The Effectiveness and Value of Esketamine for the Management of Treatment-Resistant Depression

A Summary from the Institute for Clinical and Economic Review's Midwest Comparative Effectiveness Public Advisory Council

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Major depressive disorder (MDD) is a common condition characterized by symptoms that include persistent sadness, feelings of hopelessness, loss of interest in usual activities, and thoughts of hurting oneself.[1] An estimated 7% of adults (17 million) in the United States experienced at least 1 major depressive episode in 2017.[2] Although effective pharmacologic and nonpharmacologic treatments are available for MDD, approximately 1 in 3 patients do not respond to or are intolerant to treatment and are considered "treatment-resistant." Although there is no broad consensus regarding its formal definition, treatment-resistant depression (TRD) is commonly defined as inadequate response to 2 or more trials of antidepressant monotherapies of adequate dosing and duration in the current episode.[3,4] TRD characterizes approximately 1 in 3 patients with major depression and accounts for higher health care costs and decreased productivity totaling approximately $64 billion each year.[3,5]

Treatment strategies for individuals with TRD include maximizing the dose of the existing antidepressant therapy, adding another antidepressant, adding a non-antidepressant medication such as an antipsychotic to an existing antidepressant therapy, or switching to a new antidepressant. However, many individuals still do not respond to or are intolerant of these therapeutic changes. For the most difficult-to-treat patients, commonly referred to as having refractory depression, electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) can be used. However, ECT and rTMS have major clinical or logistical constraints that make long-term use difficult. In view of these therapeutic challenges, new treatment options are needed.

A potential new therapeutic target is the N-methyl-D-aspartate (NMDA) receptor. Case reports and several small clinical trials have found that ketamine, an intravenously administered anesthetic agent that binds to the NMDA receptor, can rapidly improve depression symptoms in some patients with TRD.[6,7] Although concerns remain about its long-term safety and potential for abuse or diversion, the off-label use of ketamine for the treatment of patients with TRD has been expanding in the United States.[8] While ketamine is a racemic mixture of 2 stereoisomers, the S-enantiomer esketamine (Spravato, Janssen) was approved by the U.S. Food and Drug Administration on March 8, 2019, as a nasal inhalation treatment for adults with TRD.

The Institute for Clinical and Economic Review (ICER) performed a systematic literature review and cost-effectiveness analysis to evaluate the health and economic outcomes of esketamine for the treatment of TRD. Complete details of ICER's systematic literature search and protocol, as well as the methodology and model structure for the economic evaluation, are available on ICER's website. In this article, we present the summary of our findings and highlights of the policy discussion with key stakeholders regarding the overall value of esketamine that took place at a public meeting of the Midwest Comparative Effectiveness Public Advisory Council on May 23, 2019. The detailed report is available on the ICER website at https://icer-review.org/material/trd-final-evidence-report-and-meeting-summary/.

Summary of Findings

Clinical Effectiveness

We identified 3 similar 4-week randomized controlled trials (RCTs) of esketamine,[9-11] 2 of which were conducted in patients aged 18-65 years (TRANSFORM-1 and -2),[9,10] while the third was conducted in patients aged 65 years and older (TRANSFORM-3).[11] Patients in all 3 trials were randomized to receive either esketamine or placebo nasal spray twice weekly, each combined with 1 antidepressant that patients had not used during the current depressive episode (background antidepressant). The primary measure of clinical benefit assessed in the 4-week RCTs was change in depressive symptoms using the Montgomery–Åsberg Depression Rating Scale (MADRS). Clinical response, defined as 50% or higher reductions in MADRS scores, and remission, defined as a MADRS score of 12 or less, were also assessed. At baseline, 36%-40% of patients in the RCTs had failed 4 or more antidepressants; average duration of current episode ranged from approximately 2 to 4 years; and, on average, patients had severe depression (MADRS mean ≥ 35). In addition to the short-term RCTs, we also evaluated 1 phase 3 maintenance study of esketamine designed to primarily assess relapse prevention (SUSTAIN 1) and a 48-week open-label trial designed to assess long-term safety of esketamine.

