

Esketamine for Treatment-Resistant Major Depressive Disorder Effectiveness and Value

Final Background and Scope
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Background

Major depressive disorder (MDD) is a common psychiatric condition, with an estimated 16 million people or 7% of adults in the United States experiencing at least one major depressive episode in 2016 alone.¹ Symptoms of depression can include persistent sadness, feelings of hopelessness, loss of interest in usual activities, decreased energy, difficulty concentrating or sleeping, change in appetite and thoughts of hurting oneself. Depression can increase the risk of suicide and result in long-term suffering that impacts all aspects of life including personal relationships and ability to work. Treatment-resistant depression (TRD) refers to a major depressive episode with an inadequate response to therapy of adequate dosing and duration.² The failure of two or more trials of antidepressant monotherapies are commonly considered TRD, but the number of trials have not been standardized.³ Overall, approximately one in three patients with depression are considered “treatment-resistant.” Patients with TRD have higher costs of care, decreased work productivity and account for around \$64 billion in total costs.^{2,4}

A major depressive episode is diagnosed based upon patient-reported symptoms of at least two weeks duration; there is a lack of reliable signs or tests that confirm the diagnosis or predict response to a specific treatment.⁵ A diagnosis is typically made and treatment is often initiated by primary care clinicians, and broadly includes a range of different medications and psychological therapies in addition to supportive care such as self-help, relaxation techniques, and exercise. Second generation antidepressants including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants are commonly used for initial pharmacotherapy in patients with depression.⁶ However, patients with depression vary in terms of the severity of symptoms, course (episodic or chronic), and associated conditions such as anxiety or substance use disorders. Initial treatment may not work and switching to a different therapy is common. Since a trial of a therapy may require dose adjustments and 6-12 weeks to assess response, patients may find it difficult to remain on therapy long enough for an adequate trial of the treatment, especially if there are side effects or symptoms that are incapacitating. For this reason, TRD is difficult to define because it includes not only the number of unique treatments tried, but whether the trials were considered adequate.

In treatment trials, response to therapy is traditionally defined as a 50% or greater decrease in score from baseline on a depression rating scale.³ However, many responders may continue to have symptoms and impaired function. Remission, which refers to symptoms below a minimal level, is associated with improved quality of life and lower likelihood of relapse.^{7,8} Since initial treatment does not result in response in about one in three patients and remission in about two in three, there is a great need for therapies focused on those individuals with resistant depression. Treatment options for individuals with TRD broadly include switching therapies, augmenting existing therapies with non-antidepressant medications, combining different therapies, and attempting to optimize existing treatments by maximizing the dose used. Among those with TRD, there are patients with highly resistant depression with symptoms over long periods of time, with many sequential treatment regimens, and inadequate responses and/or multiple relapses. These patients face chronic disability and account for a disproportionate cost of care.⁴

For these most difficult to treat patients, referred to as having refractory depression, other strategies such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) may be tried.⁹ ECT has been shown to be useful in those with highly resistant depression.¹⁰ However, ECT requires anesthetic sedation and has side effects including memory loss and cognitive impairment as well as logistical constraints and preconceived notions based upon media portrayals. Though patients can relapse after ECT, it can be administered chronically to maintain remission in certain patients. TMS is another device-based treatment for refractory depression. Repetitive TMS has been shown to improve depressive symptoms but may be less effective than ECT and also has logistical constraints that make long-term therapy difficult.¹¹ If not already tried, psychotherapy may be added to pharmacotherapy, but is generally not considered stand-alone therapy.¹²

Despite available treatments, there are many individuals who do not respond to multiple therapies for whom new treatment options are needed. One potential new target for therapy is the N-methyl-D-aspartate (NMDA) receptor.¹³ Interest in agents that target this receptor have been driven by the observation that ketamine, an anesthetic, can transiently improve symptoms of depression.¹⁴ Very short-term studies have shown benefit, but this drug is usually administered intravenously and has side effects as well as the potential for abuse or diversion. A new agent, esketamine (investigational, Janssen), is under FDA review for patients with TRD. Ketamine is a racemic mixture of two stereoisomers. Esketamine is the S-enantiomer, which binds with greater affinity to the NMDA receptor and is being studied as a nasal spray.

