CADTH

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

ESKETAMINE HYDROCHLORIDE (SPRAVATO)

(Janssen Inc.)

Indication: Major Depressive Disorder in Adults

Service Line:	CADTH Common Drug Review
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CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
CANMAT	Canadian Network for Mood and Anxiety Treatments
CMHA-AB	Canadian Mental Health Association, Alberta Division
CMHA-National	Canadian Mental Health Association National
ICER	incremental cost-effectiveness ratio
LY	life-year
MADRS	Montgomery-Åsberg Depression Rating Scale
MDAO	Mood Disorders Association of Ontario
MDD	major depressive disorder
MDE	major depressive episode
NMA	network meta-analysis
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
QALY	quality-adjusted life-year
QoL	quality of life
WTP	willingness to pay

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Esketamine (Spravato), 28 mg solution for intranasal use
Submitted price	Esketamine, 28 mg solution for intranasal use: $273.00 per dose
Indication	Anticipated: In combination with an SSRI or SNRI, for the treatment of major depressive disorder in adults who have not responded adequately to at least 2 separate courses of treatment with different antidepressants, each of adequate dose and duration, in the current moderate-to-severe depressive episode
Health Canada approval status	Under review
Health Canada review pathway	Priority review
NOC date	NOD issued July 29, 2019 NOC issued May 20, 2020
Reimbursement request	As per indication
Sponsor	Janssen
Submission history	Previously reviewed: No

NOC = Notice of Compliance; NOD = Notice of Deficiency; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with MDD, who have not achieved a clinically meaningful improvement after treatment with at least 2 antidepressant agents, prescribed in adequate dosages and for adequate duration (aligned with reimbursement request)
Treatment	Esketamine in combination with newly initiated oral antidepressant
Comparator	Newly initiated oral antidepressant
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	5 years
Key data source	TRANSFORM-2 and SUSTAIN-1 clinical trials
Submitted results for base case	ICER = $43,203 per QALY (0.01 incremental LY; 0.293 incremental QALYs; $12,678 incremental costs)
Key limitations	• The sponsor inappropriately adjusted the response and remission rates for the comparator (oral antidepressant) based on the assumption that additional health care visits would result in an elevated placebo effect. Given that the placebo effect for treatment-resistant MDD may be influenced by multiple factors, this approach is subjective and substantially biases results in favour of esketamine plus oral antidepressant. • The assumption that patients achieving and maintaining recovery would discontinue esketamine due to improved outcomes was considered unlikely to occur in clinical practice based on input from the clinical experts consulted by CADTH. • Inclusion of suicide-related mortality was associated with uncertainty based on the clinical findings, and inclusion of both suicide-related and all-cause population mortality potentially overestimates mortality in the model.

Component	Description
	• Multiple structural limitations were identified that could not be addressed by CADTH including treatment effect waning and the impact of partial responders. • Due to a lack of clinical information, CADTH was unable to include relevant comparators such as IV ketamine or adjunctive treatments. • Long-term maintenance of the treatment effect for esketamine plus oral antidepressant was associated with uncertainty as current clinical information is available up to a maximum of 91 weeks.
CADTH reanalysis results	• CADTH undertook reanalyses to address the identified limitations by applying unadjusted response and remission rates for the comparator (oral antidepressant), removing discontinuation rates for recovery for esketamine plus oral antidepressant treatment, and removing all-cause population mortality. • CADTH ICER for esketamine plus oral antidepressant was $125,376 per QALY compared with oral antidepressant alone. • A price reduction of 60% for esketamine is required to achieve an ICER of $50,000 per QALY.

ICER = incremental cost-effectiveness ratio; LY = life-year; MDD = major depressive disorder; QALY = quality-adjusted life-year.

Conclusions

CADTH undertook reanalyses when possible to address limitations, including the use of unadjusted response and remission rates for the comparator (oral antidepressant), removing discontinuation rates for recovery for esketamine plus oral antidepressant treatment, and removing all-cause population mortality.

Based on the CADTH reanalyses for adult patients with major depressive disorder (MDD) who had an inadequate response to at least 2 prior antidepressant therapies, the incremental cost-effectiveness ratio (ICER) for esketamine plus oral antidepressant is $125,376 per quality-adjusted life-year (QALY), which would not be considered a cost-effective treatment at a willingness-to-pay (WTP) threshold of $50,000 per QALY. There is a 1% likelihood that esketamine plus oral antidepressant would fall below $50,000 per QALY and a 31% likelihood at a $100,000 per QALY threshold. Price reductions can improve the cost-effectiveness of esketamine plus oral antidepressant in patients with treatment-resistant MDD. At a WTP threshold of $50,000 per QALY, a price reduction of approximately 60% is required for esketamine plus oral antidepressant to be considered cost-effective.

CADTH was unable to address the impact of treatment effect waning or the impact of partial responders. Further, due to a lack of clinical data, CADTH was unable to implement comparisons with other relevant comparators including IV ketamine or adjunctive treatments. The CADTH clinical review team was unable to make conclusions regarding the effect of esketamine on health-related quality of life (QoL), suicidality, hospitalization, or emergency department visits, as the trials were not designed or powered to evaluate these outcomes. It was also noted that long-term safety of esketamine is uncertain.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process (specifically, information that pertains to the economic submission).

Four patient groups provided patient input for this review: the Mood Disorders Society of Canada; the Canadian Mental Health Association National (CMHA-National); CMHA, Alberta Division (CMHA-AB); and the Mood Disorders Association of Ontario (MDAO). Patient input was collected by each organization through either online surveys, phone interviews, or focus group follow-up of either the patient or primary caregiver.

All patient groups emphasized that depression negatively impacts a patient's emotions and QoL. Specifically, survey respondents indicated that depression affected sleep, appetite, mood, relationships, exercise, and work. Respondents' depression was also accompanied by suicidal thoughts, particularly when their depressive symptoms were compounded with life- and/or work-related stress. The financial burden was also noted, as many patients are unable to work and must rely on disability payments or savings, may have limited access to government supports and resources, or have high out-of-pocket treatment costs. In the submission by CMHA-National, CMHA-AB, and MDAO, 87% of the respondents reported experiencing financial difficulties since their diagnosis of depression.

Common adverse events (AEs) related to antidepressants included weight gain, memory loss, decreased sexual functioning, and a worsening of complications of other conditions. Consequently, medication-related side effects had an impact on patients' overall QoL and willingness and ability to seek new treatments. The joint input from the groups of CMHA-National, CMHA-AB, and MDAO emphasized that a new treatment should have a more rapid treatment response compared to the current treatments, especially for patients with suicidal ideation and MDD.

Several of these concerns were addressed in the sponsor's model.

- Treatment efficacy (proportion achieving response, remission, and recovery) and QoL (i.e., EuroQol 5-Dimensions [EQ-5D]) were incorporated using results from the TRANSFORM-2 and SUSTAIN-1 clinical trials.
- AEs were included (costs and QoL decrements); however, weight gain and decreased sexual functioning were not incorporated in the economic model.
- Mortality was adjusted based on the risk of suicide according to the patient health state (i.e., episodic, response, remission, and recovery).

In addition, CADTH addressed some of these concerns as follows:

- including unadjusted response and remission rates for oral antidepressants
- exploring the impact of removing adjusted mortality rates according to risk of suicide.

Economic Review

The current review is for esketamine (Spravato) for adult patients with MDD who have not responded adequately to at least 2 different antidepressants of adequate dose and duration in the current depressive episode.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis comparing esketamine in combination with a newly initiated oral antidepressant (esketamine plus oral antidepressant) versus newly initiated oral antidepressant alone for the treatment of MDD episodes following an inadequate response to at least 2 different antidepressants. The modelled population was consistent with the TRANSFORM-2 trial and aligned with the funding request.[1] No analyses were conducted for patient subgroups.

