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Esketamine for Depression: From Therapeutic Characteristics to Efficacy and Safety

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Abstract:

More than 280 million individuals worldwide suffer from depression, which is one of the main causes of mental disability. It has multiple subtypes, and conventional treatments have limitations such as slow onset of action, high non-response rate, and numerous side effects. For instance, it takes two to six weeks for selective serotonin reuptake inhibitors (SSRIs) to start working, and about 30% of patients experience treatment resistance. These limitations make conventional treatments unable to meet clinical needs, especially failing to address the urgent intervention needs of patients at risk of suicide. As the S-enantiomer of ketamine, esketamine exhibits a stronger binding affinity for NMDA receptors compared to its counterpart (the R-enantiomer of ketamine, or racemic ketamine). It relieves depressive symptoms rapidly through a unique mechanism of action and can also reduce suicidal ideation. Esketamine has shown therapeutic potential in various subtypes of depression, including Major Depressive Disorder (MDD) with acute suicidal ideation or behavior, Postpartum Depression (PPD), Treatment-Resistant Depression (TRD), Bipolar Depression (BD), and Atypical Depression (AD). Moreover, the combination of esketamine with oral antidepressants can improve therapeutic efficacy. Future efforts should focus on evaluating its long-term safety and dependence risks, expanding its therapeutic indications, conducting research on special populations, and developing biomarkers for predicting treatment response. This paper reviews the development and characteristics of esketamine, as well as its therapeutic applications in different types of depression, providing a new perspective for depression treatment.

Keywords: Depression; Esketamine; Suicidal Ideation; Bipolar Depression; Postpartum Depression; Atypical Depression

1. Introduction

Depression ranks among the leading causes of mental disability globally, affecting over 280 million individuals worldwide. It exerts a more severe impact on females compared to males. The disorder typically manifests during adolescence and early adulthood, with a lifetime prevalence of 15%-30% in the general population on a global scale. The incidence of depression varies across different regions [1]. In essence, depression can be classified into distinct subtypes including Major Depressive Disorder (MDD), Treatment-Resistant Depression (TRD), Bipolar Depression (BD), Postpartum Depression (PPD), and Atypical Depression (AD).

The diversity of depressive subtypes and the large patient population contribute to the emergence of significant social and public health challenges. From a statistical perspective, depression is recognized as a leading cause of the disability-adjusted life years (DALYs) among psychiatric disorders. More critically, the rising prevalence of depression correlates positively with increased suicide rates. Approximately 700,000 suicides occur annually, with a majority of these cases linked to depression [2]. In practical terms, the economic burden associated with the depression treatment not only diminishes overall societal productivity but also increases the risk of long-term mental disability for affected individuals. Concurrently, families of patients often experience strained relationships and face substantial caregiving burdens, which can sometimes lead to difficult communication dynamics.

Although a large number of therapeutic interventions have been developed for depression, these methods remain limited in their effectiveness. Serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), for instance, usually need a prolonged course of treatment for two to six weeks in order to produce therapeutic effects. This delayed onset makes them unsuitable for urgent scenarios, such as managing patients at risk of suicide. Additionally, these medications exhibit a high non-response rate, with approximately 30% of patients demonstrating resistance to treatment, and they may cause gastrointestinal issues, weight gain, and sexual dysfunction, among other adverse effects. Against this backdrop, esketamine has emerged as a novel pharmaceutical agent, which offers a promising approach to alleviate or potentially resolve depressive symptoms.

2. Development and Characteristics of Esketamine

This context has led to the identification of esketamine as a revolutionary therapeutic agent for depression. Esketamine inhibits the NMDA receptor in a non-competitive manner [3]. Glutamate release is increased, which triggers the activation of AMPA receptors. In the end, this cascade improves neural plasticity, which helps depression symptoms go away. Simultaneously, esketamine promotes the release of neurotrophic factors, which stimulate neurogenesis and synaptic remodeling. Unlike conventional treatments rooted in the monoaminergic hypothesis, esketamine introduces a novel therapeutic paradigm for depression.

