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Review Article

The Role of Ketamine in Treatment-resistant Depression: A Narrative Review

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Abstract

Ketamine, a non-competitive N-methyl-D-aspartate receptor antagonist, has emerged as an effective therapeutic agent for the management of treatment-resistant depression. Repeated treatments with ketamine show rapid, robust, and sustained antidepressant effects. Despite the large body of evidence, key concerns include adverse effects such as dissociative symptoms, hemodynamic instability, and the risk of abuse with long-term ketamine therapy. This narrative review provides an overview of the neurobiological mechanisms underlying ketamine's antidepressant effects, its basic pharmacodynamics, and its safety profile. The clinical evidence regarding ketamine's efficacy in depression is also summarized, and the need for further research on the long-term effects of ketamine therapy, the development of agents with similar antidepressant effects but fewer adverse effects or potential for abuse, and the identification of biomarkers to predict the response to ketamine is highlighted.

Introduction

Major depressive disorder (MDD) is a debilitating illness affecting up to 300 million people worldwide. It is associated with inadequate recovery, frequent relapses, and persistent functional and psychosocial disability.[1–4] It is reported to be the third leading cause of global disability and a potential risk factor for suicide.[4–7] Despite the wide range of pharmacological agents used to treat depression, a significant proportion of patients (10–20%) do not achieve remission and progress to treatment-resistant depression (TRD).[8–10]

TRD is characterized by a lack of response to at least two different classes of antidepressants administered at the maximum recommended dose for a duration longer than four weeks.[10,11] It is well known that the therapeutic effect of commonly used antidepressant drugs, which modulate the monoamine system, begins after 4–12 weeks of treatment and is associated with frequent relapses.[9,12,13] Pharmacological agents that exert a rapid antidepressant effect are urgently needed in clinical practice.[8,14]

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has proven efficacy and safety as an anesthetic and analgesic agent.[15,16] The potential use of ketamine in depression was first explored in the 1970s, and since then, various studies have reported its rapid and potent antidepressant effects.[17–20] In 2019, the United States Food and Drug Administration (FDA) approved the adjunctive use of intranasal esketamine, the *S*(+) enantiomer of ketamine, for TRD in adults.[21] Moreover, public interest in using ketamine for TRD has been rising, with a widespread positive perception of its utility in reducing symptom severity and promoting remission.[22] Nevertheless, questions have been raised about the tolerability and safety of ketamine administration in TRD, particularly in the long term. Concerns also exist regarding its efficacy with repeated treatments, variability in response duration, and the resources necessary for its safe delivery.[16,21,22] Although many studies support the efficacy of ketamine in TRD, the application of this knowledge in practical settings is limited. This narrative review summarizes the existing literature, providing a comprehensive overview of ketamine's role in depression, including its pharmacology, efficacy, and safety profile. This information is essential for educating healthcare professionals and ensuring they are equipped with up-to-date knowledge to guide their clinical practice and promote evidence-based care. The article also highlights unanswered questions and areas of uncertainty, encouraging further research to address these issues and improve our understanding of ketamine's therapeutic potential.

We performed a systematic search of PubMed, ScienceDirect, and Scopus using the following terms in combination: "Ketamine" OR "NMDA receptor antagonist" AND "Treatment-resistant depression" OR "Refractory depression" OR "Treatment-resistant major depressive disorder" OR "Treatment-resistant MDD." Rel-

Keywords: Ketamine; Depression; Treatment-resistant depression; N-Methyl-D-aspartate receptor antagonist; Refractory depression; Treatment-resistant major depressive disorder.

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evant articles were collected and analyzed. The search was restricted to meta-analyses, parallel-group, and cross-over randomized controlled trials involving ketamine as a pharmacological treatment for depression, with efficacy assessed using standard evaluation scales. The authors thoroughly analyzed all the articles before drafting this narrative review.

