Review Article ISSN 2639-944X

Journal of Medical - Clinical Research & Reviews

Ketamine's Evolving Role in Addressing Treatment Resistant Depression

Marcus Christian Rosenhagen* and Alberto Maria Forte

Department of Psychiatry, Almaval - Center of Expertise in Psychiatry and Psychotherapy, Lausanne, Switzerland.

***Correspondence:**
Marcus Christian Rosenhagen, ALMAVAL, Castel de Bois Genoud 1023 Crissier / VD, Switzerland, Tel: +41 793548745.

Received: 01 Nov 2024; **Accepted:** 11 Dec 2024; **Published:** 20 Dec 2024

Citation: Marcus Christian Rosenhagen and Alberto Maria Forte. Ketamine's Evolving Role in Addressing Treatment Resistant Depression. J Med - Clin Res & Rev. 2024; 8(12): 1-9.

ABSTRACT

Ketamine, originally developed as a safer alternative to phencyclidine, has become a groundbreaking treatment in psychiatric practice. Approved by the United States Food and Drug Administration (FDA) in 1970 for its analgesic properties and ability to induce altered consciousness while preserving vital functions, ketamine gained renewed attention in the 1990s when researchers discovered its rapid and potent antidepressant effects, particularly in treatment-resistant depression. Ketamine's mechanism of action involves blocking N-Methyl-D-Aspartate (NMDA) receptors, which leads to the release of inhibitory signals and increased glutamate levels. This cascade of events promotes neuronal growth and synaptic plasticity, both essential for its antidepressant effects. Various methods of administration have been explored, including intravenous (IV), intranasal, oral, subcutaneous, and intramuscular routes, each offering unique benefits and limitations. While IV ketamine remains the most widely used form, intranasal and sublingual formulations are increasingly popular for their improved accessibility and safety. Notably, the FDA and the European Medicines Agency (EMA) have approved intranasal S-ketamine for the treatment of resistant depression and depressive symptoms. Ketamine's safety profile is generally favorable, with side effects that are mild, temporary, and self-limiting. However, caution is necessary for individuals with uncontrolled hypertension, cardiovascular issues, a history of psychosis, or substance abuse. Pregnant women are also advised against ketamine use, and potential interactions with other medications require careful consideration. Guidelines recommend ketamine as a third-line treatment option for resistant depression, to be considered after multiple unsuccessful antidepressant therapies. While international recommendations vary slightly, ketamine is increasingly recognized as a promising intervention for addressing the challenges of treatment-resistant depression. This review underscores the expanding role of ketamine in psychiatric care, particularly its applications in treatment-resistant depression and its potential to transform acute psychiatric emergency departments. It also sheds light on administration methods, safety considerations, and international guidelines for optimizing its use in challenging psychiatric conditions.

Keywords

Psychiatry, Ketamine, S-ketamine, Treatment resistant depression.

Introduction

Ketamine stands as the first rapid-acting treatment for depression to demonstrate significant effectiveness in alleviating depressive symptoms. Its discovery has sparked a reevaluation of the biological understanding of depression, with neurobiological research shedding light on the mechanisms underpinning ketamine's antidepressant effects and offering new perspectives on its clinical efficacy [1-4].

First synthesized in 1962 as a safer alternative to phencyclidine, ketamine was designed to avoid the intense and prolonged emergence delirium associated with its predecessor [5,6]. Early clinical trials confirmed ketamine's safety and efficacy, highlighting its ability to provide analgesia and induce altered consciousness while preserving airway tone, respiration, and hemodynamic stability.

In 1970, the FDA approved ketamine for human use. Its ability to maintain vital functions during anesthesia made it a valuable tool in clinical practice. By the 1990s, researchers began investigating

its antidepressant properties after observing mood improvements in patients who received ketamine for anesthesia. Studies in the early 2000s further validated ketamine's rapid and robust antidepressant effects, particularly in individuals with treatment-resistant depression (TRD) who had not responded to conventional therapies [1,7]. These findings revealed that ketamine could reduce depressive symptoms within hours or days, in contrast to the extended periods required for traditional antidepressants.

In March 2019, the FDA approved an intranasal (IN) formulation of S-ketamine, branded as Spravato®, for use alongside oral antidepressants in adults with TRD and in 2020 in those with major depressive disorder (MDD) experiencing acute suicidal thoughts or actions [8]. Later that year, the EMA approved S-ketamine for TRD and for moderate to severe depressive episodes requiring emergency intervention when combined with an antidepressant [9].

Although intravenous (IV) racemic ketamine is not officially approved as an antidepressant by the FDA, it is increasingly prescribed off-label by clinicians, often as an adjunctive therapy for TRD and other psychiatric conditions [10]. Clinical trials for ketamine and S-ketamine in TRD have progressed to phase III and IV, underscoring their growing significance in psychiatric treatment. Sub-anesthetic doses of ketamine are also being explored as potential therapies for neuropsychiatric conditions like major depression, schizophrenia, and bipolar disorder. Moreover, combinatory approaches integrating pharmacological and non-pharmacological treatments, such as electroconvulsive therapy (ECT), psychotherapy, virtual reality, and transcranial magnetic stimulation (TMS), are becoming more common [11]. A total of 363 trials were manually assessed from clinicaltrial.gov with the search term "Ketamine" from 2014 until 2024. The highest number of trials were found for the FDA-approved indications: anesthesia (~22%) and pain management (~28%) for ketamine and TRD for S-ketamine (~29%).

A consensus de"inition for TRD with proven predictive value for clinical decision-making and health outcomes remains elusive. However, the FDA and EMA have adopted the widely accepted definition, which identifies TRD as an inadequate response to at least two antidepressants despite adequate treatment trials and adherence to therapy [12,13].

