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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
Supplemental content

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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.

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.

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 developed and followed for the delivery of ketamine treatments for major depressive episodes. The standard operating procedure should contain predosing considerations covering the following: (1) confir-

mation 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, 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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Supplementary Online Content

Sanacora G, Frye MA, McDonald W, et al; American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry.* Published online March 1, 2017. doi:10.1001/jamapsychiatry.2017.0080

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable. Comparative Numbers of Trials and Subjects in Recently Developed Mood Disorder

Modality	Number of Trials	N	Reference
rTMS (high frequency left DLPFC)	23	1156	Health Quality Ontario 2016[1]
Transcranial Direct Current Stimulation (tDCS)	10	393	Meron D, *et al.*[2]
Vagus Nerve Stimulation	1	235	Rush AJ *et al.*[3]
Deep Brain Stimulation—VC/VS	1	30	Dougherty DD, *et al.*[4]
Deep Brain Stimulation- SCC	1	75	Morishita T *et al.*[5]
I.V. or intranasal Ketamine	9	368	Han *et al.*[6]

(DLPFC) dorsolateral prefrontal cortex; (SCC) sub-callosal cingulate; (VC/VS) ventral capsule/ventral striatum

It is very difficult to make any direct comparisons across treatment modalities. It is also very difficult to obtain the true number of subjects/patients studied with each of the modalities as various versions of each treatment modality has been used in varying study designs. However, the above table provides references from the most recently published reviews or studies using the modalities. It is meant only to provide some reference on the general number of studies performed and the number of subjects studied. A review covering most of neurostimulation treatment modalities was recently provided by Milev *et al.*[7].

Preamble: The clinical guidance provided in this report may be adopted, modified, or uniformly rejected according to clinical needs and constraints, and are not intended to replace local institutional policies. This report is not supported by scientific literature to the same degree as typical standards or treatment guidelines because of the lack of sufficient numbers of adequately controlled studies involving a sufficiently large number of patients, nor has it gone through the review process normally associated with organizational policy statements.

eBox 1. Factors to be Considered in Pretreatment Evaluation

(1) **Relevance of Diagnostic Assessment:**

Data for the efficacy of ketamine infusions in treating psychiatric disorders other than major depressive episodes associated with major depressive disorder with out psychotic features are very limited. There are several studies showing a similar transient improvement of major depressive episodes in hospitalized patients diagnosed with bipolar depression[8], although these data are virtually all from single dose infusions, offering a very limited understanding of the safety and efficacy of repeated dosing. Only one small case series consisting of two subjects who received ketamine treatment for mood disorders with concurrent psychotic features has been reported to date[9]. Although the patients in this report showed improvement in symptoms and did not experience any increase in their psychotic features with the ketamine treatment, it is recommended that any patients with a past or current history of psychotic features only be considered for ketamine treatment when other standard approaches, including ECT are ineffective, and that the treatment be provided under close observation such as would be found on an inpatient psychiatric setting.

There are very few reports evaluating the use of ketamine in treating psychiatric disorders other than major depressive episodes associated with either major depressive disorder or bipolar disorder. One small proof-of-concept placebo controlled trial and a case report have been published in post-traumatic stress disorder (PTSD) patients[10,11]. The randomized crossover study using midazolam as

the control medication, contained data on 41 subjects that had received at least one dose of the study medication. The findings showed ketamine to produce a significant reduction on Impact of Event Scale–Revised scale relative to midazolam at 24 hours, serving as the primary outcome measure. Moreover, the beneficial effect appeared to be present in all 3 PTSD symptom clusters and on several secondary outcome measures. The symptoms remained significantly reduced at 2 weeks (indicated by Clinician-Administered PTSD Scale (CAPS) score of less than 50) in 6 subjects who had responded to ketamine in the first treatment compared to only 1 who had received midazolam. However, the mean CAPS score 7 days after the infusion, did not differ significantly between the two treatment conditions. Although there was evidence of transient improvement in both PTSD and associated depressive symptoms following the treatment, the evidence supporting the use of ketamine for the treatment of PTSD to date remains weak considering the size and limitations of the studies. Some researchers have expressed concern that ketamine could potentially worsen PTSD symptoms based on theoretical issues and previous work suggesting that use of ketamine analgesia in the emergency setting following a trauma may increase the symptoms of dissociation, re-experiencing, hyperarousual and avoidance 3 days after the event[12]. However, no clinically significant difference in dissociative symptoms or anxiety was observed between depressed subjects with a history of trauma and/or PTSD for 1 week after a single subanesthetic dose of ketamine in series of studies completed at the NIMH, as reviewed by Zeng *et al.*[13], and the treatment appeared to be relatively well tolerated in the two PTSD studies cited above.

