



## Research Paper

# Efficacy and safety of esketamine in treatment of drug-resistant depression: A review of clinical and survey studies and future therapeutic perspectives

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## ABSTRACT

**Introduction:** Depression, particularly medication-resistant depression, remains a global challenge, and esketamine, an innovative treatment targeting the glutamatergic system, offers a promising alternative for patients who do not respond to traditional antidepressants.

**Aim:** The study aimed to evaluate the therapeutic potential of esketamine, especially for patients who did not respond to standard antidepressant therapy.

**Material and methods:** The sample consisted of 30 patients diagnosed with medication-resistant depression, who were divided into 3 groups of 10 people each, based on blood pressure fluctuations during treatment. The study was conducted in Warsaw and Bytom (Poland), from July 9, 2024 to September 12, 2024 inclusive.

**Results and discussion:** The Montgomery-Asberg Depression Rating Scale was used to assess therapy effectiveness, with blood pressure monitored for cardiovascular reactions. Depression levels decreased over time. The 2nd group, starting with severe depression, showed the greatest improvement, reducing depression by 29 points, reaching a mild form. The 1st and 3rd groups reduced their depression by 16 and 18 points, respectively, reaching remission. During the supportive phase, all groups remained stable with minor fluctuations.

**Conclusions:** Esketamine showed a rapid and effective impact on reducing depressive symptoms. Blood pressure changes varied: the 1st group had stable levels, the 2nd showed fluctuations, and the 3rd experienced sharp increases and decreases, indicating individual responses to side effects. These findings highlight esketamine's effectiveness in treating severe depression but emphasize the need for medical supervision due to blood pressure fluctuations.

## 1. INTRODUCTION

The depression is the leading cause of disability in the world, affecting about 5% of the adult population.<sup>1</sup> One of the main challenges in treating depression is that approximately 30% of patients with depression do not respond to standard antidepressant therapy. Esketamine, an intranasal medication approved by the Food and Drug Administration (FDA) in 2019, has become an innovative way to treat patients with depression that does not respond to standard treatments. Esketamine works on the glutamatergic system, unlike monoamine antidepressants. Clinical studies have shown its rapid and significant therapeutic effect, which can significantly reduce the symptoms of depression.<sup>2</sup>

Cognitive behavioural therapy (CBT) is a popular treatment that targets negative thinking and behaviour patterns that cause depression.<sup>3–5</sup> CBT plus medication has been demonstrated to help treatment-resistant depression patients. Combining these therapies can improve treatment outcomes by targeting the biochemical and cognitive-behavioural elements of depression that persist after medication. According to Zakhour et al.,<sup>6</sup> the integration of CBT with pharmacotherapy has yielded better results in patients suffering from drug-resistant depression, leading to a reduction in depressive symptoms and providing a wider range of coping mechanisms. The effectiveness of CBT in this context lies in the fact that it provides patients with tools to overcome persistent psychological stress and cognitive distortions, which can help increase their resistance to pharmacological treatment. CBT promotes a sense of agency and self-efficacy, which can be especially helpful for those who feel trapped by their condition after repeated failures of pharmacological treatment. Rodrigues et al.<sup>7</sup> determined that an 8-week online CBT program significantly reduced depressive symptoms in individuals with medication-resistant depression, offering a feasible and accessible option, especially for those who may not respond well to pharmacotherapy.

Bennabi et al.,<sup>8</sup> studied methods such as electroconvulsive therapy, transcranial magnetic stimulation and vagus nerve stimulation continue to be used, especially for patients who do not respond to several types of drug therapy. These treatments work for severe drug-resistant depression by targeting mood-regulating brain circuitry. Kaur and Sanches,<sup>9</sup> discussed innovative experimental treatments for resistant depression, including systems biology-based approaches. Patients who don't respond to antidepressants may benefit from ketamine therapy. Their conclusion is that innovative therapeutic techniques may be more beneficial for specific subgroups of resistant depression patients, especially when biological factors are implicated. Halaris et al.<sup>10</sup> analysed the problems of treating depression that are not amenable to standard therapies. Innovative approaches, such as ketamine and transcranial magnetic stimulation (rTMS), which have shown positive results in severe cases of depression, were addressed. Researchers demonstrated that traditional treatments can be complemented by new technologies (TMS, ketamine) that demonstrate effectiveness for patients with drug resistance.