In this update, we highlight the significance of ketamine in the treatment of treatment-resistant depression. The focus is clearly on the mechanism of action of ketamine, the various administration methods of ketamine and its enantiomers, and its role in addressing suicidal ideation within the context of TRD, particularly given the highly complex nature of the studies involved. Finally, safety considerations, potential side effects, interactions, and international guidelines for ketamine usage in psychiatry are also discussed.

Biochemical Pathways

Ketamine, initially developed as an anesthetic, has emerged as a groundbreaking treatment for depression due to its rapid and significant antidepressant effects. Although its mechanism of action is not fully understood, it is believed to involve several interconnected processes. Ketamine blocks N-Methyl-D-Aspartate receptors (NMDAR), which are glutamate receptors located on γ-aminobutyric acid (GABA) interneurons [14-16]. This blockade reduces inhibitory signals, resulting in a surge of glutamate that activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. The activation of AMPA receptors initiates a cascade of events, including Increased brain-derived neurotrophic factor (BDNF) levels and activation of the mammalian target of rapamycin (mTOR) signaling pathway [15,17,18]. These pathways promote synaptogenesis and synaptic potentiation, reversing stress-induced synaptic deficits observed in the depressed brain [2,3,17,19]. Additionally, a ketamine metabolite, (2R,6R)-hydroxynorketamine (HNK), has been shown to directly activate AMPA receptors, contributing to ketamine's sustained antidepressant effects even after its short plasma half-life of 2.5 hours [20]. This unique mechanism allows ketamine's antidepressant effects to persist for up to 1-2 weeks post-infusion [16].

S-ketamine and racemic ketamine exert their primary effects through NMDAR inhibition, but emerging evidence points to additional mechanisms. These include increasing BDNF, activating mTOR signaling, and reducing inflammation by lowering pro-inflammatory cytokines like TNF-α and IL-6 [21]. These anti-inflammatory effects are particularly significant, as inflammation has been identified as a pathogenic factor in depression that reduces treatment responsiveness [22]. Ketamine's ability to counteract inflammation through cytokine suppression, modulation of the kynurenine pathway, and direct effects on microglia and monocytes may explain its unique efficacy in TRD, surpassing conventional antidepressants in addressing refractory symptoms [22].

Preclinical studies suggest distinct mechanisms between ketamine enantiomers: S-ketamine primarily modulates mTORC1 signaling, while R-ketamine influences extracellular signal-related kinase (ERK) signaling [23,24]. While R-ketamine may have a milder side effect profile, recent trials have found no significant antidepressant efficacy in TRD compared to placebo [23,25]. Over 460 biomarkers, including neurotrophic factors, ketamine metabolites, and inflammatory markers, have been studied to understand ketamine's rapid antidepressant effects. Recent research indicates that baseline plasma BDNF levels may predict ketamine's antianhedonic effects in individuals with major depressive disorder (MDD) receiving repeated doses [26,27]. Furthermore, increased mTOR protein expression in peripheral immune cells correlates with ketamine's antianhedonic effects, suggesting that peripheral immune mTOR expression could serve as a predictive biomarker for these rapid benefits [28]. These findings highlight the potential of ketamine not only as an antidepressant but also as a targeted therapy for specific symptom domains, such as anhedonia, in TRD.

Modes of Administration for Ketamine and Its Enantiomers

For the treatment with racemic ketamine or its enantiomers, the following administration routes are currently under intensive

research: intravenous (IV), in the form of a nasal spray (IN), orally in the form of tablets, subcutaneously (SC), or intramuscularly (IM), all mostly conducted in treatment of depression. The efficacy and safety of different routes of administration of ketamine have not been definitively established. When comparing these routes, it is important to consider the differences in the bioavailability of ketamine and its metabolites. Intravenous administration of ketamine typically results in complete bioavailability, meaning the drug is fully absorbed into the bloodstream. Intramuscular and subcutaneous administration have slightly lower bioavailability, estimated to be around 90% [29]. The bioavailability further decreases with intranasal administration, ranging from 8% to 45% and oral administration of ketamine has the lowest bioavailability, ranging from 8% to 29% [30].

Intravenous Administration

The first randomized study for the treatment of TRD with an NMDA antagonist was conducted using infusions and demonstrated a rapid short-term effect [7] that could be maintained with repeated treatments [31].

Racemic ketamine is administered intravenously at a significantly lower dosage compared to its use in general anesthesia, typically around 0.5-1 mg/kg over a period of 40 minutes. The treatment frequency is not clearly defined but is typically two times per week during the initial weeks and then gradually reduced based on clinical success [32,33]. Most studies have been conducted in TRD, and it is suggested that higher dosages between 0.5 to 1.0 mg/kg demonstrate greater efficacy at the group level compared to lower dosages ranging from 0.1 to 0.2 mg/kg one day after administration [29]. The maximum dosage limit for IV racemic ketamine in TRD has not been established. However, evidence from studies involving single doses indicates that both 0.5 mg/kg and 1.0 mg/kg doses are effective, with no evidence supporting the superiority of 1.0 mg/kg over 0.5 mg/kg [29].

Intranasal Administration

For IN S-ketamine, it is recommended to start with a dose of 56 mg, administered twice weekly, during an induction phase of 4 weeks. The dosing can either remain at 56 mg or be increased to 84 mg based on the patient's response to the treatment. A recent meta-analysis of nine studies involving 1752 patients with MDD and TRD found that IN S-ketamine significantly improved remission and response rates compared to placebo, particularly at 84 mg or flexible doses alongside oral antidepressants [34]. After the induction phase, the administration frequency is suggested to be reduced to once weekly during weeks 5 to 8 [35]. Following that, the frequency can be further decreased to biweekly or less frequently thereafter based on the symptoms experienced by the patient [29,36].