The pharmacology and neurobiological mechanism of action of Ketamine

Ketamine is an aryl-cyclo-alkylamine that is water-soluble, with a molecular mass of 238 g/mol and a pKa of 7.5. It is used as a hydrochloride in a relatively acidic (pH 3.5–5.5) aqueous solution, often with preservatives like chlorobutanol and benzethonium chloride.[23]

Ketamine is an optically inactive racemic mixture of two enantiomers, which are mirror images of each other. S-ketamine (esketamine), one of the enantiomers, has more potent NMDA receptor antagonistic properties, superior pharmacokinetic characteristics, and fewer psychomimetic adverse effects.[23] Ketamine is 10–30% bound to plasma proteins.[24] It is highly lipid-soluble with a large volume of distribution.[25] Its metabolism is characterized by N-demethylation via a microsomal enzyme system (cytochrome P450) in the liver, resulting in the formation of norketamine (80%). The clearance rate of ketamine is high (12–20 mL/m/kg) and dependent on liver blood flow.[24] The elimination $t_{1/2}$ of ketamine is 2–3 h, with clearance reported to be 20% higher in females.[26]

Ketamine is a high-affinity antagonist of the ionotropic NMDA receptor, which is a transmembrane ligand-gated ion channel in the glutamatergic neurotransmitter system. By blocking the NMDA receptor channel, ketamine prevents ion influx, thereby reducing action potential generation in neurons.[23] Evidence for NMDA receptor involvement includes randomized clinical trials showing that intravenous esketamine (0.2 mg/kg), the S-enantiomer of ketamine, with more potent NMDA receptor antagonistic properties, is effective in treating TRD.[27–29] A meta-analysis of eight randomized trials involving 1,488 patients with MDD reported that esketamine significantly improved the Montgomery and Åsberg Depression Rating Scale (MADRS) score compared to placebo. The effect began within 2–4 h of the first administration and lasted for the 28-day study period.[30]

The endogenous opioid neuropeptide system, particularly kappa and mu opioid receptor dysregulation, plays a key role in the pathogenesis of affective disorders, as demonstrated by various animal studies.[31–33] A double-blind crossover study randomly assigned TRD patients to two groups: 50 mg naltrexone followed by 0.5 mg/kg ketamine or placebo followed by 0.5 mg/kg ketamine. Each treatment arm was administered once, with a separation of at least two weeks. Among the 12 patients who completed both treatments, the placebo-ketamine combination was reported to be more effective in reducing the 6- and 17-item Hamilton Depression Rating Scale (HAM-D) scores on post-infusion days 1 and 3, suggesting a key role for the opioid receptor pathway.[34]

The AMPA receptor is crucial in glutamate neurotransmission. (2R,6R)-hydroxynorketamine, a ketamine metabolite, activates the AMPA receptor to produce antidepressant effects but does not exhibit NMDA receptor antagonism. An animal study reported that ketamine and (2R,6R)-hydroxynorketamine produced antidepressant effects, but the administration of (2S,6S)-hydroxynorketamine, which does not activate the AMPA receptor, did not result in any antidepressant effect. Moreover, the antidepressant effects were reduced when AMPA receptors were blocked.[35]

Various studies have identified several other molecular mechanisms of ketamine, including the inhibition of the hyperpolarization-activated cation channel, activation of the nitric oxide-guanosine monophosphate pathway, and blockade of nicotinic acetylcholine receptors. Additionally, ketamine has reported downstream effects on inflammation, neuropeptide signaling, and monoaminergic signaling.[36–38]

Functional neuroimaging studies in TRD patients suggest that ketamine's antidepressant action may be linked to the activation of the anterior cingulate cortex, along with increased connectivity between the default mode network and the insula.[39]

Dosing, route of administration, and efficacy profile of ketamine in depression

Krystal and colleagues originally assessed ketamine's role in treating MDD by infusing ketamine at 0.5 mg/kg over 40 m.[40,41] Berman *et al* conducted the first placebo-controlled double-blinded trial to assess the effect of a single intravenous ketamine infusion (0.5mg/kg) in patients with depression. They found significant improvement in symptoms of depression assessed with a reduction of the 25-item HAM-D score at 72 h post ketamine but not after placebo infusion (mean (SD),14 ± 10 points vs. 0 ± 12 points).[17]

The route of administration is an important consideration for conditions like depression, where repeated, regular dosing may be indicated, as it affects serum concentration, bioavailability, duration of action, and patient convenience.[42] Although the intravenous route is most commonly used clinically due to its dose regulation and higher bioavailability, ketamine can also be administered orally, intranasally, sublingually, and subcutaneously.[43–45] A randomized open-label parallel-group study assigned 27 MDD patients to three groups receiving ketamine at doses of 0.5 mg/kg intravenous infusion, 0.5 mg/kg intramuscular, or 0.25 mg/kg intramuscular, respectively. The study reported a similar reduction in HAM-D scores across all three groups—58.86%, 60.29%, and 57.36%, respectively—sustained for three days, with mild, transient adverse effects lasting less than an hour.[46]

