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A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders

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IMPORTANCE Several studies now provide evidence of ketamine hydrochloride's ability to produce rapid and robust antidepressant effects in patients with mood and anxiety disorders that were previously resistant to treatment. Despite the relatively small sample sizes, lack of longer-term data on efficacy, and limited data on safety provided by these studies, they have led to increased use of ketamine as an off-label treatment for mood and other psychiatric disorders.

OBSERVATIONS This review and consensus statement provides a general overview of the data on the use of ketamine for the treatment of mood disorders and highlights the limitations of the existing knowledge. While ketamine may be beneficial to some patients with mood disorders, it is important to consider the limitations of the available data and the potential risk associated with the drug when considering the treatment option.

CONCLUSIONS AND RELEVANCE The suggestions provided are intended to facilitate clinical decision making and encourage an evidence-based approach to using ketamine in the treatment of psychiatric disorders considering the limited information that is currently available. This article provides information on potentially important issues related to the off-label treatment approach that should be considered to help ensure patient safety.

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Invited Commentary page 405

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The American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments found that the data from 7 published placebo-controlled, double-blind, randomized clinical studies on ketamine hydrochloride infusion therapy in the treatment of depression comprising 147 treated patients provide "compelling evidence that the antidepressant effects of ketamine infusion are both rapid and robust, albeit transient."[1(p958)] Reports of ketamine's unique antidepressant effects, combined with frequent media coverage promulgating the potential benefits of ketamine treatment, have generated substantial interest and optimism among patients, families, patient advocacy groups, and clinicians alike. This interest has led to a rapidly escalating demand for clinical access to ketamine treatment and an increasing number of clinicians willing to provide it. However, many in the field suggest that caution should be used with this approach, as the numbers of patients included in these published studies and case series remain relatively small (the eTable in the Supplement compares other recently developed treatments), and ketamine treatment for mood disorders has not been tested in larger-scale clinical trials to demonstrate its durability and safety over time.[2,3] Moreover, the treatment approach has not been subject to the scrutiny of a US Food and Drug Administration review or approval for an on-label psychiatric indication, and, despite more than 45 years of clinical experience with ketamine as an anesthetic agent, there are no postmarketing surveillance data on the use of ketamine for any psychiatric indication to provide information on its safety and effectiveness.

The relatively unique nature of this situation presents an urgent need for some guidance on the issues surrounding the use of ketamine treatment in mood disorders. This review by the American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments Subgroup on Treatment Recommendations for Clinical Use of Ketamine is intended to complement the recent American Psychiatric Association meta-analysis[1] and other recent reviews[4-10] and aims to provide an overview and expert clinical opinion of the critical issues and considerations associated with the off-label use of ketamine treatment for mood disorders. Because relatively limited high-quality, published information on this topic exists, to our knowledge, this report is not intended to serve as a standard, guideline, clinical policy, or absolute requirement. The main intent of the report is to highlight the current state of the field and the critical issues to be considered when contemplating the use of ketamine for treatment-resistant depression. Use of this report cannot guarantee any specific outcome and is not endorsed or promulgated as policy of the American Psychiatric Association.

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Patient Selection

There are no clearly established indications for the use of ketamine in the treatment of psychiatric disorders. However, the selection of appropriate patients for ketamine treatment requires consideration of the risks and benefits of the treatment in the context of the patient's severity of depression, duration of current episode, previous treatment history, and urgency for treatment. To date, the strongest data supporting ketamine's clinical benefit in psychiatric disorders are in the treatment of major depressive episodes without psychotic features associated with major depressive disorder.[1,11] Even these data are limited by the fact that most of those studies evaluated efficacy only during the first week following a single infusion of ketamine. However, emerging studies suggest that repeated dosing can extend the duration of effect for at least several weeks.[12,13] Although some limited data on the use of ketamine in treating other psychiatric diagnoses exist (eBox 1 in the Supplement), we do not believe there are sufficient data to provide a meaningful review of the assessment of risks and benefits of ketamine use in these other disorders at present.

In addition to diagnostic considerations, appropriate patient selection requires an assessment of other medical, psychological, or social factors that may alter the risk to benefit ratio of the treatment and affect the patient's capacity to provide informed consent. For these reasons, we recommend that each patient undergo a thorough pretreatment evaluation process (Table)[14-17] that assesses several relevant features of the patient's past and current medical and psychiatric condition before initiating ketamine treatment. We also recommend that an informed consent process be completed during this evaluation. Rationale for the suggestions listed in the Table are provided in eBox 1 in the Supplement.

