



Depression and Bipolar
Support Alliance

November 20, 2018

ICER Comment: Esketamine for TRD Effectiveness and Value

As a nationally recognized and balanced voice for people with the lived experience of mood disorders, the Depression and Bipolar Support Alliance (DBSA) respectfully submits comment to the above-referenced assessment. DBSA recognizes that the aim of the project is to evaluate the health and economic outcomes of esketamine for TRD. However, treatment outcome priorities for patients are often not in alignment with the priorities of clinicians and health economists. When assessing the clinical and economic value of esketamine for TRD, we ask ICER to give equal weight to the broader impacts of TRD, look beyond the clinical and economic value of clinician-defined outcomes, and consider the entire needs of the person.

Recommendations

In 2018, DBSA created and distributed the Supporting Wellness survey—a survey to learn how peers (people living with mood disorders) define wellness. This project is a partnership between DBSA and the Milken Institute Center for Strategic Philanthropy. The survey was launched in August 2018 and has had over 6,000 responses making it one of the largest surveys that reveal peer priorities for treatment outcomes. Several peer insights from this survey will be provided in this comment. Results from this survey, coupled with over 33 years representing the peer voice, informs DBSA belief that meaningful assessment of the clinical and economic value of esketamine will be aided by understanding

1. how those receiving treatment define success, rather than simply relying upon a list of symptoms observed by clinicians with tools created by researchers several layers removed from the patient community,
2. that every person deserves the opportunity not just to survive, but to thrive,
3. whole health ramifications that lead to a patient-driven risk-benefit analysis, rather than a clinician observed tool-based benefit that doesn't incorporate the limitations of the United States health care system.

Person-Centric Treatment Outcomes

While symptom relief and side-effect management are already typically captured by clinical trials, a data gap remains in measuring well-being. Ninety percent of respondents to the Supporting Wellness survey stated that they strongly agreed or agreed that their health goal is to function as well as possible, especially in how they function at work, play and with others (84%). This stands in stark contrast to a clinician-observed improvement in symptoms and demonstrates why limiting information to clinical effectiveness is inadequate.

Adapting the assessment scope to include tools that measure wellness outcomes as defined by people with TRD has the potential to greatly improve treatment outcomes. A next logical step is the inclusion of measurable well-being outcomes that are sensitive, patient-centric, and reflect an adequate timeframe to truly capture change. It is understandable that in the time-frame of an existing clinical study these longer-

term outcomes may be difficult to capture, but we encourage ICER to continue real-world outcomes studies to better understand these potential benefits.

Several scales such as the Ryff Scale of Psychological Well-Being, the Sheehan Disability Scale, and the WHO- 5 Well-Being Index measure well-being domains. The focus of these scales is improvement in environmental autonomy from an interpersonal relationship and work/school perspective. Because these scales do not focus on the reduction of a given symptom, their use of global questions more accurately reflects an individual's unique experience living with TRD and whether the treatment is bringing improvement to their lives. Most recently, two posters were presented at the 2018 Psych Congress, demonstrating how patient-centered outcomes can be matched to traditional symptom-based scales—including one that documents the use of a Goal Attainment Scale in a clinical trial. We encourage ICER to include these posters in the review.

Beyond Surviving to Thriving

In the closing comments made at the Nov. 16, 2018 DBSA externally-led patient-focused drug development meeting, Dr. Michelle Campbell, FDA, Clinical Outcomes Assessment Staff, Office of New Drugs, Center for Drug Evaluation and Research stated she understands the request from the community to add thriving to the FDA COA roadmap describing clinical benefit in the agency's guidance to industry. Patient-focused drug development meetings are an initiative FDA has put in place to inform the assessment of benefit-risk in CDER's regulatory decisions concerning new drugs. This meeting sponsored by DBSA collected insights from peers and their supporters on preferred treatment outcomes as defined by peers.

During the meeting, participants were asked to provide further context to domains of wellness that move beyond functioning to thriving. These aspects of wellness were revealed by the respondents to the Supporting Wellness survey. In that survey, 86% of respondents selected "Ability to be independent and act according to my own will," as their highest priority. In the discussion around this priority, panelists and audience participants shared that under-employment was a barrier to achieving that priority. Other thriving domains ranked as a high priority by peers responding to the Supporting Wellness survey include:

- Purpose in Life
- Get through the day
- Self-acceptance
- Follow-through on ideas and intentions

Under-employment intersects with the ICER identified concern that "patients with TRD have higher costs of care, decreased work productivity and account for \$64 billion in total costs." When evaluating economic value, it only makes sense that ICER would include quantitative and qualitative tools that include peer-defined priority wellness domains, as positive movement along these domains have potential to significantly reduce the total costs to the U.S.