Similarly, available data regarding the use of ketamine in obsessive-compulsive disorder (OCD)[14,15] are inconclusive and inconsistent. A small controlled crossover trial of ketamine vs. saline reported 5 of 15 subjects with nearly constant intrusive obsessions had a response (>35% reduction in OCD symptoms) to the treatment within the first week following the ketamine infusion[18]. Another recently published small open-label study of 10 unmedicated OCD outpatients also found ketamine to produce reductions in OCD symptoms within 4 hours of administration. It also suggested that a brief course of intensive CBT may help to maintain the response by showing 5 of the 8 patients that completed 10 CBT sessions showed >30% reduction in OCD severity scores 2 weeks following the ketamine infusion[16]. In contrast, a small open-label study of 10 OCD subjects using broader inclusion criteria found that none of the subjects experienced a response (>35% reduction in symptoms) over the 3 days following a single ketamine infusion; however, four of the seven subjects with comorbid depression experienced a transient antidepressant response (>50% reduction in depressive symptoms) to the treatment[19]. Of note, two of the OCD patients in this open label study, both with complicated psychiatric histories including comorbid diagnosis of PTSD, presented with delayed-onset passive suicidal ideation, dysphoria and increased anxiety after receiving the ketamine treatment[17], thus suggesting special precautions are warranted in patients with complicated diagnostic issues.

At present, multiple ongoing trials are exploring the effects of ketamine treatment in other psychiatric disorders including autism spectrum disorders, social anxiety, alcohol use disorder, and Rett's syndrome (clinicaltrials.gov). However, at

present there are insufficient data to allow a meaningful review of the evidence related to these disorders, or to support the use of ketamine treatments outside of the research setting for any of these disorders.

(2) **Relevance of Symptom Severity and Treatment Resistance:** Severity and previous treatment resistance should be used as factors in calculating the risk benefit ratio for individual patients. Moreover, some form of repeated dimensional symptom assessments should be used to track clinical response to ketamine and determine if symptom improvement justifies continued treatment. To date most of the published studies and case reports have included only patients with moderate to severe major depressive episodes, and there is no high quality data clearly showing that baseline severity measures modulate ketamine treatment response. There is limited data to suggest slower processing speeds[18] and increased baseline anxiety[19,20] may predict greater response to ketamine treatment. There is also emerging evidence to suggest ketamine is effective in rapidly decreasing suicidal ideation[21-23], however the current data remain insufficient to draw any firm recommendations or comparisons to other treatment strategies at this time. Considering the currently available information the Task Force recommends, with the rare exception of unique clinical circumstances, ketamine should not be first-line treatment for any level of episode severity and more established therapies be initiated as first line treatments.

The large majority of published studies and case reports have included only patients with previously non-responsive major depressive episodes, so it is not possible to provide any information on the effects of the treatment in less refractory

patient populations. With regard to the level of treatment resistance predicting treatment outcome, a relatively small study comparing 17 patients who had previously failed a course of electroconvulsive therapy (ECT) to 23 patients not having undergone previous treatment with ECT, found ketamine was associated with transient clinical improvements in both groups with no significant difference in the percentage of responders to a single ketamine infusion between the two groups[24]. Therefore, the limited data that are available suggest that ketamine treatment may have at least transient clinical benefit in highly treatment resistant patients. However, any use in less treatment resistant patients needs to be balanced against the limited data on ketamine's efficacy and safety, and the risk of delaying other well established treatments for treatment resistant depressive disorders such as atypical antipsychotic mediations, TMS and ECT.

(3) **Relevance of Concomitant Medications:** At present there remains relatively little information regarding potential drug-drug interactions that could impact the safety or efficacy of ketamine treatment for mood disorders. Considering prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with ketamine for anesthesia (FDA label), it is also important to evaluate the potential safety implications of the potentiating interaction of these classes of medication with the use of sub-anesthetic dosing of ketamine.

