts, the most common side effects (dissociation, dizziness, nausea, sedation, headache, dizziness, dysgeusia, hypoesthesia, elevated blood pressure, anxiety, and vomiting) and potential long-term risks (cognitive impairment and interstitial cystitis). The study showed that treatment response and remission were achieved in more patients treated with esketamine in combination with an antidepressant compared to treatment with antidepressants alone. Serious side effects of the drug (mainly dissociation, vertigo, and dizziness), leading to cessation of treatment continuation, were more common with esketamine in combination with antidepressants than with antidepressants alone. However, differences in the incidence of side effects were related to the day of dosing, and the day after dosing, symptoms were similar. No cases of interstitial cystitis were reported. The incidence rate of suicidal thoughts was not significantly different in the two groups compared, and cognitive function was maintained at a similar level. In the group of patients older than 65 years, remission and response outcomes were similar, but there was a slightly higher incidence of serious side effects of the drug and the resulting discontinuation of treatment. Continuation of esketamine with an antidepressant after 16 weeks of therapy in patients with remission or response was associated with fewer relapses compared with discontinuation of therapy. Overdose, abuse, or drug-seeking behavior were not observed in any clinical trial, and the potential for abuse is addressed in a comprehensive risk reduction program. In a double-blind, randomized, multicenter placebo-controlled study conducted by Ionescu et al. [12] between June 2017 and April 2019, 47 research centers evaluated the response of patients with major depressive disorder between the ages of 18 and 64 to treatment with esketamine. The base dose was 28mg administered intranasally twice a week for 4 weeks. Patients taking esketamine experienced remission more often than those taking placebo. Blood pressure should be monitored, as a slight increase in blood pressure was noted after administration of the drug. It is also worth noting the problem of depression in minors. It is estimated that about 40% of patients in this group are refractory to SSRIs [13], and only half of them will respond to a change in treatment and psychotherapy [14]. It should be noted that relapse within a year is often observed in this population [15]. In a double-blind, randomized study conducted by B Dwyer et al. [16] ketamine was administered intravenously. Better symptom improvement was observed compared to intravenously administered midazolam. Slightly increased dissociative symptoms and hemodynamic changes could be observed after administration of the drug.

DEEP BRAIN STIMULATION

With the effects that deep brain stimulation has had on movement disorders in Parkinson's disease [17], researchers began to examine the effects of this treatment method on depression. Studies conducted on the effectiveness of this method have shown various results [18,19,20,21]. The effect of deep brain stimulation (DBS) on depression was studied by A. Sheth et al. in a 37-year-old patient with severe TRD [22]. The study used intracranial electroencephalography to create an individualized network analysis in TRD. This was to create the possibility of personalizing DBS therapy to symptomatic networks, which was expected to be associated with a higher probability of clinical success. First, 4 DBS leads were implanted intracranially - bilaterally the subcallosal cingulate (SCC) and the VC/VS and 10 sEEG electrodes. The DBS leads were externalized so that stimulation was possible. The sEEG electrodes targeted areas of the frontotemporal network associated with depression: bilateral dorsolateral prefrontal cortex, ventrolateral and ventromedial prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, and mesial temporal lobe. The patient was then continuously monitored for 9 days. After this time, another surgery was performed to remove the sEEG electrodes and internalize the DBS leads to the implanted pulse generators. Appropriate pacing parameters were then introduced, and an 8-month optimization period began. The next stage of the study was a double-blind trial in which stimulation was decreased. An increase of 25% in the Montgomery-Asberg Depression Rating Scale was observed over 2 consecutive visits, compared to the pre-withdrawal state, and the Clinical Global Impression - Improvement (CGI-I) scale score was 6 ("much worse"). Stimulation was conducted in single pulses or sequences of pulses lasting 1 second, 15 seconds, 5 minutes, and 20 minutes. The 1-second stimulation did not produce observable behavioral changes, but longer ones did. Effects of SCC stimulation included feelings of calmness and mental clarity. VC/VS effects were associated with increased talkativeness and a sense of being present. The patient reported improved mood and closer relationships with loved ones, increased concentration and productivity at work, and less anxiety during public speaking. Loved ones also noted improved health of the patient. The study by van der Wal et al. [23] attempted to evaluate the efficacy

