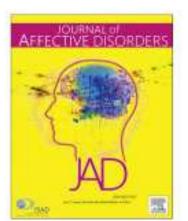
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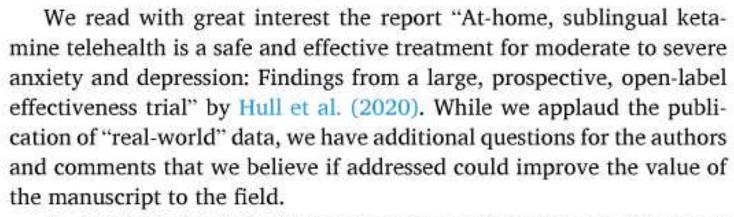
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Correspondence

At-home ketamine; still a lot to learn

Dear Sirs -



As noted by the authors, the paper does not report any efficacy or safety outcomes for at least 1573 (55.8 %) of the 2848 patients who appeared to have started the at-home ketamine treatment protocol (Fig. 1). Why were so many patients excluded from the analysis? No explanation or breakdown is provided. The authors list at least 13 exclusion criteria for this report; do these criteria apply to the administration of at-home ketamine or just to the analysis of the patients in this report? What proportion of the patients sent drug actually completed the 4 planned ketamine treatment sessions? Why was data not available for them? This information would help in determining whether this data was missing at random or not at random. The authors state in the discussion that "review of EHR for those excluded due to missing follow-up measures did not reveal any differences in rates of cancellation, dropout, or adverse events." However, they also state that drop out was essentially counted only if patients preemptively cancelled appointments (rather than not showing up, a more frequent occurrence in the clinic). A better definition of drop out-the number of patients who did not receive the intended 4 treatment sessions—would clarify whether there were safety signals that were not picked up by the report. Can the authors provide this data?

Related to safety concerns, the authors state that clinical staff—referred to as guides—were available by phone during the treatment session if a patient's peer monitor needed to reach them urgently. In what proportion of patients did this happen? This would be a critical piece of data needed to help conclude that at-home treatment is safe, as the authors state in the title. It is also noted that the guides are not licensed clinicians but hold certifications. Can the authors provide further details about this certification process? What training process is completed prior to certification? Is there training in the assessment of adverse events? The authors note that there were at least 59 patients that reported side effects. Can they give more description of what these side effects were? Were they judged mild, moderate, or severe?

For several reasons, we object to the title of the paper, which explicitly states that the paper reports data from a prospective clinical trial. The authors themselves state that the data was collected as part of a quality assurance project, which is very different than a clinical trial. Furthermore, any legitimate clinical trial requires pre-registration with a reputable database (i.e. US Clinical Trials Registry); this study was not registered and should not be considered a trial. A more accurate way to

classify this report would be a retrospective review of medical records.

The title also explicitly states that at-home ketamine is safe and effective under the protocol investigated. However, we think the authors' conclusions go well beyond the data.

Potential worrisome scenarios with at-home ketamine administration include drug diversion, abuse, and dysphoric reactions which could leave patients in a fearful and paranoid state without appropriate monitoring that could lead to harm of self or others. These events may well be rare, but it is unlikely they would be captured in the current report, which has so much missing data, does not report safety outcomes on the majority of patients treated, and does not appear to actively monitor for adverse outcomes.

For instance, it's not clear how the providers would know if a patient did not take the ketamine as directed but instead ingested all the doses together in a single 'trip.' Reselling or reformulating the ketamine would also not be observable given the surveillance procedures of the current report.

The authors report a response and remission rates of 62.8 % and 32.6 %, respectively, following 4 sessions of at-home ketamine. However, this is based on data from only 553 patients, which represents only 20 % of patients who began treatment and only 44 % of patients who were analyzed for symptom outcomes. This concern is amplified when the authors attempt to make comparisons with other reports that used much more rigorous forms of data collection.

Again, we applaud the authors' attempts at reporting real-world data and the journal for the willingness to publish this form of data; the field needs more of this. However, we also point out that the report did not show that the protocol was safe nor effective.

Credit authorship contribution statement

Both Dr. Wilkinson and Dr. Sanacora drafted the manuscript and critically revised it for content and retain responsibility for its views.

Conflict of interest

Sanacora reported receiving personal fees and serving as a consultant to Allergan, Alkermes, AstraZeneca, Avanier Pharmaceuticals, Axsome Therapeutics, Biogen, Biohaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Cowen, EMA Wellness, Engrail Therapeutics, Clexio, Denovo Biopharma, Gilgamesh, Hoffmann La-Roche, Intra-Cellular Therapies, Janssen Pharmaceuticals, Levo, Lundbeck, Merck, Navitor Pharmaceuticals, Neurocrine, Novartis, Noven Pharmaceuticals, Otsuka, Perception Neuroscience, Praxis Therapeutics, Sage Pharmaceuticals, Servier Pharmaceuticals, Seelos Pharmaceuticals, Taisho Pharmaceuticals, Teva, Valeant, Vistagen Therapeutics, and XW Labs. Dr. Sanacora also reported receiving

research contracts from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, and Usona over the past 36 months. Dr. Sanacora holds equity in BioHaven Pharmaceuticals and is a co-inventor on a US patent (8,778,979) held by Yale University and a co-inventor on US Provisional Patent Application 047162-7177P1 (00754) filed on August 20, 2018, by the Yale University Office of Cooperative Research. Yale University has a financial relationship with Janssen Pharmaceuticals and may in the future receive financial benefits from this relationship. The university has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest office. In addition, funding through support was provided in part by the George D. Gross and Esther S. Gross Endowment and the Yale New Haven Health System.

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