Whole Health

In the Supporting Wellness survey, 43% shared that their overall health was generally worse since experiencing symptoms and 37% that the stability of their health is worse. Why is this? While more research is needed, the background and scope document points to some answers.

- "treatment is often initiated by a primary care physician

- initial treatment may not work
- switching to a different therapy is common
- patients may find it difficult to remain on therapy long enough for an adequate trial
- especially if there are side-effects”

When seeking treatment for serious heart disease, patients work with a cardiologist. Treating an organ that is even more complex than the heart—the brain—requires the same level of expertise. Assessment of esketamine requires that a critical member of the team be a research psychiatrist.

Treating TRD is as complex as the number of pharmaceutical interventions currently available. Given the wide variety of medications, the different side-effects associated with them, and the fact that symptom relief is not the greatest benefit a person living with TRD is seeking, it is not surprising that people don't often take the medication as prescribed.

A central theme heard at the DBSA patient-focused drug development meeting was the necessity to weigh the benefits of taking a medication with debilitating side-effects against the risk of leaving their mental health condition untreated through a pharmaceutical intervention. People are not non-compliant when they choose to treat one health condition as a priority over another. They are weighing the clinical and economic value of the treatment options available to them to treat their whole health.

This is particularly relevant when considering co-occurring conditions. Given the realities of a siloed U.S. health care system, people are seeing a different specialist to treat each of these conditions with little to no case management. People are left with personal choices: treat my mental health condition or my diabetes, treat my mental health condition or my polycystic ovary syndrome, treat my mental health condition or treat my metabolic disorder.

Conclusion

A holistic approach is necessary. The idea of wellness cannot be embraced without considering the whole health of the individual and, untreated or under-treated TRD can disproportionately negatively affect an individual's whole health. Therefore, assessing the clinical and economic effectiveness esketamine cannot be untangled from the effects on the whole health of the person.

Eighty-nine percent of respondents to the Supporting Wellness survey shared that there should be better ways to treat and provide care. New treatments for TRD are welcome and needed. The lack of objective and quantifiable measurement tools in the clinical trial model necessitates additional acceptable measures to get a complete picture of a medicine's potential risks and benefits. Including well-being, patient-reported outcomes have the potential to move beyond the clinical trial model to capture what is truly important to patients. This model takes into consideration the lost opportunity cost when effective medication to treat TRD are not available and would enhance ICER's leadership position in understanding the cost-effectiveness of a health care intervention.

Sincerely,



Michael Pollock
Chief Executive Officer

Esketamine (investigational)

ICER Treatment-Resistant Depression DRAFT SCOPING DOCUMENT – Response to Request for Public Comments

The enclosed information has been supplied to you in response to your unsolicited request. Information contained in this response is not intended as an endorsement or promotion of any usage. This product is currently an investigational agent and is not approved by the Food and Drug Administration (FDA) in the United States. For information on ongoing clinical trials for our products, please visit www.clinicaltrials.gov.

CONTACT INFORMATION

First Name	Karen
Last Name	Johnston
Profession	PharmD
Organization	Janssen Scientific Affairs, LLC.
City, State	Titusville, NJ
Phone Number	(609) 730-6222
Email Address	kjohns33@its.jnj.com

EXECUTIVE SUMMARY

- Esketamine was granted breakthrough therapy designation by the FDA in November 2013 for treatment-resistant depression (TRD). Esketamine, a glutamate receptor modulator, is hypothesized to work differently from currently available antidepressants.¹⁻³
- Patients with MDD who have not responded to at least 2 different antidepressants of adequate dose and duration in the current depressive episode are considered to have TRD.⁴
- Compared to patients with non-TRD MDD, patients with TRD show higher healthcare costs, higher unemployment and disability rates, lower productivity, lower health-related quality of life and functioning, and higher rates of mortality.⁵⁻⁹
- The phase 3 clinical development program for esketamine nasal spray in TRD was a comprehensive program (including 3 short term double-blind studies and 2 long-term studies)¹⁰⁻¹⁴ conducted in over 1700 patients. Outcomes from the acute flexible dose study (TRANSFORM-2)¹⁰ and long-term randomized withdrawal maintenance trial (SUSTAIN-1)¹³ in adults comprise the substantial evidence submitted to the FDA for esketamine use in TRD.
- Given the lack of comparable evidence for network meta-analyses and the unique design features of the phase 3 esketamine TRD clinical program¹⁰⁻¹³ as described below, switching to a new oral antidepressant monotherapy is the most appropriate comparator for quantitative assessment.