Table. Recommended Components of Preprocedural Evaluation for Appropriateness of Ketamine Hydrochloride Treatment

Component	Recommendation
1	A comprehensive diagnostic assessment should be completed to establish current diagnosis and evaluate history of substance use and psychotic disorders
2	Assessment of baseline symptom severity should be completed to allow later assessments of clinical change with treatment[a]
3	A thorough history of antidepressant treatment should be collected and documented to confirm previous adequate trials of antidepressant treatments
4	A thorough review of systems should be performed to evaluate potential risk factors associated with ketamine treatment[b]
5	Decisions on the specific physical examination and laboratory screening assessments should be made according to established guidelines and advisories issued by the American College of Cardiology Foundation/American Heart Association and the American Society of Anesthesiologists and should be based on a patient's individual clinical characteristics[c]
6	A careful review of past medical and psychiatric records and/or corroboration of the past history by family members are strongly encouraged; all current medications and allergies should be reviewed, including histories of opiate and benzodiazepine use; the use of a baseline urine toxicology screen is strongly encouraged to ensure the accuracy of the reported substance use and medication record
7	An informed consent process, including discussion of the risks associated with the treatment,[d] the limits of the available information pertaining to the potential benefits of the treatment, the fact that this is an off-label use of ketamine, and a discussion of alternative treatment options should be completed; this discussion should be complemented with written materials, and the patient should provide written informed consent before initiating treatment

[a] Self-report versions of the Inventory of Depressive Symptomatology and Quick Inventory of Depressive Symptomatology (http://counsellingresource.com/quizzes/depression-testing/qids-depression/) are examples of scales that are available at no cost to clinicians and researchers.

[b] This review should also include questions pertaining to functional exercise capacity, which has been demonstrated to provide a good screening tool for patients that are at increased risk for adverse events associated with anesthesia exposure and surgical procedures.[14,15]

[c] American College of Cardiology Foundation and the American Heart Association guidelines for perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery[16] and practice advisory from the American Society of Anesthesiologists.[17]

[d] The Ketalar package insert (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/016812s039lbl.pdf) provides essential information related to risk of ketamine administration.

Clinician Experience and Training

There are considerable differences in the experience and clinical expertise of the clinicians currently administering ketamine to patients for the treatment of mood disorders. At present, there are no published guidelines or recommendations outlining the specific training requirements that clinicians should complete before administering doses of ketamine that are lower than those used in anesthesia. In attempting to balance the needs for treatment availability and patient safety, one must consider the information available regarding the use of ketamine at the relevant dose range in similar patient populations to formulate an advisory on clinical credentialing for ketamine administration for the treatment of mood disorders.

The peak plasma ketamine hydrochloride concentrations of 70 to 200 ng/mL seen with the typical antidepressant dose of 0.5 mg/kg delivered intravenously (IV) during 40 minutes (0.5 mg/kg per 40 minutes IV) do not produce general anesthetic effects. The concentrations are well below the peak plasma ketamine hydrochloride concentrations generally used for surgical anesthesia (2000-3000 ng/mL) and below the concentrations associated with awakening from ketamine hydrochloride anesthesia (500-1000 ng/mL).[18-20] Reporting on 833 ketamine infusions in healthy individuals resulting in peak plasma ketamine concentrations in the same general range as those achieved with a dose of 0.5 mg/kg per 40 minutes IV, Perry et al[21] found 3 individuals who became nonresponsive to verbal stimuli, but all remained medically stable during the infusion and none required any form of respiratory assistance. A second, more recent study reported no persistent medical complications or significant changes in oxygen saturation among 84 otherwise healthy patients with depression who received a total of 205 infusions of ketamine hydrochloride, 0.5 mg/kg per 40 minutes IV.[9] However, transient mean (SD) peak increases in systolic (19.6 [12.8] mm Hg) and diastolic (13.4 [9.8] mm Hg) blood pressure were reported during the infusions, with blood pressure levels exceeding 180/100 mm Hg or heart rates exceeding 110 beats per minute in approximately 30% of the patients treated. A single serious adverse cardiovascular-related event was reported in this study (0.49% of infusions), but it was considered to be attributable to a vasovagal episode following venipuncture for a blood draw, and it resolved without complications.

