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## LETTERS

### VA Ketamine Controversies

**To the Editor:** We read with interest the editorial on the clinical use of intranasal esketamine in treatment-resistant depression by Editor-in-Chief Cynthia Geppert in the October 2019 issue of *Federal Practitioner*.<sup>1</sup> A recent case report published in your journal illustrated the success of IV ketamine in alleviating refractory chronic pain caused by a rare disease.<sup>2</sup> Ketamine has been well established as an appropriate adjuvant as well as an alternative to opioids in attenuating acute postoperative pain and in certain chronic pain syndromes.<sup>3</sup> We write out of concern for the rapidity of adoption of intranasal esketamine without considering the merits of IV ketamine.

When adopting new treatments or extending established drugs for newer indications, clinicians must balance beneficence and nonmaleficence. There is an urgent need for better treatment options for depression, suicidality, posttraumatic stress disorder (PTSD), and chronic pain in the veteran population. However, one must proceed with caution before wide adoption of a treatment that lacks real-world data on sustained or long-term benefits.<sup>4</sup> Enthusiasm for this drug must also be tempered by the documented adverse effect (AE) of hepatic injury and the lack of data tracking this AE from repeated, long-term use.<sup>5</sup> With these considerations in mind, reliable dosing and predictable pharmacokinetics are of great importance.

In addition to outpatient esketamine, outpatient IV administration of racemic ket-

amine remains an advantageous option with unique benefits compared with esketamine. Pharmacokinetically, IV ketamine is superior to intranasal esketamine. The bioavailability of intranasal esketamine is likely to be variable. A patient with a poor intranasal application or poor absorption might be falsely labeled an esketamine nonresponder. Increasing intranasal esketamine dosage to avoid false nonresponders may place other patients at risk for overdose and undesired AEs, including dysphoria and hallucinations. The variable bioavailability of intranasal ketamine adds complexity to the examination of its clinical effectiveness. IV ketamine should provide a predictable drug level and more reliable data. One might retort that esketamine is not the same as ketamine. True, esketamine is the S-enantiomer of ketamine, whereas ketamine is a racemic mixture of S- and R-ketamine. However, there is no clear evidence of clinically relevant differences between these formulations.<sup>5</sup>

Psychomimetic effects and cardiovascular changes are the most common short-term AEs resulting from ketamine.<sup>5</sup> An IV infusion allows the treating physician to slowly titrate the administered ketamine to reach an effective concentration at the target site. Unlike an all-or-none intranasal administration, an infusion can be stopped at the first appearance of an AE. Psychomimetic effects, such as hallucinations, visual disturbances, and dysphoria are thought to occur in a

dose-dependent fashion and remit once a ketamine infusion is stopped.<sup>5</sup> Furthermore, cardiovascular AEs, such as hypertension and tachycardia, are commonly in patients with a body mass index > 30, with IV administration on a mg/kg basis. This suggests that calculated ideal body weight is a safer denominator, and reliable dosing is important to mitigating AEs.<sup>6</sup>

We urge caution with the widespread adoption of intranasal esketamine and suggest the advantages of the IV route, which offers predictability of AEs and titratability of dose. Questions remain regarding the appropriate dose and formulation of ketamine, rate of infusion, and route of administration for chronic pain and psychiatric indications.<sup>5,7</sup> It is our responsibility to further study the long-term safety profile of ketamine and determine an appropriate dose of ketamine. The IV route allows many veterans to be helped in a safe and controllable manner.

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