An observational head-to-head study comparing the effectiveness of IV racemic ketamine and IN S-ketamine in patients with TRD found no significant differences in baseline-to-endpoint change or response/remission rates between the two groups [37]. However, the study did find that the time to achieve remission, defined by the number of treatments, was faster for patients receiving IV racemic ketamine compared to those receiving IN S-ketamine. In another recent head-to-head study utilizing a post-hoc analysis of pooled real-world data, IV ketamine demonstrated greater short-term antidepressant efficacy, while IN S-ketamine was associated with fewer side effects. Both treatments were generally well tolerated [38].

Oral Administration

Regarding oral administration, Meshkat et al. [39] conducted a review and found that all included studies reported a significant improvement in depressive symptoms in MDD following well tolerated ketamine administration in tablet form. The dosage of ketamine varied from 0.5 to 1.25 mg/kg, and the frequency of administration ranged from daily to monthly, depending on the study [30,39].

A recent randomized placebo-controlled trial found that fixed low-dose oral S-ketamine (30 mg three times a day) was ineffective for TRD and showed no significant benefit over placebo. However, in the open-label phase with individually titrated higher doses (0.5 to 3.0 mg/kg two times a week), S-ketamine significantly reduced depressive symptoms, suggesting potential antidepressant efficacy at higher doses [40]. These results from the six weeks open-label phase are consistent with the recently published findings of a phase 2 multicenter study [41]. Extended-release ketamine tablets (R-107) demonstrated rapid-onset antidepressant efficacy, safety, and excellent tolerability in TRD, with significant improvements in MADRS scores and dose-dependent relapse prevention, particularly at 180 mg doses twice a week for 12 weeks, while minimizing common ketamine-related side effects [41]. It is important to note that in this study, patients who did not respond by day 8 were not included in the study analysis. On the other hand, another recent study with prolonged-release ketamine showed fewer promising results: Patients were randomized to receive an additional 160 mg/day or 240 mg/day of KET01 or placebo for 14 days. The findings suggest that adjunctive oral administration of prolonged-release ketamine at a dose of 240 mg/day demonstrated a positive but statistically non-significant trend toward antidepressant efficacy; however, the benefit could not be confirmed due to the premature termination of the trial after 2 weeks due to poor recruitment during the COVID-19 pandemic [42].

Intramuscular and Subcutaneous Administration

The advantages of using IM and SC routes include easier administration and reduced staff training in administering medications via IV or IN routes. When treating depression with racemic ketamine given through IM or SC injection, the recommended dose has ranged from 0.1 to 1 mg per kilogram of body weight, with a typical dose of 0.5–1 mg/kg in most studies [30,43-45]. A recent double-blind crossover study in 25 patients with TRD found that IM ketamine (0.5 and 1 mg/kg) rapidly reduced depression and anxiety ratings for up to 7 days, with similar mood improvements across doses but dose-dependent

dissociative side effects and blood pressure changes [46].

Application in Treatment Resistant Depression

One of the most remarkable breakthroughs in ketamine research is its ability to produce rapid and significant improvements in depressive symptoms, even in cases of TRD [1,7,29,31,47,48]. Building on these observed antidepressant effects, ketamine has emerged as a pivotal treatment option for TRD and is increasingly being investigated in other psychiatric areas. These studies, often small-scale or randomized, primarily focus on cases of treatment resistance. Ketamine treatment is highly clinically significant, with a number needed to treat (NNT) of less than 10 for adults with TRD across various observation periods [49].

Research has explored numerous factors influencing ketamine's effectiveness, including the use of racemic ketamine versus S-ketamine, variations in dosing strategies, session durations, administration routes, treatment frequencies, and related protocols. While most studies emphasize IV racemic ketamine (> 250 trials) and IN S-ketamine (> 25 trials), important findings have also emerged regarding alternative administration methods.

The antidepressant effects of ketamine are evident within hours of treatment and can last for several weeks, providing much-needed relief for individuals with TRD [20,30]. Importantly, these benefits extend to patients with comorbid psychiatric disorders, which are often linked to treatment resistance in MDD [50,51]. Particularly in cases of comorbidity between borderlione personality disorder and MDD, the prognosis for both disorders is negatively impacted, leading to more severe depressive and resistant symptoms, delayed remission, and shorter periods before relapse. Furthermore, available treatment options, such as antidepressants, ECT, and psychotherapy, tend to be significantly less effective in such individuals [52].

There is robust evidence supporting the persistent antidepressant effects of both intravenous and intranasal maintenance ketamine treatments with repeated administration in patients with MDD and TRD [29-31,37,39,53,54]. Notably, the long-term phase 3 study SUSTAIN-3 demonstrated that flexible, intermittent S-ketamine dosing, combined with an oral antidepressant, improved depression ratings and maintained remission in adults with TRD for up to 4.5 years. This approach showed a consistent safety profile, with common adverse events including headache, dizziness, and nausea [55]. To a lesser extent, evidence also supports the sustained therapeutic potential of oral, intramuscular, and subcutaneous maintenance ketamine treatments [54].