SCOPE

Analytic Framework

Additional key elements proposed as outcomes to capture the true value of the therapies being compared include: recovery as a health state, productivity, and the patient perspective of the impact of their depressive illness including Health Related Quality of Life (HRQoL). The concept of recovery (after 6 months of remission)^{15, 16} is based on treatment guidelines and should be considered in the model structure along with the following listed health states: i.e. Major Depressive Episode (MDE), response (without remission), remission, recovery, and relapse or recurrence. Patients achieving recovery may continue in the maintenance treatment phase with only oral antidepressants to prevent a new episode. Subsequently, patients may continue in recovery or experience a recurrence (return to the MDE health state). During recurrence, patients may receive the last treatment (including esketamine) that ended the previous episode. In contrast, patients who relapse before achieving recovery, may move on to the next treatment in the sequence.

Populations

Rather than defining treatment-resistant depression (TRD) as proposed – i.e. failure to respond to one or more prior adequate trials of therapy, TRD should be defined as non-response to at least two different antidepressants of adequate dose and duration within the current episode. This is the criteria agreed to by US, EU and other global health authorities and is consistent with the language in the AHRQ report.⁴ Specifically, in the TRD program¹⁰⁻¹⁴, *non-response* was defined as a $\leq 25\%$ improvement with treatment. Patients with current suicidal ideation should not be included as a subpopulation, as current or recent clinically significant suicidal ideation or suicidal behavior in the past year were exclusionary in the phase 3 TRD program. There is a separate phase 3 development program underway evaluating esketamine for treatment of MDD with imminent risk for suicide.

Interventions

Contingent to approval of the proposed TRD indication, esketamine nasal spray should be used after failure of at least two antidepressant treatments of adequate dose and duration within the current episode. In the landmark STAR*D trial¹⁷, one-third of treated patients with MDD progressed to 3rd-line therapy without achieving remission (e.g., TRD). Notably, the rates of remission in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)¹⁷ trial drop substantially after failure of two antidepressants, from 37% and 31% in level 1 and 2 respectively, to just 14% and 13% with the 3rd and 4th line of treatment, respectively, supporting other literature indicating earlier initiation of effective treatment is key for optimal patient outcomes.¹⁸ Additionally, in a US claims database of privately insured employees and dependents with TRD, the economic burden for TRD patients increased with the number of lines of therapy of oral antidepressants at an adequate dose and duration.⁷

Comparators

There remains limited long-term evidence supporting the use of comparators (TMS; ECT; ketamine) proposed by ICER other than oral antidepressants.^{15, 19, 20} According to the APA guideline for MDD¹⁵; if there is not an adequate response after optimizing the antidepressant dose for an adequate duration of time, options include: switching to another oral antidepressant (same or different class), augmentation with another antidepressant (different class) or another type of therapy (e.g., psychotherapy, electroconvulsive therapy [ECT]), or adjunctive non-antidepressant medication (e.g., lithium, thyroid hormone, second generation antipsychotics). According to US¹⁵ and EU²¹ guidelines, augmentation therapy should be conducted in those with partial or insufficient response to the current antidepressant. The EU guideline²¹ explicitly states that patients with TRD and non-response to antidepressant therapy (similar to the population studied in the phase 3 esketamine program) are not eligible for augmentation therapy and should be switched to an alternative antidepressant treatment.

As for the other proposed therapeutic options, the level of evidence in TRD is lacking for rTMS.^{15, 19, 20} Even though evidence is stronger for ECT, it is not commonly used due to its side effect profile and limited availability.¹² For example, in a retrospective database analysis of 6,411 patients with TRD (treatment failures with at least 2 antidepressants at adequate dose and duration), including 76.9% who received at least 4 lines of treatment, only 17 (0.3%) received ECT.⁷

Ketamine should not be considered as a comparator because it is not approved by the FDA or EMA for MDD or TRD, and because of the lack of well-controlled short term and long-term efficacy and safety studies. A recent consensus statement from the American Psychiatric Association²², highlights the importance of considering the limitations of available data and the potential risk associated with ketamine when considering it as a treatment option. Similar concerns regarding the use of ketamine were raised in recent Royal College consensus statements^{23 24}, noting that there are “*significant gaps in knowledge about dosage levels, treatment protocols and the effectiveness and safety of long-term use.*”

Robust network meta-analyses are not feasible for ketamine, ECT, or TMS due to differences in study comparators and design. Switching to a new oral antidepressant monotherapy is the most appropriate

comparator for quantitative assessment given the design of the phase 3 esketamine TRD clinical program¹⁰⁻¹³. These features include: requirement of non-response to at least two antidepressants in the current episode, with prospective confirmation of non-response to the prior oral antidepressant; simultaneous initiation of a new oral antidepressant (active comparator) rather than adjunctive treatment or use of placebo alone; use of remote, independent raters for the primary endpoint; and frequent, intensive visits. Additional support for the use of oral antidepressant as an appropriate comparator can be found in Amos et al.⁷ In this retrospective database study of 6411 patients with TRD, 87.1% received SSRIs and 48.5% received SNRIs. As such, the esketamine phase 3 program data for the oral antidepressant comparator is highly applicable.

