Is Intravenous Ketamine Better Than Intranasal Esketamine for Treating Treatment-Resistant Depression?

Letter to the Editor: According to the World Health Organization (WHO), depression is the leading cause of disability, affecting the function and quality of life of around 280 million people (3.8% of the population) globally.[1] Although there may be a reduction in depressive symptoms within a few weeks with conventional antidepressants, one-third of patients do not respond.[2] In addition, approximately 30% of patients have treatment-resistant depression (TRD). This is usually defined as a lack of response to at least 2 antidepressive monotherapies of adequate dose and duration, including the current episode.[3,4] The alternatives to medications are psychotherapy, transcranial magnetic stimulation, electroconvulsive therapy, and ketamine, which can be delivered intravenously (IV) (R-ketamine) or intranasally (S-ketamine).

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist, providing a rapid and sustained response to TRD and suicidal ideation at subanesthetic doses.[5] Glutamate transmits pain signals and regulates psychological conditions like depression, and ketamine blocks glutamate receptors. IV ketamine (R-ketamine) is a mixture of 2 mirror-image molecules, "R" and "S" ketamine given at a dose of 0.5 mg/kg twice weekly, not to exceed 6 weeks. When administered at subanesthetic doses, it resulted in rapid onset of efficacy in patients with TRD.[6] Esketamine, the S-enantiomer of ketamine, with a higher affinity for the NMDA receptor than the R-enantiomer, was approved by the US Food and Drug Administration (FDA) in March 2019 for TRD in adults. In phase 2 clinical trials, esketamine nasal spray showed fast onset and persistent efficacy in patients with TRD and depressed patients at imminent risk for suicide.[7–9]

Esketamine, also known as Spravato, is a schedule III, controlled substance and a glutamate receptor modulator that works by restoring connectivity between brain cells. Several trials were carried out before the FDA decided to approve intranasal esketamine. These include 5 phases and 3 clinical trials that observed the effects of esketamine nasal spray in TRD. Data from 3 of these studies resulted in a rapid decrease and sustained improvement in depressive symptoms with the use of esketamine plus an oral antidepressant compared to placebo plus medication.[10–12] In addition, 2 double-blind, active-controlled, multicenter short-term studies carried out in adults and elderly (aged 65 years and older) with TRD receiving esketamine or placebo nasal spray plus an oral antidepressant resulted in significant improvement in depressive symptoms over 28 days in the esketamine group among adults and clinically meaningful effects in all age groups as compared to placebo.[10] It is administered twice weekly in health care settings during weeks 1–4 (starting dose is 56 mg, and subsequent doses are 56 or 84 mg). This is called the induction phase. Depending on a patient's response, esketamine can continue during the maintenance phase. It is given once weekly during weeks 5–8 at a dose of 56 or 84 mg. This can be continued during week 9 and weekly or every 2 weeks thereafter.

On the contrary, placebo-controlled trials have provided strong evidence for the rapid-acting (within hours) and sustained (lasting up to 7 days) antidepressant effects of a single administration of a subanesthetic dose of IV ketamine in TRD.[6,13–16] A recently published systematic review and meta-analysis[17] demonstrated that IV ketamine is nearly 3 times superior to intranasal esketamine. The authors[17] reported a study of 24 randomized controlled trials, representing 1,877 participants, with 61% females (average age ranging from 36 to 70 years; 98% with major depression and 2% with bipolar depression). They included studies wherein ketamine was used alone and studies in which it was used as an augmenting agent. In three-quarters of the trials, participants had TRD. Racemic ketamine relative to esketamine demonstrated greater overall response (RR = 3.01 vs RR = 1.38) and remission rates (RR = 3.70 vs RR = 1.47), as well as lower dropout rates (RR = 0.76 vs RR = 1.37).[17]

Given these findings, we wonder why IV ketamine is still not FDA approved. Perhaps it could be due to its associated side effects, but studies[17] show a lower dropout rate due to side effects. Neither ketamine treatment is reimbursed by insurance companies, despite FDA approval for Spravato. With traditional interventions yielding no response in one-third of patients with major depressive disorder and a significant number being noncompliant with medication, advancements in alternative treatment modalities such as ketamine could enhance clinical management. This eliminates the need to question the effectiveness of antidepressants in reaching the patient, giving prescribers better information in terms of making treatment recommendations.[18] Despite ketamine not being covered by insurance, its use could still decrease costs associated with medication nonadherence, relapse, and rehospitalizations.

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