Oral ketamine undergoes high first-pass hepatic metabolism, resulting in low bioavailability.[23] However, repeated administration of oral ketamine has been reported to be well-tolerated, though clinically appreciable antidepressant effects emerge only after a delay of two to six weeks.[47] Nasal mucosal inflammation or a deviated septum may impede absorption via the nasal route, making self-administration difficult.[42]

A meta-analysis comparing intranasal, oral, and intravenous ketamine found that the peak antidepressant effect of intravenous ketamine was seen between two to six days, compared to 24 h for the intranasal route. However, the results should be interpreted with caution, as most intravenous ketamine studies involved single infusions, whereas intranasal ketamine has been evaluated in repeat-dose studies. The therapeutic benefits of oral ketamine appeared after seven to twenty days, likely due to accumulated bioavailability. Additionally, there was substantial heterogeneity across the studies included in the meta-analysis.[48]

Another meta-analysis of six trials involving 201 patients assessed the dose-dependent antidepressant effects of ketamine. It reported that ketamine, 0.5 mg/kg over 40 m intravenously, appeared more efficacious than very low doses (50 mg intranasal spray, 0.1–0.4 mg/kg intravenous, or 0.1–0.5 mg/kg intravenous, intramuscular, or subcutaneous). The antidepressant effect, including the reduction of depressive symptoms and suicidality, was apparent within 4 h. However, there was substantial variability in

response, with the therapeutic benefit lasting less than one week for most patients, though around 20% of patients remained in remission at seven days.[49]

Ketamine dose adjustments may be necessary for certain patients. For obese patients (body mass index ≥ 30 kg/m^2), it may be prudent to estimate the dose based on ideal body weight.[50] A meta-analysis of three randomized trials involving 97 patients receiving a total of 205 infusions reported that a brief increase in blood pressure (>180/100 mmHg) or heart rate (>110 beats/minute) occurred in 30% of patients, with the effect more likely in obese patients or those receiving higher doses of ketamine (46 mg versus 42 mg).[51] The rate of ketamine infusion has varied across studies (from 2 m to 100 m), with 40 m being the standard. Moderately slower infusion rates may reduce the incidence of adverse effects such as sedation.[45,48–50,52]

Efficacy and limitations of repeated ketamine therapy

Intravenous racemic ketamine has a short-term antidepressant effect, necessitating repeated ketamine therapy to maintain its therapeutic benefits.[17,48,51,53–56] There are currently no guidelines regarding the frequency of ketamine administration. A recent randomized controlled trial that used saline as a placebo studied the efficacy of intravenous ketamine at a dose of 0.5 mg/kg over 40 m, administered two and three times per week for two weeks in 68 patients with TRD. The study found that both treatment regimens exhibited a similar efficacy profile in terms of reducing the MADRS score.[57]

While various studies have shown that most benefits of ketamine occur early in the treatment course, some studies have indicated a cumulative therapeutic effect with repeated therapy.[58–68] Phillips *et al*. conducted a study in which six ketamine infusions were administered three times weekly for two weeks. Responders, identified by a ≥50% decrease in MADRS score, received weekly ketamine infusions for four weeks during the maintenance phase. A cumulative antidepressant effect was observed, with an average of three infusions needed to achieve the desired response.[59] Table 1 presents recent clinical studies on the antidepressant efficacy of ketamine in TRD.[20,58-67] These studies were selected following a comprehensive search of major databases and focused on the primary outcomes of response or remission rates following ketamine therapy.

Interaction of ketamine with other psychiatric medications

Since most patients prescribed ketamine treatment are already on other psychiatric agents, knowledge of pharmacodynamic interactions is essential.[23,68–70] Moreover, ketamine is often combined with other psychiatric drugs to prevent relapse or to serve as a rescue agent in cases of severe anxiety or agitation.

