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Role of ketamine in treatment-resistant depression

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ABSTRACT

Introduction: Depression, affecting 350 million people globally, is a leading cause of disability. Common symptoms include low mood, sadness, guilt, anxiety, and suicidalthoughts. Current treatments, mostly monoamine-based antidepressants, have limitations such as delayed effects and low efficacy, with over 60% of patients not achieving lasting remission. Ketamine, an NMDA antagonist, has shown rapid antidepressant effects, and research suggests glutamatergic dysfunction plays a role in TRD, highlighting the need for faster, more effective treatments.

Current state of knowledge: Ketamine, an NMDA receptor antagonist, has gained attention for its rapid antidepressant effects, particularly in treatment-resistant depression. It works by modulating the glutamatergic system, enhancing synaptic plasticity, and involving other systems like GABA and 5-HT. Clinical trials have shown ketamine's efficacy in reducing depressive symptoms and suicidal ideation within hours, contrasting with traditional antidepressants that take weeks. The intravenous route is most effective, with lower bioavailability in other forms. While ketamine shows promise, its potential for addiction and side effects necessitate careful monitoring.

Conclusion: Evidence supports ketamine for treating refractory depression, enhancing neuroplasticity and regulating affective symptoms through anti-inflammatory effects. Variations exist in administration route, bioavailability, and patient age. Common adverse effects include dissociative symptoms and cardiovascular issues, requiring careful monitoring and management.

Key words: treatment-resistant depression; ketamine; antidepressant; major depressive disorder; NMDA receptor

Introduction and purpose

Depression, a significant public health issue, ranks as the third leading cause of disability globally. It differs from typical mood fluctuations and occasional depressive episodes. Affecting around 350 million people worldwide, depression leads to both personal distress and substantial economic burden. Common symptoms include persistent low mood, sadness, guilt, lack of motivation, anxiety, and thoughts of suicide. [1] An estimated 3.8% of the population experience depression, including 5% of adults (4% among men and 6% among women), and 5.7% of adults older than 60 years. Approximately 280 million people in the world have depression. [2]

Current treatments for Major Depressive Disorder (MDD) primarily involve antidepressant medications, most of which are monoaminergic agents. These include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), selective norepinephrine reuptake inhibitors, dual serotonin-norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors (MAOIs). The efficacy of these drugs is based on the hypothesis that monoamine neurotransmitter systems—especially serotonin, norepinephrine, and dopamine—are hypoactive, particularly in brain regions like the hippocampus and prefrontal cortex, which are strongly implicated in the pathophysiology of MDD. [3] However, these treatments have several notable limitations, including a delayed onset of therapeutic effects and restricted efficacy. Monoamine-based drugs often require several weeks or even months to show therapeutic benefits, which is concerning given the elevated risk of suicide in individuals with depression. Moreover, over 60% of patients fail to achieve significant or sustained remission with conventional antidepressants, and approximately one-third of patients do not respond to two or more first-line treatments, making them candidates for treatment-resistant depression (TRD). Despite decades of research, the neurochemical and molecular mechanisms of MDD remain inadequately understood, and current antidepressant therapies offer limited clinical benefit. This underscores the urgent need for safer, more effective antidepressants that act more quickly and have higher response rates.[4,5].

In recent years, the urgent need for the development of pharmacological treatments for Major Depressive Disorder (MDD) that deliver rapid and sustained antidepressant effects has become increasingly evident. In this regard, the discovery that the N-methyl-d-aspartate (NMDA) antagonist ketamine induces a rapid antidepressant response has sparked exciting research into the cellular mechanisms underlying such effects. [6] Moreover, growing evidence suggests that disruptions in the regulation of glutamatergic neurotransmission play a significant role in the pathophysiology of MDD, as well as in the action of current antidepressants. This evidence is supported by: 1) observations of glutamatergic abnormalities in MDD patients, 2) the impact of existing antidepressants and mood stabilizers on the glutamatergic system, 3) preclinical studies indicating that drugs targeting various components of glutamate neurotransmission exhibit antidepressant and anxiolytic effects, and 4) recent research highlighting the efficacy of glutamate-modulating agents in treating mood disorders. [7]

Current state of knowledge

How does ketamine work?

The notion that psychedelic drugs have therapeutic potential is not a recent development. In the 1950s, substances like lysergic acid diethylamide (LSD) were found to enhance self-awareness and aid in the recall of emotional memories, offering significant benefits to psychotherapy. In 1962, ketamine emerged as a novel dissociative anesthetic and psychedelic compound, derived from its predecessor, phencyclidine (PCP). [8]

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that also affects α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, opioid receptors, and monoaminergic receptors. [9].