Esketamine is a single-use nasal spray device that delivers a total of 28 mg of esketamine in 2 sprays (1 spray per nostril).[2] It is intended for administration by the patient under the supervision of a health professional. When more than 1 device is required, a 5-minute rest between use of each device should be provided. The recommended initial dose of esketamine for adults is 56 mg (two 28 mg devices) followed by subsequent doses of 56 mg or 84 mg twice weekly for the first 4 weeks, then weekly for week 5 to week 8. From week 9 and onwards, the recommended dose is 56 mg or 84 mg weekly or every 2 weeks, based on the lowest frequency needed to maintain response or remission. The recommended initial dose for adults 65 years of age and older is 28 mg daily per week (2 treatment sessions per week).[2] The comparator included oral antidepressant which consisted of serotonin-norepinephrine reuptake inhibitors (SNRIs; desvenlafaxine, duloxetine, and venlafaxine) and selective serotonin reuptake inhibitors (SSRIs; citalopram, escitalopram, fluoxetine, paroxetine, and sertraline).[3] Treatment monitoring was only applied to esketamine and assumed to occur for the duration of treatment. Further, monitoring was assumed to be performed by a nurse for 2 hours post-treatment, and 2 patients could be observed concurrently.

The total annual drug cost of esketamine is between $18,564 to $45,591 in year 1, and $14,196 to $42,588 in subsequent years based on a unit price of $273.00 per 28 mg. In the model, the sponsor considered the average cost of esketamine as $30,019 in year 1 and $24,625 in subsequent years based on the average number of treatment sessions and devices per session obtained from the TRANSFORM-2 and SUSTAIN-1 clinical trials.

The predicted clinical outcomes included QALYs and life-years (LYs). The economic evaluation was undertaken over a 5-year time horizon using 4-week cycle lengths (half-cycle correction was applied) from the perspective of the public health care payer. Discounting (1.5%) was applied to both costs and outcomes after the first year.

Model Structure

A cohort-level Markov model was developed in Excel and consisted of a total of 3 stages: treatment of resistant depression, subsequent treatment, and a non-specific treatment mix (Figure 1 in Appendix 3). Patients entered the model in the resistant depression stage,

which consisted of the acute phase (week 1 to week 4), early maintenance (week 5 to week 8), late maintenance (week 9 to week 40), and recovery (week 41 and onward). Following the acute phase, patients could transition to the following health states based on their Montgomery-Åsberg Depression Rating Scale (MADRS) score: respond to treatment and transition to response (50% improvement from baseline in the MADRS score, excluding patients failing to achieve MADRS ≤ 12) or remission (MADRS ≤ 12); fail to respond and stay in the major depressive episode (MDE) (MADRS ≥ 28), but transition to the subsequent treatment or non-specific treatment mix; discontinue treatment early and remain in MDE; or, enter the death health state. Patients in the response health state could further improve on the MADRS scale and transition to remission, experience a loss-of-treatment response, transition to MDE and initiate subsequent or non-specific treatment mix, discontinue treatment and remain in the current health state, or transition to death. Patients achieving remission either proceeded to recovery (after 36 weeks) or followed a similar progression as patients in the response health state. Upon entering the recovery health state, patients either experienced a recurrence and initiated subsequent or non-specific treatment mix, discontinued treatment and remained in the current health state, or transitioned to death. Currently, the sponsor assumed patients failing treatment for resistant depression would directly enter the non-specific treatment mix stage which includes health states for MDE, response, and remission; however, patients were assumed to never achieve recovery.

Model Inputs

Baseline characteristics of the model population were aligned with the TRANSFORM-2 study: 61.9% of patients were female, mean age was 46 years (standard deviation [SD] = 11.89 years), and mean baseline MADRS score was 37.1 (SD = 5.67). Both all-cause and suicide-related mortality risks were included in the model, specific to each health state, and were obtained from Statistics Canada and Bergfeld et al.[4,5]

The comparative clinical efficacy of esketamine plus oral antidepressant and oral antidepressant was obtained from the TRANSFORM-2 study (week 1 to 4; measured in terms of change in MADRS for patients entering response or remission) and the SUSTAIN-1 study (week 4 onwards; response to remission, relapse, loss of response, and recurrence), based on the last observation carried forward. Although not included as part of the sponsor's base case, subsequent treatment efficacy was derived using the STAR*D study.[6] Efficacy transition probabilities (i.e., response, remission, loss of response, and relapse) for the non-specific treatment mix were obtained from the study by Edwards et al. (2013).[7] Treatment discontinuation rates were both comparator- and health state-dependent and were assumed to be independent of prior treatment, with patients in the acute treatment phase not discontinuing treatment. Using patient-level data from the SUSTAIN-1 study, the sponsor applied an exponential distribution to derive esketamine discontinuations for patients in the response and remission health states during the maintenance period (1.69% every 4 weeks). For patients in the recovery health state, 35.4% of patients were assumed to discontinue esketamine when achieving recovery (represented by the proportion of patients with ≤ 2 MDD episodes) and 99% discontinued esketamine after 2 years of maintenance therapy as aligned with the Canadian Network for Mood and Anxiety Treatments (CANMAT) and National Institute for Health and Care Excellence (NICE) guidelines for depression.[8,9] Patients discontinuing esketamine would continue to receive oral antidepressants for prevention of recurrence. AE probabilities were obtained from the TRANSFORM-2 study and assumed to only occur during the acute phase of treatment (i.e., the first 4 weeks).

The sponsor stated the remission and response rates from the TRANSFORM-2 study were high compared to other studies in depression due to the therapeutic value associated with

health care professional visits, which are expected to differ from real-world practice.[6] To account for the placebo effect, the sponsor assumed patients receiving oral antidepressants would have both a reduced number of health care visits compared to the TRANSFORM-2 study (2 vs. 8 physician visits during the first 4 weeks), and using the publication by Posternak and Zimmerman,[10] an increase of 0.804 points in the MADRS score was applied for the each additional visit in the clinical trial (total increase of 4.824 points). An overview of the adjusted response and remission rates according to the number of health care visits is provided in Table 12.

Health state utility values were obtained from the TRANSFORM-2 study using patient-level data for MDE, response, remission, and recovery, with the assumption that recovery would be the equal to remission (Table 13). Utility decrements due to AEs were also applied using the published literature and were assumed to have a duration of 1 day (Table 14). It was assumed by the sponsor that blood pressure increase, delusion, derealization, dissociation, postural dizziness, dysgeusia, hypoesthesia, nasal discomfort, and paranesthesia would have no impact on patient QoL.

The sponsor included medical costs, drug costs, treatment administration costs, and costs due to AEs. The drug price of esketamine was based on the sponsor's submitted price and the unit drug prices for oral antidepressants were obtained from the Ontario Drug Benefit Formulary using the maximum daily dosage from the respective product monographs.[11] Market shares for oral antidepressants used in resistant depression were obtained from a 2018 IQVIA new prescription (NRx) data report (Table 15). The number of administrations for esketamine were estimated using the TRANSFORM-2 and SUSTAIN-1 studies (Table 16), and administration costs were based on 2 hours of monitoring by a nurse practitioner post-treatment with esketamine ($37), with the assumption that 2 patients are monitored concurrently.[12] Health care utilization and costs were differentiated by each health state (i.e., MDE, response, remission, and recovery) based on a 2018 Canadian economic burden study commissioned by the sponsor (costs reported in 2017 CA$).[13] The sponsor assumed patients in the MDE health state would have direct medical costs (reported per 28-day cycle) as represented by the resistant depression cohort ($816.34) — response costs are represented by the MDD cohort ($697.89), and remission costs are represented by the non-MDD cohort ($430.22). The sponsor assumed patients in recovery would have the same direct medical costs as remission. Adverse event costs were assumed to be incurred on a one-off basis which included a consultation visit to a general or family physician using the Ontario Schedule of Benefits for Physician Services ($77.20; A005).[14]

Summary of Sponsor's Economic Evaluation Results

The sponsor presented both deterministic and probabilistic analyses (1,000 iterations for base-case and scenario analyses). Results were similar between the deterministic and probabilistic analyses. Only probabilistic analyses are presented as follows.