Synergistic effects of ketamine and lithium through the inhibition of glycogen synthase kinase 3 have been proposed. A study found no difference in depression rating scales between patients receiving lithium or placebo in combination with intravenous ketamine (0.5 mg/kg). It has also been reported that depressive symptoms improved significantly after intravenous ketamine (0.5 mg/kg) in both the valproate and lithium groups, with no significant differences between the two agents. Thus, clinically, lithium did not seem to potentiate ketamine's antidepressant effect in patients with depression.[71]

It has also been reported that lamotrigine might influence the effect of ketamine by reducing glutamate transmission due to sodium channel blockage. Trials have found that cerebral areas showing blood oxygenation level-dependent responses to ketamine revealed greater responses after placebo infusion than after lamotrigine infusion. Another study recorded a significant reduction in ketamine-induced total CADSS and BPRS scores when pre-treated with lamotrigine.[71]

Recent evidence suggests that higher doses of benzodiazepines may attenuate the antidepressant effect of ketamine.[72] One study found a significantly longer time for antidepressant response, a longer remission time, and a shorter time to relapse of depression with benzodiazepine medication (10 mg) after ketamine infusion (0.5 mg/kg). Certain studies have also found enhanced monoamine levels in rat brains induced by ketamine, leading to a hypothesized risk of serotonergic syndrome or hypertensive crisis when combining MAOIs and ketamine.[71]

Some trials have reported a reduction in impairment of executive cognitive functions secondary to ketamine infusion after pre-treatment with haloperidol (5 mg). Additionally, haloperidol reduces the anxiogenic and sedative effects of ketamine. Pre-treatment with risperidone significantly increased ketamine-induced perfusion changes in the prefrontal cortex, cingulate cortex, thalamus, and lateral parietal cortex, though this has yet to be correlated clinically. The strong antidopaminergic and anti-serotonergic effects of risperidone might counteract the increase in monoamines induced by ketamine. Clozapine (430 mg/day) for several weeks significantly blunted the positive symptoms induced by ketamine in 10 patients with schizophrenia.[71]

The concurrent use of antidepressant drugs that inhibit or induce the cytochrome P450 enzyme system in the liver necessitates adjustments in ketamine dosage.[23] The adjunctive use of ketamine may hasten the response to standard antidepressant drugs, which often take six to twelve weeks to show effects. A randomized clinical trial compared ketamine (0.5 mg/kg) with placebo as an add-on therapy to newly initiated escitalopram (10 mg/day). The results showed a superior response with ketamine as an adjunct compared to placebo (92% vs. 57%) in terms of shorter mean time to response (6 days vs. 27 days).[73]

Ketamine and electroconvulsive therapy

Electroconvulsive therapy (ECT) is widely recognized as the most rapid and effective treatment for TRD. However, ketamine has emerged as an appealing alternative due to its fast-acting antidepressant properties and ability to alleviate suicidal ideation.

A recent study sought to evaluate and compare the efficacy and tolerability of ECT and ketamine across various depression-related outcomes. While the ECT group experienced a greater reduction in depression scores, there was no significant difference in remission and relapse rates between the two treatments. Ketamine demonstrated better post-treatment cognitive outcomes and a lower incidence of muscle pain compared to ECT, though it was associated with a higher occurrence of dissociative symptoms. In a subgroup analysis focusing on inpatients, ketamine was less effective than ECT in terms of response rates, remission, and improvements in depression scores. These findings suggest a preference for ECT over ketamine for inpatient treatment.[66]

Anand *et al*. discovered that ketamine was similarly effective to ECT for treating treatment-resistant major depression without psychosis. In their study, 55.4% of patients in the ketamine group and 41.2% in the ECT group showed a significant treatment response (with a difference of 14.2%, $P < 0.001$, indicating ketamine's non-inferiority to ECT).[74] Another randomized controlled trial indi-

Table 1. Clinical studies on the antidepressant efficacy of ketamine in treatment-resistant depression

