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Key considerations for the use of ketamine and esketamine for the treatment of depression: focusing on administration, safety, and tolerability

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Abstract

Introduction: Racemic ketamine, a derivative of phencyclidine, has been used as a dissociative anesthetic since 1970. In 2000, the first randomized controlled trial showed a rapid relief of depressive symptoms. Since then, intravenous ketamine and intranasal S-ketamine have been validated for the treatment of depression and suicidal ideation following dose-response and double-blind placebo-controlled clinical trials. In clinical practice, after dose titration and with repeated treatments, patients may experience approximately 2–3 weeks of symptomatic relief from depression.

Areas covered: Areas covered in this narrative review include mechanism of action, dosing, safety, and tolerability. Some attention is paid to the possibility of R-ketamine as a future antidepressant.

Expert opinion: We recommend further investigation into treatment dosing and frequency strategies as well as approaches that prolong the therapeutic effects. The current fixed dosing of esketamine for obese individuals may be insufficient. Additional investigation into co-administration with somatic and neuromodulation treatments needs investigation. Finally, continuing to monitor research subjects and patients long-term for the emergence of adverse effects on cognition or other organ systems is critical.

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Declaration of interests

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Keywords

Ketamine; esketamine; depression; treatment-resistant depression

1. Introduction

Racemic ketamine, a derivative of phencyclidine (PCP), has been used as a dissociative anesthetic since 1970 [1] [2,3]. In 2000, the first randomized controlled trial published by Berman at el., showed a rapid relief of depressive symptoms [4]. Since then, i. v. ketamine has been validated for the treatment of depression and suicidal ideation following dose-response and double-blind placebo-controlled clinical trials. Saline-controlled trials were followed by midazolam-controlled trials as an active placebo [5]. The results demonstrated robust and rapid improvement in depressive and suicidal symptoms in patients with treatment-resistant depression (TRD; defined as lack of sufficient treatment response to at least two antidepressant medications [6], though this definition is evolving, see Papp, et al. [7]). Meta-analyses regarding the efficacy of i.v. ketamine have been conducted and it is largely considered to be rapidly acting antidepressant treatment [8]. Subsequently, investigations focused on safer and easier administration of ketamine [9] [10]. By 2019, intranasal (i. n.) esketamine was approved by the FDA for clinical use as an adjunctive treatment for patients with TRD and/or suicidal ideation/behavior. Currently accompanied by risk evaluation and mitigation strategies (REMS) program for monitoring its use and for adverse events [11]. Intravenous ketamine therapy and i.n. esketamine are known to have acute euphoric, anxiolytic, and dissociative effects with subacute improvements in mood and suicidality typically lasting 3–7 days [12]. Intravenous racemic ketmaine is typically initiated 2–3 times per week for 2–3 weeks, with dose titration as tolerated, and the interval duration between treatments is increased as tolerated to weekly infusions. With repeated infusions, the improvements may last up to three weeks [13]. Intranasal esketamine has fixed dose applicators and is typically given initiated 2 times per week for 2–3 weeks, then weekly and then biweekly if effective Recent meta-analyses fortify the notion that regardless of administration route, ketamine and esketamine treatments are effective, though direct comparisons have not been conducted [14]. Though ketamine and esketamine treatments reduce depressive symptoms, there are important considerations regarding safety and tolerability that one must consider when using ketamine and esketamine in clinical settings. In the following narrative review, we will discuss the use of i.v. racemic ketamine and i.n. esketamine in clinical use for the treatment of depression, accompanied by practical suggestions for delivering and optimizing these treatments. Attention is paid to safety, tolerability, and dosing of this treatment. Other administration routes and formulations are briefly discussed, as is the novel pharmacological treatment approach – arketamine.

2. Mechanism and pharmacokinetics

Racemic ketamine is an effective treatment for depression when administered intravenously, intranasally [15], orally [16], and subcutaneously [10]. Regardless of route, once administered, ketamine is rapidly disseminated throughout the body and eliminated relatively rapidly as well [17]. It has a half-life of approximately 2 hours in humans

and is not appreciably protein bound. Racemic R,S-ketamine is first meta-bolized by liver P450 cytochromes (CYP2B6 and CYP3A4) to R, S-norketamine (NK), peaking around 1 hour after i.v. infusion and then hydroxylated to a more stable (2R,6R;2S,6S)-hydroxynorketamine (HNK) and (R,S)-dehydroxynorketamine, which can be found in plasma up to 48 hours post-infusion. Interestingly, the recent discovery that HNK has antidepressant effects may help explain how the accumulation of ketamine metabolites could be responsible for the prolonged antidepressant effects of racemic ketamine [18].