Ketamine Among Current Treatments for Treatment Resistant Depression

A recent systematic review and network meta-analysis of randomized controlled trials (RCTs) involving 12,105 participants identified ECT, ketamine, esketamine, and psilocybin as superior first-line treatments for their effectiveness, with ECT and ketamine offering the best balance between effectiveness and tolerability. While esketamine and psilocybin were effective, they demonstrated lower tolerability compared to ECT and ketamine. In contrast, brexpiprazole and quetiapine showed no significant efficacy over placebo in response rates [56]. Supporting these findings, a recent study comparing IN S-ketamine and quetiapine XR for TRD highlighted that although treatment-emergent adverse events (TEAEs) were more frequent with IN S-ketamine, they were generally mild, transient, and often resolved on the same day. This led to fewer treatment discontinuations compared to quetiapine XR. With fewer days impacted by TEAEs and a consistent safety profile, IN S-ketamine demonstrated superior tolerability and efficacy, solidifying its role in TRD treatment [4]. These observations align with the outcomes of a randomized phase IIIb clinical trial published recently [57]. Additionally, a study comparing psilocybin and S-ketamine for TRD revealed that 25 mg psilocybin significantly reduced depressive symptoms at 21 days post-dose (NNT = 5), though nausea emerged as a notable side effect (number needed to harm (NNH) = 5). Meanwhile, fixed-dose S-ketamine (56 mg and 84 mg) showed significant antidepressant effects at 28 days post-dose (NNT = 7), with common side effects such as headache, nausea, dizziness, and dissociation (NNHs <10) [58]. Currently, ECT is widely regarded as one of the most effective treatments for TRD, and it is also considered a highly efficient therapeutic option for non-resistant depression. According to a recent meta-analysis, ketamine is equally effective as ECT in reducing depressive symptoms and response to therapy [59]. Another meta-analysis by involving patients with TRD, also found no significant difference in efficacy between ECT and ketamine [60]. This study was supported by an open-label, randomized, noninferiority trial, where patients with TRD were assigned to either ketamine or ECT, with ketamine showing noninferior response rates (≥50% symptom reduction) compared to ECT over a 3-week treatment phase, along with evaluations of memory and quality of life during a 6-month follow-up [61]. It is worth noting that differences in side effects were observed, with musculoskeletal adverse effects being more common in the ECT group, while ketamine was associated with dissociation [61]. A secondary analysis of the study revealed greater improvement in depression with IV ketamine in outpatients with nonpsychotic, moderately severe or severe TRD, suggesting ketamine as a potential alternative to ECT for these patients [62]. A recent review comparing ketamine and ECT for TRD found ketamine to have faster but shorter-lasting antidepressant effects with fewer cognitive deficits, while ECT showed higher long-term remission rates despite more pronounced cognitive side effects [63]. Demonstrating superiority to quetiapine and non-inferiority to ECT suggests that ketamine may be the most effective TRD intervention currently available.

Distinct Translational Properties of Ketamine

With the increasing focus of psychiatric clinical research on ketamine and its enantiomers, the exploration of various psychopathological domains specifically treatable with ketamine has gained prominence. Among these, its anti-suicidal properties stand out as particularly noteworthy [64]. Another potential area of interest is anhedonia, although the findings in this domain are

less definitive [65-67]. Despite evidence suggesting ketamine's anti-suicidal ideation effects, it is essential to emphasize that studies in this field are highly complex and must contend with the extraordinarily high placebo effect frequently observed in this area of research.

In this context, the study by Canuso et al. [68] investigated the efficacy and safety of IN S-ketamine for rapidly reducing depressive symptoms, including suicidality, in patients at imminent risk of suicide. Conducted as a double-blind, randomized, placebo-controlled trial, participants received either IN S-ketamine (84 mg) or placebo twice weekly for four weeks, alongside standard-of-care treatment. The findings revealed that while S-ketamine achieved a more rapid reduction in depressive symptoms compared to placebo, the difference in the reduction of suicidality between the two groups was not statistically significant. Adding to this body of research, the first meta-analysis evaluating the anti-suicidal effects of IV ketamine analyzed data from 10 out of 11 randomized clinical trials that used either saline or midazolam as control interventions [69]. This analysis included 167 participants with baseline suicidal ideation and demonstrated that IV ketamine rapidly reduced suicidal thoughts within one day, with effects lasting up to one week. Interestingly, these anti-suicidal effects appeared partially independent of mood improvements [69].

A broader analysis of randomized controlled trials identified 12 studies in which the reduction of suicidal ideation was the primary objective and 14 studies where it was a secondary outcome [70]. Results indicated that IV racemic ketamine exhibited significant superiority over control drugs, such as placebo or midazolam, within the first 72 hours, despite substantial placebo effects. Adverse events associated with ketamine were generally minor and transient. Conversely, IN S-ketamine did not show significant differences compared to placebo, while SC racemic ketamine demonstrated promising outcomes [70,71]. Overall, IV racemic ketamine demonstrated efficacy in reducing suicidal ideation, particularly within the initial 72 hours, although various research gaps remain. A recent review highlighted that both IV racemic ketamine and IN S-ketamine have significant anti-suicidal ideation effects [72]. Racemic ketamine produced a large anti-suicidal ideation effect within 4 to 6 hours and a medium-to-large effect within 24 hours, while S-ketamine exhibited a smaller but consistent anti-suicidal effect over the same timeframes [72].

In a recent study by Singh et al. [73], it was noted that patients with TRD and baseline suicidal ideation required more ketamine or S-ketamine treatments to achieve a therapeutic response compared to those without such ideation. This suggests that baseline suicidal ideation may correlate with a slower response to these treatments in TRD patients.

Safety and Recommendations

Side effects

The common acute side effects of ketamine and its enantiomers are generally mild, temporary, and self-limiting, including symptoms such as dissociation, hallucinations, nausea, headache, elevated heart rate, and elevated blood pressure. Among these, dissociation is the most frequently observed acute adverse event, occurring in 15% [74] up to 25% [47] of patients, while hallucinations are reported in fewer than 5% of cases [74,75]. Clinical trials of IN S-ketamine have demonstrated that cognition typically remains stable or even improves over time [53]. The administration of IV racemic ketamine and IN S-ketamine, however, must be carried out by healthcare professionals trained in cardiopulmonary resuscitation, with monitoring for two hours post-administration to include blood pressure, heart rate, respiratory rate, and oxygen saturation [75].

