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KETAMINE IN THE TREATMENT OF DEPRESSION - A REVIEW ARTICLE

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ABSTRACT

Background: Depression is a multifactorial disorder involving neurotransmitter dysregulation, HPA axis hyperactivity, neuroinflammation, and impaired neuroplasticity. While combination psychotherapy and pharmacotherapy remains first-line, ~30% of patients develop TRD. In the last few years ketamine has emerged as a rapid-acting therapeutic option for treatment-resistant cases.
Aim: To review the etiology, treatment options, and emerging interventions for major depressive disorder (MDD), with a particular focus on treatment-resistant depression (TRD) and the therapeutic potential of ketamine and ketamine-assisted psychotherapy (KAP).
Methods: A comprehensive literature review was conducted, analyzing 29 studies from the PubMed database (English-language, up to October 2025) that assess the etiology, treatment options of depression with emphasis on the therapeutic role of ketamine, especially in treatment-resistant depression (TRD).
Results: Subanesthetic intravenous or intranasal ketamine produces rapid antidepressant effects within hours, reduces suicidal ideation, and enhances synaptic connectivity through AMPA receptor, BDNF, and mTOR signaling. KAP leverages this neuroplastic window to consolidate cognitive and emotional restructuring. Intranasal esketamine has received FDA and EMA approval as adjunctive therapy for TRD. Ketamine is generally well-tolerated, though patient selection, monitoring, and adherence to safety protocols are essential.
Conclusions: Ketamine and KAP represent transformative interventions for TRD, offering rapid symptom relief and potential enhancement of psychotherapeutic outcomes. Further large-scale, randomized studies are required to optimize treatment protocols, understand long-term efficacy, and determine the additive benefits of psychotherapy.

KEYWORDS

Ketamine, Eksketamine, Depression, Treatment-Resistant Depression, Neuroplasticity

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1. Introduction

Depression is a mood disorder characterized by a persistent feeling of sadness and loss of interest. Other symptoms include anhedonia, sleep difficulties, reduced appetite and suicidal ideation. [1] It affects 350 million individuals worldwide and is the third leading cause of disability in the world. [2] According to the Global Burden of Diseases Study (GBD) conducted in 2021 depression is ranked as the second leading cause of years lived with disability among mental disorders. [3]

The etiology of depression is really complex. It is known to be a combination of hereditary, neurobiological, inflammatory, metabolic and environmental factors. Evidence from twin and adoption studies estimates heritability at approximately 31–42%, with gene–environment interactions considered central to disease development, although the identification of specific risk loci remains challenging due to the disorder's clinical and genetic heterogeneity. [4] Dysregulation of key neurotransmitter systems—including serotonin, dopamine, glutamate, and γ-aminobutyric acid (GABA)—is strongly implicated in the pathophysiology of depression. It contributes to disturbances in mood regulation, synaptic plasticity, and cognitive functioning. Alterations in 5-HT1A and 5-HT2 receptor activity, increased dopamine reuptake, abnormalities in NMDA/AMPA receptor signaling, and impaired GABAergic inhibitory control have all been associated with depressive symptomatology. In parallel, hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis and sustained hypercortisolemia reflect maladaptive stress responses and correlate with poorer clinical outcomes. Reduced levels of neurotrophins, particularly brain-derived neurotrophic factor (BDNF), further compromise neurogenesis and synaptic remodeling, whereas antidepressant interventions may partially reverse these deficits. Growing evidence also supports a role for neuroinflammation, characterized by elevated proinflammatory cytokines, microglial activation, and astrocytic dysfunction. Additionally, metabolic

abnormalities affecting amino acid, lipid, and energy metabolism contribute to disease mechanisms. Emerging research highlights the microbiome–gut–brain axis as a modulatory system influencing neurotransmission, HPA axis regulation, immune signaling, and BDNF expression, suggesting that gut dysbiosis may exacerbate depressive pathology. Together, these findings emphasize the intricate and interconnected biological networks underlying major depressive disorder. [5]

2. Treatment of depression

There are various treatment options for depression. They include psychotherapy, pharmacotherapy, relaxation techniques etc. Combination therapy including psychotherapy (especially cognitive-behavioral therapy, interpersonal therapy) and medications is most effective - it has been associated with significantly higher rates of improvement in depressive symptoms and increased quality of life. [6]

