Duman & Aghajanian (2012) in Science called the use of esketamine as an antidepressant in psychiatry “perhaps the most important discovery in half a century.” Esketamine (the S enantiomer of ketamine) is an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist that has been demonstrated to produce rapid antidepressant and antisuicidal efficacy that is sustained well beyond its half-life. On November 2013, intravenous esketamine was given breakthrough therapy designation for use in treatment-resistant depression by the FDA. More recently, on August 16, 2016, it was announced that intranasal esketamine has been given breakthrough therapy designation to expedite the drug’s path to the market for use in major depressive disorder with imminent risk of suicide. This designation could markedly affect treatment of a large, high risk patient population and fill an unmet need in the field.

The most important risk factor for suicide is major depressive disorder, and this population is in urgent need of more effective therapy than is currently in general use. Despite the growing number of medications and therapy modalities in psychiatry, the rate of suicide remains consistent at over 800,000 worldwide each year. Suicidal thoughts alone represent a huge morbidity and it has been estimated that 5.6% of the US population suffer from suicidal thoughts. This large population can escalate in risk, and currently, there are no drugs indicated to treat imminent suicidal risk. The FDA’s action of granting breakthrough therapy designation for intranasal esketamine is based on preliminary data that show great promise and represent hope for a large underserved population.

Current evidence for intravenous esketamine to treat suicidal thoughts consists of three randomized controlled trials (RCTs) and three open label studies. This is a total of 169 patients and the largest RCT contains 57 patients. The studies are underpowered, have heterogeneous patient populations and few have an appropriate control, but the majority of trials yield effect sizes in severe patients of at least 0.8 with no major side effects. Further, intranasal esketamine works within 24 hours, with some cases reporting effects lasting seven days, making it a great strategy to acutely prevent suicide and bridge patients while other treatments take effect.

The intranasal formulation of esketamine has obvious value. It has a rapid onset of action, bypasses the blood-brain barrier, has good bioavailability and is more practical and less resource-demanding than intravenous administration. The clinical evidence is limited to one RCT containing 20 subjects who were administered a single dose of 50 mg of intranasal esketamine or saline placebo at two time points, one week apart. The results were robust, with a mean MADRS decrease of 40% (p<0.001) at 24
hours after the single dose. Suicide was not a primary outcome measure\textsuperscript{11}, so the FDA’s actions are based mostly on extrapolation from evidence on intravenous esketamine, in addition to this single study and preclinical and unpublished intranasal esketamine data.

Along with the optimism, many questions still remain in the drug’s path to the patient. These are important as “imminent risk” is difficult to define, so the potential indication could include millions of patients. Long term studies to investigate side effects are needed. At the dose used for antidepressant and antisuicidal effects in the short term, esketamine is generally well tolerated with no reported long term side effects. However, the esketamine abuse literature suggests chronic use can lead to memory impairment, persistent dissociation and ulcerative cystitis. In vitro studies show a risk of hepatotoxicity\textsuperscript{12}. Further, the bulk of the evidence is around single dose treatment, and maintenance therapy data are required. Although suicidal thoughts indicate a lower functionality and quality of life on their own, the outcomes of interest when addressing imminent risk of suicide would be a decrease in suicidal behavior and actual suicides, and such studies do not yet exist. This situation is compounded by the fact that we lack accurate predictive tools for suicide. It is also considered unethical to have severely suicidal patients randomized, making clinical trials difficult to conduct.

Currently, intravenous esketamine for treatment refractory depression is in phase III trials and intranasal esketamine is in phase I trials\textsuperscript{2,13}. Overall, the preclinical, clinical and unpublished anecdotal evidence is encouraging for a rapid, robust, transient antidepressant and antisuicidal effect with few major side effects seen in the short term. The results remain preliminary, and more data are needed before formal clinical recommendations are appropriate. The breakthrough therapy designation should expedite this.

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