Base-Case Results

In the sponsor's base-case analysis, esketamine plus oral antidepressant was associated with an expected cost of $61,515 and 3.029 QALYs over the 5-year time horizon. When compared with oral antidepressant alone, esketamine plus oral antidepressant had both greater incremental costs ($12,678) and QALYs (0.293), resulting in an ICER of $43,203 per QALY gained (Table 3). At a WTP threshold of $50,000 per QALY, esketamine plus oral antidepressant has a 53.3% probability of being cost-effective and oral antidepressant has a 46.7% probability of being cost-effective.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. oral AD ($/QALY)
Oral AD	48,837	-	2.735	—	—
Esketamine plus oral AD	61,515	12,678	3.029	0.293	43,203

AD = antidepressant; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Note: The submitted analysis is based on publicly available prices of the oral AD treatments.

Source: Adapted from sponsor's pharmacoeconomic submission.[3]

Sensitivity and Scenario Analysis Results

The sponsor undertook scenario analyses of several parameters which included varying the proportion of patients discontinuing esketamine treatment after achieving recovery and altering the efficacy for oral antidepressant based on the number of visits. Based on these scenarios, the ICER ranged from $41,929 per QALY (increased adjustment of placebo effect) to $58,266 per QALY (50% of patients discontinuing esketamine by 2 years).

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis.

- **Inappropriate adjustment of treatment efficacy for placebo effect for the comparator (oral antidepressant):** The sponsor adjusted both response and remission rates in the comparator arm of the TRANSFORM-2 study (placebo plus oral antidepressant) based on the assumption of an increased placebo effect for patients as a result of additional health care visits, anticipated treatment benefits from receiving esketamine (i.e., nasal spray device for placebo), and potential unblinding of patients. CADTH noted that attributing clinical effects (response and remission) entirely to additional health care visits is speculative, as there are likely several influences on why effects may be observed.
- In the randomized design of the TRANSFORM-2 study, we could expect placebo effect to be equally prevalent in both treatment arms within the trial. As such, if 1 trial arm (i.e., comparator) is adjusted, clear rationale would be required for not conducting the same adjustment to the other arm (i.e., treatment). The clinical experts consulted by CADTH suggested increased health care visits could amplify the placebo effect, but again this is likely to occur in both comparator and treatment arms of the trial; health care visits alone could not account for inflated response and remission rates, and there is limited data and evidence to support this claim.
- The methodology used to derive response and remission rates according to the number of health care visits was also associated with substantial uncertainty. The study by Posternak and Zimmerman,[10] cited by the sponsor, used the Hamilton Depression Rating Scale to determine the impact of health care visits, therefore an additional conversion to the MADRS scale was required. It was also unclear whether the study population, primarily outpatients with MDD, is sufficiently similar to those in the TRANSFORM-2 study. Therefore, the applicability to a treatment-resistant MDD population is uncertain. In addition, the potential added benefit associated with health care visits would also apply to patients receiving esketamine plus oral antidepressant as the improved response and remission rates due to treatment are likely indistinguishable from the frequency of visits and the true benefit of esketamine is unknown. The modification of response and remission rates for the oral antidepressant treatment arm is therefore associated with substantial biases, favouring esketamine.

- CADTH applied unadjusted response and remission rates (i.e., no modification according to the number of health care visits) as part of base-case reanalyses.

- **Discontinuation of esketamine is uncertain:** It was assumed by the sponsor that patients achieving recovery and maintaining recovery after 2 years of treatment would discontinue esketamine and continue oral antidepressants alone, with a pooled risk of recurrence applied to both esketamine plus oral antidepressant and oral antidepressant alone. The clinical experts consulted by CADTH felt this would be unlikely as patients and physicians would be hesitant to withdraw an effective treatment due to the concerns of relapse or recurrence leading to a decline in overall QoL. Although the sponsor cited the CANMAT guidelines as justification for their assumption for treatment discontinuation, it was also emphasized within the guidelines that patients with risk factors including frequent, recurrent, chronic, severe, or difficult to treat episodes should consider long-term treatment (2 years or longer).[8] Given the patient population from the SUSTAIN-1 study have experienced multiple recurrent and difficult to treat episodes, it is highly likely that they would continue to receive long-term treatment despite maintaining remission, and in most cases, patients are likely to continue for the duration of their lifetime based on clinical expert feedback. CADTH did note however that patients may still discontinue treatment due to lack of efficacy (i.e., loss of response, relapse, or recurrence) or AEs which is already captured as part of the economic model.

  Further, the sponsor's assumption that patients would maintain their QoL and MADRS score after discontinuing treatment was considered highly improbable by CADTH and the clinical experts given the severity of the patient's condition, and potential patient concern for relapse and recurrence.

  - Based on the clinical uncertainty associated with patient discontinuation, CADTH considered a conservative approach where patients would only discontinue due to a loss of response, relapse, recurrence, or AEs as part of base-case reanalyses. To assess the impact of differential recurrence rates, CADTH included a recurrence rate of 0.024 for esketamine plus oral antidepressant and 0.036 for oral antidepressant alone in scenario analyses. As part of the scenario analyses, CADTH assumed 5% of patients would discontinue effective treatment annually as aligned with the Institute for Clinical and Economic Review's review of esketamine.[15] Alternate discontinuation rates upon achieving recovery were also explored, as represented by the proportion of patients with only 1 prior MDD episode (10.77%).

- **Model associated with multiple structural limitations:** The design of the sponsor's model precluded CADTH from exploring multiple areas of uncertainty such as treatment effect waning and patients achieving a partial response. The sponsor assumed that the treatment effect of esketamine plus oral antidepressant (i.e., relapse, loss of response, and recurrence) would be maintained over the duration of the analysis time horizon. Based on clinical expert feedback, patients with treatment-resistant depression are less likely to maintain a long-term durable treatment response and projections beyond the SUSTAIN-1 trial data were considered highly speculative. The impact of treatment effect waning was not explored in the sponsor's economic model and due to structural limitations, CADTH was unable to assess the impact of this assumption.

  The CANMAT guidelines suggest patients achieving a partial response (i.e., > 25% to < 50% improvement in symptom scores) are likely to benefit from adjunctive treatments and treatment optimization; however, these patients were not captured given the health states defined by the sponsor. Patients achieving a partial response without remission (MADRS score > 12) are therefore classified as nonresponders and the benefits for these patients are underestimated; however, the impact of this limitation on the cost-effectiveness of esketamine plus oral antidepressant is unknown. The clinical experts highlighted that patients achieving a partial response that is both meaningful and important would continue to receive maintenance treatment and dose adjustments with esketamine, which may be considered to optimize treatment response.

- Due to structural limitations, CADTH was unable to explore the impact of treatment effect waning or the impact of partial responders.

- **Consideration of relevant comparators:** Based on clinical expert feedback, off-label IV ketamine was considered a relevant comparator given the current use in clinical practice. Recently, a number of randomized controlled trials have examined short- (24 hours to 14 days) and long-term (15 days to 30 days) efficacy and safety of IV ketamine, with the majority of publications observing improved depression severity, response rate, and remission rates for IV ketamine versus midazolam or placebo.[16-19] However, it was noted in the CADTH Rapid Response Report[16] and the CANMAT[8] guidelines that further evidence is needed regarding efficacy and safety, with the recommendation for its use being limited to academic depression treatment centres.