Outcomes

Relevant outcomes in the model should include health states of: active MDE, response without remission, remission, recovery, relapse and recurrence, with the respective transition probabilities, associated HRQoL (utility), all-cause healthcare costs, productivity, and mortality.

Depending on the choice of comparator, additional safety parameters such as memory loss, cognition and metabolic parameters should be considered. Of note for esketamine, most adverse events in the phase 3 program occurred and resolved on the dosing day.¹⁴ Specifically, dissociation was observed post dose, but symptoms were generally transient and generally resolved within 90 minutes, with evidence of attenuation over time. A similar pattern was observed for blood pressure; with elevations observed as transient and generally limited to the dosing day.¹⁴

Timing

It is important for a drug treatment in MDD and TRD to have long-term data to demonstrate durability of response and a well-characterized safety and tolerability profile.

Settings

Esketamine will be self-administered by patients in a health care setting under supervision of a health care professional.

Potential Other Benefits and Contextual Considerations

TRANSFORM-2¹⁰ and SUSTAIN-1¹³ provide evidence of short and long-term benefits for efficacy and safety. MDD is the second leading cause of disability in the U.S.²⁵, and results in a societal cost burden of \$188 billion, higher than cancer and diabetes²⁶. Lost work productivity due to depressive symptoms accounts for most of the annual cost of MDD.²⁷ As MDD often starts in adolescence or early adulthood²⁸, it is important to capture the impact of therapies on productivity, disability, HRQoL, and other societal outcomes. Additionally, depression has been a focus of healthcare quality measurement, represented by a number of quality measures endorsed by the National Quality Forum including depression screening and symptom monitoring across the spectrum of the disease, in particular, the PHQ-9.²⁹

Comparative Value Analyses

Our recommendation is to use a minimum of a 3-year time horizon to accurately track disease progression experienced by patients with TRD through a MDE. Real world data of commercially insured US patients estimated the mean duration of a TRD episode to be 1,004 days, hence, a 3-year time horizon is considered sufficient to capture relevant outcomes.³⁰ As the model time horizon increases, treatment of patients who do not respond, or who have a relapse or recurrence becomes more relevant. In this case, it is important to have identical next line treatments across comparators after non-response and relapse. In patients who recover and experience a recurrence, the same treatment that ended the previous TRD episode should be considered. In contrast, patients who relapse before achieving recovery, may move to the next treatment in the sequence.