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The data available from these studies and other case reports in the literature suggest that the dose of ketamine hydrochloride typically used in the treatment of mood disorders (0.5 mg/kg per 40 minutes IV) does not appear to have significant effects on the respiratory status of healthy individuals or patients with depression who are otherwise generally medically healthy. However, ketamine treatment could have meaningful effects on blood pressure and heart rate for some patients. Considering the potential risks associated with ketamine hydrochloride administration at the dose of 0.5 mg/kg per 40 minutes IV, it is recommended that clinicians delivering the treatment be prepared to manage potential cardiovascular events should they occur. Based on this information, we suggest that a licensed clinician who can administer a Drug Enforcement Administration Schedule III medication (in most states this is an MD or DO with appropriate licensing) with Advanced Cardiac Life Support certification should provide the treatments.

Because it is also possible for patients to experience prominent transient dissociative or even psychotomimetic effects while being treated with ketamine,[22] clinicians should also be familiar with behavioral management of patients with marked mental status changes and be prepared to treat any emergency behavioral situations. Furthermore, it is suggested that an on-site clinician be available and able to evaluate the patient for potential behavioral risks, including suicidal ideation, before discharge to home. Finally, treating clinicians should be able to ensure that rapid follow-up evaluations of patients' psychiatric symptoms can be provided as needed.

In addition to the minimal general training requirements, it is also recommended that clinicians develop some level of experience with the specific method of ketamine administration before performing the procedure independently. Precise delineation of required experience and documentation of this experience should be based on local community standards of practice and/or clinical practice committees. Reports such as the *Statement on Granting Privileges for Administration of Moderate Sedation to Practitioners Who Are Not Anesthesia Professionals*, published by the American Society of Anesthesiologists,[23] can be used to inform the development of these standards.

Treatment Setting

Although the administration of ketamine at peak plasma concentrations similar to those produced by a dose of 0.5 mg/kg per 40 minutes IV has proven to be relatively safe to date, the potentially concerning acute effects on cardiovascular function and behavior suggest that the clinical setting should provide sufficient means of monitoring the patients and providing immediate care if necessary. Although there are relatively low levels of evidence to support the use of any specific monitoring methods in reducing the risks of ketamine treatment with doses that are lower than those used in anesthesia, it should be expected that such a facility have a means of monitoring basic cardiovascular (electrocardiogram, blood pressure) and respiratory (oxygen saturation or end-tidal CO_2) function. It should also be expected that there would be measures in place to rapidly address and stabilize a patient if an event should arise. These measures would include a means of delivering oxygen to patients with reduced respiratory function, medication, and, if indicated, restraints to manage potentially dangerous behavioral symptoms. Moreover, there should be an established plan to rapidly address any sustained alterations in cardiovascular function, such as providing advanced cardiac life support or transfer to a hospital setting capable of caring for acute cardiovascular events. Patients deemed at higher risk for complications based on pretreatment evaluation should be treated at a facility that is appropriately equipped and staffed to manage any cardiovascular or respiratory events that may occur.

Medication Delivery

Dose

Most clinical trials and case reports available in the literature have used the ketamine hydrochloride dose of 0.5 mg/kg per 40 minutes IV that was cited in the original report by Berman et al.[24] Limited information is available regarding the use of different routes of delivery and doses of ketamine. A meta-analysis of 6 trials assessing the effects of the standard dose of 0.5 mg/kg per 40 minutes IV and 3 trials assessing very low doses of ketamine hydrochloride (50-mg intranasal spray, 0.1-0.4 mg/kg IV, and 0.1-0.5 mg/kg IV intramuscularly or subcutaneously) reported that the dose of 0.5 mg/kg per 40 minutes IV appears to be more effective than very low doses in reducing the severity of depression.[4] However, there is substantial heterogeneity in the design of the clinical trials, and the total number of participants included in that analysis is very few, markedly limiting the ability to draw any firm conclusions from this report.

Although there is now a growing number of reports examining the effects of various doses and rates of ketamine infusion, including studies showing lower doses and reduced infusion rates[25-27] to be effective and studies showing higher doses and extended infusion rates[28,29] to have clinical benefit, at present we believe that insufficient information was provided in those studies to allow any meaningful analysis of any specific dose or route of treatment compared with the standard dose of 0.5 mg/kg per 40 minutes IV. Considering the lower-level evidence for doses and routes of administration other than 0.5 mg/kg per 40 minutes IV, if alternative doses are being used, that information should be presented to the patient during the informed consent process, and appropriate precautions should be made in managing any increased risk associated with the changes in ketamine administration. However, the use of alternative doses and routes of administration could be appropriate for individual patients under specific conditions.