Pharmacological management of depression is based on agents that modulate monoaminergic neurotransmission, particularly serotonin, norepinephrine, and dopamine. The principal first-line treatments are Selective Serotonin Reuptake Inhibitors (SSRIs), valued for their ease of dosing and relatively low toxicity in overdose, and commonly used in late-onset depression. This class includes medications such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline. Another major group is Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs), such as venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran, which act on both serotonin and norepinephrine pathways and are particularly beneficial in patients with prominent fatigue or pain symptoms; they also serve as second-line agents following SSRI nonresponse. Atypical antidepressants, including bupropion, mirtazapine, nefazodone, and trazodone, differ in mechanism and are effective as monotherapy or in combination for treatment-resistant depression. A newer category, Serotonin-Dopamine Activity Modulators (SDAMs), such as aripiprazole and brexpiprazole, function as partial agonists at 5-HT1A and dopamine D2 receptors and antagonists at 5-HT2A receptors; brexpiprazole is approved as adjunctive therapy in major depressive disorder. [7] Tricyclic antidepressants (TCAs), including amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine, have a well-established efficacy but are now used less frequently due to their side-effect burden and high toxicity in overdose. Finally, Monoamine Oxidase Inhibitors (MAOIs), such as isocarboxazid, phenelzine, selegiline, and tranylcypromine, are effective in refractory cases but require strict dietary restrictions because of the risk of hypertensive crisis and are associated with adverse effects including insomnia, orthostatic hypotension, weight gain, and sexual dysfunction. [8]

3. Treatment-resistant depression

Treatment-resistant depression is a major problem in psychiatry. It is generally defined as a failure to achieve adequate response following at least two trials of antidepressant medications administered at appropriate doses and duration. Approximately 30% of patients with major depressive disorder (MDD) meet criteria for treatment resistance, and only 56–60% of patients with depression respond well to active treatment with antidepressants. [9] A significant percentage of patients with TRD are actually pseudo-resistant which is caused by inadequacy of treatment trials or non-adherence to treatment. TRD is associated with greater symptom severity, increased risk of suicide, higher rates of comorbidity, functional impairment, and substantial socioeconomic burden. Management of TRD typically involves a stepwise approach.

Strategies include switching antidepressants or combining agents from different pharmacological classes. [10] Intravenous ketamine and intranasal esketamine, administered with an oral antidepressant, have been established as effective treatment options for treatment-resistant depression (TRD). Several second-generation antipsychotics (e.g., aripiprazole, brexpiprazole, cariprazine, and extended-release quetiapine) have shown effectiveness as adjunctive therapies in patients with partial response to antidepressants. Combination of olanzapine-fluoxetine has been approved by FDA-defined treatment-resistant depression. [11] pharmacotherapy may be associated with side-effects and relapse issues, so it is crucial to add other interventions. Psychotherapy, especially cognitive behavioral therapy may also be integrated. Repetitive transcranial magnetic stimulation (TMS) is established as effective and FDA-approved for individuals with TRD, with accelerated theta-burst TMS also recently showing efficacy. [12] In more severe or refractory cases, electroconvulsive therapy (ECT) remains one of the most effective treatment options. In recent years, neuromodulation techniques and glutamatergic agents such as ketamine and esketamine have emerged as important therapeutic alternatives, particularly due to their rapid onset of antidepressant effects.

4. Ketamine

Ketamine hydrochloride is a nonbarbiturate dissociative anesthetic causing profound anesthesia and analgesia. It is a mixture of two mirror-image molecules, R-ketamine and S-ketamine (arketamine and esketamine). It is used for induction and maintenance of general anesthesia via intravenous or intramuscular injection either on its own or in combination with other medications. The combination of dissociative effects and partial μ-opioid receptor agonism enables the performance of painful procedures while maintaining a stable state of sedation and patient comfort. [13]