Although the occurrence of cystitis has been reported with chronic, uncontrolled, or anesthetic doses of ketamine, this adverse event has not been documented with therapeutic dosages used in psychiatric treatments [75,76]. While ketamine is also known as a recreational drug, its use in psychiatry involves approximately one-tenth of the recreational dosage. Consequently, its addiction potential is considered low, with patients undergoing therapy reporting dissociation in about 15% of treatments rather than euphoria [74,75,77]. Nevertheless, studies specifically exploring the addiction potential of ketamine in the context of psychiatric treatment are still lacking. Additionally, an analysis of 14,606 reports from the FDA Adverse Event Reporting System on IN S-ketamine identified 518 adverse event signals, primarily involving psychiatric (33.20%) and nervous system (16.67%) disorders. Dissociation exhibited the highest occurrence rates and signal intensity, with additional strong signals for sedation, dissociative disorders, and rare events such as impaired hand-eye coordination. These findings underscore the need for close monitoring of psychiatric and nervous system effects, including those not mentioned in the product's summary of characteristics [78].

Contraindications

Although ketamine holds potential as a therapeutic agent, it is essential to carefully evaluate contraindications prior to its use. Caution is advised for individuals with uncontrolled hypertension, a history of psychosis, or cardiovascular disorders [75]. Furthermore, ketamine is not recommended for pregnant individuals or those with a history of substance abuse [75]. Ketamine is not inherently contraindicated for individuals with borderline personality disorder, especially when comorbid with TRD. However, its use in this population requires careful consideration, as no standardized protocols currently exist. Combining ketamine treatment with psychotherapy might enhance outcomes, but more research is needed to establish clear guidelines and ensure safety [52].

Medication Interactions

Ketamine is a lipophilic compound that is mainly metabolized by the enzymes CYP3A4 and CYP2B6, without inducing or inhibiting their activity [16]. Notably, it does not significantly interact with commonly prescribed traditional antidepressants, second-generation antipsychotics, lithium, or antiepileptic drugs [79].

However, recent case reports have questioned earlier conclusions, showing comparable results in patients treated with a combination of racemic IV ketamine and monoamine oxidase inhibitors (MAOIs) [79]. These observations were further corroborated by a recent case series examining the use of IN S-ketamine alongside irreversible, nonselective MAOIs [80].

In clinical settings, ketamine's efficacy has been observed to diminish when administered alongside benzodiazepines. This reduction in effectiveness may stem from increased inhibition of pyramidal neurons, which counteracts ketamine's suppression of GABA interneurons through its antagonism of extrasynaptic NMDAR [81]. To maximize treatment benefits, minimizing the use of benzodiazepines (and Z-drugs) is recommended for patients undergoing ketamine therapy for depression [81]. While ketamine does not cause respiratory depression, it can enhance the sedative effects of other substances like barbiturates, opioids, and alcohol [16,82].

Lamotrigine, a molecule of interest in conjunction with ketamine, is thought to produce psychiatric effects by blocking NMDAR [83]. Preclinical research indicates that lamotrigine may amplify ketamine's antidepressant properties by fostering neuroplasticity, reinforcing synaptic connections, and mitigating lipid damage in the hippocampus [84]. However, large-scale controlled studies exploring the combined use of ketamine and lamotrigine have yet to be conducted. Although the evidence for synergistic antidepressant effects of ketamine and lamotrigine is still limited, some reports suggest that lamotrigine may reduce ketamine-related side effects and potentially curb cravings for ketamine [85].

Recommendations

Specific guidelines for the use of ketamine in psychiatric treatment are currently available only for TRD. Even within this scope, developing clear recommendations remains challenging due to the absence of a universally accepted definition of TRD. The most commonly referenced definition, derived from the STAR*D Trial, identifies TRD as the failure to achieve a therapeutic response following two adequate antidepressant treatments [87]. However, consensus on this definition has proven difficult, largely because there are no standardized criteria for what constitutes an adequate treatment trial failure. Moreover, debates persist regarding whether non-pharmacological treatments should be factored into the definition of TRD.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) established a task force to assess the efficacy and safety of racemic ketamine and provide evidence-based clinical recommendations [82]. Their evaluation concluded that IV racemic ketamine has Level 1 evidence for efficacy in adults with TRD. However, the evidence supporting multiple infusions whether as an acute series or for maintenance therapy is limited, corresponding to Level 3 evidence. Adverse effects of ketamine infusions include behavioral issues, such as dissociation, and physiological effects, such as hypertension. Evidence for non-IV formulations of racemic ketamine is even more limited, ranging from Level 3 to Level 4. CANMAT's recommendations for IV racemic ketamine cover key considerations, including patient selection, facility and personnel requirements, treatment monitoring, and strategies to sustain treatment response.

The British National Institute for Health and Care Excellence (NICE) advises IV racemic ketamine only after five consecutive unsuccessful treatments [87]. These treatments include two trials of selective serotonin reuptake inhibitors (SSRIs), an antidepressant from another class, augmentation therapy, a combination of antidepressants, and ECT. NICE classifies racemic ketamine as a sixth-line treatment, limited to use in hospitalized patients. Additionally, NICE's 2020 guidance did not recommend the use of IN S-ketamine for TRD, citing concerns about clinical efficacy and cost-effectiveness [88]. Despite FDA approval in 2019, NICE does not endorse S-ketamine for MDD in adults at imminent risk of suicide, as Janssen, the manufacturer, did not submit the necessary evidence for evaluation. Despite these differences in guidance, an international panel of mood disorder experts reviewed the available literature on the efficacy, safety, and tolerability of racemic ketamine and IN S-ketamine in adults with TRD. They recommend considering ketamine as an augmentation therapy and suggest it be used as a third-line option after two unsuccessful antidepressant treatments [29].