  Additionally, both the CANMAT guidelines and feedback from the clinical experts recommend the use of adjunctive treatment for patients with resistant depression that are nonresponders to oral antidepressant monotherapy. Multiple clinical trials and network meta-analyses (NMA) have observed that adjunctive treatments (e.g., antipsychotic drugs) were statistically more efficacious than no treatment (placebo) in patients with treatment-resistant MDD and would be used in the same treatment setting as esketamine.[20,21] The sponsor had commissioned an NMA to inform the relative efficacy of adjunctive treatments with esketamine; however, based on multiple limitations that impact the validity of results, the NMA was not included as part of the economic analyses. The absence of adjunctive treatments as a comparator was also noted as a limitation in the evaluation of esketamine by the National Institute for Health and Care Excellence (NICE).[22]

  - CADTH was unable to include adjunctive treatments and IV ketamine as part of reanalyses as data to inform the relative clinical efficacy was unavailable or did not align with the sponsor's model structure (i.e., response and remission rate after 4-week assessments). As part of exploratory analyses, CADTH considered IV ketamine as a comparator assuming equal efficacy to esketamine. The drug costs associated with IV ketamine (assuming twice weekly treatment for acute phase and once every other week for maintenance based on clinical expert feedback), concomitant oral antidepressant, and administration were applied. Currently, IV ketamine administration costs are not covered by the public health care payer; therefore, CADTH assumed the costs of a general psychiatric consultation ($199.40; A195) and 45 minutes for an anesthesiologist ($45.03 per 3 units) from the Ontario Schedule of Benefits – Physician Services.[14] Additionally, similar monitoring costs as esketamine were applied. AEs were informed using the study by Fava et al.[23] and non-reported AEs were assumed to be similar to esketamine.

- **The long-term effects of esketamine are unknown**: The clinical experts consulted by CADTH highlighted that treatment-resistant MDD is a lifetime condition and patients are likely to continue treatment indefinitely, therefore the sponsor assumption of a 5-year time horizon may underestimate downstream costs and benefits. Given limited long-term data for esketamine plus oral antidepressant and other treatments, substantial uncertainty exists regarding the maintenance of esketamine plus oral antidepressant treatment effect as few patients were at risk beyond 52 weeks to inform treatment efficacy. Further, the clinical experts highlighted that the sponsor efficacy projections where esketamine plus oral antidepressant treatment effect is maintained over 5 years are likely optimistic given patients with treatment-resistant MDD are likely to have difficult to treat episodes. Due to the structural limitations of the sponsor's model CADTH was unable to explore the application of a treatment effect waning for esketamine plus oral antidepressant; therefore, results which use time horizons beyond 52 weeks (1 year) should be interpreted with consideration of this limitation.

  - In CADTH scenario analyses, time horizons of 1 year (aligned with the available trial evidence), 3 years, and 20 years were explored.

- **Esketamine impact on mortality is uncertain:** The sponsor applied all-cause (age and gender adjusted) and suicide-related mortality as part of the base case, indirectly increasing patient mortality for patients entering the MDE and response health states after failing to achieve or maintain remission on a previous treatment. As all-cause mortality includes death from suicide, this could double count suicide-related mortality. Given patients with treatment-resistant MDD are at an elevated risk of suicide, the inclusion of suicide-related mortality would likely capture the majority of deaths over this analysis time frame (5 years). All-cause mortality is unlikely to be substantively different between treatment groups.

  Based on the evidence from the TRANSFORM-2 and SUSTAIN-1 studies, the exclusion of patients with suicidal ideation within the previous 6 months limits the generalizability to the treatment-resistant MDD population. In addition, patients receiving esketamine plus oral antidepressant more frequently reported suicidal ideation and suicidality compared to oral antidepressant. Therefore, it was not definitively established that esketamine plus oral antidepressant would be associated with a reduced mortality. The impact on mortality is expected to be minimal based on the time horizon (5 years); however, a differential effect on mortality between esketamine plus oral antidepressant and oral antidepressant will increase with an extended time horizon and may impact cost-effectiveness.

  - CADTH removed general mortality as part of the base case and removed suicide-related mortality in scenario analyses.

- **Subsequent treatment with esketamine not explored**: Feedback from the clinical experts consulted by CADTH indicated that patients may be re-treated with a previously effective treatment (i.e., achieved response or remission) for subsequent relapses or recurrences, including esketamine plus oral antidepressant, which was not explored by the sponsor for subsequent treatment. Given the additional costs and uncertainty associated with the treatment efficacy of esketamine for treatment of subsequent episodes, the cost-effectiveness is unknown.

  - As part of exploratory analyses, CADTH included esketamine plus oral antidepressant as treatment for patients who experienced a relapse or recurrence if they received initial treatment with esketamine, with the assumption that clinical efficacy would be unaffected by line of treatment. An additional analysis was conducted where the clinical efficacy of esketamine plus oral antidepressant (for subsequent treatment) was assumed to have efficacy as reflected by step 3 of the STAR*D study.[6]

Additional limitations were identified, but were not considered to be key limitations:

- **Cost of oral antidepressant treatments may not accurately reflect the current treatment mix:** The treatment mix of oral antidepressants was not inclusive of all treatments commonly used in the Canadian setting, mainly the exclusion of fluvoxamine, bupropion, and mirtazapine, which impacts the overall treatment costs. Considering bupropion and mirtazapine are associated with relatively lower drug costs compared to other treatments (see Cost Comparison Table), oral antidepressant costs are likely overestimated.

  - The inclusion of fluvoxamine, bupropion, and mirtazapine likely has a minimal impact on cost-effectiveness and was not incorporated in the CADTH base case; however, the inclusion of all relevant oral antidepressants is recommended.

- **Individual utility decrements for AEs are not accurately represented:** The sponsor included AE utility decrements from the published literature[24,25]; however, many utility decrements for observed AEs were not reported in the studies and a weighted average of all AEs was applied for values that were not available. This approach makes evaluating the impact of harms associated with treatment challenging as an average utility decrement is unlikely to be representative of the influence that individual AEs would have on patients' QoL. Further, multiple AEs were assumed to have no effect on

patient QoL, with the majority of these AEs occurring more frequently in patients treated with esketamine plus oral antidepressant (i.e., blood pressure increase, delusional perception, derealization, dissociation, dysgeusia, hypoesthesia, and paranesthesia) compared to oral antidepressant alone, biasing results in favour of esketamine.

- CADTH explored the impact of including average utility decrements to the missing AEs as part of scenario analyses; however, given these AEs were of short duration (assumed 1 day), CADTH found the impact on results to be minimal.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (see Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Patients were assumed to receive the maximum daily dosage of oral ADs.	Uncertain. The clinical experts consulted by CADTH highlighted patient treatment is highly individualized and patients may be limited from achieving the maximum dosage due to factors such as AEs due to treatment. Additionally, the mean dose for each oral antidepressant in the TRANSFORM-2 and SUSTAIN-1 clinical trials had not reached the maximum dosage, indicating this may be overestimated in the sponsor's economic model. However, given that oral ADs were applied for both treatment arms, this is unlikely to impact results.
The sponsor assumed patients in the recovery health state would have equal direct medical costs and quality of life as patients in remission.	Reasonable. CADTH explored the impact of equal medical costs according to health state.
The number of esketamine sessions and devices per session was reflective of the TRANSFORM-2 and SUSTAIN-1 trials.	Uncertain. CADTH explored the impact of increased treatment sessions and devices per session.
Two patients could be monitored post administration of esketamine simultaneously over 2 hours by a nurse practitioner.	Reasonable based on clinical expert feedback. Due to the uncertainty with the anticipated health care resources required for esketamine, CADTH explored the impact of monitoring costs by assuming only 1 patient is monitored by a nurse practitioner, however the impact on results was minimal. It is unclear what impact the introduction would have on infrastructure changes for the health care system (i.e., waiting rooms for monitoring, equipment required for AE management) and additional assessments are needed.

AE = adverse event.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH reanalyses addressed several limitations within the economic model and are summarized in Table 5. Due to structural limitations, CADTH was unable to address the impact of treatment effect waning or the impact of partial responders.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Updated general population mortality	Statistics Canada 2017	Statistics Canada 2018
2. Direct medical costs inflated	2018 CA$	2020 CA$
Changes to derive the CADTH base case		
1. Modification of placebo treatment efficacy based on health care visits	Included placebo arm adjustment	Excluded placebo arm adjustment
2. Esketamine discontinuation rate for effective treatment	Achieved recovery: 35.4% After 2 years: 99.0%	Achieved recovery: 0.0% After 2 years: 0.0%
3. General population and suicide-related mortality	Both included	Only suicide-related mortality included
CADTH base case	-	Reanalyses 1 to 3

CA$ = Canadian dollars.