Various mechanisms of action for racemic ketamine have been illustrated [19]. Ketamine is thought to primarily an N-methyl-D-aspartate (NMDA) receptor antagonist, thereby shunting ions through AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors and engaging a multitude of neuronal signaling cascades, including synaptogenic mTORC1 (mammalian target of rapamycin complex 1) and brain-derived neurotrophic factor (BDNF) [20,21], however human studies have yet to substantiate BDNF in peripheral blood samples [22–24]. Other pharmacodynamic mechanisms have been shown as well, namely, agonism of opioid receptors and of the dopamine 2 receptor, antagonism of nicotinic and muscarinic cholinergic receptors and inhibition of serotonin, norepinephrine, and dopamine transporters, as well as a cholinesterase inhibitor [12]. It is through a combination of these, and likely other mechanisms, that ketamine facilitates the rapid improvement of mood and suicidality in individuals suffering from treatment-resistant depression.

The primary focus of this article is related to the pharmacological, biological, clinical safety and efficacy of ketamine and esketamine treatment. However, given the resurgence of interest in psychedelic treatment, the psychological effects an individual experiences when receiving ketamine and esketamine treatment cannot be ignored. As with any drug-assisted psychotherapy, the subjective experience and the clinical setting are also present with ketamine treatment [25]. There is ongoing investigation into the efficacy of ketamine-assisted psychotherapy. The underlying notion is that psychedelic therapy can be a drug-assisted form of psychotherapy rather than pure pharmacotherapy [26] [27]. With this approach, psychological factors involving the clinical context such as the preceding preparation as well as subsequent integration of the experience are thought to be important for influencing therapeutic outcome.

Additionally, as the S-enantiomer of ketamine was gaining clinical interest as ‘esketamine,’ the R-enantiomer (referred to as ‘arketamine’) was gaining preclinical interest as it appeared to elicit antidepressant effects without NMDA-blockade [28], and therefore without the dissociative experience. This effort is particularly intriguing as it offers the possibility of a novel antidepressant without the psychedelic and dissociative effects associated with S-ketamine. There have been encouraging results from an open-label clinical trial [29] and future investigation will determine its validity and potential clinical use.

3. Efficacy

Many clinical trials investigating i.v. ketamine use for patients with TRD have been conducted, most of which had less than 100 participants, yet meta-analyses have substantiated its clinical utility [30] [31]. According to STAR*D, the chance of a patient

responding to a third class of medication after failing two adequate trials is less than 25% [32]. The European Group for the study of Resistant Depression recently found that there is futility in rotating antidepressant medications and that patients with TRD most likely have a combination of genetic as well as specific patient factors such as severity and duration of illness, including psychosis and/or melancholic or anxious features, among others, that determine treatment-resistance [33]. Practically, most patients seeking ketamine treatment have failed four or more antidepressants and many augmentation strategies, including psychotherapy, leading to high morbidity rates in many cases [34] [35]. Therefore, it is important to consider the degree of treatment resistance when interpreting the data presented in clinical trials as many trials include patients who failed a minimum of two medication trials, though some failed four [5]. For someone with little improvement after 2–4 pharmacotherapies and likely one or more psychotherapy trials to then have an up to a 50% chance of rapid antidepressant response to ketamine or esketamine is quite remarkable [20]. The main drawback from these treatments is the short duration of response and the likely need for maintenance treatments in many patients [36]. Although many doses have been investigated, there are many open questions about the dosing and frequency of ketamine administration. Lastly, the use of i.v. ketamine in adolescent populations has been investigated with encouraging results [37] [38]; however, long term and frequent use should be met with caution given the concern for adverse cognitive effects that would occur during the neurodevelopmental period. This should be balanced with the adverse effect of severe depression and suicidal ideation in a developing adolescent.