Author (s), Year, Country	Study design	Sample characteristics	Results	Response rate and remission rate	Limitations	Conclusion
Murrough *et al*,[60] 2013, Egypt	A two-site, parallel-arm, randomized placebo-controlled trial	Patients (n = 73) with TRD experiencing a major depressive episode were randomly assigned to receive a single intravenous infusion of ketamine (0.5mg/kg over 40 m) or midazolam in a 2:1 ratio	Greater improvement in the MADRS score along with lower MADRS score in the ketamine group than in the midazolam group by 7.95 points (95% confidence interval [CI], 3.20 to 12.71) 24 h after treatment.	A response rate of 64%.	Patients with psychotic symptoms/substance abuse were excluded. Moreover, a significant percentage (17.2%) of screened patients refused/were unable to tolerate psychotropic medication washout prior to randomization.	Ketamine showed a rapid antidepressant effect after a single infusion in TRD patients.
Mandal *et al*,[61] 2019, India	Open-label prospective study	Male patients (n = 25) with severe depression received 0.5 mg/kg intravenous ketamine bolus and were assessed using HAM-D, HAM-A, and CGI. Six doses were given over two weeks and final assessments were made after one month of the last dose.	There was a significant reduction in mean scores (HAM-D) at the 1st h of the 1st dose ($P < 0.01$), at the end of two weeks ($P < 0.001$) and after one month during follow-up ($P < 0.001$). No significant change in mean scores of CGI severity after 1st h of 1st dose. However, there was a significant reduction in mean scores at the end of two weeks ($P < 0.001$) and after one month ($P < 0.001$).	–	Open-label design, absence of female patients limits the interpretation and generalisability of results.	Ketamine has a robust and rapid effect on depression, which was seen immediately after the administration of ketamine and sustained at the end of one month.
Zarate *et al*,[62] 2006, United States	Randomized placebo-controlled, double-blind crossover study	Patients with TRD (n = 18) were randomized to receive ketamine hydrochloride (0.5 mg/kg) or placebo on two days, a week apart, and assessed using. HAM-D score at baseline and at 40, 80, 110, and 230 m and one, two, three, and seven days post-infusion.	A significant improvement in HAM-D score was seen with ketamine at 110 m compared to placebo. 71% of those treated with ketamine met response and 29%-35% of these subjects continued to respond for at least one week.	The response rate is 71% and the remission rate is 29% the day following ketamine infusion.	The relatively small study population. Pharmacological responses may be different from those with a less severe or shorter course of illness. Limitations in preserving blinding potentially confounding results.	A robust and rapid antidepressant effect resulted from a single intravenous infusion of ketamine with onset within 2 h sustained for one week.

(continued)

Table 1. *(continued)*

Author (s), Year, Country	Study design	Sample characteristics	Results	Response rate and remission rate	Limitations	Conclusion
Phelps *et al*,[63] 2009, United States	Open-label study	Patients with TRD (n = 26) were treated with a single intravenous ketamine (0.5 mg/kg) and rated with MADRS at baseline, 40, 80, 120, and 230 m post-infusion.	Overall, 43% of patients had at least a 50% decrease from baseline MADRS scores and 26% had a MADRS below 10 at 230 m post-infusion. Patients with a positive family history of alcohol abuse/dependence group had a significantly higher response rate (67% v/s 18%, $P = 0.02$) and a higher remission rate (42% v/s 9%, $P = 0.08$)	The response rate is 43% and the remission rate is 26%.	The small sample size limited the generalization of findings. There was no control group. Self-reporting was used to determine the family history.	A family history of alcohol dependence was a predictor of a rapid initial antidepressant response to ketamine.
Machado-Vieira *et al*,[64] 2009, United States	Open-label study	Patients with TRD (n = 23) received a single infusion of intravenous ketamine hydrochloride (0.5 mg/kg) and response was rated using MADRS score at baseline and at 40, 80, 120, and 230 m post-infusion. BDNF samples were taken at the same time points	A significant improvement in MADRS scores after ketamine treatment was obtained ($F_{4,81} = 24.70$, $P < 0.001$). There were no changes in BDNF levels in subjects receiving ketamine compared to baseline.	The response rate is 47.8%.	There is a possibility that BDNF levels might alter at later time points.	Ketamine demonstrated rapid antidepressant effects not mediated by BDNF.
Phillips *et al*,[59] 2019, Canada	A single-site randomized double-blind placebo-controlled crossover study	Patients with TRD (n = 41) received single infusions of ketamine and midazolam. On relapse, a course of six open-label ketamine infusions was administered thrice weekly over two weeks Four additional infusions were administered once weekly in responders.	11 participants (27%) met antidepressant response criteria, and two participants (5%) achieved remission 24 h after the first ketamine infusion. Responders had a mean decrease of 22.3 points (SD = 5.3) MADRS score. With once-weekly maintenance ketamine infusions, participants had no significant change in depression severity ($P = 0.49$).	Response rate of 59%, Remission rate of 23% on repeated therapy	Questionable integrity of the blinding in the crossover comparison. Open label with no active control. Modest sample size.	Repeated ketamine infusions have cumulative and sustained antidepressant effects.
aan het Rot M *et al*,[58] United States	Placebo-controlled crossover study	Symptomatic patients with TRD (n = 10) not on antidepressants, received a 40-min IV infusion of ketamine (0.5 mg/kg). Responders (> or =50% reduction in MADRS scores on day 2), received five more infusions (days 3, 5, 8, 10, and 12)	The response criterion was met by nine patients after the first infusion as well as after the sixth infusion. An 85% reduction in MADRS scores after the sixth infusion was seen. Post ketamine, eight of nine patients relapsed, on average, 19 days after the sixth infusion.	Response rate of 90%.	Limited sample size	This study demonstrated the feasibility of repeated-dose IV ketamine for the acute treatment of TRD.