Over the past two decades, ketamine has shown rapid onset with sustained (up to several days) antidepressant effects in patients whose MDD has not responded to conventional antidepressant drugs. [10]

The rapid antidepressant effects of ketamine are believed to be mediated primarily by the glutamate system, with synaptic plasticity playing a key role. Additionally, other mechanisms are thought to involve the γ-aminobutyric acid (GABA)ergic and 5-HTergic systems. Recent studies have also implicated astrocytes in the rapid antidepressant-like effects of ketamine.

The interactions between these systems produce a synergistic, fast-acting antidepressant effect through neural circuits and molecular mechanisms. [11]

What are ketamine's clinical effects?

The first clinical trial demonstrating the antidepressant effects of ketamine was published in 2000. In this study, ketamine was administered intravenously via a 40-minute infusion at a sub-anesthetic dose of 0.5 mg/kg, in contrast to the typical anesthetic dose of up to 2 mg/kg. Remarkably, a significant antidepressant effect was observed within four hours post-infusion, compared to depressed individuals who received a placebo. [12]

A subsequent double-blind randomized clinical trial demonstrated the efficacy of ketamine in treatment-resistant major depressed patients, who failed at least two conventional antidepressant treatments. The antidepressant effects of ketamine were observed within 2 hours post-infusion, and 35% of patients sustained their response for at least 7 days. [13]

Ketamine's ability to induce rapid antidepressant effects stands in stark contrast to the delayed onset of action seen with currently approved antidepressant treatments. This is particularly crucial for patients with suicidal ideation, as the delayed onset of traditional antidepressants has been linked to an increased risk of suicidal behavior. Additionally, ketamine has been shown to quickly alleviate suicidal thoughts in patients with major depression and to rapidly reduce anhedonia. [14, 15] Reduced suicidal ideation, induced by intravenous administration of ketamine, is noted already within 40 minutes after the infusion, whereas SSRIs (selective serotonin reuptake inhibitors) induce such antidepressant effects as late as after two weeks. [16]

What is the most effective route of drug administration?

Ketamine is available in several formulations, with intravenous and intranasal administration showing the most robust evidence of effectiveness in treatment-resistant depression (TRD). The Bioavailability of ketamine varies depending on the route of delivery, with a gradient observed as follows: intravenous > intramuscular > subcutaneous > intranasal > oral. Ketamine's plasma protein binding is around 10%–15%, and its elimination half-life is approximately 2–4 hours for racemic ketamine and about 5 hours for esketamine. Intravenous ketamine has nearly 100% bioavailability, while intranasal esketamine has a bioavailability of

approximately 30%–50%. While the dosing equivalence between intravenous ketamine and intranasal esketamine has not been definitively established, it is estimated that 0.5 mg/kg of intravenous ketamine provides a bioavailability roughly equivalent to 56 mg of esketamine, given that racemic ketamine contains an equal molar ratio of S- and R-ketamine. [17]
Intravenous ketamine administration has been shown to significantly reduce depressive symptoms in both unipolar and bipolar affective disorders. Oral administration is associated with low bioavailability. The rate of absorption is influenced by genetic factors, food intake, variable intestinal motility, and gastric conditions. Furthermore, ketamine undergoes extensive first-pass metabolism in the liver, meaning that only 17-23% of the administered dose reaches the circulatory system. [18]

Are ketamine treatments safe?

Treatment-emergent adverse events associated with ketamine and esketamine in major depression can be classified into several categories: psychiatric (e.g., dissociation, psychotomimetic effects), neurologic/cognitive, hemodynamic, genitourinary, and abuse potential. The side effects observed with ketamine and esketamine in major depression often overlap, although there may be differences in the frequency and severity of these events. Variations in the occurrence and intensity of adverse events are influenced by factors such as the specific ketamine formulation, route of administration, patient population, concurrent medications, and the design of the studies, including safety assessment methods.[19]
Ketamine increases the risk of nausea, vomiting, headache, hallucinations, and dizziness compared to placebo, particularly following a single-dose administration. In future clinical practice, determining the most effective approach to achieve the best antidepressant effects of ketamine while minimizing adverse effects remains a significant challenge. [20]

How addictive is ketamine?