4. Response

To constitute a response to i.v. ketamine during treatment, we would expect a temporary decrease in a patient's depression and anxiety symptoms (>20–50% reduction), typically lasting up to a week, with the most pronounced response within the first 24 hours [14]. In clinical practice, to achieve sufficient reduction in depressive symptoms for a week post-infusion, many individuals need doses higher than 0.5 mg/kg (up to 1.0 mg/kg). Individuals are generally thought to be non-responders if they display less than a 20% reduction in their symptoms by their sixth infusion, typically assayed with a Quick Inventory of Depression Symptomatology (QIDS) or Patient Health Questionnaire-9 (PHQ-9) [20].

Intravenous ketamine doses ranging from 0.5 to 1.0 mg/kg have been shown to remit depressive and suicidal symptoms for 3–7 days. With repeated doses of weekly i.v. ketamine or i. n. esketamine, efficacy has been shown to increase the treatment interval duration to 2–3 weeks [39] [40]. Additional research into maintenance is needed as the median time to relapse after i.v. ketamine is approximately a month (median 18 days) [13,41,42]. Importantly, there has been varied data regarding gender differences in response to ketamine treatments [43,44]. On balance, the gender difference to treatment response may favor women, but be less of an issue compared to dosing and to side effects. More improtantly, there have been differences observed in degree of discontinuation symptoms, which can play a role in morbidity and adverse outcomes [45]. Therefore, given the potential for rapid relapse because of ketamine's the lack of sustained improvement, care should be taken to ensure appropriate outpatient infrastructure is in place. Furthermore, due to the instability of

response, this rapidly acting antidepressant approach may be contraindicated in some patient populations, though this has yet to be determined.

4.1. Considerations for dosing and frequency

While doses of i.v. racemic ketamine as low as 0.1 mg/kg have been shown to be effective in controlled trials, the data supports the notion that consistent and effective remission of depressive symptoms is between 0.5 and 1.0 mg/kg. Dosing at 1.0 mg/kg is generally well tolerated and is associated with more intense psychedelic experiences and increases the risk of adverse events. One approach would begin with a 2–3 week 'titration' phase starting at 0.5 mg/kg as infused over 40 minutes and increasing by 0.1 mg/kg as tolerated to 1.0 mg/kg for each of the subsequent titration doses (up to first six treatments). Most patients can undergo maintenance treatment at a 1–3-week interval. Dosing with i.n. esketamine has far less flexibility due to commercially available products [46]. Currently, i.n. esketamine can be delivered in two doses, 56 mg and 84 mg, typically administered 2 times per week for the first 2–4 weeks and then weekly or every other week [20]. Most patients begin with 56 mg and then titrate to the higher dose as tolerated. A trial of ketamine or esketamine treatment is considered failed if there is a minimal response (<20%) after four weeks of treatment.

It is not currently known how long patients should remain on maintenance ketamine or esketamine treatment and whether 1–3-week maintenance is safer in the long term than rescue treatments as relapse prevention. A clinic may not have sufficient resources to provide titration treatments while also amassing a large cohort of maintenance patients. This may limit access to treatment. Threfore, it may be safe to assume that once a patient can have a consistent interval of 3–4 weeks without a significant deterioration in their mood, those individuals could consider a rescue/relapse prevention approach in the event of another impending major depressive episode, though this approach has not been investigated.

4.2. A practical protocol for ketamine infusion therapy would be as follows

Have the patient fast for three hours prior to infusion to limit nausea. Then upon the patient's arrival, obtain weight and baseline vital signs, then conduct a brief psychiatric interview, determine the dose, place the IV and begin ketamine infusion over 40 minutes, obtain vital signs at 20 mins and at conclusion of infusion (40 min timepoint), then again at 60 minutes to monitor for downtrend in heart rate and blood pressure. After the final blood pressure measurement at 40 minutes post-infusion, offer the patient an assisted/supervised walk to the restroom. This will allow for the opportunity to assess gait and dizziness. Encouraging hydration and urination after infusion may help prevent genitourinary complications. We recommend patients have a trusted chaperone to escort them home after treatment as one should not drive after receiving anesthesia. Intranasal esketamine has a thorough protocol for administration and information can be found on the esketamine REMS website. It is similar to the i.v. ketamine protocol, except there is a two-hour requirement for the treatment in order to monitor for adverse events. Blood pressure is monitored before, during and after esketamine treatment and there are treatment and observation forms to be submitted to the REMS database.