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TABLE 1 Health Care Sector Perspective Results Compared with No Additional Treatment in Patients with TRD on Background Antidepressant

Interventions	Drug Cost, $	Total Cost, $	LYs	QALYs	ICER vs. background AD alone	
					Cost/LY, $	Cost/QALY, $
Background AD	0	410,200	20.64	12.47	–	–
Esketamine plus background AD	42,600	448,600	20.66	12.66	2,592,000	198,000

AD = antidepressant; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life-year; TRD = treatment-resistant depression.

Esketamine plus background antidepressant (AD) demonstrated statistically significant improvement in MADRS score relative to placebo plus a background AD at 4 weeks in TRANSFORM-2 (mean difference 4.0, 95% confidence interval [CI] = −7.31 to −0.64; $P = 0.01$).[9] However, a statistically significant difference was not observed between esketamine and placebo in TRANSFORM-1 and TRANSFORM-3.[10,11] We conducted a random effects meta-analysis of the 2 RCTs that were homogenous in patient population (TRANSFORM-1 and -2), and the result favored esketamine, showing a greater improvement on MADRS score for esketamine plus background AD compared with placebo plus background AD (mean difference −3.84; 95% CI = −6.29 to −1.39). On the secondary outcomes, results of the meta-analysis showed that patients on esketamine plus background AD were more likely to achieve clinical response compared with placebo plus background AD (relative risk [RR] 1.30; 95% CI = 1.08-1.56), while the relative risk of clinical remission was also superior but was not statistically significant (RR 1.37; 95% CI = 0.99-1.91). In the relapse prevention study (SUSTAIN 1), maintenance esketamine plus background AD decreased the risk of relapse by 51% among stable remitters (hazard ratio [HR] 0.49; 95% CI = 0.26-0.84).[12]

Patients receiving esketamine were more likely to experience dissociation, sedation, dizziness, and have clinically important increases in systolic and diastolic blood pressure, but these adverse events were mostly mild to moderate and resolved within a day of administration. A total of 6 esketamine-treated patients across all trials died during the esketamine development program, 3 of whom committed suicide. There was no evidence of misuse or abuse of esketamine in any of the esketamine trials.

Limitations of the Clinical Evidence

First, there is a lack of data on how esketamine compares with ketamine and other commonly used therapies for TRD. Second, while esketamine appears to offer favorable short-term results in the trials, patient blinding of treatment allocation to esketamine may have been compromised because of prominent side effects such as dissociation. Information on maintenance of blinding was not reported in any of the trials. Third, data on the long-term safety of esketamine are limited at this time. Although the trials did not report issues related to misuse or abuse, this remains a concern given the similarity to ketamine, which is reported to have these risks. As such, esketamine is currently available only through a Risk Evaluation and Mitigation Strategies (REMS) program in order to monitor its abuse potential. Finally, MDD patients with psychotic features or other coexisting psychiatric conditions were excluded, thus, limiting the generalizability of the findings.

Long-Term Cost-Effectiveness

We evaluated the cost-effectiveness of esketamine plus background AD compared with background AD alone in patients with TRD using a de novo decision analytic model from a U.S. health care sector perspective. The base-case Markov model was developed with 3-month cycles and ran over a lifetime horizon. The baseline characteristics of the modeled cohort reflected the weighted average across the 2 RCTs of esketamine conducted in patients aged 18-65 years (TRANSFORM-1 and -2), with a mean age of 46.0 years and a mean MADRS score of 37.4.

Patients entered the model receiving esketamine plus background AD or background AD alone and could either have an effective (i.e., remitters), partially effective (i.e., clinical responders who did not achieve remission), or insufficient response to treatment. Patients were treated with up to 3 alternative oral ADs if they had an insufficient response to treatment. Clinical inputs regarding the efficacy of esketamine plus background AD and background AD alone were derived from the meta-analysis of the key trials of esketamine (TRANSFORM-1 and -2), while the efficacy of alternative oral ADs were derived from the STAR*D trial, a pragmatic study evaluating numerous treatments for depression.[13]

Results from our base-case cost-effectiveness analysis showed that compared with background AD alone, esketamine plus background AD had incremental cost-effectiveness ratios of approximately $198,000 per quality-adjusted life-year (QALY) gained and approximately $2.6 million per life-year (LY) gained, which exceeds the commonly accepted cost-effectiveness threshold range of $100,000-$150,000 per QALY gained or per LY gained (Table 1).