Major depressive disorder (MDD) is a prevalent mental condition that causes persistent sorrow, poor energy, loss of interest in activities, and cognitive impairment, including trouble concentrating or making decisions.<sup>11–13</sup> These symptoms endure at least 2 weeks and impair daily life. Biological, psychological, and social factors cause this syndrome. Brain chemical imbalances such as serotonin, norepinephrine, and dopamine, along with neural circuit alterations, particularly in the mood, cognitive, and behaviour domains, are associated with depression.<sup>14–16</sup> Trauma, loss, and prolonged stress can also cause depression. Depression affects 5% of adults worldwide, or 280 million.<sup>17</sup> Females have a higher frequency due to biological, psychological, and social factors. Hormonal changes during menstruation, pregnancy, postpartum, and menopause are important biological factors. These alterations can impact mood and cause depression. The mix of job and household duties, gender discrimination, and social pressure can increase stress among women. Depression increases suicide risk and is linked to cardiovascular disease and diabetes.<sup>18–21</sup>

Depression causes continuous unhappiness, pessimism, and apathy towards daily tasks.<sup>22</sup> The diagnosis requires at least 2 weeks of symptoms. Depressed people experience weariness, irritation, sleep difficulties, and suicidal thoughts. Causes include biological, psychological, and environmental aspects.<sup>23</sup> Depression disrupts daily life and alters brain structure and function. This condition is associated with abnormalities in the frontal, temporal, and limbic lobes, according to neuroimaging.<sup>24,25</sup> Treatment-resistant depression is a subtype of MDD in which patients do not respond adequately to at least 2 different types of antidepressants prescribed at the appropriate dose and duration.<sup>26</sup> Drug-resistant depression is associated with increased morbidity, comorbidities, and increased healthcare costs. It affects about 20%–40% of patients with MDD and is associated with poor response to pharmacological and non-pharmacological interventions.<sup>27</sup> There are several definitions of medication-resistant depression, but the most common one involves the absence of a response to at least 2 trials of antidepressants from different classes. Lack of treatment response in medication-resistant depression can be due to various factors, such as treatment adherence, comorbid conditions, and biological or genetic factors.<sup>28</sup>

Treatment-resistant depression is commonly characterised as a situation in which a MDD patient does not react to at least two antidepressants in suitable doses and for a sufficient time (6–8 weeks).<sup>30</sup> A more comprehensive approach to treating treatment-resistant depression is becoming apparent. This occurs when a MDD patient does not improve after 2 acceptable antidepressant courses in proper doses and duration. This mental condition raises the risk of chronic diseases and suicide, requiring more extensive treatment.<sup>29</sup> The drug-resistant depression occurs when a depressed patient does not respond to normal antidepressant medication. It is commonly described as the lack of clinically significant improvement despite prescribing at least two antidepressants of different classes at a sufficient dose and

period. Biological, genetic, psychological, and other factors can cause therapy-resistant depression. Alternative or combined therapies are needed to treat this disease.

## 2. AIM

Many researchers have examined drug-resistant depression treatments, but few have used esketamine, necessitating this study. Esketamine was tested for its effects on blood pressure and depression symptoms in drug-resistant depression. To achieve this goal, the following research objectives were set: to characterise depression and drug-resistant depression, to analyse esketamine's mechanism of action and main side effects, to analyse clinical trials evaluating its efficacy in psychiatric treatment, and to empirically investigate its effect on patients' depression and blood pressure.

## 3. MATERIAL AND METHODS

Esketamine's pharmacological characteristics and central nervous system receptor interactions were examined to determine its mechanism of action. Esketamine was tested specifically on N-methyl-D-aspartate (NMDA) receptors, which regulate glutamate neurotransmission. Studies showing how these pathways reduce depressive symptoms rapidly in drug-resistant depression patients were also examined. Clinical investigations addressing the short- and long-term effects of esketamine, including mood changes and side effects, were also reviewed. Side effects were examined to determine how the medicine works and how it treats depression that doesn't respond to other drugs. This was done to determine which patient reactions are normal and short-term and which are active ingredient-specific and require medical attention. Reviewing similar research on pharmacological efficacy helped determine the relevance and need for the current study.