Based on current scientific understanding, esketamine possesses both advantages and limitations as a depression treatment. A major revolutionary trait of esketamine lies in its fast-acting nature—therapeutic effects can be detected within hours, as opposed to the weeks required for many other antidepressant medications to take effect. It can be administered in combination with oral antidepressants to enhance overall treatment response and exhibits a unique capacity to reduce suicidal ideation [4]. Strict administration protocols for esketamine also help prevent unauthorized or improper use. However, several limitations persist, which indicate areas for future research. Concerns remain regarding the long-term safety profile of esketamine and its potential for abuse. Additionally, the cost associated with esketamine treatment represents a practical barrier to accessibility. As technological progress continues to advance, there exists substantial potential to reduce these drawbacks to a minimum, and in turn, support the widespread acceptance of esketamine as an effective therapeutic option for depression.

3. Esketamine in the Treatment of Different Types of Depression

3.1 Treatment-Resistant Depression (TRD)

TRD is defined as the failure to achieve an adequate response following two or more courses of antidepressant treatment. Electroconvulsive therapy (ECT) demonstrates some efficacy in treating TRD but is associated with side effects including cognitive impairment. Esketamine exhibits significant efficacy in treating TRD and is generally well-tolerated by patients. The TRANSFORM-3 trial validated the efficacy and safety of esketamine in elderly patients with TRD. Patients with TRD who were 65 years of age or older were recruited for this phase 3 trial, and they were randomly divided into two groups following a 1:1 ratio. Flexible-dose esketamine nasal spray (28 mg, 56 mg, or 84 mg) was administered to one group together with a recently started oral antidepressant, whereas a placebo nasal spray was administered along with a newly

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started oral antidepressant to the other group. After four weeks of treatment, a long-term open-label extension study was conducted. Results indicated that at the primary endpoint (day 28), the between-group difference in Montgomery-Åsberg Depression Rating Scale (MADRS) scores among patients aged 65-74 years was -4.9 (p=0.017) [5]. Several safety precautions are necessary when administering esketamine. Common side effects, which require further research to address, include sedation, high blood pressure, dizziness, and dissociation. Usually, these adverse effects are temporary and controllable, but continuous monitoring is required during esketamine administration. TRD diagnosis requires documentation of prior treatment failure with two or more antidepressants, or stratification based on the number of failed treatment attempts. In clinical trials, the comparator group typically consists of placebo plus standard care, with statistical analyses focusing on response rates and survival analysis for time to treatment response.

3.2 Major Depressive Disorder with Acute Suicidal Ideation or Behavior

MDD frequently presents with suicidal ideation or behavior. Conventional oral antidepressants require 4-6 weeks to exert therapeutic effects and demonstrate limited efficacy in patients with suicide attempts history. Functioning as a glutamatergic NMDA receptor antagonist, esketamine offers a crucial new choice for meeting urgent psychiatric care requirements and stopping suicide. Previous small-scale studies have suggested that esketamine can rapidly alleviate depressive and suicide-related symptoms. Canuso et al. pooled data from two phase 3 randomized controlled trials, ASPIRE I and ASPIRE II, which featured an identical study design before evaluating efficacy through the use of analysis of covariance (ANCOVA). According to the results, within 24 hours after the first esketamine administration, the MADRS scores of the esketamine group were significantly lower than those of the placebo group. The least squares mean differences in MADRS scores at 4 hours and 24 hours were -3.4 and -3.8 (95% confidence interval: -5.75 to -1.89), respectively, and this difference remained significant at -3.4 by day 25. Common adverse events (occurring in ≥20% of patients) in the esketamine group included dizziness (38.3%), dissociation (33.9%), and nausea (26.9%), with most symptoms resolving on the day of administration. Furthermore, a real-world analysis of US insurance claims data provided additional support for these trial findings. This analysis demonstrated the accessibility, utilization, and clinical outcomes of esketamine in routine clinical practice, which revealed that some patients who do not exhibit an early response to treatment may still achieve clinical benefits with continued esketamine use in later stages [6]. Clinical protocols for this patient population often involve emergency enrollment and the evaluation of rapid-acting agents. The comparator group typically includes placebo plus standard care, and occasionally ketamine or midazolam.

