

Supplementary Online Content

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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, <i>et al.</i> ²
Vagus Nerve Stimulation	1	235	Rush AJ <i>et al.</i> ³
Deep Brain Stimulation—VC/VS	1	30	Dougherty DD, <i>et al.</i> ⁴
Deep Brain Stimulation- SCC	1	75	Morishita T <i>et al.</i> ⁵
I.V. or intranasal Ketamine	9	368	Han <i>et al.</i> 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 depression⁸, 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 date⁹. 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, hyperarousal and avoidance 3 days after the event¹². 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 infusion¹⁸. 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 infusion¹⁶. 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 treatment¹⁹. 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 treatment¹⁷, 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 speeds¹⁸ 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 ideation²¹⁻²³, 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 groups²⁴. 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 medications, 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 release²⁵, 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 observations²⁶ and a small post hoc sub-analyses of other studies²⁷, 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 infusion²⁸. 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 drug²⁹, 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 \geq 150 mmHg or DBP \geq 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 function³⁰, 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 memory³¹, 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 Indices³⁸ or the Bladder Pain/ Interstitial Cystitis Symptom Score³⁹ could be used to follow patients for possible progression of symptoms with ongoing ketamine treatment.

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