See article by Oliver et al

Ketamine in the Real World:
Where Do We Go From Here?

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In their article in the *Journal*, Oliver and colleagues[1] report outcomes from a sample of 424 patients receiving ketamine therapy from community clinics. The clinicians used a 6-infusion treatment approach, given over 2–3 weeks. Some 30% of patients discontinued treatment prior to completing the 6-infusion protocol. The authors report a 50% response rate and a 20% remission rate by 6 weeks following initiation of treatment.

Despite the US Food and Drug Administration (FDA) approval of esketamine, it appears that racemic ketamine—most commonly delivered intravenously but also via other routes of administration—will continue as a therapeutic option for the foreseeable future.[2,3] At this point, it is likely that many tens of thousands of patients have received racemic ketamine from community providers. For many years, several key leaders in the field have been calling for a registry to collect data on the use of ketamine for mood disorders.[4,5] Unfortunately, no funding or accreditation body has stepped forward to take on this challenge. Short of this, reports like the one from Oliver and colleagues are the next best thing. The field would benefit from additional reports from similar groups and clinics that provide racemic ketamine on a clinical basis.

These reports can provide valuable clinical information. For instance, Oliver and colleagues report that among responders, the median number of treatments until response was 6. The reports also notes that 30% of patients discontinued the treatment protocol prior to the 6 prescribed infusions (a breakdown of reasons for discontinuation would also be extremely helpful). Details that characterize the patient population—in this report, the proportion of patients who had failed two or more antidepressant therapies, the proportion who had received ECT, and the proportion who had attempted suicide—can also help contextualize response and remission rates as well as other outcome data.

There are, of course, limitations to these reports. In general, reports from community clinics will not have a control/comparator group. Because of key differences between research and clinical care settings, comparison of response or remission rates between these types of reports and studies that are conducted as clinical trials is fraught with nuances and pitfalls. These comparisons should be done with extreme reticence and caution, if done at all. This is especially the case because most—if not all—patients who are treated by community providers with racemic ketamine are paying out of pocket (as was the case with the report by Oliver and colleagues); this means that these patients likely differ in important ways from samples of patients who enroll in clinical trials, in which finances are not a barrier to treatment.

It is also important to recognize that these clinics have limited resources to devote toward data collection and, hence, will inevitably yield fewer data that are generally of lower quality than data from clinical trials. It is therefore important to highlight the data that are most reliable and achievable in this setting. Building on Oliver and colleagues' report, key clinical data that could realistically be collected in such clinical settings include—in addition to data collected by Oliver and colleagues—documentation of a history of psychiatric hospitalization, current or recent antipsychotic use, unipolar versus bipolar depression, reasons for discontinuation, and race. Perhaps most important to improve reports such as the one by Oliver and colleagues is the standardized documentation of serious adverse events. Without funding for a registry, it is highly unlikely that community clinics would have the resources to rigorously document all adverse events in the same way they are documented in clinical trials. However, further training and organization to facilitate the rigorous documentation of serious adverse events (including attribution of causality to the treatment) according to FDA definitions would be invaluable for the field. Documenting and reporting the proportion of patients who experience dysphoric reactions during the infusion (sometimes colloquially termed *k-holes* in the literature on ketamine abuse) would also be an important piece of information.

One of the questions implied by Oliver and colleagues' report is whether there is a meaningful clinical difference between racemic ketamine and intranasal esketamine, the latter having regulatory approval as a psychotropic therapy. There seems to be an abundance of strong opinions on this matter but little high-quality data. A meta-analysis by Bahji and colleagues[6] concluded that racemic ketamine was superior to esketamine. However, this analysis included only one head-to-head comparative study and did not account for some systematic differences between ketamine and esketamine trials, including multisite versus single-site, FDA-registration, academic versus community sites, and multidose versus single-dose protocols. My own clinic recently

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published clinical outcome data based on medical records review in over 200 patients treated with either ketamine or esketamine.[7] Like the report by Bahji and colleagues, our data suggested a signal in favor of racemic ketamine. However, there were several nuances in our report—most especially the lack of randomization—that prevent firm conclusions from being drawn. The ongoing controversy in the field regarding the comparative effectiveness of ketamine versus esketamine has provided inconsistent messaging to patients, contributed to many providers' being unwilling to adopt the FDA-indicated treatment (which is more likely to have insurance coverage and therefore be more affordable from the patient perspective), and confused third-party payers on what policies they should adopt regarding ketamine/esketamine treatment coverage. A fully funded, well-powered comparative effectiveness study to provide data to resolve this controversy should be a priority for the field.

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