4.1. NMDA Receptor Antagonism and Glutamate Modulation

Ketamine is a noncompetitive *N*-methyl-D-aspartate (NMDA) and glutamate receptor antagonist that blocks HCN1 receptors. At the molecular level, ketamine acts by binding within the channel pore of spontaneously active ("resting") NMDA receptors, thereby limiting calcium (Ca^{2+}) entry into the postsynaptic neuron. By preferentially blocking NMDARs located on GABAergic interneurons, ketamine disinhibits pyramidal glutamatergic neurons, resulting in a transient surge in glutamate release. [14]

This glutamate burst enhances α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor throughput, which appears critical for antidepressant efficacy. Downstream signaling activates intracellular pathways including:

- mTOR (mammalian target of rapamycin)
- ERK (extracellular signal-regulated kinase)
- Increased brain-derived neurotrophic factor (BDNF) release

These processes promote rapid synaptogenesis and restoration of functional connectivity within prefrontal–limbic circuits.

4.2. Neuroplasticity and Synaptic Remodeling

Ketamine appears to promote synaptogenesis in brain regions such as the medial frontal cortex and hippocampus. Preclinical models demonstrate that chronic stress reduces dendritic spine density in the prefrontal cortex. Ketamine reverses these structural deficits within hours, restoring synaptic strength and network integrity. Several studies showed that a single dose of ketamine increases the number of dendritic spines by elevating their formation rate in the frontal cortex. The underlying mechanism remains unknown. [15]

More recent evidence has demonstrated that optogenetic stimulation of neurons expressing the dopamine D1 receptor (Drd1) induces sustained antidepressant-like effects lasting up to seven days, closely resembling the behavioral effects observed after ketamine administration. Conversely, selective inhibition of Drd1-expressing neurons abolishes ketamine's antidepressant response. These findings indicate that Drd1-positive neuronal populations play a critical role in mediating ketamine's behavioral effects. However, it remains unclear whether the antidepressant action is driven primarily by the specific neuronal cell type itself or by D1 receptor–dependent signaling mechanisms within these cells. [15]

4.3 The Role of the Lateral Habenula

The lateral habenula (LHb) has emerged as a critical node in depression-related circuitry. Often referred to as the brain's "anti-reward" center, the LHb exerts inhibitory control over dopaminergic neurons in the ventral tegmental area and serotonergic neurons in the raphe nuclei.

In depression models, LHb neurons exhibit pathological bursting activity mediated by NMDA receptor overactivation. This hyperactivity suppresses monoaminergic reward pathways and contributes to anhedonia and negative affect.

Ketamine blocks NMDA receptor–dependent bursting activity in the LHb, thereby reducing its inhibitory influence over reward circuits. This disinhibition restores dopaminergic and serotonergic signaling, which may underlie ketamine's rapid antidepressant effects. Notably, suppression of LHb activity persists beyond ketamine's immediate pharmacokinetic presence, potentially due to sustained channel-level interactions within NMDAR pores. [16]

4.4 Opioid System Involvement

Emerging evidence suggests that ketamine's antidepressant effects may partially involve the endogenous opioid system. Ketamine interacts with μ-opioid receptors, consistent with its established use in acute and chronic pain management.

A pivotal clinical study demonstrated that pretreatment with oral naltrexone (50 mg), an opioid receptor antagonist, significantly attenuated the acute antidepressant effects of intravenous ketamine in patients with depression. These findings suggest that opioid receptor activation may contribute to the rapid mood-elevating response. [17]

However, the precise role of opioid signaling remains debated. Some subsequent investigations have yielded mixed results, indicating that opioid mechanisms may modulate, rather than fully mediate, ketamine's antidepressant action.

4.5 Additional Mechanisms

Beyond NMDA antagonism, ketamine may exert antidepressant effects through:

- Sigma receptor modulation (Sigma-1 receptor (S1R) is a unique multi-tasking chaperone protein in the endoplasmic reticulum. Because S1R agonists demonstrate strong antidepressant-like effects, the sigma-1 receptor (S1R) has emerged as a promising target for developing novel antidepressant therapies. [18]
- Anti-inflammatory activity. Animal studies further support the link between ketamine's rapid antidepressant effects and its anti-inflammatory properties. In a chronic unpredictable mild stress model of depression, ketamine alleviated stress-induced depressive-like behaviors, including anhedonia, behavioral despair, and neurovegetative changes, which were accompanied by elevated hippocampal levels of proinflammatory cytokines IL-1β, IL-6, and TNF-α. Ketamine's antidepressant and anti-inflammatory effects were mediated by multiple mechanisms: it reduced the number of activated microglia in the hippocampus, lowered IL-1β, IL-6, and TNF-α levels, suppressed cytokine synthesis via the TLR4/p38 signaling pathway, and inhibited cytokine release from microglia through downregulation of P2X7 receptors. [19]
- Enhancement of synaptic homeostasis
- Network-level functional connectivity normalization.