The 2nd stage involved choosing study tools and qualifying respondents. The Montgomery-Asberg Depression Rating Scale (MADRS) assessed respondents' depression dynamics during therapy.<sup>30</sup> This methodology includes 10 assessment statements: visible signs of depression, subjectively expressed depression, internal tension, poor sleep quality, appetite changes, difficulty concentrating, decreased work motivation, emotional sensitivity loss, pessimism, and suicidal ideation. The interviewer rates each remark from 1 to 6 during a direct chat with the patient. The maximum score for this questionnaire is 60 points, thus grading is: 0–15 points – no symptoms of depression, 16–25 points – mild depression, 26–30 points – moderate depression, and more than 30 points – severe depression. This survey was done before esketamine administration, and then every 7 days during the 4-week induction phase. We measured weekly during the 4-week maintenance period. Esketamine was increased in dose and frequency based on MADRS scores. It was given twice a week during the induction phase, once a week at the

doctor's advised dose during maintenance, and once a week or every two weeks starting in week 9, depending on the doctor's recommendation. Esketamine was administered twice a week during the induction phase, which lasted 4 weeks; once a week during the maintenance phase, which lasted 4 weeks; and once a week or every 2 weeks after the 9th week. Another method was to test blood pressure (BP) to determine if the medicine affected this indication. Induction blood pressure was checked every 2 to 5 days, and maintenance blood pressure was measured every 7 days. A doctor used an automated tonometer to check each patient.

The next step was to select respondents. The criteria were as follows: a diagnosis of medication-resistant depression, not using other treatments or medications to test the effectiveness of this treatment, being between the ages of 18 and 60, and living in Warsaw and Bytom (Poland). All participants who met the above criteria were tested with the MADRS to assess their baseline depression. The total sample size was 30 people, ranging in age from 20 to 56 years. All respondents agreed in writing to participate in this treatment, they and were familiarised with the treatment plan. For ethical reasons, this consent guaranteed the complete anonymity of both the participants and the institution where the study took place.

## 4. RESULTS

The study on treatment discontinuation showed that esketamine had a significant advantage in prolonging the time to relapse compared to placebo. However, the level of evidence for long-term effectiveness is low, as some studies have a medium to high risk of bias. These results indicate that although esketamine has the potential to be a fast-acting treatment for treatment-resistant depression, its long-term efficacy remains poorly understood. The main positive aspect of esketamine is its rapid onset of antidepressant action, which can be critical for patients with severe depression who need a rapid response to treatment. However, the results of long-term treatment remain preliminary, and more research is needed to confirm its effectiveness in the long term. Table 1 shows the average values of the respondents' initial assessments of depression.

The results indicate that all 3 groups with a score of more than 30 points have a severe form of depression. It is worth noting that Group 1 and Group 3 have the same average score and are the closest to the moderate depression score, while Group 2 had a significantly higher average score of 51 points, which corresponds to a more pronounced level of depression

**Table 1. Initial average MADRS scores for the 3 groups.**

Group	MADRS result
Group 1	31
Group 2	51
Group 3	32

Source: compiled by the authors.

**Table 2. Dosing of esketamine (in mg) during the induction phase for the 3 groups.**

Group	9 July	11 July	16 July	18 July	23 July	25 July	30 July	1 August
Group 1	56	56	56	56	56	56	84	84
Group 2	56	56	84	84	84	84	84	84
Group 3	56	56	56	56	84	84	84	84

**Table 3. Blood pressure levels (in mm Hg) during the induction phase in 3 groups.**

Group	9 July	11 July	16 July	18 July	23 July	25 July	30 July
Group 1	130/80	130/80	125/83	117/85	128/73	130/23	128/72
Group 2	135/80	111/69	126/78	131/89	112/74	120/70	141/87
Group 3	140/90	130/80	115/77	132/80	139/94	144/89	147/85

**Table 4. Changes in MADRS (in points) during the induction phase in 3 groups.**

Group	9 July	16 July	23 July	30 July	1 August
Group 1	31	23	17	15	15
Group 2	51	51	38	22	22
Group 3	32	24	22	20	14

among respondents in this group. The difference in baseline scores between the groups suggests that the Group 2 was in a more severe condition at baseline, which may affect the dynamics of changes in depression levels because of treatment. Table 2 provides information on the dosage of esketamine prescribed by a doctor for each of the groups of respondents during the induction phase of therapy. The body forms its initial response to therapeutic intervention during this crucial stage of treatment. The appropriate dosage was determined by the physician based on baseline depression, blood pressure, age, and other clinical characteristics of the patients to ensure an individualised approach to treatment.