Ketamine is classified as a Schedule III controlled substance by the DEA (U.S. Drug Enforcement Administration). Substances in this category have recognized therapeutic uses but also carry the potential for physical and psychological dependence, particularly in cases of ketamine abuse.[21]
Both preclinical and clinical studies suggest that repeated low-dose ketamine infusions can lead to addictive behaviors and cognitive impairments. Animal research indicates that female

rodents, both adolescent and adult, are more prone to ketamine's abuse potential, while male rodents of the same age groups are more susceptible to the memory-impairing effects of repeated ketamine exposure. Additionally, ovarian hormones appear to increase sensitivity to the abuse potential of low-dose ketamine. [22]

A meta-analysis of studies administering acute ketamine infusions at doses ranging from 0.5 to 1.3 mg/kg intravenously found that men are more susceptible to ketamine-induced memory and verbal recall deficits. In particular, men who received a single ketamine infusion showed greater impairments in verbal and subjective memory, as assessed by the Hopkins Verbal Learning Task and the Clinician-Administered Dissociative States Scale (CADSS). [23]

The safety of repeated ketamine infusions remains uncertain, particularly regarding whether ketamine treatment for treatment-resistant depression (TRD) increases the risk of addiction. While further investigation into the addictive potential of ketamine is essential, repeated low-dose infusions have shown significant therapeutic benefits in reducing suicidal ideation in individuals with TRD. The literature suggests that low doses of ketamine possess addictive properties; however, it is still unclear whether repeated infusions will heighten the risk of ketamine abuse or relapse to other addictive substances following antidepressant treatment. To address this, studies on the effects of slow, low-dose ketamine infusions on subsequent self-administration of ketamine are needed. Additionally, evidence indicates that (R)-ketamine may have fewer addictive properties compared to (S)-ketamine, but (S)-ketamine is currently being tested in clinical trials due to its reduced psychotomimetic effects and enhanced antidepressant efficacy. [24]

Who is eligible for ketamine therapy?

Children and adolescents

Depression and anxiety are common conditions in childhood and adolescence. When depression is diagnosed in elementary school, the therapeutic approach becomes a complex challenge due to the difficulty in predicting the course of the illness and the impact of changing environmental factors. Recent research has suggested that depression in preschool-aged children is a strong predictor of major depressive disorder (MDD) in both prepubertal and mid-to-late pubertal stages. Suicide is the second leading cause of death in the United States for individuals aged 10 to 24. [25].

The first-line treatment for moderate to severe depression in youth recommends a multimodal approach, combining psychotherapy with pharmacotherapy, such as selective serotonin reuptake inhibitors (SSRIs). While SSRIs are generally effective, in cases where patients do not respond, switching to an antidepressant with a different mechanism, such as venlafaxine, along with cognitive behavioral therapy (CBT), has been shown to result in a higher clinical response rate compared to switching to another medication without CBT. However, a significant number of adolescents do not respond even after two medication trials combined with CBT, and these individuals may be categorized as having treatment-resistant depression (TRD). These patients require careful diagnostic evaluation, clinical attention, and potentially innovative therapeutic approaches. [26]

Among new therapies, several studies investigated the efficacy of ketamine in children and adolescent. Ketamine (0.5 mg/kg; six intravenous infusions over two weeks) was administered to 13 adolescents with treatment-resistant depression (TRD) aged 12–18. Overall, the study found that five participants responded to the treatment and remained in remission at a six-week follow-up, while two continued to maintain remission after six months.[27]

An interesting case report described the use of repeated intravenous ketamine in a 16-year-old male with a history of treatment-resistant major depressive disorder (MDD). The patient experienced an immediate reduction in depression symptoms, suicidal ideation, and hopelessness within just one day, with improvements lasting throughout the 8-week hospitalization. This enabled the patient to be discharged after psychiatric stabilization, with a plan for continued ketamine infusions every 3–6 weeks, alongside pharmacotherapy and psychotherapy support. [28] Repeated intravenous ketamine infusions were also shown to be effective in a 15-year-old female adolescent with treatment-resistant depression (TRD), generalized anxiety disorder, and post-traumatic stress disorder (PTSD) secondary to sexual trauma. [29]

Mothers with symptoms of postpartum depression

Postpartum depression is a prevalent and debilitating psychosocial condition that can negatively impact the well-being of the mother, infant, and family. Although traditional treatments for postpartum depression typically involve therapy and medication, recent research has demonstrated promising outcomes with the use of ketamine. Multiple studies have indicated that ketamine can be beneficial in alleviating postpartum depression (PPD)

symptoms. One study found that when ketamine was administered as an intraoperative agent within five minutes of cord clamping, it led to improvements in mothers with Edinburgh Postnatal Depression Scale (EPDS) scores greater than 9 one week postpartum. [30] Additionally, ketamine has shown protective effects. When given 10 minutes after a C-section, it was found to reduce the risk of PPD and associated factors, including suicidal ideation, antenatal depression symptoms, and stress. [31]