Limitations of the Cost-Effectiveness Model

Our analysis was limited to the cost-effectiveness of esketamine plus background AD versus background AD alone due to the lack of comparative effectiveness data on esketamine compared

TABLE 2 Other Benefits or Disadvantages

Does treating patients with esketamine plus background antidepressant offer 1 or more of the following potential "other benefits or disadvantages" compared with other approved treatments for TRD?

Potential Benefit	Panel Votes
a. This intervention will significantly reduce caregiver or broader family burden.	9/17
b. This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	14/17
c. This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity.	12/17
d. There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	4/17

TRD = treatment-resistant depression.

with other commonly used treatments of TRD. In addition, we had very limited data on how the number of treatments failed during a person's lifetime, pattern and frequency of depression episodes, and how severity of the episodes affected treatment effectiveness and cost of care.

Policy Discussion

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) is one of the independent appraisal committees convened by ICER to engage in the public deliberation of the evidence on clinical and cost-effectiveness of health care interventions. The Midwest CEPAC is composed of medical evidence experts, including practicing clinicians, methodologists, and leaders in patient engagement and advocacy. Their deliberation includes input from clinical experts and patient representatives specific to the condition under review, as well as formal comment from manufacturers and the public. A policy roundtable concludes each meeting during which representatives from insurers and manufacturers join clinical experts and patient representatives to discuss how best to apply the findings of the evidence to clinical practice, insurance coverage, and pricing negotiations.

The ICER report on esketamine was the subject of a Midwest CEPAC meeting in May 2019. Following discussion, the CEPAC panel members voted 14-3 that the evidence was adequate to demonstrate the superiority of esketamine plus background AD versus background AD alone. The CEPAC panel also voted on "other potential benefits" and "contextual considerations" as part of a process intended to signal to policymakers whether there are important considerations when making judgments about long-term value for money not adequately captured in analyses of clinical and/or cost-effectiveness. The results of these votes are shown in Table 2 and Table 3 and serve to highlight several factors that the CEPAC panel felt were particularly important for judgments of value, including the novel mechanism of action of esketamine and the high severity and lifetime burden of illness suffered by patients with TRD.

As described in ICER's recent value assessment framework,[14] questions on long-term value for money are subject to a value vote when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $150,000 per QALY in the primary "base case" analysis. As previously described, the estimate of $198,000 per QALY exceeds the higher end of this range, thus, esketamine was deemed "low value" without a vote of the panel.

The policy roundtable discussion explored how best to translate the evidence and broader perspectives discussed into clinical practice and into pricing and insurance coverage policies. The full set of policy recommendations can be found in the final evidence report on the ICER website at https://icer-review.org/material/trd-final-evidence-report-and-meeting-summary/. However, the key policy recommendations are as follows:

1. Manufacturers and researchers should conduct studies directly comparing esketamine and other treatment options using standardized research protocols and outcomes that reflect what matters most to patients; this would allow real-world, long-term assessment of comparative effectiveness.
2. Given the considerable uncertainty that remains regarding the longer-term benefits and risks of esketamine, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure that patients are carefully selected and managed by clinicians with the necessary expertise to ensure appropriate care. Considerations for prior authorization include:
   a. *Patient eligibility:*
      - *Diagnosis:* Adult patients with TRD defined as having tried 2 or 3 medications from 2 or more drug classes in the current episode with inadequate response or intolerance.
      - *Exclusion:* Due to concerns about abuse and misuse, patients with active substance use disorders may be excluded from consideration for esketamine, but criteria should not be so stringent as to exclude patients with TRD and a history of substance use who may benefit from esketamine when used as directed.
      - *Step therapy:* For patients meeting the criteria previously suggested, the addition of step therapy through treatments such as ECT, rTMS, and antipsychotics were not recommended due to uncertainty about relative risks, benefits, and logistical constraints compared with esketamine.

