Notice of correction 2/19/2020: The conflict of interest statement now reflects that Dr Swainson has been on advisory boards for, received speaker honoraria from, and provided consultancy services to Lundbeck, Otsuka, Sunovion, and Janssen and that Dr Khullar has been on advisory boards for, received speaker honoraria from, and provided consultancy services to Lundbeck, Otsuka, Sunovion, Janssen, Shire, Bausch, Takeda, and Eisai.

Sublingual Ketamine: An Option for Increasing Accessibility of Ketamine Treatments for Depression?

To the Editor: A recent review on oral ketamine for depression[1] described an antidepressant effect that was delayed in the range of 2–6 weeks, as compared to the rapid action of intravenous (IV) ketamine treatment. This differs from our clinical experience using sublingual (SL) ketamine to treat patients with severely treatment-resistant depression (TRD). In our experience, SL ketamine can both provide and sustain rapid antidepressant effects. We suspect this difference may be a dose effect, and we wish to note that to determine appropriate dosing for future prospective studies, bioavailability of each formulation of ketamine must be considered.

Sublingual ketamine is more bioavailable (30%) than oral ketamine (20%).[2] A recent study[3] described safety and efficacy of IV ketamine at doses of 0.5 mg/kg and 1.0 mg/kg and no benefit to lower doses. This translates to 1.5 or 3.0 mg/kg if dosed sublingually, and 2.5 or 5.0 mg/kg if dosed orally. With this in mind, only 2[4,5] of 7 retrospective studies from the systematic review included patients with appropriately dosed ketamine. All others were below the equivalent expected SL and oral doses. Two prospective studies also underdosed ketamine at 25 mg bid[6] or or 0.5 mg/kg daily,[7] and 1 prospective study used a potentially adequate total daily dose of 50 mg tid,[8] but divided doses may have contributed to a reduced or slower ketamine response.

Rosenblat and colleagues suggest that until further studies are completed, use of oral ketamine cannot be recommended, and they caution regarding risks of addiction and diversion. However, in our experience, SL ketamine has been of great benefit for carefully selected patients. We would consider judicious prescribing of ketamine similar to cautious prescribing of other potential substances of abuse.

In our practices, patients who have responded to IV ketamine have typically required maintenance ketamine. This is consistent with previous literature describing a median time to relapse of 18 days.[9,10] Potential risks of stopping ketamine have recently been outlined,[11] so programs offering ketamine treatments should ethically offer ongoing treatment in some form. Intravenous ketamine is difficult to access within public health care systems around the world, so long-term maintenance IV treatment may be impractical.

As such, we have had success transitioning IV ketamine responders to maintenance SL ketamine, dosed at 1.5 mg/kg. We also have numerous TRD patients started on sublingual ketamine in the community when they have been unable to access IV ketamine treatments. Tolerability has been excellent. Efficacy has yielded response approximately one-third of the time, in keeping with response rates for IV ketamine in similar populations of severely treatment-resistant patients reported previously.[12]

With this in mind, SL ketamine may provide a reliable and accessible alternative for appropriate patients. Future prospective studies should consider bioavailability to extrapolate dosing from the IV ketamine literature. Data to look at blood levels and kinetics of absorption would also be of benefit. Proper data on this would go a long way toward increasing the range of ketamine use for all psychiatrists and may increase accessibility of this treatment for patients.

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