Stakeholder Input

This scoping document was developed with input from diverse stakeholders, including patient advocacy organizations, clinicians, researchers, and manufacturers of the agent of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders, open input submissions from the public, and public comments on the draft scoping document.

Patient advocacy organizations and clinicians highlighted the impact of depression on quality of life and helped to inform the research direction outlined in this scope. Stakeholders indicated that depression, especially that which has been resistant to prior treatments, can be a serious and disabling condition. Though there are a range of treatment options available including medicines, talk therapy, and devices, some individuals do not obtain relief or reach a point where their depression is in a remission. It is difficult to identify which treatments are most likely to benefit a specific patient, so it may take several tries to find a medicine that helps and does not have unacceptable side effects. Moreover, most treatments, including medicine and talk therapy can take weeks to begin helping, adding to the uncertainty of whether the treatment will eventually be effective. Though many patients will respond to treatment, for a substantial number that response will not fully eliminate their symptoms of depression and may diminish over time. Thus, for patients whose symptoms are not adequately controlled, there is a recognized need for therapies that target depression in novel ways.

Report Aim

This project will evaluate the health and economic outcomes of esketamine for TRD. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

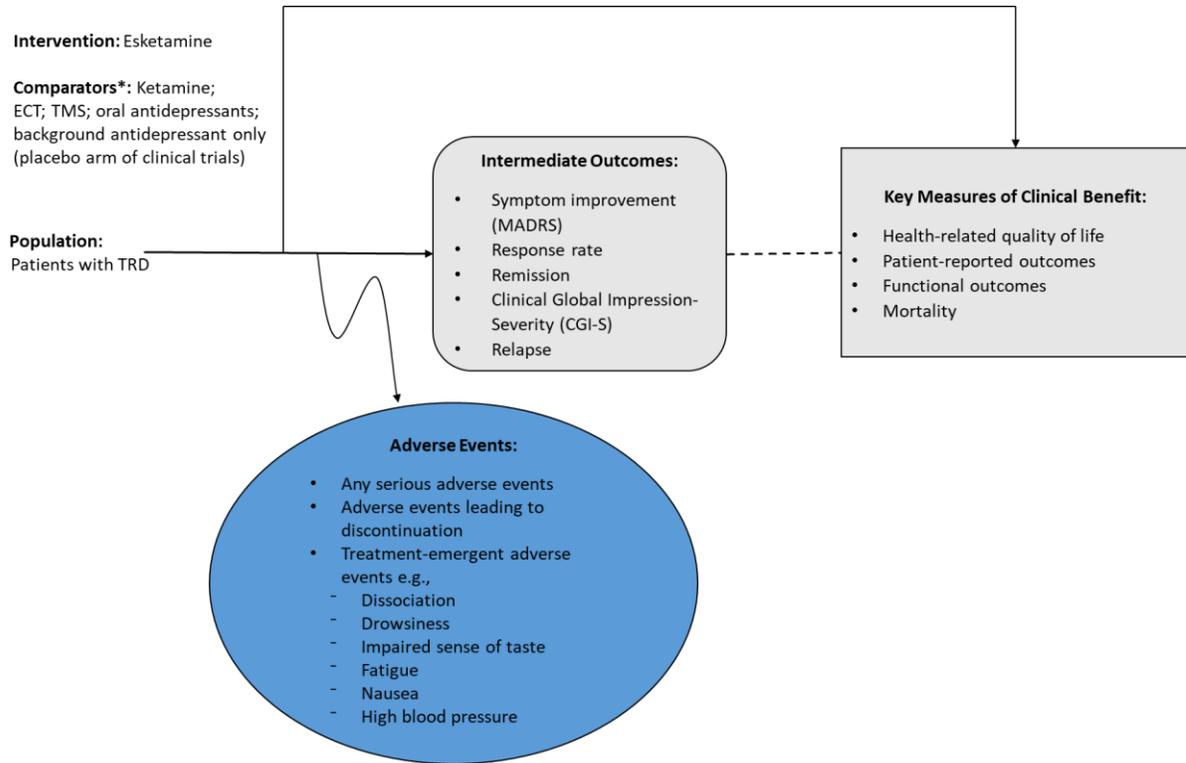
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see <https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/>).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (<https://osf.io/7awvd/>).