(continued)

Table 1. *(continued)*

Author (s), Year, Country	Study design	Sample characteristics	Results	Response rate and remission rate	Limitations	Conclusion
M fava *et al*,[20] 2020, United States	A multi-site, double-blind, placebo-controlled study	Patients with TRD (n = 99) were randomly assigned to one of the five arms 1:1:1:1:1 (Ketamine -a single intravenous dose of 0.1 mg/kg (n = 18), 0.2 mg/kg (n = 20), 0.5 mg/kg (n = 22), 1.0 mg/kg (n = 20), and a single dose of midazolam 0.045 mg/kg (n = 19) and assessed on days 0, 1, 3, 5, 7, 14, and 30.	The overall group × time interaction effect was significant for the primary outcome measure, the HAM-D-6. In post hoc pairwise comparisons controlling for multiple comparisons, standard dose (0.5 mg/kg) and high dose (1 mg/kg) of intravenous ketamine were superior to active placebo.	0.5 mg/kg and 1.0 mg/kg had higher response rates as compared to lower doses.	A small sample size and the large corresponding confidence intervals around the estimates of effect sizes. The results may have been confounded by the variability in the degree of responsiveness across the treatment groups.	The study provided evidence for the efficacy of the 0.5 mg/kg and 1 mg/kg doses of IV ketamine and no clear or consistent evidence for the efficacy of lower doses of IV ketamine.
Shiroma *et al*,[65] 2020, United States	A randomized, double-blind, active placebo-controlled study	Patients with TRD (n = 54) received either six ketamine or five midazolam infusions (placebo) followed by a single ketamine for 12 days followed by up to a six-month post-treatment period.	There was no significant difference between single versus six ketamine treatments at 24 h post-treatment. The median time-to-relapse was nominally but not statistically different (two and six weeks for the single and six ketamine groups, respectively	Response rate of up to 75% and remission rate of 54%.	The study for the primary outcome was underpowered. Concomitant psychiatric drugs were continued for at least six weeks prior to study onset. The population studied was predominantly male (85%). Around 20% of patients had sub-syndromal PTSD.	Acute repeated ketamine showed greater antidepressant efficacy than midazolam.
Ibrahim *et al*,[66] 2011, USA	Open-label study	Patients with MDD who previously did not respond to ECT (n = 17) and patients with TRD who had not previously received ECT (n = 23) were administered ketamine (0.5 mg/kg) and evaluated using the MADRS	The ECT-resistant group had significantly higher scores than the non-ECT-exposed group. The proportion of patients exhibiting a substantial improvement in depressive symptoms (50%) did not significantly differ between the two groups ($P = 0.33$)	Response rate of 50%	It is an open-label study.	Ketamine appears to improve depressive symptoms in patients with MDD who had previously not responded to ECT.
Cullen *et al*,[67] 2018, United States	Open Label Study	Patients with TRD (n = 13) were administered six ketamine (0.5 mg/kg) infusions over two weeks and the response was evaluated using the Children's Depression Rating Scale-Revised (CDRS-R).	Average decrease in CDRS-R was 42.5% ($P = 0.0004$). Five (38%) adolescents met the criteria for clinical response. Three responders showed sustained remission at the six-week follow-up; relapse occurred within two weeks for the other two responders.	Response rate of 38% and remission rate of 23%.	It is an open-label design with a small sample size	This study demonstrates the potential role of ketamine in treating adolescents with TRD

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cated that ECT was more effective than ketamine, especially after six sessions for severe depression.[75] A recent meta-analysis found no evidence to favor ketamine over ECT in reducing depressive symptoms or improving response rates.[76]