References

1. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000; 47: 351-354.
2. Duman RS, Aghajanian GK. Synaptic dysfunction in depression potential therapeutic targets. Science. 2012; 338: 68-72.
3. Krystal JH, Abdallah CG, Sanacora G, et al. Ketamine A Paradigm Shift for Depression Research and Treatment. Neuron. 2019; 101: 774-778.
4. McIntyre RS, Jain R. Glutamatergic Modulators for Major Depression from Theory to Clinical Use. CNS Drugs. 2024, 38: 869-890.
5. Domino EF. History and pharmacology of PCP and PCP-related analogs. J Psychedelic Drugs. 1980; 12: 223-227.
6. Greifenstein FE, Devault M, Yoshitake J, et al. A study of a 1-aryl cyclo hexyl amine for anesthesia. Anesth Analg. 1958; 37: 283-294.
7. Zarate CA, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006; 63: 856-864.
8. Singh JB, Daly EJ, Mathews M, et al. Approval of esketamine for treatment resistant depression. Lancet Psychiatry. 2020; 7: 232-235.
9. https://www.ema.europa.eu/en/medicines/human/EPAR/spravato
10. Wilkinson ST, Toprak M, Turner M, et al. A survey of the clinical off-label use of ketamine as a treatment for psychiatric disorders. Am J Psychiatry. 2017; 174: 695.

11. Vekhova KA, Namiot ED, Jonsson J, et al. Ketamine andEsketamine in Clinical Trials FDA-Approved and Emerging Indications Trial Trends With Putative Mechanistic Explanations. Clin Pharmacol Ther. 2024.
12. Sforzini L, Worrell C, Kose M, et al. A Delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials. Mol Psychiatry. 2022; 27: 1286-1299.
13. McIntyre RS, Alsuwaidan M, Baune BT, et al. Treatment-resistant depression definition prevalence detection management and investigational interventions. World Psychiatry. 2023; 22: 394-412.
14. Anis NA, Berry SC, Burton NR, et al. The dissociative anaesthetics ketamine and phencyclidine selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. Br J Pharmacol. 1983; 79: 565-575.
15. Zanos P, Moaddel R, Morris PJ, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature. 2016; 533: 481-486.
16. Zanos P, Moaddel R, Morris PJ, et al. Ketamine and ketamine metabolite pharmacology insights into therapeutic mechanisms. Pharmacol Rev. 2018; 70: 621-660.
17. Kim JW, Suzuki K, Kavalali ET, et al. Ketamine Mechanisms and Relevance to Treatment of Depression. Annu Rev Med. 2024, 75: 129-143.
18. Strasburger SE, Bhimani PM, Kaabe JH, et al. What is the mechanism of Ketamines rapid-onset antidepressant effect A concise overview of the surprisingly large number of possibilities. J Clin Pharm Ther. 2017; 42: 147-154.
19. Duman RS, Aghajanian GK, Sanacora G, et al. Synaptic plasticity and depression new insights from stress and rapid-acting antidepressants. Nat Med. 2016; 22: 238.
20. Kim JW, Suzuki K, Kavalali ET, et al. Bridging rapid and sustained antidepressant effects of ketamine. Trends Mol Med. 2023; 29: 364-375.
21. Halaris A, Cook J. The Glutamatergic System in Treatment-Resistant Depression and Comparative Effectiveness of Ketamine and Esketamine Role of Inflammation. Adv Exp Med Biol. 2023; 1411: 487-512.
22. Johnston JN, Greenwald MS, Henter ID, et al. Inflammation stress and depression An exploration of ketamines therapeutic profile. Drug Discov Today. 2023; 28: 103518.
23. Johnston JN, Henter ID, Zarate CA Jr. The antidepressant actions of ketamine and its enantiomers. Pharmacol Ther. 2023; 246: 108431.
24. Scotton E, Antqueviezc B, Vasconcelos MF, et al. Is (R)-ketamine a potential therapeutic agent for treatment-resistant depression with less detrimental side effects? A review of molecular mechanisms underlying ketamine and its enantiomers. Biochem Pharmacol. 2022; 198: 114963.
25. Leal GC, Souza-Marques B, Mello RP, et al. Arketamine as adjunctive therapy for treatment resistant depression A placebo-controlled pilot study. J Affect Disord. 2023; 330: 7-15.
26. Kang MJY, Vazquez GH. Association between peripheral biomarkers and clinical response to IV ketamine for unipolar treatment-resistant depression: An open label study. J Affect Disord. 2022; 318: 331-337.
27. Zheng W, Gu L, Zhou Y, et al. Baseline Plasma BDNF Levels are Associated with Antianhedonic Effects of Repeated-Dose Intravenous Ketamine in Major Depressive Disorder. Curr Neuropharmacol. 2023; 21: 1013-1021.
28. Singh B, Vande Voort JL, Riva-Posse P, et al. Ketamine-Associated Change in Anhedonia and mTOR Expression in Treatment-Resistant Depression. Biol Psychiatry. 2023; 93: e65-e68.
29. McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression an international expert opinion on the available evidence and implementation. Am J Psychiatry. 2021; 178: 383-399.
30. Andrade C. Ketamine for Depression 4: In What Dose at What Rate by What Route for How Long and at What Frequency. J Clin Psychiatry. 2017; 78: e852-e857.
31. Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 2013; 74: 250-256.
32. Marcantoni WS, Akoumba BS, Wassef M, et al. A systematic review and meta-analysis of the efficacy of intravenous ketamine infusion for treatment resistant depression: January 2009-January 2019. J Affect Disord. 2020; 277: 831-841.
33. McMullen EP, Lee Y, Lipsitz O, et al. Strategies to Prolong Ketamines Efficacy in Adults with Treatment-Resistant Depression. Adv Ther. 2021, 38: 2795-2820.
34. Oraee S, Alinejadfard M, Golsorkh H, et al. Intranasal esketamine for patients with major depressive disorder A systematic review and meta-analysis. J Psychiatr Res. 2024; 180: 371-379.
35. SPRAVATO esketamine nasal spray CIII HIGHLIGHTS OF PRESCRIBING IN FORMATION. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211243s004lbl.pdf.
36. Peters EM, Halpape K, Cheveldae I, et al. Intranasal racemic ketamine for patients hospitalized with treatment-resistant depression: A retrospective analysis. Exp Clin Psychopharmacol. 2023; 31: 593-598.
37. Singh B, Kung S, Pazdernik V, et al. Comparative Effectiveness of Intravenous Ketamine and Intranasal Esketamine in Clinical Practice Among Patients with Treatment-Refractory Depression An Observational Study. J Clin Psychiatry. 2023; 84: 22m14548.
38. Andrea G, Pettorruso M, Di Lorenzo G, et al. The rapid antidepressant effectiveness of repeated dose of intravenous ketamine and intranasal esketamine A post-hoc analysis of pooled real-world data. J Affect Disord. 2024; 348: 314-322.