Analytic Framework

The general analytic framework for assessment of esketamine for TRD is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Esketamine for Treatment-resistant Depression



ECT: Electroconvulsive therapy; MADRS: Montgomery-Åsberg depression rating scales; TMS: Transcranial Magnetic Stimulation; TRD: Treatment-resistant depression; * Comparators may be used alone or in combination with background antidepressant (see below).

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., remission), and those within the squared-off boxes are key measures of benefit (e.g., mortality). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.¹⁵

Populations

The population of focus for this review will be adults ages 18 years and older with major depressive disorder, without psychotic features, and for whom prior antidepressants prescribed at adequate

dose and duration during the current episode have failed, termed treatment-resistant depression. As data permit, we will also plan to examine subgroups of patients suggested by patients and clinical experts. These include subgroups defined by:

1. Age: Adults 18 – 64 years; Adults 65 years and older
2. Number of prior treatment failures (e.g., 2-3; 3-5; ≥5)

Interventions

The intervention of interest will be esketamine nasal spray plus background antidepressant (continued or new administration). In addition, we will seek clinical evidence on all forms of the product, including the intravenous form.

Comparators

Feedback from clinical experts suggests that esketamine will be used in patients for whom numerous antidepressants have failed. As such, our comparators for this review include treatments commonly used in this setting. These comparators may be used alone or in combination with background antidepressant (continued or new administration):

- Ketamine, an anesthetic agent used off-label for treatment-resistant depression
- Electroconvulsive therapy (ECT)
- Transcranial Magnetic Stimulation (TMS)

In addition, we will seek evidence on the following comparators:

- Other oral antidepressants (plus background antidepressants)
- No additional therapy beyond background antidepressants (i.e. placebo arm of clinical trials)

Outcomes

We will look for evidence on the following outcomes of interest.

Efficacy outcomes:

- Symptom improvement measured on Montgomery–Åsberg depression rating scales (MADRS) or other depression rating scale
- Rate of response
- Rate of remission
- Rate of relapse

- Symptom improvement as assessed by the clinician (Clinical Global Impression of Severity [CGI-S]) and patient (Patient Global Impression of Severity [PGI-S])
- Health-related quality of life assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L)

Safety outcomes:

- Serious adverse events (including suicidality)
- Discontinuation due to adverse events
- Treatment-emergent adverse events (e.g.,)
 - Dissociation
 - Dizziness
 - Headache
 - Fatigue
 - Somnolence
 - Nausea
 - Impaired sense of taste
 - High blood pressure
 - Metabolic
 - Substance use disorder
 - Memory loss

Timing

Evidence on intervention effectiveness and safety will be derived from studies of at least seven days, as long as they meet the study design criteria set forth above and measure an outcome of interest.

Settings

Evidence from all relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Table 1.1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
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.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
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.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to “the comparator,” there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to “the comparator,” there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will ideally develop a Markov model to assess the lifetime cost-effectiveness of esketamine compared with other commonly used therapies for treatment-resistant depression, namely a new antidepressant, ketamine, ECT, or TMS. If data are not available to support such an analysis, we will compare a newly prescribed oral antidepressant plus esketamine to a newly prescribed oral antidepressant with no additional active treatment (i.e. placebo arm of esketamine trials) for treatment-resistant depression. The *de novo* model structure will be designed based on a comprehensive literature review of prior published models of major depressive disorder or treatment-resistant depression, as well as on available data from esketamine trials and other published information on treatments for treatment-resistant depression identified in the evidence review.¹⁶⁻²⁵ The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only). Data permitting, productivity losses will be considered in a separate analysis taking a limited modified societal perspective. The target population will consist of adults aged 18 years and older with treatment-resistant depression defined as patients with