Neuroimaging studies reveal rapid changes in connectivity within the default mode network, salience network, and prefrontal–limbic circuits following ketamine administration.

5. Ketamine in psychiatry

First potential antidepressant effects of ketamine were described in the 1970s by Trullas and Skolnick. They suggested that NMDA receptor pathways might be involved in behavioral changes caused by stress. [20]

The first study including ketamine was published in 2000, where ketamine was administered intravenously via 40-min infusion at the sub-anesthetic dose of 0.5 mg/kg. It led to a robust antidepressant effect of ketamine within four hours post-infusion compared with depressed subjects who received placebo. Reduction in depressive symptoms was measured by the Hamilton Depression Rating Scale (HAM-D). [21] In another double-blind randomized study with resistant major depressed patients, who failed at least two conventional antidepressant treatments ketamine manifested antidepressant effect within 2 hours post-infusion. 35% of patients maintained response for at least 7 days. [20] Several other clinical trials have shown similar results - one of them showed that ketamine demonstrated rapid antidepressant properties in treatment-refractory patients. [21] Ketamine has been shown to reduce suicidal ideation and anhedonia. According to studies, it lowers suicidal ideation within 2 hours of administration in inpatient, outpatient, and emergency settings, patients with TRD. [22]

Unlike traditional antidepressants, which require weeks to achieve clinical efficacy, subanesthetic doses of ketamine can produce symptom improvement within hours. It has been shown that ketamine may be more effective in patients with with higher level of basal suicidal cognition or with a previous history of suicide attempt. The most common practice is to administer the IV ketamine twice or thrice weekly. The benefits of ketamine are transient, they last up to 1–2 weeks after infusion. Its long-term effect is less reported. [2] Preliminary findings suggest that patients with anxious depression may experience more benefit from ketamine treatment compared with those with non-anxious depression. Furthermore, both melancholic (typical) and atypical depressive features appear to improve following ketamine administration, although melancholic symptoms may show larger effect sizes at earlier time points (e.g., 24 hours post-infusion). [23] Nonetheless, further studies are required to systematically validate these observations.

5.1. Ketamine-assisted psychotherapy

Ketamine-assisted psychotherapy (KAP) is an emerging approach that combines ketamine's rapid pharmacological effects with structured psychotherapeutic support, with the aim of enhancing and prolonging clinical benefits beyond those achieved with ketamine alone. The underlying rationale is that ketamine temporarily increases neuroplasticity and psychological openness, creating a "therapeutic window" in which psychotherapeutic interventions can more effectively facilitate cognitive and emotional restructuring. This may allow patients to engage more deeply with therapy and consolidate gains in mood and behavior during periods of heightened neural receptivity. [24]

Preliminary clinical evidence supports the potential of KAP to reduce symptoms of depression, anxiety, and post-traumatic stress disorder, with sustained improvements observed up to three to six months

post-treatment in large observational cohorts. These studies, often using multiple ketamine doses integrated with psychotherapy, have reported moderate to large effect sizes, with a substantial proportion of patients achieving clinically meaningful symptom reduction. However, outcome data are limited by high attrition, lack of randomization, and methodological heterogeneity. [25]

Systematic reviews confirm that combining ketamine with psychotherapy is associated with significant reductions in psychological distress across a range of psychiatric conditions, and that KAP may enhance treatment engagement and possibly maintain ketamine's therapeutic effects. Yet, the evidence base remains small and variable: only a minority of studies have randomized designs or standardized protocols, and results are mixed regarding whether psychotherapy adds significant benefit over ketamine treatment alone. Larger, rigorously designed randomized controlled trials are needed to clarify the efficacy, mechanisms, and optimal integration strategies for KAP in treatment-resistant depression and other disorders. Ongoing trials are currently underway to compare KAP with ketamine alone to determine additive effects. [25]