39. Meshkat S, Haikazian S, Di Vincenzo JD, et al. Oral ketamine for depression An updated systematic review. World J Biol Psychiatry. 2023; 31: 1-13.
40. Smith-Apeldoorn SY, Veraart JKE, Kamphuis J, et al. Oral esketamine in patients with treatment-resistant depression a double-blind randomized placebo-controlled trial with open-label extension. Mol Psychiatry. 2024; 29: 2657-2665.
41. Glue P, Loo C, Fam J, et al. Extended-release ketamine tablets for treatment-resistant depression a randomized placebo-controlled phase 2 trial. Nat Med. 2024; 30: 2004-2009.
42. Colla M, Offenhammer B, Scheerer H, et al. Oral prolonged-release ketamine in treatment resistant depression A double-blind randomized placebo-controlled multicentre trial of KET01, a novel ketamine formulation Clinical and safety results. J Psychiatr Res. 2024; 173: 124-130.
43. Tham JCW, Do A, Fridfinnson J, et al. Repeated subcutaneous racemic ketamine in treatment resistant depression case series. Int Clin Psychopharmacol. 2022; 37: 206-214.
44. Loo C, Glozier N, Barton D, et al. Efficacy and safety of a 4-week course of repeated subcutaneous ketamine injections for treatment-resistant depression KADS study randomized double-blind active-controlled trial CORRIGENDUM. Br J Psychiatry. 2024; 225: 349.
45. Palhano-Fontes F, Cavalcanti-Ribeiro P, da Costa Gonçalves KT, et al. Repeated subcutaneous esketamine on treatment-resistant depression An open-label dose titration study. J Affect Disord. 2025; 369: 155-163.
46. Glue P, Neehoff S, Beaglehole B, et al. Ketamine for treatment-resistant major depressive disorder Double-blind active-controlled crossover study. J Psycho pharmacol. 2024; 38: 162-167.
47. Popova V, Daly EJ, Trivedi M, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined with a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression A Randomized Double-Blind Active-Controlled Study. Am J Psychiatry. 2019, 176: 428-438.
48. Vasiliu O. Esketamine for treatment-resistant depression A review of clinical evidence Review. Exp Ther Med. 2023; 25: 111.
49. Calder CN, Kwan ATH, Teopiz KM, et al. Number needed to treat NNT for ketamine and esketamine in adults with treatment-resistant depression A systematic review and meta-analysis. J Affect Disord. 2024; 356: 753-762.
50. Johnson DE, Rodrigues NB, Weisz S, et al. Examining the impact of comorbid posttraumatic stress disorder on ketamines real-world effectiveness in treatment-resistant depression. Eur Neuro psycho pharmacol. 2024, 91: 69-77.
51. Danayan K, Chisamore N, Rodrigues NB, et al. Real world effectiveness of repeated ketamine infusions for treatment-resistant depression with comorbid borderline personality disorder. Psychiatry Res. 2023, 323: 115133.
52. Więdłocha M, Marcinowicz P, Komarnicki J, et al. Depression with comorbid borderline personality disorder could ketamine be a treatment catalyst. Front Psychiatry. 2024, 15: 1398859.
53. Nikayin S, Murphy E, Krystal JH, et al. Long-term safety of ketamine and esketamine in treatment of depression. Expert Opin Drug Saf. 2022; 21: 777-787.
54. Smith-Apeldoorn SY, Veraart JK, Spijker J, et al. Maintenance ketamine treatment for depression a systematic review of efficacy, safety, and tolerability. Lancet Psychiatry. 2022; 9: 907-921.
55. Zaki N, Chen LN, Lane R, et al. Long-term safety and maintenance of response with esketamine nasal spray in participants with treatment-resistant depression interim results of the SUSTAIN-3 study. Neuro psycho pharmacology. 2023; 48: 1225-1233.
56. Guo Q, Guo L, Wang Y, et al. Efficacy and safety of eight enhanced therapies for treatment resistant depression A systematic review and network meta-analysis of RCTs. Psychiatry Res. 2024; 339: 116018.
57. Young AH, Llorca PM, Fagiolini A, et al. Efficacy of esketamine nasal spray over quetiapine extended release over the short and long term sensitivity analyses of ESCAPE-TRD a randomized phase IIIb clinical trial. Br J Psychiatry. 2024; 1-7.
58. Wong S, Kwan ATH, Teopiz KM, et al. A comparison between psilocybin and esketamine in treatment-resistant depression using number needed to treat NNT: A systematic review. J Affect Disord. 2024; 350: 698-705.
59. de A Simoes Moreira D, Gauer LE, Teixeira G, et al. Efficacy and adverse effects of ketamine versus electroconvulsive therapy for major depressive disorder A systematic review and meta analysis. J Affect Disord. 2023; 330: 227-238.
60. Rhee TG, Shim SR, Forester BP, et al. Efficacy and Safety of Ketamine vs Electroconvulsive Therapy Among Patients with Major Depressive Episode A Systematic Review and Meta-analysis. JAMA Psychiatry. 2022; 79: 1162-1172.
61. Anand A, Mathew SJ, Sanacora G, et al. Ketamine versus ECT for Nonpsychotic Treatment Resistant Major Depression. N Engl J Med. 2023; 388: 2315-2325.
62. Jha MK, Wilkinson ST, Krishnan K, et al. Ketamine vs Electroconvulsive Therapy for Treatment Resistant Depression A Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open. 2024; 7: e2417786.
63. Chaudhri SI, Amin A, Panjiyar BK, et al. Comparison of the Efficacy and Adverse Effects of Ketamine and Electroconvulsive Therapy in the Management of Treatment Resistant Depression A Systematic Review. Cureus. 2024, 16: e55596.
64. Jawad MY, Di Vincenzo JD, Badulescu S, et al. The therapeutic role of ketamine and esketamine in treating psychopathological domains of depression. Neuro pharmacology. 2023; 223: 109299.