CADTH's base-case results are presented in Table 6 and additional reanalyses are presented in Table 17.

In CADTH's base case, oral antidepressant was the least costly option (total cost of $49,108) and provides 2.818 QALYs over the 5-year time horizon. When compared with oral antidepressant, esketamine plus oral antidepressant had both higher incremental costs ($31,266) and QALYs (0.249), resulting in an ICER of $125,376 per QALY gained. At a WTP of $50,000 per QALY, 1% of simulations resulted in esketamine plus oral antidepressant being cost-effective.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER vs. oral AD ($/QALYs)
Sponsor's base case	Oral AD	48,837	2.735	–
	Esketamine plus oral AD	61,114	3.029	41,839
Sponsor's corrected base case	Oral AD	49,589	2.737	–
	Esketamine plus oral AD	61,918	3.039	40,831
CADTH reanalysis 1: Health care visit adjusted efficacy	Oral AD	48,784	2.799	–
	Esketamine plus oral AD	62,066	3.040	54,978
CADTH reanalysis 2: Discontinuation rate	Oral AD	49,621	2.733	–
	Esketamine plus oral AD	78,469	3.024	99,436
CADTH reanalysis 3: Mortality	Oral AD	49,985	2.756	–
	Esketamine plus oral AD	62,586	3.063	41,001
CADTH base case (reanalysis 1 to 3)	Oral AD	49,108	2.818	–
	Esketamine plus oral AD	80,374	3.068	125,376

AD = antidepressant; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Note: CADTH reanalyses are based on publicly available prices of the oral AD treatments.

Scenario Analysis Results

Scenario analyses were conducted using the CADTH base case to investigate the impact of treatment discontinuation, differential recurrence rates, time horizon, health state medical costs, number of sessions and devices per session, AE utility decrements, and mortality adjustments (Table 18).

Based on CADTH scenario analyses, the application of both increased sessions and number of devices to the maximum recommended doses had the largest impact on esketamine plus oral antidepressant results, making esketamine less cost-effective with an ICER of $208,999 per QALY (Table 19). A 1-year time horizon had the second largest impact on esketamine plus oral antidepressant results, with an ICER of $208,949 per QALY.

Exploratory Analysis Results

CADTH conducted exploratory analyses to assess the use of esketamine as part of subsequent therapy and the inclusion of IV ketamine was assessed (Table 20). Based on CADTH analyses, esketamine plus oral antidepressant was dominated by IV ketamine (i.e., esketamine is associated with more costs and fewer QALYs) and the ICER for esketamine plus oral antidepressant ranged from $108,754 per QALY to $161,611 per QALY for subsequent treatment scenarios (Table 21).

Given the lack of data to inform the relative efficacy between IV ketamine and esketamine, the application of equal efficacy represents a conservative estimate and may not necessarily reflect the true cost-effectiveness between these treatments. Additionally, the inclusion of esketamine as subsequent treatment was applied to all patients failing initial treatment and therefore results are not specific to patients experiencing a relapse or recurrence where re-treatment with esketamine would be used. These results are associated with high uncertainty but provide a context for the relative cost-effectiveness of esketamine plus oral antidepressant in these treatment settings.

Price Reduction Analyses

Price reduction analyses were conducted using the sponsor's and CADTH's base cases (Table 7). Based on the sponsor's base case, no price reductions would be required to achieve a WTP threshold of $50,000 per QALY. When using the CADTH base case at a WTP of $50,000 per QALY, esketamine would require a price reduction of approximately 60% to be considered cost-effective versus oral antidepressant.

Table 7: CADTH Price Reduction Analyses for Esketamine Plus Oral AD Versus Oral AD

	ICER ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	43,203	125,376
10%	36,905	112,877
20%	31,706	**100,624**
30%	26,507	85,563
40%	21,308	73,499
50%	16,109	59,944
60%	10,910	**47,121**
70%	5,712	33,049

	ICER ($/QALY)	
Price reduction	Sponsor base case	CADTH reanalysis
80%	513	20,804
90%	Dominates oral AD	7,556

AD = antidepressant; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Issues for Consideration

- **Nonpharmacological interventions:** The clinical experts consulted by CADTH noted that both psychological[26] and neurostimulation[27] interventions would likely be used in conjunction with oral antidepressants for treatment-resistant MDD. This was also reported in the STAR*D study, where patients could receive cognitive behavioural therapy in addition to citalopram treatment.[6] As the sponsor's model does not account for the impact of nonpharmacological interventions, it was not possible to estimate any benefit, harm, QoL, or cost differences which may occur between treatment strategies.
- **Accessibility of esketamine:** The sponsor has indicated esketamine will be provided through a controlled distribution system where only pharmacies enrolled in the program can prescribe esketamine. Limited details were provided in the esketamine product monograph and it is uncertain to what extent this program will inhibit patient access.[2]

Overall Conclusions

CADTH undertook reanalyses when possible to address limitations, including the use of unadjusted response and remission rates for the comparator (oral antidepressant), removing discontinuation rates for recovery for esketamine plus oral antidepressant treatment, and removing all-cause population mortality.

In CADTH base-case reanalyses for adult patients with MDD who had an inadequate response to at least 2 prior antidepressant therapies, esketamine plus oral antidepressant would not be considered a cost-effective treatment at a WTP threshold of $50,000 per QALY. The probability of esketamine plus oral antidepressant being considered the most cost-effective intervention was 31% at a $100,000 per QALY threshold and 1% for $50,000 per QALY. Price reductions can improve the cost-effectiveness of esketamine plus oral antidepressant in patients with treatment-resistant MDD. At a WTP threshold of $50,000 per QALY, a price reduction of approximately 60% is required for esketamine plus oral antidepressant to be considered cost-effective.

CADTH was unable to address the impact of treatment effect waning or the impact of partial responders. Further, due to a lack of data, CADTH was unable to implement comparisons with other relevant comparators including IV ketamine or adjunctive treatments. The CADTH clinical review team was unable to make conclusions regarding the effect of esketamine on health-related QoL, suicidality, hospitalization, or emergency department visits, as the trials were not designed or powered to evaluate these outcomes. It was also noted that long-term safety of esketamine is uncertain.

Appendix 1: Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and, as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Treatment-Resistant Major Depressive Disorder

Drug/comparator	Strength (mg)	Dosage form	Price ($)	Recommended dose (mg)	Average weekly drug cost ($)	Average annual drug cost ($)
Esketamine (Spravato)	28	Intranasal spray	273.0000[a]	Week 1 to week 4: 2 sessions per week; day 1: 56; subsequent days: 56 or 84 Week 5 to week 8: 56 or 84 once weekly Weeks ≥ 9: 56 or 84 every 2 weeks or once weekly	Week 1: 1,092 to 1,365 Weeks 2 to 4: 1,092 to 1,638 Weeks 5 to 8: 546 to 819 Weeks ≥ 9: 273 to 819	Year 1: 18,564 to 45,591 ≥ 2 Years: 14,196 to 42,588
NMDA receptor antagonist						
Ketamine (generic)	10 mg/mL 50 mg/mL	Vial	1.6454[b] 5.1975[b]	0.5 mg/kg intravenously infused for 40 minutes 1 to 3 times weekly[c]	5.20 to 15.59[c]	270 to 811[c]
SNRIs						
Desvenlafaxine (generic)	50 100	ER tablet	2.3409 2.3409	50 to 100 daily	16.39	854
Duloxetine (generic)	30 60	DR capsule	0.4814 0.9769	60 daily	6.84	357
Venlafaxine (generic)	37.5 75 150	ER capsule	0.0913 0.1825 0.1927	75 to 225 daily	1.28 to 2.63	67 to 137
SSRIs						
Citalopram (generic)[d]	20 40	Tablet	0.1332	20 to 60 daily	0.93 to 1.86	49 to 146
Escitalopram (generic)	10 20	OD tablet	1.3199 1.4052	10 to 20 daily	9.24 to 9.84	482 to 513
	10 20	Tablet	0.3109 0.3310		2.18 to 2.32	114 to 121