REFERENCES

1. Sanacora G, Zarate CA, Krystal JH, et al. Targeting the glutaminergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov*. 2008;7(5):426-437.
2. Duman RS, Li N, Liu RJ, et al. Signaling pathways underlying the rapid antidepressant actions of ketamine. *Neuropharmacology*. 2012;62(1):35-41.
3. Duman RS, Aghajanian GK, Sanacora G, et al. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med*. 2016;22(3):238-249.
4. Agency for Healthcare Research and Quality. Technology Assessment Program. Definition of Treatment-Resistant Depression in the Medicare Population. Rockville, MD: U.S. Department of Health and Human Services; 2017.
5. DiBernardo A, Lin X, Zhang Q, et al. Humanistic outcomes in treatment resistant depression: a secondary analysis of the STAR*D study. [published on line ahead of print 29October2018]. *BMC Psychiatry*. 2018. doi:10.1186/s12888-018-1920-7.
6. Amos TB, Witt EA, Alphas L, et al. Health-related quality of life, productivity, and health care resource use burden in treatment-resistant depression: results from a US health survey. *Poster presented at the 29th Annual US Psychiatric & Mental Health Congress; October 21-24, 2016; San Antonio, TX*. Poster 101.
7. Amos T, Tandon N, Lefebvre P, et al. Direct and indirect cost burden and change of employment status in treatment-resistant depression: a matched-cohort study using a U.S. commercial claims database. *J Clin Psychiatry*. 2018;79(2).
8. Li G, Fife D, Wang G, et al. All-cause mortality of treatment-resistant depression patients: a retrospective observational analysis in the US. *Poster presented at: American Psychiatric Association; May 5-9, 2018; New York City, NY*.
9. Chow W, Doane MJ, Sheehan J, et al. Economic Burden Among Patients With Major Depressive Disorder: An Analysis of Health Care Resource Use, Work Productivity, and Direct and Indirect Costs by Depression Severity. *Poster presented at: Academy of Managed Care Pharmacy (AMCP) Nexus Meeting; October 22-25, 2018; Orlando, FL*.
10. Popova V, Daly EJ, Trivedi M, et al. Randomized, double-blind study of flexibly-dosed intranasal esketamine plus oral antidepressant vs. active control in treatment-resistant depression. *Presented at: the 2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP); May 30, 2018; Miami, FL*. Poster: W30.
11. Fedgchin M, Trivedi M, Daly EJ, et al. Randomized, double-blind study of fixed-dosed intranasal esketamine plus oral antidepressant vs. active control in treatment-resistant depression. *Poster presented at: the 9th Biennial Conference of the International Society for Affective Disorders (ISAD); September 20-22, 2018; Houston, TX*.
12. Ochs-Ross R, Daly EJ, Lane R, et al. Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression. *Poster presented at: the 2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP), May 29-June 1, 2018*. 2018. Poster: W27.
13. Daly EJ, Trivedi M, Janik A, et al. A randomized withdrawal, double-blind, multicenter study of esketamine nasal spray plus an oral antidepressant for relapse prevention in treatment-resistant depression. *Poster presented at: the 2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP); May 30, 2018; Miami, FL*. Poster: W68.
14. Wajs E, Aluisio L, Morrison R, et al. Long-term safety of esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: phase 3, open-label, safety and efficacy study (SUSTAIN-2). *Poster presented at: the Annual Meeting of the American Society of Clinical Psychopharmacology; 29 May-1 June, 2018; Miami, FL*. Poster: T67.
15. Work Group on Major Depressive Disorder, Gelenberg, AJ, Freeman, MP, et al. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd. Washington, DC: American Psychiatric Association; 2010.

16. Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP task force on response and remission in major depressive disorder. *Neuropsychopharmacol.* 2006;31:1841-1853.
17. Rush AJ, Trivedi MH, Wisniewski S.R., et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163(11, pt 1905):1905-1917.
18. Stassen HH, Angst J, Hell D, et al. Is there a common resilience mechanism underlying antidepressant drug response? Evidence from 2848 patients. *J Clin Psychiatry.* 2007;68(8):1195-1205.
19. Medical Advisory Secretariat. Repetitive transcranial magnetic stimulation for the treatment of major depressive disorder: an evidence-based analysis. *Ontario Health Technology Assessment Series.* 2004;4(7).
20. Health Quality Ontario. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis of randomized controlled trials. *Ont Health Technol Assess Ser.* 2016;16(5):1-66.
21. European Medicines Agency (EMA). *Guideline on clinical investigation of medicinal products in the treatment of depression.* 2013. https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-depression_en.pdf.
22. Sanacora G, Frye MA, McDonald W, et al. A consensus statement on the use of ketamine in the treatment of mood disorders [published online March 1, 2017]. *JAMA Psychiatry.* 2017;74(4):399-405. doi:10.1001/jamapsychiatry.2017.0080.
23. The Royal Australian & New Zealand College of Psychiatrist Committee for Therapeutic Interventions and Evidence-based Practice. *Clinical Memorandum: Use of ketamine for treatment-resistant depression.* December 2017. https://www.ranzcp.org/Files/Resources/College_Statements/Clinical_Memoranda/CM-Use-of-ketamine-for-treatment-resistant-depress.aspx.
24. Royal College of Psychiatrists Committee on ECT and Related Treatments. *Statement on ketamine to treat depression.* February 2017. <https://www.rcpsych.ac.uk/pdf/Ketamine%20to%20treat%20Depression%20-%20ECT%20ctee%20statement%20Feb17.pdf>.
25. Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA.* 2013;310(6):591-608.
26. Mrazek DA, Hornberger JC, Altar CA, et al. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatr Serv.* 2014;65(8):977-987.
27. The Institute for Clinical and Economic Review. *Nonpharmacologic interventions for treatment-resistant depression: supplementary data and analyses to the comparative effectiveness review of the agency for healthcare research and quality.* Final meeting report December 22, 2011. https://icer-review.org/wp-content/uploads/2016/01/Final-Report-TRD_FINAL2.pdf.
28. American Psychiatric Association. Major Depressive Disorder. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013. p. 160-168.
29. NQF-Endorsed Behavioral Health Measures. Available from: http://www.qualityforum.org/Projects/a-b/Behavioral_Health_Phase_1_and_2/Table_of_Endorsed_Measures.aspx Accessed: 29October2018.
30. Kubitz N, Mehra M, Potluri RC, et al. Characterization of treatment resistant depression episode in a cohort of patients from a US commercial claims database. *PLoS One.* 2013;8(10):e76882.