recurrent major depressive disorder without psychotic features who have failed to respond to prior (two or more) adequate trials of therapy in the current depressive episode. The Markov model will consist of health states describing treatment response (“Initial treatment”; “Response”; “Maintenance” (i.e. long-term response); “Non-response” – alternative therapy prescribed and death) combined with level of depression (severe; mild to moderate; and none). “Initial treatment” will be defined as the beginning period of therapy prior to evaluation of treatment response. Patients in “initial treatment” state will have a level of depression corresponding to population estimates for the Montgomery- Åsberg Depression Rating Scale (MADRS) in patients with treatment-resistant depression. Patients responding to therapy will transition to the “Response” state at a level of depression corresponding to results from clinical trials evaluating esketamine and other comparator therapies. The “Maintenance” state will be defined as a state where the initial therapy (e.g. esketamine) has been discontinued among responders and patients remain on background oral antidepressant or no therapy with continued response. Patients in the “Maintenance” state will continue to maintain the same level of depression as during the “Response” state. Patients not responding to the “Initial treatment” will transition to a “Non-response” state at the same level of depression they had in the initial treatment state. Among responders and those in maintenance therapy, at any time, patient response to therapy may change, resulting in patients transitioning to “Non-response” and a poorer level of depression. Patients may transition to the “Death” state at any time in the model. Response will be based on the observed proportion of patients changing levels of depression using the MADRS (and possibly other depression rating scales). Thresholds for different levels of depression will be determined based on a comprehensive literature search, input from experts in the field, and esketamine trial data. Costs will be based on treatment and level of depression while utilities will be based on level of depression. Costs and utilities will be obtained from a comprehensive review of the literature. Depending on available evidence, additional transitional health states may be needed to model relevant situations that affect costs, utilities, or probabilities of important outcomes, such as drug-related adverse events, hospitalizations, and death from depression-related causes. A cohort of patients will transition between states during predetermined one-month cycles over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons.

Base-case model inputs will include the probability of initial and maintained symptom improvement, deterioration of initial response, and death, quality-of-life estimates, and health care costs (drug and non-drug treatment costs) associated with the modeled health states. The effects of esketamine and comparators will be modeled by altering probabilities, costs, and other inputs to reflect comparative responses to those therapies from clinical trials. Treatment effectiveness of esketamine and its comparators will be estimated using network meta-analyses, if feasible.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and the associated direct medical costs and utility (expressed as quality-

adjusted life years (QALYs)) assigned to each state. The health outcome of each intervention will be evaluated in terms of time spent in response, life-years gained, and quality-adjusted life years (QALYs) gained. Quality-of-life weights will be applied to each health state, including quality-of-life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug, condition-related care, and serious adverse events. In addition, productivity losses associated with TRD and gains from treatment will be included in a separate analysis if data allow. All costs and outcomes will be discounted by a rate of 3%. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the incremental cost per QALY gained, incremental cost per life-year gained, and incremental cost per year spent in response. If indicated, threshold analyses will be conducted using cost per QALY gained and cost per year spent in response to assess cost and benefit thresholds needed for a variety of willingness to pay thresholds. One-way sensitivity analyses will be conducted on all model inputs to assess their individual impact on outcomes. Probabilistic sensitivity analyses will be conducted to assess the impact of important model parameters simultaneously.

In separate analyses, we will explore the potential health system budgetary impact of esketamine over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: <http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf>.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see <https://icer-review.org/material/final-vaf-2017-2019/>). These are services that would not be directly affected by esketamine (e.g., psychiatric hospitalization), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of MDD beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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