Drug/comparator	Strength (mg)	Dosage form	Price ($)	Recommended dose (mg)	Average weekly drug cost ($)	Average annual drug cost ($)
Fluoxetine (generic)	10 20	Capsule	0.3404[e] 0.3311	20 to 60 daily	2.32 to 2.98	121 to 363
Fluvoxamine (generic)[d]	50 100	Tablet	0.2105 0.3783	100 to 300 daily[f]	2.65 to 7.94	138 to 430
Paroxetine (generic)	20 30	Tablet	0.3250 0.3453	20 to 50 daily	2.28 to 4.69	119 to 245
Sertraline (generic)[d]	25 50 100	Capsule	0.1516 0.3032 0.3303	50 to 200 daily	2.12 to 4.62	111 to 241
Vortioxetine (Trintellix)	5 10 20	Tablet	2.8148 2.9484 3.2011	10 to 20 daily	20.64 to 22.41	1,077 to 1,169
Norepinephrine -dopamine reuptake inhibitor						
Bupropion (generic)	100 150	SR capsule	0.1547 0.2298	100 to 150 daily	1.08 to 1.61	57 to 84
	150 300	ER capsule	0.1463 0.2927	150 to 300 daily	1.02 to 2.05	53 to 107
Alpha-2 adrenergic agonist						
Mirtazapine (generic)[d]	15 30 45	OD tablet	0.0975 0.1950 0.2925	15 to 45 daily	0.68 to 2.05	36 to 107
	15 30 45	Tablet	0.0975[g] 0.3100 0.2925[g]			

DR = delayed release; ER = extended release; NMDA = N-methyl-D-aspartate; OD = orally disintegrating; SNRI = serotonin-norepinephrine reuptake inhibitor; SR = sustained release; SSRI = selective serotonin reuptake inhibitor.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed February 2020) unless otherwise indicated and do not include dispensing fees.[11] Annual costs are based on 365 days per year.

[a] Sponsor-submitted price.

[b] BC PharmaCare Formulary (February 2020). Prices for 10 mg/mL vials ($1.7770) and 50 mg/mL vials ($5.6133) were reduced based on the 8% markup for non-high drugs (daily cost less than $40.00).[28]

[c] Dosing based on the mean baseline patient weight of 81.61 kg from the SUSTAIN-1 study and dose frequency based on clinical expert feedback. The current dosing is reflective of treatment in the acute phase, with reductions in dose (once weekly or once every 2 weeks) as part of maintenance.

[d] Indicated for "depressive illness."

[e] Alberta Formulary (February 2020).[29]

[f] According to the fluvoxamine product monograph, dosages above 150 mg should be divided so a maximum of 150 mg is given as the bedtime dose.[30]

[g] Saskatchewan Formulary (February 2020).[31]

Table 9: CADTH Cost Comparison Table for Treatment-Resistant Major Depressive Disorder – Second-Line or Third-Line Treatment

Drug/comparator	Strength (mg)	Dosage form	Price ($)	Recommended dose (mg)	Average weekly drug cost ($)	Average annual drug cost ($)
SNRIs (second line)						
Levomilnacipran (Fetzima)	20 40 80 120	ER capsule	3.7007[a] 3.8400[a] 4.0947[a] 4.3720[a]	40 to 120 daily	26.88 to 30.60	1,401 to 1,596
Serotonin reuptake inhibitors (second line)						
Trazodone (generic)[b]	50 100 150	Tablet	0.0554 0.0989 0.1453	150 to 300 daily	1.02 to 2.03	61 to 106
Vilazodone (Viibryd)	10 20 40	FC tab IR tab IR tab	3.1257[a] 3.1257[a] 4.1603[a]	20 to 40 daily	21.88 to 29.12	1,141 to 1,519
Reversible MAO-A inhibitor (second line)						
Moclobemide (generic)[b]	100 150 300	Tablet	0.3400 0.5295 1.0399	300 to 600 daily	7.28 to 14.56	380 to 760
Tricyclic antidepressants (second line)						
Amitriptyline (generic)[b]	10 25 50 75	Tablet	0.0435 0.0829 0.1540 0.3634[c]	75 to 150 daily	2.54 to 3.23	91 to 169
Clomipramine (generic)[b]	10 25 50	Tablet	0.2949 0.4020 0.7401	25 to 200 daily	2.81 to 20.72	147 to 1,081
Desipramine (generic)[b]	10 25 50 75 100	Tablet	0.4056[d] 0.3880 0.6838 0.9093 0.9507[d]	100 to 300 daily	6.65 to 19.96	347 to 1,042

Drug/comparator	Strength (mg)	Dosage form	Price ($)	Recommended dose (mg)	Average weekly drug cost ($)	Average annual drug cost ($)
Doxepin (generic)[b]	10 25 50 75 100	Capsule	0.2397 0.2940 0.5455 0.8066 1.3438	100 to 150 daily	7.64 to 11.29	398 to 589
Imipramine (generic)[b]	10 25 50 75	Tablet	0.1397 0.2573 0.5021 0.6727[c]	25 to 200 daily	1.80 to 12.93	94 to 674
Nortriptyline (Aventyl)[b]	10 25	Capsule	0.2570 0.5193	75 to 100 daily	10.91 to 14.54	569 to 759
Trimipramine (generic)[b]	12.5 25 50 75 100	Tablet Tablet Tablet Capsule Tablet	0.2156 0.2960 0.5795 0.7800 0.9889	150 to 300 daily	10.98 to 20.77	572 to 1,083
Irreversible MAO inhibitor (third line)						
Phenelzine (Nardil)	15	Tablet	0.4667	45 to 90 daily	9.80 to 19.60	511 to 1,023
Tranylcypromine (Parnate)[b]	10	Tablet	0.4055	20 to 60 daily	5.68 to 17.03	296 to 889

ER = extended release; FC = film coated; IR = immediate release; MOA = monoamine oxidase; SNRI = serotonin-norepinephrine reuptake inhibitor.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed February 2020) unless otherwise indicated and do not include dispensing fees.[11] Annual costs are based on 365 days per year.

[a] National wholesale price from Delta PA (accessed February 2020).[32]

[b] Indicated for "depressive illness."

[c] Alberta Formulary (accessed February 2020).[29]

[d] Saskatchewan Formulary (accessed February 2020).[31]

Table 10: CADTH Cost Comparison Table for Treatment-Resistant Major Depressive Disorder – Adjunctive Treatment

Drug/comparator	Strength (mg)	Dosage form	Price ($)	Recommended dose (mg)	Average weekly drug cost ($)	Average annual drug cost ($)
First line						
Aripiprazole (generic)	2 5 10 15 20 30	Tablet	0.8092 0.9046 1.0754 1.2692 1.0017 1.0017	2 to 15 daily	5.66 to 8.88	296 to 464
Quetiapine (generic)[a]	50 150 200 300 400	IR tablet	0.2501 0.4926 0.6661 0.9776 1.3270	150 to 300 daily	3.45 to 6.84	180 to 357
Risperidone (generic)[a]	0.25 0.5 1 2 3 4	Tablet	0.1036 0.1735 0.2397 0.4795 0.7180 0.9574	1 to 3 daily	1.68 to 5.03	87 to 262
Second line						
Bupropion (generic)	100 150	SR capsule	0.1547 0.2298	100 to 150 daily	1.08 to 1.61	57 to 84
	150 300	ER capsule	0.1463 0.2927	150 to 300 daily	1.02 to 2.05	53 to 107
Liothyronine (Cytomel)[a]	5 mcg 25 mcg	Tablet	1.3632[b] 1.4818[b]	25 mcg to 50 mcg daily	10.37 to 20.75	541 to 1,082
Lithium carbonate (generic)[a]	150 300	Capsule	0.0667 0.0657	600 to 1,200 daily	0.92 to 1.84	48 to 96
Mirtazapine (generic)[a]	15 30 45	OD tablet	0.0975 0.1950 0.2925	15 to 45 daily	0.68 to 2.05	36 to 107
	15 30 45	Tablet	0.0975[c] 0.3100 0.2925[c]			