Based on a proposed mechanism of ketamine's antidepressant action, whereby ketamine selectively inhibits the activation of subsets of GABAergic interneurons leading to increased levels of presynaptic glutamate release[25], it has been hypothesized that the concomitant use of benzodiazepines or other gamma

amino butyric acid A (GABA A) potentiating agents may attenuate the antidepressant effects of ketamine. This has found some support in a report of clinical observations[26] and a small post hoc sub-analyses of other studies[27], but remains speculative and preliminary. This is an important consideration in light of the fact that rapid acting benzodiazepines are frequently used to attenuate the potential emergence and anxiogenic effects of ketamine, or may be commonly used in patients with major depressive episodes accompanied by anxiety. At present, it is not possible to provide a strong specific recommendation regarding the concomitant use of benzodiazepines, but considering the limited information available it would not be unreasonable to minimize the use of benzodiazepines prior to the time of the ketamine infusions, and to allow adequate time after last dose for benzodiazepine washout prior ketamine dosing.

(4) **Rationale for Assessing Medical and Demographic Risk Factors:** As discussed in more detail below, ketamine, even at sub-anesthetic doses, can have physiologically meaningful effects on cardiovascular function. A study of 84 unique patients receiving 205 intravenous ketamine infusions (0.5 mg/kg over 40 minutes) for treatment of mood disorders reported transient increases in mean peak blood pressure measures (mean peak increases of 19.6 ± 12.8 mm Hg systolic, and 13.4 ±9.8 mmHg diastolic blood pressure). Approximately 14% of the patients received treatment with antihypertensive medications during the infusions, and 30% of the sample had blood pressures exceeding 180 mmHg systolic, 100 mmHg diastolic, or heart rate greater than 110 bpm at some point during the infusion[28]. Although changes in cardiovascular status are not specifically reported in many of

the other published studies, the recent findings by Wan et al. are generally in agreement with the existing reports in showing a significant and potentially meaningful increase in blood pressure, but no associated serious adverse cardiovascular events.

Based on this information, it is important to screen for baseline hypertension and tachycardia in order to anticipate potential cardiovascular complications of treatment, and to ensure that the patient has received adequate treatment for these conditions, if they do exist, prior to initiating treatment. It is also advised that some assessment of a patients' exercise capacity be collected and documented. Additionally, patients should be specifically asked about any recent changes in exercise tolerance. These measures should be used to better predict potential risks associated with the ketamine-induced cardiovascular changes and to understand the risk benefit ratio of the treatment. The choice of other physical and laboratory screening procedures should be determined according to the patients' individual risk factors based on demographics, medical history and review of systems. Similarly, decisions on whether to obtain consults from cardiologist or other medical specialist should be made based on the patient's individual risk factors.

Since ketamine has been abused as a recreational drug[29], strong efforts should be made to evaluate potential factors that may increase a patient's risk of developing substance abuse issues with ketamine. These factors should include history of substance abuse, level of past and current alcohol use, smoking history, any previous history of medication misuse or inappropriate use of medical care, and a positive result on a screening urine toxicology panel. While there is no clear

evidence of a recent substance abuse to be associated with the risk of relapse with ketamine, we recommend the length of sobriety be strongly considered in evaluating the risks of ketamine treatment.

eBox 2. Suggested Acceptable Baseline Parameters

Blood Pressure: Ketamine is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard. The most common physiological response to ketamine is an increase in SBP, DBP and HR. SBP can frequently rise >20mmHG and DBP can rise >15 mmHG during infusions. Considering the goal of keeping BP values less than 180/110 at all times during the infusion process, it is suggested that patients, even if otherwise in generally good health, with SBP≥150 mmHg or DBP≥95 mmHg at baseline, be considered at higher risk, and treatment of hypertension should be considered prior to initiating treatment if possible. Patients with a history of cardiopulmonary or cerebrovascular diseases, poor exercise capacity (<6 metabolic equivalent of tasks (METs); Bicycling—light effort (10–12 mph) = 6.0), or any disease that could be associated with increased risk of acute cardiac demand or blood pressure or respiratory depression should all be considered on a personalized basis, considering the individual risk/benefit ratios. It is reasonable to consider seeking necessary consultations or referring these subjects to appropriately staffed and equipped facilities with specific medical expertise.