TABLE 3 Contextual Considerations

Are any of the following contextual considerations important in assessing the long-term value for money of esketamine plus background antidepressant?

Contextual Consideration	Panel Votes
a. This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	14/17
b. This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	13/17
c. Compared with other treatments for TRD, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	12/17
d. Compared with other treatments for TRD, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	13/17
e. There are additional contextual considerations that should have an important role in judgments of the value of this intervention	4/17

TRD = treatment-resistant depression.

b. *Potential provider criteria:* Esketamine may be covered only if prescribed by, or in consultation with, a specialist clinician with formal training in psychiatry

3. Payers should develop mechanisms to adequately compensate clinicians for the expenses associated with monitoring and delivering esketamine within the specification of the REMS program.

Conclusions

Current evidence demonstrates short-term clinical benefit of esketamine versus placebo. However, concerns remain about its safety with long-term use. Furthermore, at current pricing in the U.S. market, the incremental cost-effectiveness ratio for esketamine is above the commonly cited cost-effectiveness thresholds and thus was judged to represent low long-term value for money. Further research is needed to evaluate whether there are subgroups of patients that can be identified who are most likely to benefit from esketamine in the short term. Further research is also needed to evaluate the outcomes of esketamine use beyond the very short duration of existing trial data. Having a new treatment for TRD is important given significant unmet clinical need, but evidence about the relative benefits and risks of esketamine compared with other treatments remains quite limited.

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Dissociating the Clinical Role and Economic Value of Intranasal Esketamine

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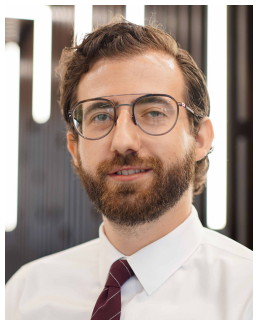
COMMENTARY

Approximately 2 decades ago, the first study to evaluate the use of ketamine for depression was published and disrupted how we think about depression treatment.[1] The study was conducted with intravenous ketamine and has been replicated many times in robust study settings.[2] Although ketamine had been used as an anesthetic since the 1960s, it was not until the 2000s that the psychiatric utility of ketamine gained mainstream attention.[3] The majority of the evidence base for the antidepressive and antisuicidal effects of ketamine were documented with intravenous or intramuscular racemic ketamine.[2,4] Esketamine, an S-enantiomer, was given breakthrough therapy designation by the U.S. Food and Drug Administration (FDA) in 2013 for the treatment of treatment-resistant depression (TRD) and was approved as an intranasal formulation for this indication in 2019.



In June 2019, the Institute for Clinical and Economic Review (ICER) published its final evidence report on the clinical and economic implications of intranasal esketamine approval.[5] The final report notes that intranasal esketamine provides a clinical benefit to patients that have TRD and are being treated with a background antidepressant as compared with a background antidepressant alone. Of course, there are no direct comparison trials available with other modalities for treating TRD (i.e., antidepressant augmentation, transcranial magnetic stimulation, electroconvulsive therapy, or parenteral racemic ketamine). Although the clinical utility of this new therapy is positive, the ICER report demonstrates that the value and pricing of the new intranasal esketamine product may be less than ideal.

The ICER report uses a standard metric of cost-effectiveness, the quality-adjusted life-year (QALY). Typically, medications with a cost per QALY of $50,000-150,000 are considered a reasonable value.[6] The new intranasal esketamine product delivers a cost per QALY of $198,000. The ICER analysis used a de novo decision analytic model with clinical inputs derived from the TRANSFORM-1 and -2 and SUSTAIN-1 and -2 trials of intranasal esketamine and from the STAR*D trial (the largest trial of real-world antidepressant therapy, augmentation, and switching). There are certainly some important factors that can be attributed to the high cost per QALY that was reported;

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