However, the use of ketamine in obstetric anesthesia requires further investigation. As a lipophilic drug, ketamine can cross the placenta, so determining the optimal dosing is crucial to ensure the safety of both the mother and fetus. Most studies have kept the dosage below 1.5 mg/kg to minimize risks. Animal research has shown that ketamine possesses neuroprotective properties, including anti-inflammatory effects and a reduction in neuronal loss. Also, there is not enough information about ketamine and breastfeeding; thus, its use as a long-term agent may not be possible until more research has been done. [32]

Older Patients

The results provide preliminary evidence supporting the efficacy and safety of ketamine in treating depression in the elderly. Dose titration is recommended to optimize both antidepressant effects and safety on an individual basis. Subcutaneous injection is a practical method for administering ketamine, and repeated treatments may enhance remission rates.[33] George et al. conducted a double-blind, randomized, multiple-crossover, controlled trial to evaluate different subcutaneous doses of ketamine in individuals over 60 years of age with major depressive disorder (MDD). An ascending dose schedule was used, with subcutaneous injections administered one week apart, and a single dose of midazolam served as an active control. The participants in this study were highly treatment-resistant, with an average current major depressive episode lasting 9 years. They had not responded to a mean of four antidepressant trials during the current episode and had undergone an average of eight lifetime antidepressant trials. Additionally, 12% of participants had failed electroconvulsive therapy (ECT) during the current episode. The study found that single doses of subcutaneously administered ketamine were effective, safe, and well tolerated in older patients. At various time points, 11 participants (69%) met the criteria for both response and remission after receiving ketamine. [34]

Discussion

This scoping review examined the existing medical literature on the effectiveness and safety of ketamine for treating DRT. The studies included in the review indicated that ketamine led to an improvement in depressive symptoms in patients with DRT compared to those receiving a placebo or midazolam. The most commonly administered dose in the treatment groups was 0.5 mg/kg intravenously. Some studies also highlighted the effectiveness of alternative administration routes, such as subcutaneous injection, particularly in the elderly population. Additionally, both anesthetic and antidepressant effects were noted in patients who also received complementary ECT. While self-limited adverse effects were most commonly reported, more complex reactions such as hallucinations, restlessness, and alterations in the perception of body, time, colors, and sounds were also observed. [35, 36]

Ketamine can be administered through various routes, with the intravenous route being the most studied for treatment-resistant depression (TRD). Other routes, including oral, subcutaneous, sublingual, and intranasal, have also been evaluated. The oral route has low bioavailability (only 8%) [37], which improves to 24%-30% with liquid sublingual formulations. Subcutaneous ketamine has nearly complete bioavailability, and its intravenous plasma concentration can be twice as high as that of other administration routes. However, oral ketamine is often criticized for its unpleasant taste, intranasal ketamine can cause nasal pain or discomfort, and subcutaneous ketamine may lead to local irritation at the injection site, all of which can reduce patient adherence to the treatment. [38]

Neuroinflammation and oxidative stress are key factors in the neuroprogression of major depressive disorder (MDD) and the response to treatment. Ketamine exerts anti-inflammatory and immunomodulatory effects by lowering plasma levels of interleukin-6 (IL-6), inhibiting phosphorylation, and inactivating transcription factor B. [39] It is also thought to modulate tumor necrosis factor alpha, IL-6, and nitric oxide synthase, potentially leading to an increase in bone density. Additionally, ketamine has been shown to reduce the levels of pro-inflammatory adipokines, such as resistin. [40] Some studies suggest that mood disorders are linked to a systemic pro-inflammatory state and reduced neuroplasticity, although further research is needed to better understand ketamine’s role in modulating inflammatory processes in patients with treatment-resistant depression (TRD). [41]

Conclusion

The evidence supports the use of ketamine in treating refractory depression. Its anti-inflammatory and immunomodulatory effects help restore signaling in neurocognitive pathways and enhance neuroplasticity, which positively influences the regulation of affective symptoms. There are variations in terms of the route of administration, bioavailability, and age group. The most commonly reported adverse reactions include dissociative symptoms and cardiovascular issues, which are generally self-limited. However, some of these adverse effects are more complex and require careful monitoring and clinical management by experienced healthcare providers.

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