Heart Rate: There are no high quality data to guide the decision on acceptable minimal and maximal resting heart rates at baseline assessments. However,

patients experiencing baseline bradycardia (<60 beat per minute) or tachycardia (>100 beats per minute) should be considered on an individual basis for the relative risks associated with ketamine treatment.

SpO2 level: Baseline SpO2 should be >94

Other Laboratory Measures: Other physiological and laboratory measures should be decided on a personalized basis, considering individual risk factors.

eBox 3. Suggested Stopping/Intervention Parameters

Blood Pressure: The goal is to keep BP values < 180 mmHg for SBP and <110 mmHg for DBP at all times during the infusion process. This should be kept as a conservative maximum level to trigger an intervention or stopping criteria, especially in non-hospital based settings. Based on existing evidence showing a rapid decrease in blood pressure following infusion discontinuation, it is possible to simply stop the infusion if either SBP or DBP meets the criteria. Blood pressure should be monitored closely after this time to insure that the decrease occurs. In some situations, considering the experience of the clinician providing the treatment and the setting where it is provided, it is also possible to provide antihypertensive medications to manage the transient blood pressure increases while continuing the infusion.

Perhaps more concerning than an increase in blood pressure, is a reduction in SBP from baseline blood pressure, despite evidence of an increased cardiac demand. Sudden drops in SBP>10 mmHg associated with increased heart rate or any evidence of distress should be considered a stop criteria. However, it is not uncommon for SBP to decrease with the termination of the infusion or if the patient was extremely anxious at the beginning of the infusion session.

Again**,** any disease that places a patient at an increased risk of having a serious adverse event related to an acute increase in cardiac demand or blood pressure, should all be considered on a personalized basis considering the individual risk/benefit ratios.

Heart Rate: There is no high quality data to guide monitoring of heart rate with ketamine treatments, however using the American Heart Association recommendations of target heart rate with exercise (www.heart.org/HEARTORG/HealthyLiving/PhysicalActivity/FitnessBasics/Target-Heart-Rates_UCM_434341_Article.jsp#.WCaAr1tgbiM) and considering 70% of maximum heart rate to be consistent with the higher level obtained during moderately intense activities, we suggest age adjusted maximum heart rates of 20yrs<140bpm, 30yrs<133, 40yrs<126, 50yrs<119, and 60yrs<112. Patients over the age of 65 should be considered on an individualized basis based on exercise capacity and other risk factors.

Other Factors to Consider: The appearance of any of the following symptoms should also be grounds for immediate termination of the infusion: (1) pallor, cyanosis, or any symptoms suggesting poor perfusion, (2) respiratory symptoms such as shortness of breath, wheezing, (3) the appearance of chest, jaw or arm pain suggesting cardiac involvement, or (4) the patient's desire to stop.

eBox 4. Suggested Ongoing Assessments of Cognitive Function and Urinary Symptoms

Ongoing Evaluation of Cognitive Function

There is no clear agreement on the type or frequency of cognitive assessment that should be performed to evaluate potential changes in cognitive function. Although there is strong evidence that ketamine can have transient adverse effects on cognitive function [30], and that chronic ketamine abuse is associated with cognitive impairment in several domains including verbal fluency, verbal memory, verbal learning, visual recognition memory, cognitive processing speed and deficits in working and episodic memory[31], the available studies examining the effects of ketamine treatment of mood disorders on cognition have not demonstrated any evidence of cognitive decline[18,32,33]. However, these studies have a number of limitations including small numbers of subjects, and treatment periods of less than 1 month, limiting the ability to make strong claims on the relative risks of the treatment on cognitive performance. Considering the preclinical literature suggesting that ketamine could produce cognitive dysfunction and potentially even excitotoxic degeneration [34,35], and the limited safety data currently available, it is recommended that some assessment of cognition, probing several different domains function be used to follow patients receiving ongoing ketamine for the treatment of mood disorders.

Ongoing Evaluations of Urinary Symptoms

In light of the identified risk of cystitis associated with chronic high frequency ketamine use[36,37], it is also suggested that some assessment of urinary symptoms and pelvic pain be included in the follow up of patients receiving ongoing ketamine treatment. Questionnaires such as the O'Leary/Sant Voiding and Pain Indices[38] or the Bladder Pain/ Interstitial Cystitis Symptom Score[39] could be used to follow patients for possible progression of symptoms with ongoing ketamine treatment.

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