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.

REFERENCES

1. Newport DJ, Carpenter LL, McDonald WM, et al: Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am J Psychiatry 2015; 172:950–966
2. McGirr A, Berlim MT, Bond DJ, et al: A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol Med 2015; 45:693–704
3. Sassano-Higgins S, Baron D, Juarez G, et al: A review of ketamine abuse and diversion. Depress Anxiety 2016; 33:718–727
4. Morgan CJ, Muetzelfeldt L, Curran HV: Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. Addiction 2010; 105:121–133
5. Sanacora G, Heimer H, Hartman D, et al: Balancing the promise and risks of ketamine treatment for mood disorders. Neuropsychopharmacology 2017; 42:1179–1181

Samuel T. Wilkinson, M.D.
Mesut Toprak, M.D.
Mason S. Turner, M.D.
Steven P. Levine, M.D.
Rachel B. Katz, M.D.
Gerard Sanacora, M.D., Ph.D.

From the Department of Psychiatry, Yale School of Medicine, New Haven, Conn.; Kaiser Permanente Northern California, San Francisco; and Ketamine Treatment Centers, Princeton, N.J.

Address correspondence to Dr. Sanacora (gerard.sanacora@yale.edu).

Dr. Wilkinson receives research and salary support from NIMH (T32MH062994-15), the Brain and Behavior Research Foundation, and the Robert E. Leet and Clara Guthrie Patterson Trust.

Over the last 36 months, Dr. Sanacora has received consulting fees from Allergan, Alkermes, AstraZeneca, Avanier Pharmaceuticals, BioHaven Pharmaceuticals, Bristol-Myers Squibb, Hoffmann La-Roche, Janssen, Merck, Naurex, Novartis, Noven Pharmaceuticals, Servier Pharmaceuticals, Taisho Pharmaceuticals, Teva, Valeant, and Vistagen Therapeutics. He has also received additional research contracts from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Hoffmann La-Roche, Merck, Naurex, and Servier over the last 36 months. No-cost medication was provided to Dr. Sanacora for an NIH-sponsored study by Sanofi-Aventis. In addition, he holds shares in BioHaven Pharmaceuticals Holding Company and is a coinventor on a patent (Glutamate agents in the treatment of mental disorders, number 8778979). Dr. Levine is the owner of Ketamine Treatment Centers. The other authors report no financial relationships with commercial interests.

This letter was accepted for publication in May 2017.

Am J Psychiatry 2017; 174:695–696; doi: 10.1176/appi.ajp.2017.17020239

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

antidepressant trials of children and adolescents, placebo response rates should be well controlled by strict implementation of trials, which will help studies of antidepressants obtain correct results.

REFERENCE

1. Walkup JT: Antidepressant efficacy for depression in children and adolescents: industry- and NIMH-funded studies. Am J Psychiatry 2017; 174:430–437

Lujin Li, Ph.D.
Yanfei Li, M.D.
Qingshan Zheng, Ph.D.

From the Center for Drug Clinical Research, Shanghai University of Traditional Chinese Medicine, Shanghai.

Address correspondence to Dr. Lujin Li (lilujin666@163.com).

The authors report no financial relationships with commercial interests.

This letter was accepted for publication in April 2017.

Am J Psychiatry 2017; 174:696–697; doi: 10.1176/appi.ajp.2017.17030347