6. Indications and route of administration

In 2019, The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the IN esketamine spray Spravato as an additional treatment to conventional antidepressants in MDD patients, when at least two other treatments have failed. In 2020, FDA approved Spravato for the treatment of major depressive disorder with acute suicidal ideation and behavior. [26] It is recommended to begin with one or two sprays per nostril on the first day, followed by up to three sprays administered twice weekly for four weeks. If symptoms improve, Spravato is then given once weekly for an additional four weeks, after which dosing is reduced to a single administration every one to two weeks for at least six months as maintenance therapy. Intravenous ketamine is used off-label for the treatment of TRD. In the United States, a recent study by Brendle et al. (2022) compared the cost-effectiveness of IV ketamine and intranasal (IN) esketamine, demonstrating greater cost-effectiveness of IN esketamine from the patient perspective.

Patients considered for ketamine treatment must meet the following criteria: [27]

- suffer from treatment-refractory non-psychotic unipolar or bipolar depression and other psychiatric conditions where ketamine has shown effectiveness, such as suicidality
- Have previously tried at least three different classes of antidepressant medications, each for a minimum of six weeks at an adequate therapeutic dose, without sufficient clinical response.
- Have undertaken at least one form of psychological therapy, such as Cognitive Behavioral Therapy (CBT), Cognitive Analytic Therapy (CAT), or Mindfulness-based interventions. In addition, patients should have either received, or been considered for, electroconvulsive therapy (ECT) and/or pharmacological augmentation strategies.
- Be formally referred to the ketamine service by their treating psychiatrist.
- Be able to travel safely to attend treatment and assessment appointments.
- Be willing and able to complete regular clinical questionnaires and outcome measures.
- Be able to understand the nature and purpose of the treatment, its potential benefits, and possible side effects, and provide informed consent.

7. Safety and precautions

Whereas anesthetic dosing of ketamine usually falls between 1 and 3 mg/kg, the dose for TRD is markedly lower (approximately 0.5 mg/kg), which is associated with a lower incidence of adverse events. The effects of ketamine can be felt minutes after usage. The most common adverse drug reactions associated with single-dose IV ketamine infusion are nausea, vomiting, dizziness, diplopia, drowsiness, dysphoria, and confusion. [28] It may cause allergic reactions or injection site reactions such as erythema, localized pain, and morbilliform rash. It can also lead to drug-induced liver injury. Ketamine is metabolised by the hepatic cytochrome CYP450, so it can interact with many drugs. [29]

Ketamine is contraindicated in patients with: [22]

- heart diseases such as uncontrolled hypertension, myocardial infarction, aneurysmal vascular disease or arteriovenous malformation,
- intracerebral hemorrhage
- during obstetrics, pregnancy, or breastfeeding
- with schizophrenia (a due to the potential for exacerbating the underlying condition)
- children ≤3 years (it can lead to pediatric neurotoxicity and cognitive deficits)
- hypersensitivity to esketamine, ketamine, or any of their excipients.

Before starting treatment with ketamine, it is recommended to perform a set of laboratory tests covering parameters such as: peripheral blood count, CRP, AST, ALT, creatinine, urea, ionogram, glucose, TSH, urine test for drugs (toxicology), general urine test, betaHCG (in women of childbearing age), electrocardiogram (ECG). It is advisable to assess blood pressure, heart rate, and oxygen saturation. It is important to remember to obtain the patient's informed written consent to the treatment before starting it.

8. Conclusions

Depression is a complex disorder, and many patients do not respond adequately to standard treatments such as antidepressants and psychotherapy. For individuals with treatment-resistant depression (TRD), ketamine has become a promising new option. It can reduce depressive symptoms and suicidal thoughts much faster than traditional medications, sometimes within hours. Both intravenous ketamine and intranasal esketamine have shown meaningful benefits in patients who previously did not improve with other treatments.

However, although ketamine is an important breakthrough, its exact mechanisms are still not fully understood. More research is needed to determine its long-term safety, how long its effects last, and which patients benefit the most. Further studies will help clarify its role in the future treatment of depression.

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