5. Tolerability

Esketamine was initially introduced as an anesthetic in Germany in 1997 and has been shown to cause somnolence, dizziness, and vertigo [47]. A recent and large meta-analysis (eight double-blind, randomized controlled clinical trials with 1,488 subjects) comparing efficacy and safety of i.n. esketamine and placebo in patients with Major Depressive Disorder revealed that i.n. esketamine had higher total adverse events (AEs) than the placebo group. Similarly, patients frequently experience transient sedation, dissociation, dizziness, and gait instability after ketamine infusion [48]. Therefore, care must be taken to ensure safety after treatment. In combination with altered mental status, a patient in an treatmentinduced dissociative state is at risk of falling and should be monitored until they have recovered. Older patients, or others at risk of falling, should remain in their chair or bed for at least an hour post-treatment until they demonstrate that they are safe to ambulate.

Although most people experience anxiolytic effects from i. v. ketamine or i.n. esketamine, over 70% of patients experience dissociation [49]. This psychedelic/dissociative experience may be too intense for some and can be mitigated with dose reductions or with lorazepam administration [50]. Additionally, up to 40% of patients experience nausea from i.v. ketamine and esketamine [51]. It is typically treated or prevented with the coadministration of ondansetron (IV or oral dissolving tablet) and other medications such as prochlor-perazine or haloperidol for refractory cases (with consideration paid to the QT interval). Patients may also experience blurred vision and dry mouth, which typically return to baseline within an hour of treatment. A two-year naturalistic study showed that approximately 50% of patients who started i.v. ketamine treatments dropped out within their induction period, but this was mainly due lack of clinical benefit and cost, not intolerability [34]. Lastly, it must be noted that practitioners should avoid ketamine and esketamine treatment in pregnant and lactating mothers due to lack of evidence of adverse outcomes. Pregnancy tests or confirmation of compliance with contraception is highly recommended before administering such treatments.

5.1. Long-term safety and tolerability of esketamine

In a recent open-label, multicenter, long-term study (up to 1 year) [52] including 802 TRD patients, i.n. esketamine plus new antidepressant combination showed a safety profile consistent with those reported in the short-term placebo-controlled studies. The majority of adverse events were mild or moderate in severity, and most patients with serious adverse events (AEs) either recovered or were recovering at study closure. Common side effects included dizziness (32.9%), dissociation (27.6%), nausea (25.1%), and headache (24.9%) and 76 patients (9.5%) discontinued i.n. esketamine due to adverse events as 55 patients (6.9%) experienced serious AEs. Interestingly, the results of an Asian subgroup analysis [53], including patients from South Korea, Malaysia, and Taiwan also showed similar side effect profile without occurring new AEs in comparison with those in the SUSTAIN-2 study, and likewise, the most common AEs were dizziness (37.2%), nausea (29.5%), dissociation (28.2%), and headache (21.8%), possibly indicating no racial differences in the safety and tolerability issues in the use of i.n. esketamine in patients with TRD.

5.2. Considerations for potential adverse events

5.2.1. Cardiovascular—Intravenous ketamine and intranasal esketamine have well-known effects on the cardiovascular system [54]. Both ketamine and esketamine treatments increase heart rate (HR) and blood pressure (BP) through direct sympathetic activation and antagonism of muscarinic receptors [12] [48]. Persistent high blood pressure (>161/110) can be treated with oral clonidine or i.v. hydralazine and persistent elevated HR (>130) can be treated with labetalol [55]. Care should be taken to evaluate patients for comorbid cardiovascular disease (CVD) including but not limited to, uncontrolled hypertension, severe kidney disease, previous signs or symptoms of cerebrovascular events, i.e. strokes and transient ischemic attack, aneurysms, stage III heart failure, and coronary artery disease including history of myocardial infarction and the status of stents and anticoagulation. Those followed by a cardiologist for CVD would benefit from a stress echocardiogram, obtaining an electrocardiogram, or close follow-up as there may be cryptic lesions unmasked by the acute increase in cardiac demand from ketamine and/or esketamine treatment. In patients with a history of CVD, a frank discussion about the risks is necessary. Additionally, assessment of angina symptoms would be recommended during or immediately following ketamine or esketamine treatment in patients with a history of CVD.