One example of a rationale for dose adjustment is related to the dosing of ketamine for patients with a high body mass index (calculated as weight in kilograms divided by height in meters squared). The fact that greater hemodynamic changes were observed in patients with a body mass index of 30 or higher who were receiving a dose of 0.5 mg/kg per 40 minutes[9] suggests that adjusting the ketamine dosing to ideal body weight (using the person's calculated ideal body weight and not actual body weight to determine dosing) may be an appropriate step to help ensure safety for patients with a body mass index of 30 or higher. However, there is currently very limited information supporting this approach.

Delivery Procedure

To help best ensure patient safety and to minimize risks, it is strongly advised that site-specific standard operating procedures be devel-

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oped and followed for the delivery of ketamine treatments for major depressive episodes. The standard operating procedure should contain predosing considerations covering the following: (1) confirmation of preprocedural evaluation and informed consent; (2) assessment of baseline vital signs, including blood pressure, heart rate, and oxygen saturation or end-tidal CO_2; (3) criteria for acceptable baseline vital signs before initiation of medication delivery (eBox 2 in the Supplement); and (4) incorporation of a "time-out" procedure in which the name of the patient and correct dosing parameters are confirmed.

Standard operating procedures should also include specifically defined ongoing assessments of patients' physiological and mental status during the infusion process, including the following: (1) assessment of respiratory status (ie, oxygen saturation or end-tidal CO_2); (2) assessment of cardiovascular function (blood pressure and heart rate, reported on a regular basis); (3) assessment of the level of consciousness (ie, Modified Observer's Assessment of Alertness/Sedation Scale[30]) or other documented assessment of responsiveness; and (4) delineation of criteria for stopping the infusion (eBox 3 in the Supplement) and a clear plan for managing cardiovascular or behavioral events during treatment.

Immediate posttreatment evaluations, assessments, and management should ensure that the patient has returned to a level of function that will allow for safe return to his or her current living environment. This assessment should include documentation of return to both baseline physiological measures and mental status. It is also critical to ensure that a responsible adult is available to transport the patient home if the treatment is being administered on an outpatient basis. Recommendations regarding driving and use of heavy machinery, as well as use of concomitant medications, drugs, or alcohol, should also be reviewed before discharge. It is also important to review follow-up procedures and ensure that the patient has a means of rapidly contacting an appropriately trained clinician if necessary.

Follow-up and Assessments

Efficacy Measures of Short-term Repeated Administration

The existing data surrounding the benefits of repeated infusions of ketamine remain limited.[1,11] Although an increasing number of small case series evaluate the efficacy of repeated ketamine administration for the treatment of major depressive episodes, there is a very small number of randomized clinical trials in the literature.[1] The lack of clinical trials in this area makes it difficult to provide suggestions on the frequency and duration of treatment with even moderate levels of confidence. Most studies and case reports published to date on this topic have examined the effects of less than 1 month of treatment.[12,26,31-34]

A recent randomized, placebo-controlled clinical trial (using saline as the placebo) of 68 patients with treatment-resistant major depressive disorder examined the efficacy of ketamine, 0.5 mg/kg per 40 minutes IV, both 2 and 3 times weekly for up to 2 weeks and found both dosing regimens to be nearly equally efficacious (change in mean [SD] Montgomery-Åsberg Depression Rating Scale total score for ketamine 2 times weekly, −18.4 [12.0] vs placebo, −5.7 [10.2]; and ketamine 3 times weekly, −17.7 [7.3] vs placebo, −3.1 [5.7]).[13] After 2 weeks of treatment, patients treated with ketamine 2 times weekly showed a 69% rate of response and 37.5% rate of remission vs placebo, at 15% and 7.7%, respectively, and those treated with ketamine 3 times weekly had a 53.8% rate of response and 23.1% rate of remission vs placebo, at 6% and 0%, respectively. In the ensuing open-label phase of the study, patients were allowed to continue with active medication at the dose frequency they were originally assigned for an additional 2-week period. At the end of 4 weeks of treatment, the 13 patients who received ketamine 2 times weekly and continued to receive the additional 2 weeks of treatment had a mean 27-point reduction in the Montgomery-Åsberg Depression Rating Scale score compared with a 23-point decrease for the 13 patients who received ketamine 3 times weekly. Although this was clearly not a definitive study, it is the best evidence currently available, to our knowledge, to suggest that twice-weekly dosing is as efficacious as more frequent dosing for a period of up to 4 weeks. In general, most of the available reports describing the effects of repeated treatments showed the largest benefits occurring early in the course of treatment, but some reports did show some cumulative benefit of continued treatment.[31]

Very limited data exist to suggest a clear point of determining the futility of treatment, but there are a few reports of patients responding after more than 3 infusions. Based on the limited data available, patients should be monitored closely using a rating instrument to assess clinical change to better reevaluate the risk to benefit ratio of continued treatment. In addition, only 1 report suggests that an increased dose of ketamine (beyond 0.5 mg/kg per 40 minutes) may lead to a response to treatment in patients who had previously not responded.[28] Equally few data are available to suggest a standard number of treatments that should be administered to optimize longer-term benefit of the treatment.