The distribution of dosages by date was used to track the escalation of therapy. In the Group 1, the dosage remained at 56 mg for the first 6 sessions, and from July 30 it increased to 84 mg. This indicates a stable initial condition of patients in this group and gradual adaptation to the drug before increasing the dosage. In the Group 2, a more aggressive dose increase was observed, namely, at the 3rd session (July 16), the dosage increased to 84 mg and remained so until the end of the induction phase. This indicates that the patients in this group had more severe symptoms of depression and required a faster increase in dosage, which may also be since Group 2 had much higher initial MADRS scores than the other 2, which was the impetus for increasing the dose of esketamine as quickly as possible to improve the respondents' condition. The Group 3 started out on the same dose as the first two, but on July 23, they were given an increased dose of 84 mg, the same as the Group 2. This shows that they need more intensive therapy in later stages, which could be because their depressive disorder was getting worse or not getting better enough, as measured by the MADRS, and their blood pressure was going up and down. Thus, the dosage regimen in each group demonstrates a differenti-

ated approach to treatment, depending on the patient's initial parameters and clinical dynamics during therapy. The blood pressure monitoring during the induction phase was essential to determine the effect of esketamine on the cardiovascular system and to monitor the physical condition of patients. The data obtained by measuring patients every 2 and 5 days are shown in Table 3.

The Group 1 had stable blood pressure throughout observation. Small alterations within the usual range may indicate that these people handled esketamine well and that it didn't affect their cardiovascular systems. Systolic and diastolic pressure fluctuated sharply in the other group, especially the second. The patient's blood pressure fluctuated, which may reflect esketamine reactivity or other haemodynamic variables. Such instability requires close monitoring and therapeutic changes for this population. In the Group 3, blood pressure spiked and then dropped. Esketamine may cause these alterations due to an acute cardiovascular reaction, a cumulative effect, or other patient-specific causes. The total research demonstrates that esketamine responsiveness differs by patient category. The Group 1 has stable blood pressure; however, the 2nd and 3rd groups fluctuate, which can impair patient health and therapy. This highlights the need for specific therapy and cardiovascular monitoring during esketamine administration. Due to its drug resistance, it was required to document changes in respondents' subjective well-being during the induction phase to assess if esketamine reduces depressive symptoms. Thus, patients' symptoms were examined weekly using the MADRS. Table 4 shows survey results.

During the induction phase, all 3 groups showed a decrease in MADRS scores, indicating a reduction in depression symptoms. In the Group 1, there was a gradual decrease in the level of depressive symptoms, followed by stabilisa-

**Table 5. Changes in blood pressure (in mm Hg) for the 3 groups during the maintenance phase.**

Group	6 August	13 August	20 August	29 August	5 September	12 September
Group 1	130/87	120/13	116/84	130/80	128/77	–
Group 2	149/87	136/79	136/95	120/80	129/86	–
Group 3	140/86	126/75	130/90	140/80	118/88	120/80

**Table 6. Changes in MADRS (in points) during the maintenance phase in 3 groups.**

Group	6 August	13 August	20 August	29 August	5 September	12 September
Group 1	17	16	14	15	15	–
Group 2	22	18	18	22	20	–
Group 3	14	14	14	14	14	14

