Letters to the Editor

A Survey of the Clinical, Off-Label Use of Ketamine as a Treatment for Psychiatric Disorders

TO THE EDITOR: Since 2000, several small randomized controlled trials have demonstrated that ketamine has potent and rapid-acting antidepressant effects in patients with treatment-resistant depression (1). Despite a lack of long-term data or Food and Drug Administration indication, many community providers and academic centers have begun offering ketamine treatment to patients with major depressive disorder and with other psychiatric disorders, determining the existing evidence justifies use for some individuals. The practice patterns of such providers have not been studied.

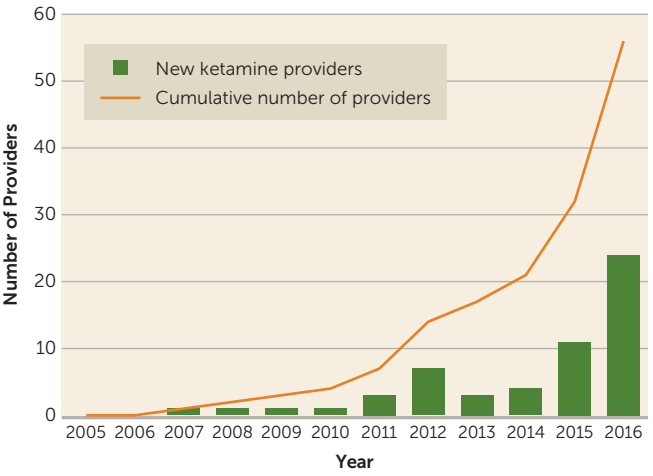
Method

From September 2016 through January 2017, a web-based survey was sent to physicians nationwide inquiring whether their clinical practices use ketamine for psychiatric disorders. Physicians were identified through a systematic web search for sites advertising ketamine treatments for depression and through our relationships with academic and community colleagues. The study was considered exempt from a full evaluation from an institutional review board.

Results

We identified 85 providers through our search. Survey requests were sent to 76 providers (e-mail addresses could not be acquired for nine), and responses were received from 57 (75.0%). Most (73.7%) survey respondents worked in private practice, with a minority in academic settings (14.0%) or in health maintenance organizations (8.8%), with a regional distribution as follows: West Coast (31.6%), Northeast (19.3%), Southeast (15.8%), Mountain West (10.5%), Mid-Atlantic (10.5%), and Midwest (8.8%). Most (66.7%) providers were trained in psychiatry, with others trained in anesthesiology (22.8%), emergency medicine (3.5%), or family medicine (3.5%). Most providers (73.7%) administered ketamine in an office-based setting, with a minority (21.1%) administering ketamine in a hospital-based setting or in a surgical or procedural suite. The majority of practitioners reported starting to provide ketamine for psychiatric disorders relatively recently, with a notable increase in the cumulative number of such providers since 2012 (Figure 1).

FIGURE 1. Total Number of Physicians Initiating the Practice of Providing Ketamine Off Label for the Treatment of Psychiatric Disorders per Calendar Year (Bars), and Cumulative Number of Ketamine Providers Over Time (Line)



The most commonly reported diagnosis treated was major depressive disorder (72.2%), followed by bipolar disorder (15.1%) and posttraumatic stress disorder (5.7%). Most providers (87.7%) reported administering ketamine via an intravenous route, with a minority reporting using an oral (22.8%) or an intranasal (19.3%) formulation. Among providers reporting intravenous administration, 44.0% reported using a dosage of 0.5 mg/kg infused over 40–45 minutes, the typical dosage in most research protocols (2); a minority reported using a range of dosages between 0.5 and 1.0 mg/kg (12.0%) or between 0.5 and 3.0 mg/kg (14.0%).

Approximately half of providers reported monitoring heart rate (48.1%) and pulse oximetry (54.0%) at least every 5 minutes during the infusion, with 25.9% monitoring blood pressure at least every 5 minutes. Most providers reported monitoring heart rate (77.8%), pulse oximetry (80.0%), and blood pressure (75.9%) at least every 15 minutes during the infusion. Few providers reported no monitoring of heart rate (1.9%), pulse oximetry (10.0%), and blood pressure (1.9%).

Most providers (89.5%) reported offering ketamine on a continuation or maintenance basis (defined as a time period greater than 1 month). Providers reported the average frequency of maintenance treatments as monthly (29.8%), once per 3 weeks (21.1%), once per 2 weeks (12.3%), or less than monthly (15.8%). Providers reported that 64% of patients paid for the ketamine treatment out of pocket, with 23% of patients having a portion of the cost reimbursed by insurance and 13% of patients having other payment structures.

Discussion

This is the first attempt to characterize practice patterns among physicians providing ketamine as a treatment for psychiatric disorders. Although there are limitations to this approach, including the inability to ensure that this is a representative sample of all ketamine providers across the country, we identified a rapidly growing number of physicians in a variety of specialties and geographic locations offering ketamine treatment for psychiatric disorders. Various dosing protocols were reported, although the majority of research studies have used only one protocol (2). These results underscore the urgent need for more research on the use of ketamine in psychiatric disorders in clinical settings in order to establish evidence-based treatment regimens and the safety of long-term use. The growing use of ketamine in this population, coupled with the concern for potential adverse clinical consequences of repeated dosing (e.g., abuse liability [3], cognitive impairment [4]), argues for the importance of a registry (5) to longitudinally follow psychiatric patients who receive ketamine.

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High Placebo Response Rates Hamper the Discovery of Antidepressants for Depression in Children and Adolescents

TO THE EDITOR: We read with interest the article by John T. Walkup (1), published in the May 2017 issue of the *Journal*. The author has presented an important viewpoint that the conclusions of meta-analyses, which suggest that antidepressants for depression in children and adolescents are not effective or are minimally effective, should be highly suspect because those meta-analyses include improperly designed industry-sponsored studies. To shorten the time frame in these studies, unqualified subjects had been recruited, leading to high placebo response rates and a negative conclusion. On the contrary, studies funded by the National Institute of Mental Health are characterized by their methodological strengths, lower placebo response rates, and meaningful intergroup differences that support the efficacy of antidepressants.

However, we need more data to back this claim. Therefore, we conducted a comprehensive literature search of public databases, and eight placebo-controlled randomized controlled trials of fluoxetine were included for analysis. There were two trials (N=459) with high placebo response rates (≥50%) and six trials (N=885) with low placebo response rates (<50%). The trials with high placebo response rates yielded small differences between fluoxetine and placebo of only 1% (95% CI=−13 to 15). However, in the trials with low placebo response rates, the significant differences between fluoxetine and placebo were found to be 19% (95% CI=11–28). The results showed that even fluoxetine, the only drug approved by the Food and Drug Administration for the treatment of children and adolescents with depression, was invalid in the trials with high placebo response rates, which suggests that the results from the trials with high placebo response rates are unreliable.

In 19 placebo-controlled randomized controlled trials of other newer antidepressants (excluding fluoxetine) for children and adolescents with depression, we found the number of trials in which the placebo response rate was higher than 50%, between 40% and 50%, and lower than 40% to be 10, seven, and two, respectively. We hypothesized that the high placebo response rates may be the reason for the efficacy debate of these newer antidepressants for the treatment of depression in children and adolescents.

We support the author's viewpoint and reinforce it with data from a comprehensive literature review. In the