Given the burdens associated with ECT, such as the risk of transient cognitive side effects, repeated exposure to general anesthesia, stigma, and limited accessibility, ketamine might be considered a more tolerable option. However, ketamine also presents risks, including the potential for abuse and possible bladder and neurotoxicity. Therefore, individual patient factors will significantly influence the choice of treatment for both patients and providers.[77] The American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments stated conclusively that ketamine should not be considered a substitute for ECT, as the potential risk of relapse is nearly twice as high with ketamine after successful therapy with either ECT or ketamine.[78]

Side effects of ketamine therapy used in depressive disorders

Ketamine is classified as a Schedule III controlled substance under the Controlled Substance Act and is approved by the FDA for anesthetic purposes, (https://pubchem.ncbi.nlm.nih.gov/compound/Ketamine). A short duration of ketamine therapy for TRD is generally well tolerated and considered relatively safe. Early termination due to severe adverse effects, such as hemodynamic instability, psychotomimetic symptoms, and anxiety, was observed in only 2% of patients.[52]

Dissociative symptoms and psychotomimetic effects were reported in more than 70% of the trials.[68,79] Visual hallucinations, unusual thought content, and conceptual disorganization were observed to peak shortly after ketamine infusion and typically resolved within 2 h.[78,80–83] Dysphoria, treatment-emergent suicidal ideation, and transient mania or hypomania were also reported.[82,83] Transient increases in anxiety, which typically resolve within 80–120 m, are also frequently reported.[69] Non-dissociative side effects associated with ketamine administration include agitation, mild sedation, nausea, vomiting, headaches, blurred vision, dizziness, dry or numb mouth, irritability, delirium, sensory changes, vertigo, and drowsiness.[81,84,85]

Cardiovascular side effects include an average increase in systolic blood pressure (8–19 mmHg) and diastolic blood pressure (13 mmHg), with onset typically within 40 m of infusion and resolution within 2–4 h.[28,52] A retrospective analysis of 66 patients who received approximately 10 infusions of ketamine (0.5 mg/kg over 40 m) reported a 30% incidence of pharmacotherapy-controlled essential hypertension, which generally resolved within 70 m.[86]

Heart rate increased by an average of nine beats per minute within two hours of infusion and returned to baseline within 60 m. More severe cardiac effects, such as intermittent atrial fibrillation and ventricular extrasystoles, were also observed.[86,87]

Ketamine exhibits agonist activity at opioid receptors and shares structural similarities with phencyclidine, which can result in euphoric or hallucinogenic effects and a potential for abuse and addiction.[50,88] Ketamine abuse has been associated with bladder dysfunction and liver injury. Symptoms of lower urinary tract involvement include nocturia, painful hematuria, urinary urgency, incontinence, and dysuria.[88]

According to available data, the most common side effects of ketamine are generally mild, short-lived, and self-limiting. However, emerging evidence suggests that high doses of ketamine may lead to long-term cognitive impairment. Despite this, numerous clinical trials have demonstrated that cognitive function tends to remain stable or even improve over time, indicating no increased risk of cognitive impairment when ketamine is used at appropriate doses and frequencies.[89]

Concerns about the long-term safety of ketamine treatment primarily arise from studies on individuals with ketamine use disorder, which have shown significant adverse effects, including persistent dissociative and psychotic symptoms, cognitive impairment, and interstitial cystitis.[90] Long-term recreational use of ketamine has also been linked to reduced grey matter volume, decreased white matter integrity, and impaired thalamocortical and corticocortical connectivity. These changes may contribute to the long-term cognitive and psychiatric effects observed, such as memory impairment and executive dysfunction.[91] However, further research is needed to definitively establish the safety profile of long-term ketamine use.

Limitations of ketamine therapy in depression

Further investigations are required to determine whether the antidepressant effects of ketamine are sustained in the long term. The study of biomarkers may enhance our understanding of heterogeneous and complex psychiatric disorders like MDD.[92] Functional neuroimaging studies conducted by Salvadore *et al*. have demonstrated that increased activation of the anterior cingulate cortex could serve as a reliable biomarker for identifying ketamine responders.[93]

Another issue that needs to be addressed is the variability in the duration of response, as well as whether repeated ketamine therapy leads to habituation or tolerance of its antidepressant effects. The optimal dosing strategy (weekly, biweekly, or monthly) also remains unclear, given the variable response duration. Additionally, the utility of ketamine in other forms of depression has not been thoroughly evaluated. Moreover, most studies and randomized trials have not fully assessed the long-term implications of repeated ketamine therapy. Since many of the studies included in this narrative review are short-term trials, caution should be exercised when interpreting the findings.