3.3 Bipolar Depression

Conventional treatments for bipolar depression face challenges related to the risk of inducing mania and the presence of other adverse effects. Esketamine demonstrates both strengths and limitations in the treatment of this subtype. Specifically, case reports and small-scale open-label studies have provided evidence that esketamine can reduce depressive symptoms without triggering mania. When administered in combination with mood stabilizers, esketamine exhibits an acceptable safety profile [7]. A key limitation, however, is the lack of large-scale randomized controlled trials (RCTs), which represents an important area for future research. Clinical protocols for bipolar depression often involve esketamine as an adjunct to mood stabilizers. The comparator group typically consists of placebo plus a mood stabilizer, with efficacy assessed based on changes in depression rating scale scores.

3.4 Postpartum Depression (PPD)

The impact of PPD should not be underestimated, as it affects both mothers and infants—with approximately 10%-15% of new mothers experiencing the condition. PPD is associated with impaired maternal functioning and adverse outcomes for infants. Traditional treatment with SSRIs raises concerns about drug transfer into breast milk, which may compromise infant health and development. This issue can potentially exacerbate the clinical situation and may delay the onset of effective treatment [8]. In this context, esketamine offers significant therapeutic promise. The rapid symptom relief provided by esketamine is critical for fostering healthy mother-infant bonding. Given the severe consequences of PPD, other innovative treatments have also been developed, but esketamine remains distinguished by its unique advantages. Li et al. conducted a meta-analysis involving 14 studies and 2,916 patients to evaluate the effects of ketamine and esketamine on the prevention of PPD following cesarean delivery [9]. The results demonstrated that at 1 week and 4 weeks after surgery, the incidence of Postpartum Depression (PPD) in the esketamine group was significantly lower than that in the control group. Specifically, the risk ratios (RR) at these two time points were 0.41 and 0.39, respectively. Furthermore, at these time points, the esketamine group's Edinburgh Postnatal Depression Scale (EPDS) ratings were

1.25 and 0.76 points lower than those of the control group. When esketamine was administered via patient-controlled intravenous analgesia (PCIA), the risk ratios for PPD incidence at 1 week and 4 weeks postoperatively were 0.36 and 0.40, respectively. The side effects of esketamine primarily included dizziness, diplopia, hallucinations, and headache, with occurrences that were 2.74 times, 5.25 times, 6.53 times, and 2.54 times higher than those in the control group, respectively. This meta-analysis represents the first large-scale study to confirm the preventive effect of esketamine on PPD following cesarean delivery. Subgroup analyses examining administration routes and dosages helped identify optimal treatment regimens, which provide a new direction for the prevention of perinatal PPD. Brexanolone, another recently approved therapeutic agent for PPD, requires intravenous infusion and hospitalization. In contrast, esketamine-based treatments, such as esketamine nasal spray, offer a more convenient administration route.

3.5 Atypical Depression

Atypical depression is characterized by distinct clinical features including hypersomnia, hyperphagia, weight gain, and marked sensitivity to rejection [10]. Current treatment options for this subtype are limited, as atypical depression often exhibits resistance to SSRIs. The scarcity of clinical cases further complicates the development and evaluation of targeted therapies. However, existing evidence suggests that esketamine may alleviate symptoms of atypical depression by targeting glutamatergic system dysfunction. Since there are currently no extensive clinical trials, more research is required to verify esketamine's effectiveness in treating this subtype of depression.

4. Conclusion

Esketamine represents a significant breakthrough in the management of acute suicidal ideation and depression. Its rapid onset of action and novel mechanism of action distinguish it from conventional antidepressants. While esketamine exhibits both advantages and limitations, there is considerable potential to enhance its strengths—including rapid therapeutic effects, efficacy in previous treatment-refractory patients, and suicide prevention capabilities—while addressing its weaknesses, such as high treatment costs, potential side effects, and unresolved long-term safety concerns. The future research direction for esketamine is clearly defined. First, priorities should be placed on establishing the long-term safety profile of esketamine and evaluating its potential for dependence—with special attention to its cognitive effects and risk of misuse. Second, research should explore the expansion of esketamine's therapeutic indications to include additional depressive subtypes. Third, targeted studies involving special populations—including adolescents, the elderly, and pregnant women—should be conducted, with a focus on upholding ethical principles and ensuring mutual respect. Finally, the development of biomarkers to predict treatment response will be essential for optimizing the therapeutic efficacy of esketamine. In summary, when compared to conventional treatments, esketamine holds substantial promise for the future and may offer effective therapeutic options for certain treatment-refractory subtypes of depression.

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