A growing number of small clinical trials have demonstrated that subanesthetic doses of ketamine can produce antidepressant effects in patients with mood disorders who have demonstrated refractoriness to standard therapies. Patients in these trials have been diagnosed with major depressive disorder and bipolar disorder, and the sample sizes have ranged from 8 to 99. While there is broad agreement that ketamine-like drugs hold considerable promise as novel antidepressant agents, the increasing number of clinicians from a variety of medical specialties offering ketamine as an off-label treatment for psychiatric disorders has raised concern.

Although ketamine has been approved by the US Food and Drug Administration (FDA) as an anesthetic for more than 45 years, there remain concerns about the safety of repeated ketamine dosing. These concerns stem in part from reports of cognitive impairment and bladder dysfunction associated with repetitive administration of the drug in rodent models and in humans with ketamine use disorder. Furthermore, concerns of spawning a substantial increase in iatrogenic ketamine use disorder related to wider use of ketamine for treating mental health disorders have led some to suggest more restricted use until additional data are available.

However, the lack of patent protection surrounding the use of racemic ketamine hydrochloride as a treatment for mood disorders makes it unlikely that larger phase 3 trials required for FDA consideration or standard postmarketing surveillance studies addressing issues of longer-term safety and effectiveness will ever be completed. In light of these facts, the American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments issued a consensus statement on the off-label use of ketamine for the treatment of mood disorders. This Viewpoint summarizes a number of important issues related to the clinical use of ketamine for the treatment of psychiatric disorders addressed in the consensus statement and provides suggestions for addressing remaining concerns.

Who Should Be Considered for Ketamine Treatment

There was strong agreement among the contributors to the consensus that appropriate patient selection is a critical and necessary factor in optimizing the risk/benefit ratio of this novel treatment strategy. This requires a comprehensive evaluation and thorough consideration of the individual's potential risks and benefits, considering the medical, psychological, and social factors specific to each patient. Considering the limited longer-term safety and efficacy data, only patients who have not responded to adequate trials of more standard antidepressant treatments should be candidates. Agreement was also reached that patients should be informed of the extent of the existing evidence regarding the use of ketamine in the treatment of psychiatric disorders before they provide consent to treatment. This should include acknowledgment of the relative dearth of published data on any diagnosis other than major depressive episodes, the limited evidence of long-term effectiveness, the possible or likely need for repeated administrations to maintain response, and the concerns regarding cognitive impairment, cystitis, and abuse liability.

Clinical Experience, Training, and Treatment Setting

No published guidelines exist delineating required clinician training prior to providing subanesthetic doses of ketamine as a treatment. Considering the delivery regimen most commonly used in published research protocols (0.5 mg/kg infused intravenously over 40 minutes) typically results in peak ketamine serum levels that are an order of magnitude below the peak levels used for anesthesia, it does not seem reasonable to impose the same training requirements as would be used in the case of ketamine anesthesia. However, even subanesthetic doses of ketamine can induce potentially concerning transient elevations in both heart rate and blood pressure.

In addition, patients may also experience prominent psychoactive effects (such as perceptual and cognitive disturbances, derealization, and depersonalization) that can persist for 30 to 120 minutes following infusion cessation.

In consideration of these risks, the consensus statement recommended that, at a minimum, clinicians who administer ketamine be prepared to manage both cardiovascular and behavioral events should such arise, and suggested certification in Advanced Cardiac Life Support for clinicians delivering the treatment. The consensus statement also suggests that ketamine be provided by a clinician who can administer Drug Enforcement Agency Schedule III medications (in most states, this is a licensed physician with an MD or DO degree). The treatment facility should have a means of providing basic cardiac and respiratory monitoring as well as an established plan for providing stabilization and rapid transfer of patients with sustained alterations in cardiac functioning.

Dose and Delivery Procedure

Most evidence available to date has supported the use of 0.5-mg/kg ketamine hydrochloride given intravenously over 40 minutes. Comparatively little research has been published on other doses, routes of administration, or infusion durations. The only available randomized clinical data comparing various doses come from 2 small trials of 99 and 71 patients that suggest both lower and higher ketamine doses (0.1-1.0 mg/kg) may have some efficacy. Nevertheless, it should be noted that in both studies, the more commonly used 0.5-mg/kg dose was at least numerically...
more efficacious. Furthermore, the increased efficacy of the 0.5 mg/kg dose may be more pronounced in patients with severe depression compared with lower doses. However, lower doses do appear to have few associated adverse events. Thus, because of limited data, it is not possible to clarify the relative benefits and risks of doses other than 0.5 mg/kg delivered intravenously over 40 minutes.

To ensure patient safety, site-specific standard operating procedures should be developed and should include assessments of baseline vital signs, confirmation of preprocedural informed consent, criteria for acceptable baseline vital signs prior to initiating treatment, and criteria for prematurely stopping an infusion. Posttreatment assessments should confirm that each patient returns to a mental state that will allow for a safe return to the current living situation and a responsible adult should be available to transport the patient home if treatments are done on an outpatient basis.

Course of Treatment Planning
The only existing study to date examining dosing frequency suggests that dosing thrice weekly is no better than twice weekly induction dosing, although this evidence comes from a comparatively small (n = 68) randomized clinical trial. While some clinicians have reported more frequent dosing strategies, there is currently no published evidence to support the benefits of this practice over lower-frequency treatments.

Most published data supporting the use of ketamine as a treatment for mood disorders are based on trials that have followed up patients for just 1 week after a single administration of the drug. While a few small trials (7 trials with sample sizes ranging from 9 to 68) have demonstrated the relative safety of repeated infusions (4-6 total infusions over a couple of weeks), there is very little published data on the efficacy and safety of longer-term use. Most of these repeated dosing trials have shown that the majority of benefit experienced by patients occurs within the first 2 weeks of treatment. Hence, it may be reasonable to discontinue treatment after 2 weeks if no meaningful benefit is achieved.

As most trials to date suggest that a short course of ketamine does not usually provide long-lasting benefits to patients with a chronic disease, many clinicians currently offer maintenance ketamine treatment. However, there is insufficient evidence to meaningfully inform long-term treatment with ketamine. Considering the liability of the potential for abuse as well as concerns for cognitive impairment and cystitis associated with chronic high-frequency exposure, it is reasonable to suggest that clinicians limit the administration to the minimum effective dosing frequency and use recurring assessments of cognition, bladder functioning, and substance use when long-term treatment is provided until more information on the longer-term safety is available. Moreover, during this early stage of clinical development, the consensus statement strongly cautions against the practice of take-home, self-administration of ketamine.

Conclusions
While the discovery of ketamine’s robust and rapid-acting antidepressant effects has appropriately led to considerable enthusiasm among some clinicians and considerable hope among some patients, this enthusiasm for this promising treatment should be coupled with caution given the limitations of the existing knowledge base and the potential adverse effects of long-term treatment. However, considering the tremendous individual and societal burden of mood disorders, the high percentage of patients that do not achieve satisfactory responses from the currently available approved treatments, and the recent evidence of rising rates of suicide, expedited research into this potentially transformative treatment is needed. Several ongoing studies (such as NCT01945047, NCT03113968, and NCT00088699) are attempting to address these knowledge gaps and enrollment in these trials should be encouraged when possible. In addition to the standard randomized clinical trials, the creation of a registry of patients receiving ketamine off-label as a treatment for mood disorders could serve as an efficient way to learn more about the longer-term effectiveness and safety of the treatment and could be beneficial in guiding the rational use of the treatment.

ARTICLE INFORMATION
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