65. Patarroyo-Rodriguez L, Cavalcanti S, Vande Voort JL, et al. The Use of Ketamine for the Treatment of Anhedonia in Depression. CNS Drugs. 2024; 38: 583-596.

66. Nogo D, Jasrai AK, Kim H, et al. The effect of ketamine on anhedonia improvements in dimensions of anticipatory consummatory and motivation-related reward deficits. Psychopharmacology Berl. 2022; 239: 2011-2039.

67. Kwaśny A, Cubała WJ, Włodarczyk A. Anhedonia and depression severity measures during ketamine administration in treatment-resistant depression. Front Psychiatry. 2024; 15: 1334293.

68. Canuso CM, Singh JB, Maggie Fedgchin, et al. Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide Results of a Double-Blind, Randomized, Placebo-Controlled Study. Am J Psychiatry. 2018; 175: 620-630.

69. Wilkinson ST, Ballard ED, Bloch MH, et al. The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation A Systematic Review and Individual Participant Data Meta-Analysis. Am J Psychiatry. 2018; 175: 150-158.

70. Jollant F, Colle R, Nguyen TML, et al. Ketamine and esketamine in suicidal thoughts and behaviors a systematic review. Ther Adv Psychopharmacol. 2023; 13: 1-25.

71. Anzolin AP, Goularte JF, Pinto JV, et al. Ketamine study Protocol for naturalistic prospective multicenter study on subcutaneous ketamine infusion in depressed patients with active suicidal ideation. Front Psychiatry. 2023; 14: 1147298.

72. Chen CC, Zhou N, Hu N, et al. Acute Effects of Intravenous Sub-Anesthetic Doses of Ketamine and Intranasal Inhaled Esketamine on Suicidal Ideation A Systematic Review and Meta-Analysis. Neuro psychiatr Dis Treat. 2023; 19: 587-599.

73. Singh B, Vande Voort JL, Pazdernik VK, et al. Treatment-resistant depression patients with baseline suicidal ideation required more treatments to achieve therapeutic response with ketamine/esketamine. J Affect Disord. 2024; 351: 534-540.

74. Williamson D, Turkoz I, Wajs E, et al. Adverse Events and Measurement of Dissociation After the First Dose of Esketamine in Patients With TRD. Int J Neuro psycho pharmacol. 2023; 26: 198-206.

75. Schep LJ, Slaughter RJ, Watts M, et al. The clinical toxicology of ketamine. Clin Toxicol Phila. 2023; 2: 1-14.

76. Belal M, Downey A, Doherty R, et al. Consensus statements on the management of ketamine uropathy. BJU Int. 2024; 134: 148-154.

77. Orsolini L, Salvi V, Volpe U. Craving and addictive potential of esketamine as side effects. Expert Opin Drug Saf. 2022; 21: 803-812.

78. Liu R, Liu C, Feng D, et al. Pharmacovigilance of esketamine nasal spray an analysis of the FDA adverse event reporting system database. Front Pharmacol. 2024; 15: 1414703.

79. Veraart JKE, Smith-Appledorn SY, Bakker IM, et al. Pharmacodynamic interactions between ketamine and psychiatric medications used in the treatment of depression a systematic review. Int J Neuro psycho pharmacol. 2021; 24: 808-831.

80. Wallner MA, Eloge JC, Mackey IV, et al. Safety and Tolerability of Concomitant Intranasal Esketamine Treatment with Irreversible Nonselective MAOIs A Case Series. J Clin Psychiatry. 2023; 84: 22cr14598.

81. Andrashko V, Novak T, Brunovsky M, et al. The antidepressant effect of ketamine is dampened by concomitant benzodiazepine medication. Front Psychiatry. 2020; 11: 1.

82. Swainson J, McGirr A, Blier P, et al. The Canadian Network for Mood and Anxiety Treatments CANMAT Task Force Recommendations for the Use of Racemic Ketamine in Adults with Major Depressive Disorder. Can J Psychiatry. 2021; 66: 113-125.

83. Ramadan E, Basselin M, Rao JS, et al. Lamotrigine blocks NMDA receptor-initiated arachidonic acid signalling in rat brain implications for its efficacy in bipolar disorder. Int J Neuro psycho pharmacol. 2012; 15: 931-943.

84. Réus GZ, Matias BI, Maciel AL, et al. Mechanism of synergistic action on behavior oxidative stress and inflammation following co-treatment with ketamine and different antidepressant classes. Pharmacol Rep. 2017; 69: 1094-1102.

85. Wilkowska A, Wiglusz MS, Jakuszkowiak-Wojten K, et al. Ketamine and Lamotrigine Combination in Psycho-pharmacology Systematic Review. Cells. 2022; 11: 645.

86. Rush AJ, Warden D, Wisniewski SR, et al. STAR*D revising conventional wisdom. CNS Drugs. 2009; 23: 627-647.

87. López-Díaz Á, Murillo-Izquierdo M, Moreno-Mellado E. Off-label use of ketamine for treatment resistant depression in clinical practice European perspective. Br J Psychiatry. 2019; 215: 447-448.

88. Mahase E. NICE reconsiders esketamine for depression. BMJ. 2020; 370: m3479.