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Invited Commentary

Use of Ketamine in Clinical Practice A Time for Optimism and Caution

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Increasing evidence, primarily from small studies, supports the idea that the dissociative anesthetic ketamine has rapid antidepressant effects in patients with treatment-refractory major depression.¹ The beneficial effects of ketamine are observed



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within hours of administration and can last approximately 1 week. Given that up to one-third of patients with major depression fail current treatments,² there is a clear need for novel and more effective treatments. Results to date have led to increasing off-label use of ketamine in clinical practices, with little guidance about clinical administration. In this issue of the *JAMA Psychiatry*, Sanacora and colleagues³ provide a much-needed consensus statement to help guide clinical use of ketamine.

Sanacora et al³ provide a thoughtful overview of ketamine use, including commentary about patient selection, risks, clinician experience, treatment setting, drug administration, and follow-up. The authors acknowledge the major limitations in the available data: limitations that should give pause to clinicians considering the use of ketamine in their practices. Sanacora and colleagues³ state that data on ketamine in psychiatric practice, especially longer-term use of ketamine, are limited or nonexistent. Thus, their recommendations are purposefully vague in places.

There is little doubt that ketamine is having a major effect on psychiatry. If clinical studies continue to support the antidepressant efficacy of ketamine, psychiatry could enter an era in which drug infusions and deliveries with more rapid responses become common. Basic science studies examining the mechanisms underlying ketamine are advancing rapidly, providing hope for even better treatments in the future.⁴ Although ketamine is an uncompetitive antagonist of *N*-methyl-D-aspartate glutamate receptors (NMDARs), rodent studies indicate that ketamine produces its antidepressant-like effects by enhancing transmission mediated by the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid class of glutamate receptors through modulation of intracellular signaling.⁴ Studies are under way to understand how ketamine alters human brain networks, as well as efforts to develop other

NMDAR antagonists for use in psychiatry.⁴ Recent data question whether ketamine itself, and NMDAR antagonism specifically, are key mediators of antidepressant actions.⁵ Ketamine metabolites that are not active at NMDARs show antidepressant-like effects in rodents,⁵ suggesting that alternative mechanisms could be important. Determining the role of NMDARs and alternative mechanisms could perhaps lead to antidepressants that are better tolerated by patients.

Despite great enthusiasm, the limitations highlighted by Sanacora et al³ are noteworthy and should be emphasized. Because of limited data to guide clinical practice, these limitations extend to almost every recommendation in the consensus statement, including, perhaps most importantly, patient selection. The bulk of the literature describes the effects of ketamine in patients with treatment-refractory major depression. The definition of treatment-refractory major depression and where treatments such as ketamine fall in the algorithm for managing treatment-refractory major depression remain poorly understood.² Even within the literature on ketamine treatment, there is considerable variability in defining treatment-refractory major depression (some studies required only 1 antidepressant failure, and others studied patients who failed electroconvulsive therapy). It is unclear whether patients with depression that is not treatment-refractory or patients with other psychiatric illnesses are appropriate candidates for ketamine treatment, and extreme caution must be exercised in patients with psychotic or substance use disorders.

There are also major limitations in what is understood about the dose, duration of infusion, and route of administration for ketamine. Most studies examining ketamine for depression use intravenous infusions of 0.5 mg/kg for 40 minutes. This dosing derives directly from a study by Krystal and colleagues⁶ in the early 1990s in which they used this same dosage to induce psychotic and cognitive symptoms in healthy adults. Fortunately, psychotic symptoms last only a few hours and have not been a major problem in studies of ketamine in depression. What is unknown is whether other ketamine dosing regimens would have more or fewer beneficial and adverse effects.

A major problem with ketamine is that its antidepressant effects following a single infusion are transient, usually abating in about 1 week. Efforts to prolong these effects have involved repeated infusions (several times per week with maintenance infusions) or longer durations of infusion (eg, 96 hours).^{7,8} The risks and benefits of such altered dosing schemes are poorly understood. As noted by Sanacora et al,³ long-term ketamine abuse is associated with cognitive impairment; whether that will be an issue with longer-term therapeutic dosing of ketamine is unknown.

Several agents have been used to dampen the psychotomimetic effects of ketamine, including γ -aminobutyric acid-enhancing drugs, antimuscarinics, and α -adrenergics. It is unknown how these dampening agents influence the antidepressant effects of ketamine, although clonidine has been used effectively in 1 study⁸; this finding could be important because ketamine is associated with elevations in blood pressure. Most studies of ketamine in psychiatry have used intravenous infusions. Although ketamine can be administered intramuscularly, intranasally, and perhaps orally, these alternative methods remain understudied.

It is also unclear what training is needed for psychiatrists to administer ketamine safely. Because ketamine is an anesthetic, credentialing in conscious sedation should be consid-

ered. At a minimum, psychiatrists must be prepared to handle cardiovascular and respiratory emergencies when administering ketamine, and thus have training in advanced cardiac life support. Given the suggestion by Sanacora et al³ to monitor respiratory function (eg, end-tidal CO₂ levels) along with vital signs, it may be prudent to have joint anesthesia and psychiatry teams administer intravenous ketamine, especially in patients with complex medical conditions.

Sanacora and colleagues³ conclude with several key recommendations that include the need for more research to address the major gaps outlined. They highlight the importance of enrolling patients in systematic studies to advance the field, rather than simply using ketamine in open and uncontrolled ways. We strongly endorse the authors' call for a registry of patients treated with ketamine to allow coordinated data collection and to provide a monitor about ketamine use.

Ketamine provides new excitement for psychiatry and offers the hope of much-needed novel and perhaps more effective treatments. The consensus statement by Sanacora and colleagues,³ however, provides a sobering cautionary guide, especially as we move toward attempting to sustain the gains achieved by acute doses of ketamine. This consensus statement will not be the final word on this topic, and similar considerations will be needed for other novel treatments.

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