5.2.2. Genitourinary—There is consistent evidence detailing adverse genitourinary effects when ketamine is used recreationally. It has been shown to cause urinary symptoms such as dysuria, nocturia, hematuria, urgency, and incontinence in 20–40% of people using illicit ketamine [56,[57,58]. There does appear to be a dose-dependent relationship in the urinary adverse outcomes and hence consideration should be taken in patients receiving higher doses of i.v. ketamine and for longer periods of time. There have also been similar adverse effects observed with esketamine [59] [60]. Therefore, patients should be counseled and encouraged to drink fluids and use the restroom after treatment to decrease bladder accumulation.

5.2.3. Neurocognitive—Preclinical data in rodents suggest that there are potential neuropathological consequences to repeated ketamine infusions, however the doses used in this study were much higher (5–20 mg/kg) than used clinically [61]. Additionally, there are data from individuals using ketamine recreationally suggesting adverse effects on cognition, including deficits in attention, working and episodic memory [62,[63,64]. This concern has led to a thorough evaluation of patients receiving subanesthetic ketamine for the treatment of depression in clinical settings [65–67]. There are safety concerns regarding cognitive performance and attention within 24 hours of i.v. ketamine infusion [68] [69]; however, thus far, there is no evidence of long-term adverse effects on cognition in patients receiving subanesthetic doses of ketamine or esketamine for the treatment of depression [70] [71]. It is well known that depression, particularly treatment-resistant depression, can have a significant adverse effect on aspects of cognition including attention, memory, and processing speed [72], so careful balance must be taken when comparing baseline depressed patients with responding and remitting patients after ketamine and esketamine treatment.

5.3. Considerations for improving outcomes

There is evidence that ketamine facilitates the striatal dopamine release [73,74], which may be responsible for the therapeutic effects [75]. Therefore, dopaminergic agents such as bupropion and stimulants may help improve the efficacy of i.v. ketamine, though no controlled trials have been conducted. Benzodiazepines are known to attenuate or delay efficacy of i. v. ketamine [76] [77], and other agents that interfere with NMDA receptor activity or neurotransmitter release such as gabapentin and pregabalin, may do so as well. Because of its inhibition of glutamate release, lamotrigine appears to attenuate efficacy [78] andsurprisingly, the addition of lithium did not improve long-term outcomes [79]. Naltrexone possibly attenuates ketamine response likely due to its antagonism of ketamine's action on kappa opioid receptors [80]. However, decisions about decreasing naltrexone should be weighed with the risk of substance use relapse. Interestingly, a recent and encouraging study showed that ketamine can be helpful along with psychotherapy in the treatment of alcohol use disorder [81]. The increased incidence of medical and recreational cannabis use by patients may also have variable effects on outcomes, and this is an area needing future investigation.

Due to adverse effects on HR and BP, care must be taken in patients with a history of recreational ketamine, cocaine, and/ or amphetamine abuse, and clinicians could consider urine drug monitoring on a weekly basis in patients at high risk for abuse or who have had a recent relapse. These clinical scenarios can be challenging when patients emphasize the role of depression and anxiety as a driver for their substance use. Esketamine has not been shown to increase the likelihood of recreational ketamine abuse [52]; though the same was initially said about opiate-based medications used for pain management [82].

Lastly, antidepressant treatments have a risk of affective switch in patients with bipolar affective disorder [83]. When this occurs, it can be particularly alarming when a patient has a history of severe depression without a history of mania as they have been suffering from bipolar depression. Typically, prior to ketamine treatment, patients have had trials with serotonergic agents and even transcranial magnetic stimulation [84] [85], both of which have risks of affective switch. Effectiveness, safety, and tolerability of ketamine treatment of bipolar depression in the clinical setting have been encouraging [86]. A recent systematic review of patients with bipolar depression undergoing i.v. ketamine displayed a response rate for depression over 60% with one patient from each of the groups – treatment and placebo – experienced affective switch [87]. While there have not been certain cases of frank affective switch from depression to mania in patients receiving ketamine and esketamine, data are generally limited, though encouraging, and monitoring continues to be necessary.