tion. The Group 2, starting with the highest depression scores, initially showed no changes, but after the second assessment, there was a significant improvement, which subsequently stabilised. The Group 3 was characterised by a steady decrease in symptoms throughout the period, reaching the lowest final values among all groups. After 4 weeks of the induction phase, the patients moved on to the maintenance phase. Firstly, it is worth noting that the dosage of esketamine stabilised after this phase and amounted to 84 mg for each group. This may indicate that all groups reached a stable state or response to treatment during this period. Compared to the previous period, there were significant changes in the amount of esketamine dosage. Previously, the groups started with a lower dose and moved to a higher dose at different times. The Group 2 increased the dose earlier than the others, followed by the Group 3, and the Group 1 was the last to increase the dose. This staggered approach could be used to assess the tolerability or effectiveness of different doses. Currently, all groups are receiving a consistently higher dose, indicating successful adaptation to this dose level. The homogeneity of the parameters between the groups indicates stabilisation of the treatment response after dose adjustment. There were also some changes in blood pressure fluctuations compared to the induction phase (Table 5).

The Group 1 had consistent blood pressure measurements throughout the observation period, with modest swings within normal physiological limits. New data show this stability pattern continues. This group's blood pressure remained steady despite slight variations, demonstrating good esketamine tolerance and minimal cardiovascular effects. These patients had no significant blood pressure side effects from esketamine medication. The Group 2 had known systolic and diastolic blood pressure oscillations with abrupt spikes and drops. New data showed a continuance of this tendency, suggesting esketamine's sustained effect or other variables. These patients continued to have unstable blood pressure readings, highlighting the necessity for regular and careful monitoring and therapeutic modifications to avoid major cardiovascular consequences. In the 3rd group, blood pressure spiked and dropped, indicating

unstable haemodynamics. The new data showed that this group's blood pressure grew more constant and less fluctuating. The cardiovascular system may be adapting to esketamine medication. All treatment focused on detecting the biggest changes, especially in depression (Table 6).

The final results show that each of the study groups made a lot of progress, which shows that esketamine is very good at treating depression that doesn't respond to other medications. The Group 2 showed the most significant improvement, with a 31-point reduction in scores, allowing patients to move from severe to mild depression. Although the results in the other 2 groups were not as large, they are still significant. In particular, the Group 1 showed a 16-point decrease, which led to the complete disappearance of depression symptoms in this phase of the study. A similar result was recorded in the 3rd group, where the decrease was 18 points, also reaching the level of no symptoms of depression on the MADRS scale. The study demonstrated significant improvements in depression symptoms across all three groups following esketamine treatment, as evidenced by decreases in MADRS scores. Group 2, which started with the highest depression scores, showed the most substantial reduction, moving from severe to mild depression. Groups 1 and 3 also exhibited notable improvements, with Group 1 achieving complete symptom remission by the end of the maintenance phase. Blood pressure monitoring revealed stable readings in Group 1, while Groups 2 and 3 experienced fluctuations, highlighting the need for individualized monitoring and potential therapy adjustments. Overall, the results underscore the efficacy of esketamine in managing treatment-resistant depression, with all groups responding positively to the treatment regimen.

## 5. DISCUSSION

Esketamine and racemic ketamine were examined in treatment-resistant depression by Correia-Melo et al.<sup>31</sup> Participants received esketamine or ketamine. Both medications performed similarly. Esketamine remitted depression 24 h after injection in 29.4% of patients, compared to 24.1% in

the ketamine group. MADRS ratings dropped significantly in both groups. Esketamine was as effective as ketamine, researchers found. Even while both medicines behaved similarly, esketamine may have fewer mental negative effects than the Renantiomer. Esketamine is safer when used regularly, making it better for resistant depression. Esketamine is a ketamine isomer used to treat depression that resists other medications and anaesthetics. NMDA receptor antagonists influence brain glutamate transmission. Regular ketamine can be used in lesser doses, but esketamine is stronger. It modulates NMDA receptors to re-establish brain neuronal connections that reduce depressive symptoms. A nasal spray of esketamine has a faster therapeutic effect than other methods. It works well for severe depression when other antidepressants fail.

