VIEWPOINT

Psychiatric Practice Patterns and Barriers to the Adoption of Esketamine

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Major depressive disorder (MDD) affects approximately 17.3 million adults in the United States,[1] with a 12-month and lifetime prevalence of 10.4% and 20.6%, respectively.[2] Conducting clinical trials and developing new treatments for depression can be difficult because of spontaneous recovery rates and placebo effects.[3] In addition, many patients with chronic and refractory MDD do not experience clinical improvement even after several treatment courses. There is growing interest in the use of exercise and improved nutrition to treat depression,[4] but these approaches may not be effective for patients with MDD because lack of motivation is a core symptom. Recently, the US Food and Drug Administration (FDA) approved 2 new therapies, one for MDD that has not responded to previous therapies (esketamine) and another for postpartum depression (brexanolone), that have novel mechanisms of action and different routes of administration compared with traditional antidepressant drugs. This Viewpoint addresses the implications of esketamine for psychiatric practice in light of the unique FDA requirements for administration and postadministration patient monitoring.

The FDA approval of esketamine (Spravato) for treatment-resistant depression in March 2019 was welcome news to the 7% to 44% of patients whose symptoms fail to achieve remission with traditional antidepressant drugs.[5] The New Drug Application for FDA approval was based on 5 phase 3 clinical trials (3 short-term randomized trials, 1 open-label long-term study, and 1 long-term randomized withdrawal trial wherein esketamine responders/remitters were randomized to continue receiving esketamine or receive placebo). Based on data from the US Clinical Trials Registry, a total of 702 patients participated in short-term studies and approximately 1239 patients participated in long-term studies, which provided data for up to 1 year of drug exposure. One of the short-term trials and the randomized withdrawal trial achieved their primary end points ($P < .05$); 2 of the short-term trials did not achieve statistically significant improvement in symptoms in the esketamine group vs the placebo group ($P = .058$ and $P = .088$). All patients enrolled in the studies began taking a new oral antidepressant at the time of study initiation regardless of randomization assignment. Hence, esketamine administered as a nasal spray (plus an antidepressant) was compared with standard treatment (an antidepressant plus placebo nasal spray), whereas the majority of antidepressant trials have compared the intervention vs a true inert placebo.

Esketamine is the s-enantiomer of ketamine, which has been approved as an anesthetic agent since 1970, and has been increasingly used for the off-label treatment of depression since 2010.[6] Unlike traditional antidepressant drugs, which take 6 to 8 weeks to produce a full clinical effect, esketamine may lead to rapid effects in hours or days. Because of its unique administration requirements, esketamine will be more difficult for patients to access and clinicians to provide. Esketamine is a self-administered nasal spray that must be used at a health care facility. Patients' mental status and vital signs must be monitored for 2 hours postadministration, and patients cannot drive until the next day. Extensive monitoring is required because esketamine may have transient effects on blood pressure and heart rate and can produce feelings of dissociation lasting 1 to 2 hours. In short-term FDA-registered clinical trials, dissociation was reported as an adverse event in 12.5% to 26.8% of adults and transiently elevated blood pressure was reported in 8.2% to 13.9% of adults. For psychiatrists and other clinicians who treat patients with depression, adoption of esketamine may require fundamental changes to the organization and reimbursement of their medical practice. In other cases, these requirements may exacerbate already existing disparities in patient access to treatment.

Psychiatrists have resisted the trend toward large group practice and hospital employment that have characterized many specialties. In 2016, about one-third of psychiatrists were solo practitioners, and many others were in small group practices.[7] For smaller practices, adoption of esketamine may be cost prohibitive. Practices that offer esketamine will need to have additional space and clinical staff to monitor patients following administration. These practices also must establish systems and infrastructure for buying and storing the schedule III drug and report data to a FDA-mandated Risk Evaluation Management Strategy (REMS) reporting system to ensure a favorable risk to benefit ratio. These barriers may limit administration of this drug to only the largest practices or clinics.