6. Expert Opinion

There has been much interest recently in rapidly acting antidepressant treatments [88]. The prototypical agent is ketamine. Intravenous ketamine has been investigated for over 20 years for rapidly improving depressive and suicidal symptoms. More recently, intranasal esketamine has been gaining use as it is easier and safer to administer in outpatient clinics. Importantly, i.v. ketamine is an off-label treatment and an out-of-pocket expense, which has limited its use until recently as some insurance providers are now covering it. Intranasal

esketamine is currently covered by Medicare among other insurance providers; but because its reimbursement is low for clinician time and resources, widespread use by providers in community outpatient clinics will take time. These concerns confound naturalistic studies because treatments are limited to those with severity of illness high enough or the means/willingness to pay for such treatments. Finally, given the concern for adverse events of i.v. ketamine and i.n. esketamine, outpatient community practitioners may be reluctant to provide care. Taking an overly conservative clinical approach would limit the access of an effective treatment to a vulnerable population. Additional concerns include the appropriate clinical setting to deliver these treatments, the predictors leading to better and sustained responses, the monitoring of potential long-term adverse events, augmentation strategies and what to do when either ketamine or esketamine is either abused or ineffective. It is currently unclear where ketamine and esketamine fall in the algorithm for treating depression and how to pay for it. A balance must be struck between the economic cost of prolonged functional disability from TRD and the financial cost of ketamine and esketamine treatments.

There are many unanswered questions about the practical role of i.v. ketamine and i.n. esketamine in the treatment of TRD. There are limitations to fixed dosing of i.n. esketamine in a population with a significant portion having comorbid obesity. Worldwide, the average person weighs 62 kg, however Americans have an average weight of 80 kg (177.9 lbs). Assuming 40% bioavailability of i.n. esketamine, it is estimated that 0.5 mg/kg racemic ketamine administered intravenously to an average person is equivalent to 56 mg intranasal esketamine. To achieve equivalent dosing of esketamine to the average American, one would need to administer approximately 80 mg (the current highest esketamine dose is 86 mg). Many American patients of average weight may need the equivalent of 1.0 mg/kg i.v. ketamine to achieve adequate symptom reduction, of which an equivalent dose i. n. esketamine is unattainable with commercially available products. Given the lower bioavailability of i.n. esketamine, trials investigating higher doses such as 112 mg (equivalent to approximately 100 mg i.v. racemic ketamine) may provide benefit to severely treatment-resistant patients with a higher body-mass index (BMI). Considering i.v. ketamine dosing is weight-based, it may be clinically helpful to have higher doses of i.n. esketamine commercially available for patients with comorbid obesity.

It is not currently known to what degree psychiatric comorbidities confound the efficacy of ketamine and esketamine treatment for depression. There are ongoing investigations into the role of ketamine and esketamine treatment for additional psychiatric illnesses such as posttraumatic stress disorder, obsessive compulsive disorder, generalized anxiety disorder, and substance use disorders. Initial depression studies excluded patients with these comorbidities, particularly substance use, and therefore for clinical practice, it will be helpful to understand which comorbidities improve or worsen outcomes.

It is not known what the direct impact from long-term ketamine treatment is on cognition or on other organ systems such as cardiovascular and genitourinary. Importantly, there have been no long-term controlled trials for maintenance i.v. ketamine directly investigating these adverse outcomes. A recent open-label trial comparing electroconvulsive therapy (ECT) to i.v. racemic ketamine at a dose of 0.5 mg/kg for induction and maintenance treatments showed ketamine almost as effective as ECT without adverse effects on cognition

or the need for general anesthesia [89]. This line of investigation is very promising and would benefit from reproduction and there are ongoing trials to do this [90]. Additionally, there have been no robust head-to-head trials of ketamine compared to other somatic treatments such as transcranial magnetic stimulation (TMS), vagal nerve (VNS) or deep brain stimulation (DBS). Additionally, it would be particularly interesting to study ketamine augmentation of such somatic treatments for depression. Would this approach lead to faster improvement in the VNS or TMS response? Or a more stable ketamine response? Questions such as these remain open areas for investigation.

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Article highlights

- Intravenous ketamine and intranasal esketamine are effective treatments for treatment-resistant depression
- Intravenous ketamine and intranasal esketamine are effective treatments for acute suicidal ideation
- There are constraints to esketamine dosing that may limit treatment options

This box summarizes key points contained in the article.