Di Vincenzo et al.<sup>32</sup> and Krystal et al.<sup>33</sup> noted that esketamine, the S-enantiomer of ketamine, has a clear effect, primarily targeting the glutamatergic system. It acts as a non-competitive NMDA receptor antagonist, leading to a cascade of effects that enhance synaptic plasticity and neurogenesis and provide a rapid antidepressant effect. After inhibiting NMDA receptors, esketamine increases the activation of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, which triggers subsequent signalling pathways, including the release of brain-derived neurotrophic factor, critical for promoting synaptic plasticity and stability in mood-regulating brain regions such as the prefrontal cortex. These studies demonstrate its ability to significantly improve the condition of patients who have not previously responded to traditional antidepressants. In addition, esketamine has shown potential benefits for patients with major depressive disorder with acute suicidal thoughts and behaviour, making it an important tool in crisis therapy. The drug is administered intranasally, which ensures a rapid onset of action but at the same time requires medical monitoring to manage side effects such as dissociation, dizziness, nausea, and increased blood pressure.

Respiratory disturbances may occur in patients with concomitant respiratory diseases; therefore, it is important to consider this factor before prescribing the drug. Although such reactions are rare, they require close medical supervision. As for more serious side effects, they are much less common than the above. Zaki et al.,<sup>34</sup> who determined that the short-term side effects mentioned above were short-lived, while the more serious ones included the most common one – the worsening of depression. Other serious side effects were less common, with some patients discontinuing the study due to side effects, most commonly worsening depression, increased blood pressure, dissociation, anxiety, mania, fatigue, and suicidal ideation. In general, the safety of esketamine is quite high when used correctly, but it is necessary to address the individual risks for each patient.<sup>45</sup>

Khorassani and Talreja<sup>35</sup> analysed the use of intranasal esketamine as an innovative treatment for drug-resistant depression. Esketamine is used as an adjunct to oral antidepressants. Patients receive the drug under medical supervision and are monitored for 2 h after administration to pre-

vent adverse reactions. In this case, esketamine has shown a rapid reduction in the symptoms of depression in patients who have not responded to traditional treatments. Side effects, such as dizziness and dissociation, usually occur immediately after ingestion and disappear within a few hours. The researchers note that intranasal esketamine is a promising option for rapid relief of depression symptoms, although its use requires careful monitoring. These findings are consistent with the current study, although it is worth noting that patients' responses to the drug are highly variable and individual, making monitoring, especially during the first weeks of taking new medications, a necessary measure. Esketamine was chosen as the most relevant and effective drug for the current study due to its novelty and versatility in the treatment of drug-resistant depression.<sup>36,37</sup> Swainson et al.<sup>38</sup> covered the main aspects of the use of esketamine for the treatment of depression resistant to medication. The main objective was to assess the efficacy and safety of esketamine as a new therapeutic option for patients that have failed other traditional antidepressants. The authors of the study focused on the key pharmacological properties of esketamine, its mechanism of action, and the main clinical trials conducted in this regard.

Fedgchin et al.<sup>39</sup> evaluated the efficacy and safety of intranasal esketamine in patients with drug-resistant depression. Patients received esketamine or a placebo in combination with a new antidepressant. Esketamine showed a significant reduction in depression symptoms on the MADRS scale as early as day 28 of treatment. Side effects included nausea, dissociation, and dizziness, but their intensity was moderate, and they disappeared within a few hours of taking the drug. The authors concluded that esketamine shows encouraging results as a fast-acting antidepressant for patients with treatment-resistant depression, although questions about safety and duration of effect remain. Overall, this study confirms the effectiveness of esketamine in the treatment of drug-resistant depression, although symptoms decreased more slowly than in the current study.

As noted by Kaur et al.,<sup>40</sup> one of the key findings of the review is that esketamine acts very quickly compared to traditional antidepressants, which may take several weeks to achieve a clinical effect. Patients with medication-resistant depression who had not responded to other treatments experienced significant improvements in symptoms within hours or days of starting esketamine treatment. This is especially important for patients with severe depression, as a rapid reduction in depression symptoms, such as suicidal thoughts or emotional instability, can be vital. The most common of these were dizziness, headache, high blood pressure, and dissociative states. These effects usually occur immediately after administration of the drug and do not last long. However, the authors note that safety precautions should be taken when administering the drug and that the patient should be monitored for at least 2 h after administration.