Drug/comparator	Strength (mg)	Dosage form	Price ($)	Recommended dose (mg)	Average weekly drug cost ($)	Average annual drug cost ($)
Modafinil (generic)[a]	100	Tablet	0.9293	100 to 400 daily	6.51 to 26.02	339 to 1,357
Olanzapine (generic)[a]	2.5 5 7.5 10 15	Tablet	0.1772 0.3544 0.5316 0.7088 1.0631	2.5 to 10	1.24 to 4.96	65 to 259
	5 10 15	OD tablet	0.3574 0.7143 1.0711		5.00	261
Third line (psychostimulants)						
Methylphenidate (generic)	18 27 36 54	IR tablet	0.5246 0.6055 0.6863 0.8479	18 to 54 daily[d]	3.67 to 5.94	191 to 309

CANMAT = Canadian Network for Mood and Anxiety Treatments; ER = extended release; IR = immediate release; OD = orally disintegrating; SR = sustained release.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed February 2020) unless otherwise indicated and do not include dispensing fees.[11] Annual costs are based on 365 days per year. Comparators were based on atypical antipsychotic drugs recommended as adjunctive agents for nonresponse or partial response to an antidepressant as listed in the CANMAT 2016 Guidelines.[8]

[a] Dosing from the CANMAT 2016 Guidelines.[8]

[b] Alberta Formulary (accessed February 2020).[29]

[c] Saskatchewan Formulary (accessed February 2020).[31]

[d] Dosing obtained from the study by Ravindran et al. (accessed 2008).[33]

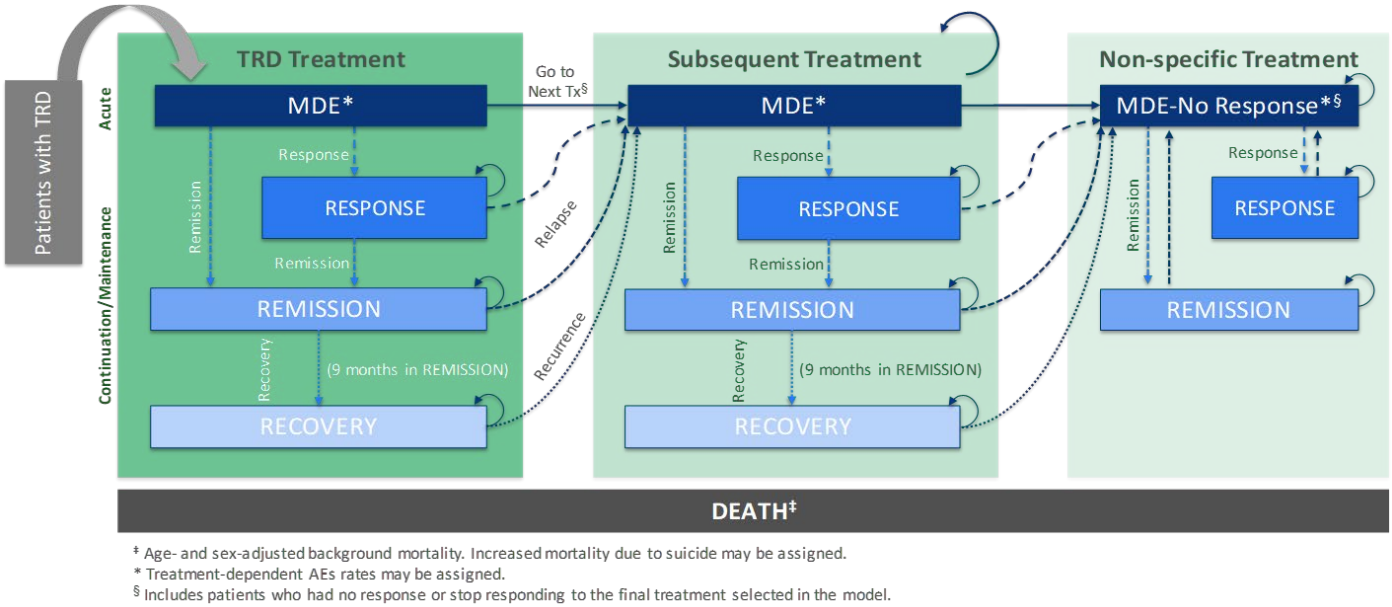
Appendix 2: Submission Quality

Table 11: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☐	☒	The clinical experts consulted by CADTH stated adjunctive treatments and IV ketamine would be considered relevant treatment comparators.
Model has been adequately programmed and has sufficient face validity	☒	☐	None.
Model structure is adequate for decision problem	☒	☐	None.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☒	☐	The use of 1,000 iterations was associated with minor variability in incremental costs. CADTH used 5,000 iterations in the base-case reanalyses. The sponsor also used a seeded random number generation model; however, the use of non-seeded values in the probabilistic analyses is preferred and was applied in the CADTH base-case reanalyses.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☒	☐	As per the CADTH Guidelines for the Economic Evaluation of Health Technologies,[34] discounting should be explored in scenario analyses which were not conducted by the sponsor.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough detail)	☒	☐	Probabilistic results disaggregated by health state and cost category are preferred.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Model Structure



‡ Age- and sex-adjusted background mortality. Increased mortality due to suicide may be assigned.
* Treatment-dependent AEs rates may be assigned.
§ Includes patients who had no response or stop responding to the final treatment selected in the model.

MDE = major depressive episode; TRD = treatment-resistant depression; Tx = treatment.

Source: Sponsor's pharmacoeconomic submission.[3]

Detailed Results of the Sponsor's Base Case

Table 12: Response and Remission Rates Adjusted According to the Number of Health Care Visits

Health state	Unadjusted	3 visits	4 visits	5 visits	6 visits	7 visits	8 visits
Remission	31%	21%	19%	18%	18%	18%	16%
Response	52%	45%	41%	36%	34%	31%	30%

Source: Sponsor's pharmacoeconomic submission.[3]

Table 13: Health State Utilities

Health state	Utility	SE	Source
MDE	[redacted]	[redacted]	TRANSFORM-2
Response	[redacted]	[redacted]	TRANSFORM-2
Remission	[redacted]	[redacted]	TRANSFORM-2
Recovery	[redacted]	[redacted]	Same as remission

MDE = major depressive episode; SE = standard error.

Note: Sponsor assumed recovery would be equal to remission.

Source: Sponsor's pharmacoeconomic submission.[3]

Table 14: Utility Decrements Due to Adverse Events

Adverse events	Utility decrement, estimate (SE)	Duration (weeks)	Source
Anxiety	–0.129 (0.03225)	0.14	Sullivan et al. (2004)[25]
Diarrhea	–0.044 (0.011)	0.14	Sullivan et al. (2004)[25]
Dizziness	–0.085 (0.02125)	0.14	Sullivan et al. (2004)[25]
Dry mouth	–0.010 (0.0025)	NR	Revicki and Wood (1998)[35]
Fatigue	–0.085 (0.02125)	0.14	Assumed same as dizziness
Feeling abnormal	–0.085 (0.02125)	0.14	Assumed same as dizziness
Feeling drunk	–0.085 (0.02125)	0.14	Assumed same as dizziness
Headache	–0.115 (0.02875)	0.14	Sullivan et al. (2004)[25]
Illusion	–0.085 (0.02125)	0.14	Assumed same as dizziness
Insomnia	–0.129 (0.02875)	0.14	Sullivan et al. (2004)[25]
Nausea	–0.065 (0.01625)	0.14	Sullivan et al. (2004)[25]
Somnolence	–0.085 (0.02125)	0.14	Sullivan et al. (2004)[25]
Throat irritation	–0.010 (0.0025)	0.14	Assumed same as dry mouth
Vertigo	–0.085 (0.02125)	0.14	Assumed same as dizziness
Vision blurred	–0.050 (0.02125)	0.14	Sullivan and Ghushchyan (2006)[24]
Vomiting	–0.065 (0.01625)	0.14	Assumed same as nausea

NR = not reported; SE = standard error.