Esketamine has a relatively high price vs traditional antidepressant drugs, costing $590 to $885 per treatment visit or an estimated $7080 to $10 620 (excluding physician, facility, and other nondrug charges) for the initial 2-month treatment episode when treatments should be provided 1 to 2 times per week per the FDA label.[8] Most practices that offer esketamine will operate under the buy-and-bill model in which they will purchase the drug and submit claims to payers for reimbursement. Unlike traditional antidepressant drugs (sold directly to patients), esketamine will provide practices with an additional revenue source. Medicare pays the average sales price of physician-administered drugs plus 4.3% to 6.0%, whereas private payers often pay the average sales price plus 10.0% or more.[9] Some physician specialties (eg, rheumatology and oncology) have developed lucrative practice models based on cost-plus reimbursement.

The provision of esketamine under the buy and bill model may be especially profitable for hospitals and clinics that qualify for discounts under the 340B program, which was intended to allow health care centers that serve low-income populations to receive drugs at discounted prices. If the 340B program continues in its present form, esketamine may present an opportunity for hospitals to generate additional revenue. Hospitals qualifying for the program can purchase drugs at discounts of 23% or more, yet are reimbursed by insurers based on a drug's average sales price. The 340B program may provide an incentive for large hospital systems to acquire smaller psychiatric practices to expand their network of clinics offering esketamine. It may be unlikely that a single drug will reshape psychiatric practice, but if there is sufficient patient demand and financial incentive, psychiatrists in solo practices and small group practices may feel pressure to join or partner with larger groups to be able to offer esketamine.

Practices will also need to be reimbursed for the treatment visit. Despite the passage of the Mental Health Parity and Addiction Equity Act, psychiatric services continue to be reimbursed at low rates compared with services provided by other specialties. If the reimbursement for patient monitoring is set too low, clinicians will be reluctant to adopt esketamine. Currently, there is no Current Procedural Terminology code for esketamine postadministration monitoring. Physicians can bill evaluation and management codes for the visit, but these cover only face-to-face patient-physician interactions.

Another potential barrier to adoption is that approximately one-third of psychiatrists do not accept commercial insurance.[10] If few patients are willing to pay the high out-of-pocket price for esketamine, these clinicians may face a decision of whether to continue to operate outside the third-party payer system or instead sign contracts with insurers. In the meantime, patients who can afford these high costs may have the easiest time gaining access to esketamine, whereas patients at other practices must wait for clinicians and health care centers to resolve the reimbursement issues and establish the infrastructure for buying and storing the drug.

If psychiatrists prove reluctant to adopt esketamine, nonpsychiatrists (ie, primary care physicians), who currently provide depression treatment to the majority of individuals with depression, could open specialty clinics focused on esketamine administration. Anesthesiologists and other nonpsychiatrists account for one-third of the clinicians who offered off-label intravenous ketamine for depression prior to the approval of esketamine.[6] Although administration of esketamine by nonpsychiatrists can expand patient access, it carries risks. Esketamine has a much riskier adverse effect profile than traditional antidepressant drugs. Clinics specializing in esketamine may be motivated to recruit large numbers of patients. However, the REMS reporting system requirement, if implemented thoughtfully, may balance the tension between increasing access to an effective treatment for a potentially devastating disease and minimizing the risk of drug abuse or diversion and other adverse effects.

The discovery of ketamine's rapid-acting properties, culminating most recently with the FDA's approval of esketamine, offers hope to the large numbers of patients whose symptoms do not resolve with traditional treatments. However, many traditional psychiatric practices may be reluctant to invest in the costly infrastructure necessary to provide this therapy, especially because of the uncertainty regarding the reimbursement for patient monitoring. Patients who do not live near a larger practice that is accepting new patients may have trouble accessing the drug. Clinics that specialize in providing esketamine can help provide access to fill the void, but may be inclined to overprescribe the drug. Payers should carefully monitor the use of esketamine to limit inappropriate prescribing. A registry that tracks patient outcomes and adverse effects would be invaluable to public health. Given that approximately one-third of patients with MDD do not achieve remission of their symptoms with traditional antidepressant drugs, many could potentially benefit from esketamine; however, long-term follow-up data are currently quite limited. Whether these patients can access the medication depends on the ability of psychiatric practice to adapt to a new model of drug delivery.

ARTICLE INFORMATION

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