Pitfalls of Cost-Effectiveness Analysis in Practice: A TRD Case Example in the United States with Esketamine Versus Oral Antidepressants

We read with interest the article by Agboola et al. published in the January issue of *JMCP*,¹ which reiterates the base case cost-effectiveness (CE) analyses results from the Institute for Clinical and Economic Review (ICER) evidence report. We believe that ICER's CE model has several key flaws and therefore should not be used in assessing the value of esketamine in treatment-resistant depression (TRD). While each flaw is problematic alone, appropriate correction of the flaws collectively has a significant impact on the incremental cost-effectiveness ratio estimate such that the conclusion changes to become cost-effective per ICER's own criteria.

First, clinical assumptions underpinning the model are flawed. Regardless of treatment, the ICER model does not allow for a representative proportion of patients in long-standing remission to exit a major depressive episode (i.e., achieve recovery) and so is inconsistent with the nature of the disease.² In addition, in clinical practice risk of symptom relapse or episode recurrence declines the longer a patient stays in remission, yet the ICER model does not account for this.

Second, the ICER model overestimates how long patients will stay on medication.³ In the model, the median duration of treatment is 13 years among patients who remain in remission, driven by the low discontinuation assumption of only 1.3% per 3-month period. This highly unrealistic estimate does not reflect length of therapy among patients in remission.

Third, ICER disregards the flexible dosing recommendation in the Spravato label when it chose to estimate the treatment effect of esketamine by including a clinical trial with fixed dosing, a less effective dosing practice. Clinicians routinely flexibly dose antidepressants.

Finally, although Janssen shared actual values from the esketamine trials with ICER, in some cases, ICER chose to ignore those values and used alternative inputs of an unknown source to estimate esketamine effectiveness. Further detail is available here: https://icer-review.org/wp-content/uploads/2018/10/ICER_TRD_Public_Comments_050919.pdf.

Furthermore, the ICER summary proposes a prior authorization strategy not driven by evidence-based medicine and not in the interest of patients with TRD who have high unmet need and a poor prognosis. For example, trial evidence in depression shows no benefit of between- versus within-class antidepressant switches at lines 1 and 2.⁴ However, the proposed prior authorization forces between-class switches and consequently a longer than necessary period before patients with TRD can access esketamine.

In summary, because of these flaws, this model should not be used to inform value discussions on esketamine. That the conclusion of the ICER analysis *changes* when the model's flaws are corrected collectively further highlights the pitfalls of these types of analyses in decision making. Furthermore, the

ICER model in the article does not include numerous beneficial effects of esketamine. At the CEPAC meeting, the majority of the panel believed that esketamine could significantly improve patients' ability to return to work and/or overall productivity and caregiver/family burden, yet these components are not incorporated into ICER's model in the article. The panel also endorsed the high severity, lifetime burden, and significant unmet need of patients with TRD.

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The Authors Respond

We thank Karkare et al. for their thoughtful comments on our article titled “The Effectiveness and Value of Esketamine for the Management of Treatment-Resistant Depression,” published in the January issue of *JMCP*.¹ In developing the model, we followed the Institute for Clinical and Economic Review’s model technical summary and internal policies and recommendations for conducting economic reviews.^{2,3} Systematic literature reviews were conducted to identify key model inputs. Patient, clinician, and research experts provided guidance. The model was shared with interested stakeholders. Where deemed appropriate, changes were made based on feedback received. However, as with all complex models, there may be disagreement among stakeholders as to the optimal model design and inputs. We detail below why specific inputs were selected.

With regards to treatment discontinuation in patients with sustained treatment response, we found no published evidence addressing discontinuing successful treatment in patients with treatment-resistant depression (TRD). Including data from less severe depressive disorders would introduce bias. When consulting clinician experts, we heard that patients with TRD often cycle through depressive episodes and that clinicians would be unlikely to discontinue successful treatment, even with sustained symptom improvement over concerns of rapid depression relapse and difficulty treating those relapses. Therefore, we assumed that a minority of patients (5% per year), those with milder symptoms or infrequent cycles, would be considered for treatment discontinuation. Increasing this model input from 5%-20% resulted in an incremental cost-effectiveness ratio of \$167,300 per quality-adjusted life-year (QALY) gained. Importantly, the model did not include the higher costs of reinitiating treatment with esketamine when compared with maintenance treatment, which would eliminate some or all of the potential reduced costs of discontinuing treatment. Overall patient discontinuation included sustained treatment effect, loss of treatment effect, and adverse events. The median time in effective treatment was 2.25 years and not 13 years. The relatively high proportion of patients in whom esketamine was effective and then relapsed underscores the severity of TRD and the need to maintain treatment in those patients who respond to esketamine.⁴

The fixed dose and variable dose trials both met a priori eligibility criteria that were established prospectively in our scoping document.^{5,6} Both of these included trials were phase 3 evaluations with similar study populations, outcomes, and follow-up periods. In the fixed dose trial, within-trial remission (36.0% for 56 mg and 38.8% for 84 mg) and response rates (54.1% for 56 mg and 53.1% for 84 mg) for esketamine were nearly identical at day 28 regardless of which dose patients received, suggesting similar effectiveness.⁵

Finally, we assert that the proposed prior authorization strategy on diagnostic eligibility is evidence based. Clinical evidence and input from clinical experts and patient groups supported that diagnostic eligibility for esketamine should be patients with TRD (consistent with the U.S. Food and Drug Administration label), defined as patients who had tried 2 or 3 medications from 2 or more drug classes in the current depressive episode with inadequate response or intolerance. This definition is consistent with generally accepted criteria for TRD: failure to produce a significant clinical improvement after at least 2 trials with antidepressants from different pharmacologic classes (assuming appropriate dosing and treatment duration).⁷

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