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## The APA Guidelines on Ketamine Use for Depression CME / ABIM MOC / CE

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### Clinical Context

Ketamine and esketamine have grown in popularity as agents to manage treatment-resistant depression (TRD). Although ketamine has several routes of administration, the best record for efficacy against TRD has been recorded with the intravenous (IV) and intranasal routes. Although IV ketamine is 100% bioavailable, intranasal esketamine is only 30% to 50% available. The elimination half-lives for ketamine and esketamine are 2 to 4 hours and 5 hours, respectively. Ketamine has mild effects in inducing the cytochrome P450 system, and coadministration with medications that affect the CYP3A4 or CYP2B6 system may affect functional concentrations of ketamine.

The current review by McIntyre and colleagues highlights the efficacy and safety of ketamine and esketamine in the management of TRD.

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### Study Synopsis and Perspective

An international panel of mood disorder experts has published guidance on how to safely and effectively use ketamine and esketamine to treat adults with TRD.

"Ketamine and esketamine are the first rapid-onset treatments for adults with TRD, and there was an international need for best-practice guidance on the deft and safe implementation of ketamine and esketamine at the point of care, as none previously existed," first author Roger McIntyre, MD, professor of psychiatry and pharmacology, University of Toronto, Toronto, Ontario, Canada, told *Medscape Medical News*.

"This need has only been amplified by the significant increase in the number of clinics and centers providing this treatment," added McIntyre, head of the Mood Disorders Psychopharmacology Unit.

Their article was published online March 17 in the *American Journal of Psychiatry*.

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### Insufficient Evidence of Long-Term Efficacy

As reported by *Medscape Medical News*, the FDA approved esketamine nasal spray (Spravato®) for TRD in March 2019.

In August 2020, the FDA updated the approval to include adults with major depression and suicidal thoughts or actions.

To provide clinical guidance, McIntyre and colleagues synthesized the available literature on the efficacy, safety, and tolerability of ketamine and esketamine for TRD.

The evidence, they noted, supports the rapid-onset (within 1-2 days) efficacy of esketamine and ketamine in TRD.

The strongest evidence of efficacy is for intranasal esketamine and IV ketamine. There is insufficient evidence for oral, subcutaneous, or intramuscular ketamine for TRD, they reported.

Intranasal esketamine demonstrates efficacy, safety, and tolerability for  $\leq 1$  year in adults with TRD. Evidence for long-term efficacy, safety, and tolerability of IV ketamine for patients with TRD is insufficient, the group noted.

They also noted that esketamine is approved in the United State for major depression in association with suicidal ideation or behavior and that it has been proven to reduce suicide completion.

Safety concerns with ketamine and esketamine identified in the literature include, but are not limited to, psychiatric, neurologic/cognitive, genitourinary, and hemodynamic effects.

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## Implementation Checklist

The group has developed an "implementation checklist" for use of ketamine/esketamine in clinical practice.

Starting with patient selection, they noted that appropriate patients are those with a confirmed diagnosis of TRD for whom psychosis and other conditions that would significantly affect the risk:benefit ratio have been ruled out.

They suggested that a physical examination and monitoring of vital signs be undertaken during treatment and during posttreatment surveillance. A urine drug screen should be considered if appropriate.

The group advised that esketamine and ketamine be administered only in settings with multidisciplinary personnel, including, but not limited to, persons with expertise in the assessment of mood disorders.

Clinics should be equipped with appropriate cardiorespiratory monitoring and be capable of psychiatric assessment of dissociation and psychotomimetic effects.

Depressive symptoms should be measured, and the authors suggested assessing for anxiety, cognitive function, well-being, and psychosocial function.

Patients should be monitored immediately after treatment to ensure cardiorespiratory stability, clear sensorium, and attenuation of dissociative and psychotomimetic effects.

The United States and some other countries require a risk evaluation and mitigation strategy (REMS) when administering esketamine. Regarding the REMS, it is advised that all patients be monitored for a minimum of 2 hours before discharge.

Patients should arrange for reliable transportation for each appointment, and they should be advised not to operate motor vehicles or hazardous machinery without at least one night of sleep.

"The rate of [TRD] as well as suicide is extraordinary and rising in many parts of the world, only worsened by COVID-19," said McIntyre.

"Clinicians of different professional backgrounds have been interested in ketamine/esketamine, and we are extraordinarily pleased to see our international guidelines published," he added.

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## "Extremely Useful"

Reached for comment, Alan Schatzberg, MD, professor of psychiatry and behavioral sciences at Stanford Medicine, Stanford, California, said this document "puts a lot of information in one place as far as what we know and what we don't know right now, and that's helpful. I think it's an attempt to have a kind of a somewhat objective review of the literature, and it's in a good journal."