The role of Esketamine in the treatment of depression

Esketamine, the S-enantiomer of ketamine, was approved by the FDA for use in depression in 2019, (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211243lbl.pdf). The dosing model for esketamine includes an induction phase of twice-weekly dosing (intranasal esketamine effective doses: 56 mg and 84 mg), tapering down to a weekly maintenance phase for four weeks, and later to every one to two weeks thereafter, with no maximum duration specified.[93,94] The efficacy of intranasal esketamine as an augmentation therapy in TRD was established in a meta-analysis (five trials, n = 774 patients), which reported that adjunctive esketamine was significantly more effective compared to placebo in treatment response, changes in MADRS scores, and remission. This finding was consistent despite differences in the study samples and baseline standard antidepressants.[95]

Esketamine has also demonstrated a 51% reduction in relapse among those achieving stable remission when used as an adjunct with a standard antidepressant, compared to a placebo.[96] The relative efficacies of intravenous racemic ketamine and intranasal esketamine have yet to be established due to the lack of adequately powered comparator trials.[97,98] A recent meta-analysis compared intravenous and intranasal ketamine/esketamine formulations and found no significant difference in efficacy between the two formu-

lations at 24 h, one week, and four weeks.[99] Another meta-analysis (24 trials, 1,877 participants) revealed that intravenous ketamine had a superior response rate (rate ratio (RR) = 3.01 vs. 1.38), a better rate of remission (RR = 3.70 vs. 1.47), and a lower dropout rate (RR = 0.76 vs. 1.37) compared to intranasal esketamine.[100] However, the substantial heterogeneity among the component studies makes it challenging to draw definitive conclusions.

Guidelines and recommendations for the use of ketamine in depression

The use of ketamine in treating depression is expanding rapidly, emphasizing the need for standardized guidelines to regulate its application. This is particularly important as ketamine for TRD is not FDA-approved, despite substantial evidence supporting its safety and efficacy.

The Canadian Network for Mood and Anxiety Treatments has recommended ketamine as a third-line treatment option for adults with TRD. They recommend intravenous ketamine (0.5 mg/kg over 40 m), administered as a single infusion or as a course of repeated therapy two to three times per week for a total of four to eight infusions (Level 3 evidence). There is limited evidence regarding the efficacy of a longer course of six to eight repeated infusions. Additionally, Level 3 evidence supports the use of oral ketamine, while Level 4 evidence supports sublingual and intranasal formulations of racemic ketamine.[101]

JAMA Psychiatry and the American Journal of Psychiatry have also published evidence-based guidelines and detailed recommendations for ketamine therapy in depression.[50,92] It is generally advised that racemic ketamine should only be administered by specialist physicians with adequate knowledge and experience in its use, and in centers equipped with sufficient resources for patient monitoring and immediate care.[101]

Future directions

The urgent need is to identify or develop agents with an efficacy profile similar to that of ketamine but without its associated adverse effects or the risk of addiction and abuse. Agents with common mechanisms of action that avoid these issues are essential. Potential alternatives under investigation include the (*R*)-enantiomer of ketamine, arketamine, and ketamine metabolites such as (2*R*,6*R*)-hydroxynorketamine. Animal studies have shown that arketamine may have a longer-lasting and more potent antidepressant effect compared to ketamine/esketamine, with a reduced risk of behavioral or psychotomimetic effects and a lower potential for abuse.[22,36]

Conclusions

Ketamine has been found to play an essential role in the effective management of patients with TRD. A robust body of evidence supports its rapid and potent antidepressant action, and emerging studies suggest that repeated therapy may prolong its effects. However, future multi-center studies are needed to establish the long-term efficacy, optimal route, dosing protocol, and safety profile of ketamine, particularly with extended use.

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Conflict of interest

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Author contributions

Contributed to study concept and design (AR and AB), acquisition of the data (SP and KJ), assay performance and data analysis (AR, PT, KK, RC, and AL), drafting of the manuscript (AR, AB and YL), critical revision of the manuscript (AR, PT, KK and SP), supervision (AB, KJ, RC and AL).

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