Source: Adapted from sponsor's pharmacoeconomic submission.[3]

Table 15: Oral Antidepressant Market Share and Daily Dosage

Oral antidepressant	Market share (%)	Daily dosage (mg)
Duloxetine	[redacted]	120
Escitalopram	[redacted]	20
Sertraline	[redacted]	200
Venlafaxine	[redacted]	225
Paroxetine	[redacted]	50
Fluoxetine	[redacted]	80
Citalopram	[redacted]	60
Desvenlafaxine	[redacted]	50

Source: Adapted from sponsor's pharmacoeconomic submission.[3]

Table 16: Average Number of Esketamine Doses

Phase	Number of sessions (per week)	Number of devices (per week)	Average dose (mg per week)
Acute	[redacted]	[redacted]	[redacted]
Optimization	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]
Recovery	[redacted]	[redacted]	[redacted]

Source: Adapted from sponsor's pharmacoeconomic submission.[3]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Detailed Results of CADTH Base Case

Table 17: Disaggregated Summary of CADTH's Results (Deterministic)

Parameter	Esketamine plus oral AD	Oral AD	Incremental
Total	4.763	4.755	0.008
MDE	3.231	3.797	–0.566
Response	0.259	0.307	–0.048
Remission	0.530	0.406	0.124
Recovery	0.743	0.245	0.498
Discounted QALYs			
Total	3.027	2.800	0.227
MDE	1.667	1.959	–0.292
Response	0.216	0.256	–0.040
Remission	0.476	0.364	0.112
Recovery	0.667	0.220	0.447
AE	0.000	0.000	0.000
Discounted costs ($)			
Total	78,387	49, 363	28,959
Drug acquisition	31,701	1,315	30,316
Drug administration/monitoring	1,600	0	1,596
Medical costs	44,969	48,010	–3,031
AEs	117	38	78
ICER ($/QALY)	127,942		

AD = antidepressant; AE = adverse event; ICER = incremental cost-effectiveness ratio; MDE: major depressive episode; QALY = quality-adjusted life-year.

Note: Due to limitations of the sponsor's model, disaggregated results are presented deterministically. Results were generally aligned with the probabilistic results.

Scenario Analyses

Table 18: CADTH Scenario Analyses

Scenario	CADTH base case	CADTH scenario
Scenario analyses		
1. Treatment discontinuation after 2 years	0%	5% annually (10% after 2 years)
2. Treatment discontinuation upon achieving recovery	0%	10.77%
3. Recovery recurrence rate	Esketamine plus oral AD: [redacted] Oral AD alone: [redacted]	Esketamine plus oral AD: [redacted] Oral AD alone: [redacted]
4. Time horizon	5 years	1, 3, and 20 years
5. Health state medical costs	Specific medical costs for each health state	Equal medical costs for each health state
6. Number of treatment sessions and devices per session	Sessions 1. Acute: [redacted] 2. Maintenance (week 5 to week 8): [redacted] 3. Maintenance (week 9 to week 40): [redacted] 4. Maintenance (recovery): [redacted] Number of devices per session 1. Acute: [redacted] 2. Maintenance (week 5 to week 8): [redacted] 3. Maintenance (week 9 to week 40): [redacted] 4. Maintenance (recovery): [redacted]	Scenario 1 (increased sessions) 1. Acute: 2 2. Maintenance (week 5 to week 8): 1 3. Maintenance (week 9 to week 40): 1 4. Maintenance (recovery): 1 Scenario 2 (increased devices) 1. Acute: 3 2. Maintenance (week 5 to week 8): 3 3. Maintenance (week 9 to week 40): 3 4. Maintenance (recovery): 3 Scenario 3 (both increased sessions and devices)
7. AE utility decrements	Excluded for blood pressure increase, delusional perception, derealization, dissociation, dizziness, dysgeusia, hypoesthesia, nasal discomfort, and paresthesia	Included for blood pressure increase, delusional perception, derealization, dissociation, dizziness, dysgeusia, hypoesthesia, nasal discomfort, and paresthesia
8. Mortality	Suicide-related mortality included	Suicide-related mortality excluded

AD = antidepressant; AE = adverse event.

Table 19: CADTH Scenario Analyses Results

Drug	Total costs ($)	Total QALYs	ICER vs. oral AD ($/QALY)
Treatment discontinuation after 2 years – 5% annually			
Oral AD	49,144	2.818	—
Esketamine plus oral AD	78,025	3.064	117,556
Treatment discontinuation upon recovery – 10.77%			
Oral AD	49,124	2.818	—
Esketamine plus oral AD	77,787	3.058	119,472
Differential recovery recurrence rate			
Oral AD	49,537	2.798	—
Esketamine plus oral AD	80,054	3.064	114,885
Time horizon – 1 year			
Oral AD	9,897	0.987	—
Esketamine plus oral AD	25,685	0.688	208,949
Time horizon – 3 years			
Oral AD	29,753	1.739	—
Esketamine plus oral AD	55,293	1.923	138,596
Time horizon – 20 years			
Oral AD	174,021	9.651	—
Esketamine plus oral AD	216,041	10.030	110,942
Equal medical costs by health state			
Oral AD	53,243	2.817	—
Esketamine plus oral AD	87,151	3.059	140,200
Increased number of sessions (scenario 1)			
Oral AD	49,045	2.818	—
Esketamine plus oral AD	92,792	3.063	178,776
Increased number of devices per session (scenario 2)			
Oral AD	49,082	2.817	—
Esketamine plus oral AD	85,501	3.062	148,714
Increased number of sessions and devices per session (scenario 3)			
Oral AD	49,167	2.817	—
Esketamine plus oral AD	100,132	3.061	208,999
AE utility decrements included			
Oral AD	49,023	2.819	—
Esketamine plus oral AD	80,099	3.065	126,414
Suicide mortality excluded			
Oral AD	49,584	2.843	—
Esketamine plus oral AD	80,449	3.081	129,625

AD = antidepressant; AE = adverse event; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Exploratory Analyses

Table 20: CADTH Exploratory Analyses

Analysis	CADTH base case	CADTH scenario
1. Included comparators	Oral AD only	Oral AD and IV ketamine
2. Subsequent treatment with esketamine – treatment efficacy unaffected by line of treatment	Esketamine subsequent treatment excluded	Remission: [redacted] Response: [redacted] Response to remission: [redacted] Relapse: [redacted] Loss of response: [redacted] Recurrence: [redacted]
3. Subsequent treatment with esketamine – treatment efficacy as per step 3 of the STAR*D study	Esketamine subsequent treatment excluded	Remission: [redacted] Response: [redacted] Response to remission: [redacted] Relapse: [redacted] Loss of response: [redacted] Recurrence: [redacted]

AD = antidepressant.

Note: CADTH assumed the costs associated with esketamine for subsequent treatment (i.e., number of sessions and devices per session) remained unchanged from the initial treatment for treatment-resistant major depressive disorder.

Table 21: CADTH Exploratory Analyses Results

Drug	Total costs ($)	Total QALYs	ICER vs. oral AD ($/QALY)
Inclusion of IV ketamine			
Oral AD	49,105	2.816	—
Esketamine plus oral AD	79,969	3.059	Dominated by IV ketamine
IV ketamine	52,631	3.081	13,306
Esketamine subsequent treatment – initial TRD efficacy			
Oral AD	48,039	2.906	—
Esketamine plus oral AD	106,534	3.444	108,754
Esketamine subsequent treatment – subsequent TRD efficacy			
Oral AD	47,983	2.905	—
Esketamine plus oral AD	85,680	3.138	161,611

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

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