The VA Ketamine Controversies

Extreme remedies are very appropriate for extreme diseases.
Hippocrates Aphorisms

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On March 5, 2019, the US Food and Drug Administration (FDA) approved a nasal spray formulation of the drug ketamine, an old anesthetic that has been put to a new use over the past 10 years as therapy for treatment-resistant severe depression. Ketamine, known on the street as Special K, has long been known to cause dissociation, hallucinations, and other hallucinogenic effects. In many randomized controlled trials, subanesthetic doses administered intravenously have demonstrated rapid and often dramatic relief of depressive symptoms.

Neuroscientists have heralded ketamine as the paradigm of the glutamatergic modifying drug class, which represents the first real breakthrough in the pharmaceutical treatment of depression in decades.[1] There have been 2 major pharmacologic limitations attached to this promising new treatment: the IV form of the drug and the short duration of its antidepressant effect. Pharmaceutical companies and neuroscientists predictably have been engaging in a fast and furious race to successfully overcome these obstacles, hoping to win fame and fortune and bring hope and help to the millions of patients who have failed to fully respond to or been unable to tolerate existing therapies for mood disorders.[2]

When the FDA approved Spravato (esketamine), a nasal administration of ketamine, many people hoped that researchers had succeeded in overcoming these barriers. The risks of serious adverse events (AEs) as well as the potential for abuse and diversion led the FDA to limit prescriptions under a Risk Evaluation and Mitigation Strategy (REMS).[3] Patients self-administer the nasal spray but only in a certified medical facility under the observation of a health care practitioner. Patients also must agree to remain on site for 2 hours after administration of the drug to ensure their safety. The FDA recommends the drug be given twice a week for 4 weeks along with a conventional monoamine-acting antidepressant.

When the US Department of Veterans Affairs (VA) cleared the way for use of esketamine, less than 2 weeks after the FDA approval, it also launched a series of controversies over how to use the drug in its massive health care system, which is the subject of this editorial. On March 19, 2019, the VA announced that VA practitioners would be able to prescribe the nasal spray for patients who were determined to have treatment-resistant depression but only after appropriate clinical assessment and in accordance with their patients' preferences.

A number of controversies have emerged surrounding the VA adoption of esketamine, including its cost/benefit/risk ratio and who should be able to access the medication. Each of these issues has onion layers of political, regulatory, and ethical concerns that can only be superficially noted here and warrant fuller unpeeling. In June *The New York Times* featured a story alleging that in response to the tragic tide of ever-increasing veteran suicides, the VA sanctioned esketamine prescribing despite its cost and the serious questions experts raised about the data the FDA cited to establish its safety and efficacy. Although the cost to the VA of Spravato is unclear, it is much higher than generic IV ketamine.[4]

The access controversy is almost the ethical inverse of the first. In June 2019, a Veterans Health Administration advisory panel voted against allowing general use of esketamine, limiting it to individual cases of patients who are preapproved and have failed 2 antidepressant trials. Esketamine will not be on the VA formulary for widespread use. Congressional and public advocacy groups have noted that the formulary decision came in the wake of ongoing attention to the role of the pharmaceutical industry in the VA's rapid adoption of the drug.[5,6] For the thousands of veterans for whom the data show conventional antidepressants even in combination with other psychotropic medications and evidence-based psychotherapies resulted

in AEs or only partial remission of depression symptoms, the VA's restriction will likely seem unfair and even uncaring.[7]

As a practicing VA psychiatrist, I know firsthand how desperately we need new, more effective, and better-tolerated treatments for severe unipolar and bipolar depression. Although I have not prescribed ketamine or esketamine, several of my most respected colleagues do. I have seen patients with chronic, severe, depression respond and even recover in ways that seem just a little short of miraculous when compared with other therapies. Yet as a longtime student of the history of psychiatry, I have also seen that often the treatments that initially seem so auspicious, in time, turn out to have a dark side. Families, communities, the country, VA, and the US Department of Defense and its practitioners in and out of mental health cannot in any moral universe abide by the fact that 20 plus men and women who served take their lives every day.[8]

As the epigraph to this column notes, we must often try radical therapies for grave cases in drastic crises. Yet we must also in making serious public health decisions fraught with unseen consequences take all due and considered diligence that we do not violate the even more fundamental dictum of the Hippocratic School, "at least do not harm." That means trying to balance safety and availability while VA conducts its own research in a precarious way that leaves almost no stakeholder completely happy.

Author disclosures

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CORRECTIONS

In: Dean W, Talbot S, Dean A. Reframing clinician distress: moral injury not burnout. *Fed Pract.* 2019;36(9):400-402, the first sentence incorrectly referred to *moral injury* instead of *burnout*. The sentence should read: "For more than a decade, the term *burnout* has been used to describe clinician distress." It has been corrected online.

In the article, A veteran presenting with leg swelling, dyspnea, and proteinuria. *Fed Pract.* 2019;36(9):420-424, Madeline DiLorenzo, MD, should have been listed as the first author. Madeline DiLorenzo is a Resident in the Department of Internal Medicine at Boston University Medical Center in Massachusetts. It has been corrected online.