The article, Schatzberg added, "could be extremely useful for someone who is considering whether ketamine is useful for a patient or what they can tell a patient about ketamine, that is, about how long they might need, is it going to work, will it continue to work, and the level of data we have either on benefits or side effects."

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and is listed as an inventor on patents for pharmacogenetics and anti-glucocorticoid use in the prediction of antidepressant response.

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## Study Highlights

- IV ketamine has usually been studied as monotherapy or adjunctive treatment for depression, and intranasal esketamine has been investigated as co-treatment with a newly initiated antidepressant medication. Randomized controlled trials demonstrate the efficacy of these agents in these settings.
- The efficacy of IV racemic ketamine has been demonstrated at a dose of 0.5 mg/kg, with little added efficacy at a dose of 1 mg/kg. There is limited evidence that the rate of adverse effects (AEs) associated with ketamine is dose-dependent.
- The ideal frequency of treatment with IV ketamine has not been established.
- A meta-analysis of 5 clinical trials of intranasal esketamine demonstrated pooled risk ratios of 1.4 and 1.45 for response and remission of depression, respectively, vs placebo. These results translated into numbers needed to treat of 6 and 7, respectively.
- Intranasal esketamine also reduced the risk for depression relapse by 51% to 70% among patients who developed remission or a response on therapy, respectively.
- Still, the efficacy of intranasal esketamine has not been established in adults at age  $\geq 65$  years.
- There is a lack of data comparing intranasal esketamine and IV ketamine, but in one study, the IV formulation was shown to be possibly superior to the intranasal form.
- Ketamine is associated with a rapid reduction in suicidal ideation, which appears to last  $\leq 7$  days since the last administration. With repeated IV dosing, ketamine has been demonstrated to reduce suicidality for  $\leq 6$  weeks.
- Nonetheless, ketamine and esketamine have not yet been proven to reduce the risk for completed suicide.
- The most common AEs reported with ketamine in TRD include dissociation, perceptual disturbances, abnormal sensations, derealization, and depersonalization. IV racemic ketamine promotes dissociation in nearly three-quarters of patients treated for TRD. Dissociation peaks within 40 minutes after ketamine administration, and it resolves within 1 to 2 hours.
- The risk for sustained psychosis after ketamine administration seems very remote.
- Exposure to intranasal esketamine for 1 year has not been associated with cognitive deficits; however, dizziness and drowsiness are common short-term neurologic AEs related to the use of ketamine.
- Ketamine is associated with increases in blood pressure and pulse rate among 10% to 50% of patients treated. These effects usually resolve within 2 to 4 hours after drug administration.
- While ketamine is a schedule III agent in the United States and is associated with increased drug liking in healthy volunteers, there is no evidence that treatment with ketamine or esketamine in TRD is associated with a higher risk for substance use disorders.
- The concomitant use of benzodiazepines may attenuate or delay the antidepressant response to ketamine.
- The standard starting dose of IV ketamine is 0.5 mg/kg infused over 40 minutes.
- Intranasal esketamine can be initiated at a dose of 56 mg, and then continued at 56 to 84 mg twice weekly through 4 weeks. The treatment frequency is usually tapered to every 1 to 2 weeks thereafter.
- The efficacy of treatment with ketamine or esketamine should be assessed at around 4 weeks, and treatment should be discontinued if ineffective.
- All patients under consideration for treatment with ketamine should have an evaluation of depression symptom severity by a professional experienced in this area. Assessments for anxiety and well-being are recommended as well.
- Staff should be able to handle potential complications of treatment with ketamine. Patients should be monitored for 2 hours after treatment with esketamine, and this period should also apply to patients who receive IV ketamine.

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## Clinical Implications

- IV ketamine and intranasal esketamine both appear effective in improving rates of response and remission in cases of TRD. Intranasal esketamine has been demonstrated to reduce the risk for relapse of depression, but its efficacy among adults at age  $\geq 65$  years is unproven. There is insufficient evidence to compare these medications in terms of efficacy.
- Patients treated with IV ketamine and intranasal esketamine should be monitored for  $\geq 2$  hours after administration. Ketamine is associated with a reduction in suicidal ideation. The majority of patients receiving IV ketamine experience dissociation, and ketamine can also raise blood pressure and pulse.

- Implications for the healthcare team: The healthcare team needs to work together to ensure patient safety and a good patient experience among patients taking ketamine for TRD.

### Earn Credit

AE = adverse effect

IV = intravenous

REMS = risk evaluation and mitigation strategy

TRD = treatment-resistant depression

### References

1. 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*. Published online March 17, 2021. Accessed March 25, 2021. Article abstract. <https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2020.20081251>

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