and safety of DBS targeting the ventral anterior inner capsule (vALIC) in 25 patients with TRD during a one-year open-label maintenance treatment period that followed a one-year optimization period [24]. All patients were implanted with four-contact electrodes on both sides, with the lowest contact point in the seminiferous nucleus and three upper contact points in the vALIC. After surgery, patients proceeded to an open optimization phase, which lasted up to a year, followed by a double-blind, controlled crossover phase. Patients then proceeded to an open maintenance phase. During this period, the DBS setting was regularly evaluated and adjusted, and drug treatment or psychotherapy was introduced as needed. Of the 25 patients treated with DBS, 21 entered and 18 completed the maintenance phase. Of these 18 patients, 8 achieved a response to treatment, and 5 of the 8 achieved remission. Three patients experienced four serious side effects in the maintenance phase, but these cannot be directly linked to DBS. One patient experienced an increase in depressive symptoms and suicidal thoughts due to battery depletion, and improved several months after battery replacement. Ramasubbu et al. [25] in their study compared the efficacy and safety of short pulse width (SPW) and long pulse width (LPW) subcortical cortex DBS in depression. Patients diagnosed with major depressive disorder and bipolar depression were bilaterally implanted with DBS into the white matter of the cingulate cortex, and for six months 12 patients were stimulated with SPW and 10 with LPW. After this time, if no response to treatment was observed, patients were assigned to the opposite group for another 6 months. A significant reduction in symptoms was observed in both groups, but there were no significant differences between the groups. Side effects did not differ between groups (most commonly anxiety and depression severity). Another study by Brown et al. [26] examined the metabolic activity of the SCC as a predictor and marker of response to DBS treatment. DBS electrodes were implanted bilaterally into the white matter of the SCC. All patients underwent MRI and FDG-PET before surgery, and FDG-PET was performed again 6 months after the start of stimulation. FDG-PET measures the cerebral rate of glucose metabolism (CMRGlu). SPW was used in 11 patients and LPW in nine. The results of the study show that higher baseline SCC metabolic activity is associated with greater change in symptom severity. The mean CMRGlu value in SCC can accurately distinguish responders from non-responders with a precision of 80%, providing strong support for the use of CMRGlu in SCC as a potential biomarker of DBS treatment outcome in SCC.

**Table 1.** Summary of Clinical Studies, Outcomes, and Safety Profiles of Esketamine, Ketamine, and Deep Brain Stimulation in Treatment-Resistant Depression.

| Treatment | Common Side Effects | Serious / Rare Risks | Safety Considerations | Clinical Notes |
|---|---|---|---|---|
| **Intranasal Esketamine** | Dizziness, dissociation, nausea, headache | Acute hypertension (4%), tachycardia, potential cognitive deficits, bladder toxicity (long-term), hepatotoxicity | Monitor blood pressure, caution in patients with hypertension; administered under supervision | Rapid antidepressant effects; higher response and remission rates compared to antidepressants alone; no observed abuse, overdose, or drug-seeking behavior in clinical trials |
| **IV Ketamine** | Mild dissociative symptoms, transient hemodynamic changes | Limited long-term safety data; potential for substance misuse | Monitor cardiovascular status during infusion; avoid in patients with severe cardiovascular disease | Rapid symptom improvement, often within hours; effects can be temporary; particularly useful for suicidal ideation |
| **Deep-Brain Stimulation (DBS)** | Anxiety, transient depressive symptoms during parameter adjustment | Surgical risks, battery depletion, infection, hardware-related complications | Requires surgical implantation and long-term device management; stimulation parameters optimized individually | Effective in long-term TRD management; benefits may take weeks to months; combining with sEEG allows personalized network-targeted stimulation; LPW and SPW show similar efficacy and risk |

**Conclusions**

In conclusion, depression (especially treatment-resistant depression) is a serious problem in society, which poses a threat to the lives of patients suffering from it. It reduces the quality of life and hinders daily functioning. In order to improve the quality of life of patients suffering from depression, newer and more effective methods of achieving remission are being sought to ensure long-term improvement. One of these methods is intranasally applied esketamine. In studies, it has been shown to produce positive results, with depressive symptoms being less severe or the disease going into complete remission. Compared to classical antidepressants taken orally, esketamine has shown better results, with a higher percentage of patients responding to treatment. Side effects (mainly dissociation and dizziness) were not severe, tended to show low intensity, did not impede function, and disappeared on the same day the drug was administered. One concern was the risk of esketamine addiction. However, as the study showed, symptoms of addiction, overdose, or drug-seeking did not occur. An increase in blood pressure could be observed in some patients, so special attention should be paid to patients with ongoing hypertension.

The second discussed method is deep brain stimulation, which has also shown promising results in treating depression. Patients have reported improved well-being, and their symptoms have diminished or the disease has entered a stage of regression that has persisted for a long time. No serious side effects were noted that suggested a risk to patients. LPW and SPW stimulation were associated with similar risks and showed similar efficacy in reducing depressive symptoms. Research indicates that both adjusting pulse width and regulating amplitude may be crucial in enhancing clinical outcomes among patients grappling with TRD. When combined with sEEG, it has the extra advantage of bypassing the step of searching for parameters that will adequately respond to the treatment. Patients whose condition did not improve after the first year of therapy also failed to see improvement in the second year of treatment. However, an important limitation of DBS is the remoteness of the change in parameters and the noticeable effects of that change over time, unlike DBS for movement disorders, where changes are seen immediately.

In summary, the diverse approaches discussed in this review article, including esketamine and deep brain stimulation, offer valuable strategies to address the complex challenges posed by depression and its associated health risks. These interventions provide a multifaceted toolkit for healthcare practitioners and individuals seeking effective ways to manage the risks that come with depression, improve quality of life, and enhance overall well-being.

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