November 20, 2018

Attn: Midwest Comparative Effectiveness Public Advisory Council (CEPAC)
Institute for Clinical and Economic Review
Two Liberty Square
Ninth Floor
Boston, MA 02109

Dear Members of the Midwest CEPAC:

Mental Health America (MHA) thanks Institute for Clinical and Economic Review (ICER) for inviting public comment on the draft scoping document for a review of esketamine for treatment-resistant depression, and for the opportunities for ongoing engagement. MHA recommends that ICER enrich its current approach through additional scenario analyses that model the unique cost considerations of public health care payers.

MHA – founded in 1909 – is the nation's leading community-based nonprofit dedicated to addressing the needs of those living with mental illness and to promoting the overall mental health of all Americans. Our work is driven by our commitment to promote mental health as a critical part of overall wellness, including prevention services for all, early identification and intervention for those at risk, integrated care, services, and supports for those who need it, with recovery as the goal.

Federal and state governments are the largest payers of depression care in the United States. Because governments only cover individuals when they reach certain thresholds of income or disability, public health care payer cost-effectiveness works differently than commercial payer cost-effectiveness. When a public payer invests in effective depression care for an individual, the individual may be more able to work and increase their earnings. If the increased earnings causes the individual to cross over the thresholds of income or disability (or not reach them in the first place), the individual will no longer be eligible for public health care coverage, and be able to seek commercial coverage instead. From the perspective of the public payer then, the cost in the cost-effectiveness of depression care is not just driven by a potential decrease in later health care utilization related to better depression outcomes, but also the possibility of not having to pay for any further health care services as the individual transitions to commercial coverage. Thus, meaningfully investments in depression care can be extremely cost-effective for public payers, and modeling should reflect this where possibly.

Modeling public payers is important not only to ensure descriptive accuracy, but also to advance an important normative goal – that the government invest in the long-term functioning of its citizens. By making the analysis described here common practice, it can shift the paradigm for how CMS and state Medicaid agencies view costs and benefits – away from trimming health

care costs and toward making critical investments that alleviate poverty and disability. Where there is not good evidence for these relationships in the literature, MHA urges the use of estimates in scenario analyses, and would assist with any attempts to parameterize such models.

MHA thanks ICER for its consideration on how additional scenario analyses could enrich the field's understanding of costs and benefits. For additional information, please do not hesitate to contact us.

Sincerely,

A handwritten signature in black ink, appearing to read "Nathaniel Counts". The signature is fluid and cursive, with a large initial "N" and a long, sweeping tail.

Nathaniel Counts, J.D.
Senior Policy Director
Mental Health America

Comments on Draft ICER Background and Scope of Review of Esketamine for Treatment-Resistant Major Depressive Disorder

November 20, 2018

On behalf of the National Alliance on Mental Illness (NAMI), the nation's largest grassroots organization dedicated to improving the lives of people with mental illness and their families, I am pleased to offer the following comments on the Institute for Clinical and Economic Review (ICER) Draft Background and Scope of Review of Esketamine for Treatment-Resistant Major Depressive Disorder Draft Background and Scope, released on October 31, 2018. NAMI appreciates the opportunity to offer its thoughts on the announced review and hope that our suggestions and concerns are addressed in the final design of the review.

As the draft scoping document makes clear, treatment-resistant depression (TRD) is a devastating condition associated with an enormous public health burden in terms of both mortality and morbidity, as well as lost productivity and poorly managed co-morbid chronic medical conditions. People living with TRD often experience months and even years of trial and error with multiple medications without significant symptom relief and regaining quality of life. This is not an isolated or narrow population – about one-third of patients diagnosed with depression are considered to have TRD.ⁱ

The economic impact of higher costs of care and decreased productivity alone total about \$64 billion.ⁱⁱ According to the World Health Organization, depression is the leading cause of disability in the world and a major contributor to the global burden of disease.ⁱⁱⁱ It is also important to recognize that chronic mental illnesses, such as TRD, often incur a significant strain on family caregivers. In fact, there are about 8.4 million family caregivers of adults with mental illness in the United States. According to the National Alliance for Caregiving report (2016), *On Pins & Needles*, 74% of caregivers report feeling high emotional stress and four in ten say they find it difficult to take care of their own health. Only one in three (33%) report having excellent or very good health. These impacts on both patients and caregivers underscore the need for new treatment options to improve the effectiveness and tolerability of treatments for TRD.