Smith-Apeldoorn et al.<sup>41</sup> tested low-dose oral esketamine in chronic and severe medication-resistant depression patients. The trial gave 7 individuals 1.25 mg/kg esketamine



daily for 3 weeks. The Hamilton Depression Rating Scale (HDRS) was used to measure findings. The average HRSD score was 23.6 before therapy and 19.7 after 3 weeks, a 16.5% drop. 3 participants' HRSD scores dropped over the clinically relevant level (8 points), however only 2 responded partially to treatment. No subjects obtained complete remission, i.e., a fall in HRSD scores to a level without substantial depressive symptoms. Psychotomimetic occurrences dominated moderate adverse reactions in the research, which had no significant adverse events. Oral esketamine is safe for drug-resistant depression, although its efficacy is limited, especially in chronic disease patients. The prior study included only 7 individuals, which limits its validity for general conclusions. The current study comprised 30 depressed people of various levels. Lower-depressed participants' ratings dropped from 31 to 23 and 32 to 24 in the 1st week, but those with severe depression (51) took 2 weeks to decline to 38. This shows that esketamine's mode of action is varied but effective.

Singh et al.<sup>42</sup> compared intravenous ketamine (0.5 mg/kg) and nasal esketamine (56 mg or 84 mg) for drug-resistant depression. The clinical trial comprised 62 adult patients who got up to 8 esketamine or 6 ketamine treatments. The 16-item self-rating scale of the Quick Inventory of Depressive Symptoms (QIDS-SR) examined depressive symptoms before and 24 h after treatment. Remission rates were identical comparing the two groups, indicating that both approaches had similar possibilities of reducing or eliminating depression symptoms. Compared to nasal esketamine, intravenous ketamine caused faster remission and required fewer treatments. Even after controlling for age, gender, and beginning depression, this impact persisted. Unlike the current study, this one examined depression symptoms using a self-rating scale (QIDS-SR), which can introduce subjective bias. Patients may overestimate or underestimate symptoms, affecting study outcomes. The present study used MADRS, where the patient's doctor assessed depression, which yielded more objective results. Consider the short- and long-term negative effects of ketamine before using it. Hallucinations, dissociation, agitation, and decreased mind control are common short-term psychiatric and psychotomimetic symptoms. In this trial, esketamine had no negative effects, suggesting it is more adaptive and less likely to harm patients.

Based on an analysis of studies on this topic by other authors, it is worth noting that the current study selected esketamine as the optimal treatment for drug-resistant depression, given its rapid efficacy, convenient form of administration, and better safety profile compared to other drugs. Esketamine demonstrated a significant reduction in depression symptoms in the early stages of treatment, although individual patient responses varied. One of the advantages of the drug is its rapid action, which is especially important for patients with severe depression. However, given the possible side effects noted by most researchers, such as changes in blood pressure and dissociation, careful monitoring of patients during therapy remains an important aspect.

## 6. CONCLUSIONS

- (1) The study found esketamine effective and safe for treating drug-resistant depression. Esketamine dramatically reduced depression in patients who did not react to conventional antidepressants, as shown by MADRS scores. All three groups improved, but the 2nd group, with the highest baseline depression, improved the most. Esketamine reduced MADRS depression symptoms by 16–31 points. Many patients went from severe to moderate or mild depression. The study also found that some patients improved quickly, while others needed prolonged treatment to stabilise.
- (2) The main side effects were fluctuations in blood pressure, which was the focus of the current study. The 2nd and 3rd groups of patients showed significant fluctuations in blood pressure, while the 1st group was stable in both the induction and maintenance phases, highlighting the need for careful monitoring during esketamine treatment, especially for patients at increased risk of cardiovascular disease.
- (3) Important limitations of the study are the small sample size (30 people) and the short period of follow-up after completion of therapy, which cannot be used to draw definitive conclusions about the long-term effectiveness of esketamine. Further research should focus on the long-term evaluation of the efficacy of esketamine and the study of its mechanisms of action in different patient groups, and the combination of esketamine with other therapeutic methods and classical antidepressants should be investigated to improve the results of treatment of drug-resistant depression.

## Conflict of interest

Authors declare no competing interest.

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No funding was received for conducting this study.

## Ethics

The study was approved by Ethics Commission of the Provincial Specialist Hospital No. 4 in Bytom, No. 0002938. Informed consent was obtained from all individuals included in this study.

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