Efficacy of Longer-term Repeated Administration

To our knowledge, there are extremely limited published data on the longer-term effectiveness and safety of ketamine treatment in mood disorders. This literature is confined to a few case series that do not allow us to make a meaningful statement about the longer-term use of ketamine.[35,36] Several clinics providing such treatments are currently using a 2- or 3-week course of ketamine delivered 2 or 3 times per week, followed by a taper period and/or continued treatments based on empirically determined duration of responses for each patient. However, there remain no published data that clearly support this practice, and it is strongly recommended that the relative benefit of each ketamine infusion be considered in light of the potential risks associated with longer-term exposure to ketamine and the lack of published evidence for prolonged efficacy with ongoing administration. The scarcity of this information is one of the major drawbacks to be considered before initiating ketamine therapy for patients with mood disorders and should be discussed with the patient before beginning treatment.

Safety Measures and Continuation of Treatment

Based on the known or suspected risks of cognitive impairment[37] and cystitis[38] associated with chronic high-frequency use of ketamine and the known substance abuse liability of the drug,

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assessments of cognitive function, urinary discomfort, and substance use[39] should be considered if repeated administrations are provided (eBox 4 in the Supplement).

Considering the known potential for abuse of ketamine[40] and recent reports of abuse of prescribed ketamine for the treatment of depression,[41] clinicians should be vigilant about assessing the potential for patients to develop ketamine use disorder. Close clinical follow-up with intermittent urine toxicology screening for drugs of abuse and inquiries about attempts to receive additional ketamine treatments at other treatment centers should be implemented when clinical suspicion of ketamine abuse is present. Moreover, the number and frequency of treatments should be limited to the minimum necessary to achieve clinical response. Considering the evidence suggesting that the mechanism of action requires some delayed physiological effect to the treatment and does not appear to require sustained blood concentrations of the drug to be present, there is no evidence to support the practice of frequent ketamine administration. The previously mentioned report showing twice-weekly dosing to be at least as effective as dosing 3 times a week[13] for up to 4 weeks appears to support this idea instead of more frequent dosing schedules.

At this point of early clinical development, we strongly advise against the prescription of at-home self-administration of ketamine; it remains prudent to have all doses administered with medical supervision until more safety information obtained under controlled situations can be collected. Discontinuation of ketamine treatment is recommended if the dosing cannot be spaced out to a minimum administration of 1 dose per week by the second month of treatment. The goal remains to eventually taper and discontinue treatment until more long-term safety data can be collected.

Future Directions

The rapid onset of robust, transient antidepressant effects associated with ketamine infusions has generated much excitement and hope for patients with refractory mood disorders and the clinicians who treat them. However, it is necessary to recognize the major gaps that remain in our knowledge about the longer-term efficacy and safety of ketamine infusions. Future research is needed to address these unanswered questions and concerns. Although economic factors make it unlikely that large-scale, pivotal phase 3 clinical trials of racemic ketamine will ever be completed, there are several studies with federal and private foundation funding aiming to address some of these issues. It is imperative that clinicians and patients continue to consider enrollment in these studies when contemplating ketamine treatment of a mood disorder. It is only through these standardized clinical trials that we will be able to collect the data necessary to answer some of the crucial questions pertaining to the efficacy and safety of the drug. A second means of adding to the knowledge base is to develop a coordinated system of data collection on all patients receiving ketamine for the treatment of mood disorders. After such a registry is created, all clinicians providing ketamine treatment should consider participation.

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Outfitters, and Takeda; and holding patent No. 6,375,990B1 related to the method of and devices for transdermal delivery of lithium and patent No. 7,148,027B2 related to the method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay.

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Invited Commentary

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

Charles F. Zorumski, MD; Charles R. Conway, MD

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 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 colleagues[3] provide a much-needed consensus statement to help guide clinical use of ketamine.

Related article page 399

Sanacora et al[3] 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 colleagues[3] 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 al[3] 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 colleagues[6] 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.

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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 study[8]; 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 considered. 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 al[3] to monitor respiratory function (eg, end-tidal CO_2 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 colleagues[3] 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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