While there are numerous medications approved to treat depression in several therapeutic classes – SSRIs, SNRIs and MAO inhibitors—the common experience for people living with TRD is a repetitive cycle of trial and error with multiple combinations of these existing medications. It is significant that antidepressants can take 4-6 weeks to show any clinical effect – prolonging an individual's suffering with severe symptoms that negatively impact on work, relationships and engagement with life activities, as well as management of other health conditions and risk of suicide.

Currently, the only FDA-approved adjunctive therapy (a supplemental therapy added onto an antidepressant) for TRD are antipsychotic medications that carry significant risk of negative side effects such as weight gain, sedation, metabolic syndrome and akathisia. The challenges with current medications and adjunctive therapy results in some people seeking out interventions such as Electroconvulsive therapy (ECT) and Transcranial Magnetic Stimulation (TMS). While these interventions can provide some clinical benefit in symptom relief for an acute episode, they have significant limitations as tools for managing TRD as a chronic condition.

In NAMI's experience, people living with TRD are desperate for novel therapies that offer immediate symptom relief. With over 4 million adults in the U.S. estimated to live with TRD, it is imperative to expand treatment options that offer symptom relief, quicker relief, clinical remission, or relief from side effects of existing treatments.

Esketamine Not Yet Approved by the FDA for Treatment of TRD

NAMI is concerned that ICER is undertaking a review before the FDA has granted approval of Esketamine to treat TRD. It is premature to undertake this review given that the most compelling scientific data about this product – the results from 5 randomized controlled trials, including three short-term studies, one withdrawal maintenance of effect study and one long-term safety study – are not yet available as they are under review at the FDA. Further, undertaking this review before FDA approval prevents examination of any evidence of how this novel therapy is being used in real world treatment settings.

In addition, this ICER review is limited to the single indication of Esketamine for TRD as an adjunctive therapy with a newly-prescribed oral antidepressant. According to published reports, the sponsor is undertaking additional clinical trials to demonstrate efficacy for acute suicidal ideation in adults with TRD. Given the enormous public health burden associated with suicide, NAMI would recommend that ICER wait until the full picture of the potential clinical promise of Esketamine is revealed and reviewed by the FDA.

Use of QALYs to Measure Symptom Improvement in TRD

NAMI has strong concerns about the use of QALYs to measure the current and emerging therapies to treat mental illness. Because existing therapies are not disease-modifying in nature and do not cure the underlying condition, QALYs are an inappropriate measure. Being able to demonstrate extended life expectancy in mental health treatment over a 5-year projection (as ICER is proposing in this review) is likely to result in a low value per QALY gained for all of the comparators in this review. Instead, what is needed is the ability to capture what is meaningful to patients: improvement in individual symptoms, functioning and quality of life—including for caregivers.

This past week, NAMI joined with our colleagues at the Depression Bipolar Support Alliance (DBSA) in conducting a "Patient Focused Drug Development" (PFDD) meeting at the FDA where people living with depression shared their personal experiences with TRD and expressed what outcomes really mattered to them. Many of the priorities expressed by patients at this meeting were beyond achievement of single clinical endpoint on a depression scale, such as MADRS, and included side effects of medications, being able to work, spend quality time with family and friends, and enjoy hobbies. NAMI remains very concerned that cost per QALY gained is unable to satisfactorily integrate these important patient priorities into a review of these interventions.

Health-related quality of life assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L)

NAMI would also like to note that the scoping document proposes to measure health-related quality of life using the EQ-5D-5L. However, recent research concludes that the anxiety/depression (A/D) dimension of the EQ-5D-3L shows limited responsiveness to changes in depressive symptoms measured by PHQ9 and anxiety symptoms measured by GAD2.^{iv} Of note, the researchers state that 31.7% of patients who had an improvement in depressive symptoms based on the PHQ9, and 40.0% of those who

had deterioration, showed no changes in the A/D dimension of the EQ-5D-3L.^v This suggests that use of the EQ-5D will not capture clinically important changes in the mental health of patients with TRD.

Potential Other Benefits and Contextual Considerations

NAMI appreciates the opportunity to comment, as well, on potential other benefits and contextual considerations. Given the very debilitating nature of TRD, it is important for other benefits to reflect not just “significantly” improved patient outcomes, caregiver burden, or impact on returning to work (or seeking work) or productivity, but *any* improvement that is meaningful to the patient. NAMI recommends that ICER include, as important benefits, interventions that result meaningful reduction of one or more symptoms that are important to a patient that may not be captured by the MADRS depression rating scale, such as irritability, anger, agitation, sexual problems, and unexplained aches and pains.

