Esketamine 5 Years After Approval: Welcome New Data With Continuing Questions

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The article in this issue by Sanacora et al. (1) presents data on the safety of esketamine during the treatment period in the United States, based largely on the Risk Evaluation and Mitigation Strategy (REMS) program for the product as well as other reporting to the manufacturer. Overall, the data presented point to the safety of esketamine nasal spray since the time of its release. The data cover 58,483 patients and nearly 1,500,000 treatment sessions corresponding to 37,862.7 patient-years. Data are presented on both the more acute phase and the later maintenance phase of treatment. The results indicate no major surprises in the acute-phase trials. The effects on blood pressure are in keeping with previous reports and are reassuring. The incidences of dissociation and nausea are as expected, and for the acute effects there does appear to be accommodation over time.

The issue of premature death and suicide among patients treated with esketamine has received considerable attention and been under some debate since the original review by the U.S. Food and Drug Administration (FDA). At that time, the brochure for the FDA advisory committee (2) noted that at least three individuals had died by suicide within 3 weeks of stopping the medication in clinical trials. These events were reportedly from open-label continuation studies and were of special concern because none of the three individuals had a history of suicidal activity. The FDA noted that the suicides were not likely related to effects of esketamine because they occurred days after esketamine was stopped. However, we have argued that these events could be related to stopping the medication, given that ketamine and esketamine have opioid properties, as demonstrated in humans by our group and in preclinical studies by Michaelides and colleagues (3–6). We also argued that a REMS should not follow patients only while they are taking the medication but also for limited periods after they stop treatment, in line with the pharmacological properties of the enantiomer.

Sanacora et al. note that 70 suicides during the esketamine treatment period were reported to the manufacturer. That number (equivalent to 0.18 per 100 person-years) is close to the number expected from samples of patients with treatment-resistant depression, so an easy conclusion could be that esketamine treatment has no effect on suicidality. This is in accord with the results of our recent meta-analysis (7). However, an additional 28 of the total 228 deaths (12.28% of all deaths) are suspect; their causes may be related to suicidality (e.g., overdose, drug and alcohol abuse, road traffic and other accidents, fall, toxicity to various agents, failure to thrive). Taken together, the number of deaths by suicide and deaths due to suspicious causes is 98 (42.98% of all deaths and 0.26 per 100 patient-years). This is 18.18% higher than the 0.22 per 100 patient-years expected among patients with treatment-resistant depression receiving treatment as usual (8). What is not emphasized in the Sanacora et al. article is that for 52 of the 70 patients who died by suicide, data were available as to where in their treatments they were at the time of suicide. Surprisingly, 50% of those 52 patients died by suicide within a week of the most recent dosing. The article does not indicate whether they had completed their trials. The relationship to recent dosing appears to be in keeping with the previous FDA report that suicides occurred within 4–20 days after the last dose and treatment cessation. This is of concern even if the overall rates of suicide may seem to be within the acceptable range.

An impressive observation is that the number of suicide attempts reported in the Sanacora et al. article is surprisingly low (N=21; 0.05 per 100 person-years). Even more surprising is the fact that the number of attempts is lower than the number of suicides, and not vice versa. The rate of suicide attempts would be expected to have been as high as 4.66 per 100 person-years in a population with treatment-resistant depression (9). Therefore, the number of suicide attempts in this study sample would be expected to have been as high as 1,141, much higher than the 21 cases reported. That could suggest that suicidal behavior was reduced either as an effect of the drug or as an effect of the increased vigilance associated with the protocol; however, this unexpected result may raise questions regarding the accuracy and validity of the numbers observed. This concern is reinforced by the low number of deaths from all causes (N=228; 0.6 per 100 person-years) observed in the Sanacora et al. study. According to our calculations, while

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the expected number of all-cause deaths would be about 200 if this were a general population sample, in a population with treatment-resistant depression, one would expect an increased risk for death, with a relative risk of 1.62 (10). Based on a sample with treatment-resistant depression, the expected number of deaths thus would be 324 (0.85 per 100 person-years), or 100 more than were observed. Thus, the interpretation of the data reported in the Sanacora et al. article is unclear, and what the results really mean remains a matter of debate. The suicide rate is in the expected range, but the number of suicide attempts and the number of all-cause deaths are relatively low. Is the number of suicides underreported? That would fit the observation noted above regarding suspicious deaths.

The data on the timing of suicide raise a number of questions that should be followed up on:

1. Where in their overall course of treatment were the patients who died by suicide? Were they in the acute twice-per-week phase or the once-per-week phase? In the maintenance phase?
2. Had they reached the point of stopping esketamine? Were there any deaths after the end of the scheduled treatment plan?
3. Had these patients been considered responders or nonresponders to acute therapy?
4. Were these patients previously suicidal, or were their symptoms and behavior emerging de novo?
5. When was the last dose administered for the patients whose suicides did not occur within a week of stopping? How close were they to their most recent treatment, and how long were the intervals between the most recent treatments?

These questions should be explored rather than stating that the numbers were in the expected range. This is of importance for the field and for future patients undergoing treatment with the drug. Also of note is that if the rate of suicide is within the expected range, data would suggest that esketamine is not effective in reducing suicide risk. In our recent meta-analysis (7), we saw virtually no effect of esketamine plus treatment as usual versus placebo plus treatment as usual in reducing suicidal behavior or ideation at 4 weeks, in keeping with the lack of an approved indication for reducing suicidal behavior specifically.

The study by Sanacora et al. adds much to the literature on esketamine, and the authors are to be commended on their collection and presentation of the data. While the data are a welcome addition, they raise questions that are of concern to us and are worthy of further clarification.

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