Intranasal esketamine: A primer

Maxwell Zachary Price, BA, and Richard Louis Price, MD

Intranasal esketamine is an FDA-approved ketamine molecule indicated for use together with an oral antidepressant for treatment-resistant depression (TRD) in patients age ≥18 who have had an inadequate response to ≥2 antidepressants, and for depressive symptoms in adults with major depressive disorder with suicidal thoughts or actions.[1] Since March 2019, we've been treating patients with intranasal esketamine. Based on our experiences, here is a summary of what we have learned.

REMS is required. Due to the potential risks resulting from sedation and dissociation caused by esketamine and the risk of abuse and misuse, esketamine is available only through a Risk Evaluation and Mitigation Strategy (REMS) program. The program links your office Drug Enforcement Administration number to the address where this schedule III medication will be stored and given to the patient for self-administration. Requirements and other details about the REMS are available at www.spravatorems.com.

Treatment. Start with the online REMS patient enrollment/consent form. Contraindications include having a history of aneurysmal vascular disease, intracerebral hemorrhage, or allergy to ketamine/esketamine. Adjunctive treatment with esketamine plus sertraline, escitalopram, venlafaxine, or duloxetine are comparably effective.[1] We have found that adding magnesium to block glutamate action at *N*-methyl-D-aspartate (NMDA) receptors, bupropion, and the oral NMDA receptor antagonist dextromethorphan may amplify and prolong esketamine's therapeutic effects. Titrate to a maximum tolerated dose of 3 devices (84 mg total), 5 minutes apart. Administer esketamine twice weekly for 4 weeks, then weekly for the next 4 weeks (for TRD), and continue weekly or twice monthly.[1] Open-label clinical trial data over 4 years support continuing treatment for relapse prevention, and have not reported the long-term cognitive impairment or ulcerative/interstitial cystitis associated with frequent, chronic ketamine use.[2] TRD clinical trials have shown a response rate (>50% reduction in baseline Montgomery-Åsberg Depression Rating Scale score) of 70% by the end of Week 4, emerging at 4 hours, independent of dissociation.[3]

Iatrogenic effects rarely lead to dropout. The first session is critical to allay anticipatory anxiety. Sedation, blood pressure increase, and dissociation are common but transient adverse effects that typically peak at 40 minutes and resolve by 90 minutes. Record blood pressure on a REMS monitoring form before treatment, at 40 minutes, and at 2 hours. Avoid administering sedative or prohypertensive medications together with esketamine.[1] Dissociation is more common in patients with a history of trauma. Combine music, guided

Mr. Price is a first-year medical student, Hackensack Meridian School of Medicine, Nutley, New Jersey. Dr. Price is Assistant Professor, Department of Psychiatry, Weill Cornell Medical College, New York, New York.

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imagery, or psychotherapy to harness this for therapeutic benefit. Sleepiness can last 4 hours; make sure the patient has arranged for a ride home, as they cannot drive until the next day. Verify normal blood pressure before starting treatment. Clonidine or labetalol for hypertension/severe dissociation and ondansetron or prochlorperazine for nausea are rarely needed. Advise patients to use the bathroom before treatment and keep a trash can nearby for vomiting. Other transient adverse effects found in TRD clinical trials that occurred >5% and twice that of placebo were dizziness, vertigo, numbness, and feeling drunk.[1]

Reimbursement for treatment with esketamine is available through most insurances, including copay cards, rebates, deductible support, and free assistance programs. Coverage is either through pharmacy benefit, assignment of medical benefit (pharmacy handles the medical benefit), or medical benefit with remuneration above wholesale price.

Zeitgeist shift. Emergency departments are backlogged and patients languish waiting to feel the effects of oral antidepressants. Intranasal esketamine could help alleviate this situation by producing a more immediate response. We also have observed improvements in comorbid posttraumatic stress disorder and in cognitive deficits of dementia, possibly due to rapidly enhanced neuroplasticity, neurogenesis, and astrocyte functioning, which NMDA receptor antagonism, AMPA activation, and downstream mediators (eg, brain-derived neurotrophic factor) may promote.[4]

We also have observed improvement in comorbid PTSD in patients receiving esketamine

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