NAMI also believes it is important to consider, as a benefit, whether an intervention offers fewer or more tolerable side effects for any given patient and, importantly, the time from initial treatment to symptom relief.

Concerns About the Comparators in the Proposed ICER Review

NAMI has a number of concerns about the four interventions for which Esketamine will be compared to. ICER is proposing to use following four intervention:

- 1) Intravenous Ketamine (used off-label)
- 2) Electroconvulsive Therapy (ECT)
- 3) Transcranial Magnetic Stimulation (TMS)
- 4) Continued or new administration of antidepressants

NAMI would like to raise a few specific concerns about three of these comparators:

- 1) Intravenous Ketamine – Intravenous ketamine clinics can be found across the United States, largely outside of the federal and state regulation and payment systems. Nearly all of this treatment is off-label and outside peer-reviewed, evidence-based treatment guidelines. As a result, there are few if any reliable guidelines on dosing and timing and duration of administration. By contrast, if Esketamine is approved by the FDA as safe and effective, it will come with robust scientific evidence about dosing and possibly even a REMS (Risk Evaluation Mitigation Strategy) from the FDA to address possible safety concerns. NAMI would be extremely concerned if an ICER review resulted in payors incentivizing or directing providers to prescribe off-label intravenous ketamine with no reliable guidance on dosing and administration and no patient safety protocols over an FDA approved on-label indication.
- 2) Electroconvulsive Therapy (ECT) – ECT has been around for decades as treatment for TRD and recognize that there are many people with TRD that have benefited greatly from ECT, typically individuals that have long histories of being unable to benefit from medication. It is important to note, however, that symptom relief is often short-lived. Moreover, side effects associated with ECT can be significant – headaches, seizures, nausea, muscle aches and soreness, disorientation and confusion. Even more concerning is the high incidence of short-term—and even permanent—memory loss. In addition, ECT is an intervention that frightens many individuals. Given the side effects and fear associated with this intervention, NAMI is concerned about using ECT as a comparator.

- 3) Transcranial Magnetic Stimulation (TMS) – TMS is a form of neurostimulation, i.e. a non-invasive procedure in which a changing magnetic field is used to cause electric current to flow in a small targeted region of the brain via electromagnetic induction. Unlike ECT, TMS does not require sedation or anesthesia and is not associated with many of the adverse side effects of ECT. In 2008, the FDA authorized use of TMS for TRD. However, it is important to note that the process for the FDA “authorizing” use of a medical device for particular disease or condition is very different than the more rigorous process of approving a medication as “safe and effective.” As a result, not all health plans currently pay for TMS, which makes it unavailable for many.

Potential Candidates for Low Value Service Reductions

NAMI is pleased that the ICER review process will allow for an innovative therapy to demonstrate how an existing low value, high cost intervention can be minimized, if not eliminated, for patients prescribed the innovative therapy. In the case of Esketamine, NAMI would like to suggest that ICER consider the high costs associated with poorly managed co-morbid chronic medical conditions in the TRD population. When these patients are in the grip of a major depressive episode, their ability to engage in adherence to treatment for their diabetes, heart disease, asthma, or other chronic medical condition can be severely compromised. As a result, their risk of an acute episode of a co-occurring medical condition rises significantly. Immediate symptom relief of their depression can allow for the reduction of high cost services to treat co-morbid medical conditions.

With over 4 million adults experiencing the debilitation of TRD, it is important to have new treatment options that address people’s differential responses to treatment and their unique sets of symptoms and side effects. With the goal of better and expanded treatment options in mind, NAMI appreciates your consideration of our comments and welcome the opportunity to call on us and our community of people living with mental illness as you move forward.

Sincerely,



Mary Giliberti, J.D.
Chief Executive Officer

ⁱ Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatric services (Washington, DC)*. 2014;65(8):977-987.

ⁱⁱ *Ibid.*

ⁱⁱⁱ World Health Organization. *Depression. Key Facts*. March 22, 2018. Accessed online at <http://www.who.int/news-room/fact-sheets/detail/depression>.

^{iv} Crick K, Al Sayah F, Ohinmaa A, Johnson JA. Responsiveness of the anxiety/depression dimension of the 3- and 5-level versions of the EQ-5D in assessing mental health. March 3, 2018. *Quality of Life Research*. Accessed online at https://www.researchgate.net/publication/323615070_Responsiveness_of_the_anxietydepression_dimension_of_the_3-_and_5-level_versions_of_the_EQ-5D_in_assessing_mental_health.

^v *Ibid.*