Cost-effectiveness of esketamine nasal spray for patients with treatment-resistant depression in the United States

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Abstract

Objective: The aim of this study was to estimate the cost-effectiveness of esketamine, a novel intranasally-dosed antidepressant, for patients in the United States with treatment-resistant depression.

Methods: A decision-analytic model, parameterized with efficacy data from phase III randomized trials of esketamine, was used to simulate the effects of treatment with esketamine versus oral antidepressants over a 5-year horizon, from both societal and healthcare sector perspectives. Outcomes included remission and response of depression, quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness ratios (ICERs) for esketamine. In addition, value-based prices were calculated, defined as the per-dose price at which esketamine would become cost-effective given cost-effectiveness thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY. Uncertainty in these outcomes was assessed using probabilistic sensitivity analyses. Key model parameters included the efficacy of esketamine versus oral antidepressants (relative risk 1.39 for remission, 1.32 for response) and the monthly cost of esketamine ($5,572 for month 1, $1,699–2,244 thereafter).

Results: Over 5 years, esketamine was projected to increase time in remission from 25.3% to 31.1% of life-years, resulting in a gain of 0.07 QALYs. Esketamine increased societal costs by $16,617 and healthcare sector costs by $16,995. Base case ICERs were $237,111/QALY (societal) and $242,496/QALY (healthcare sector). In probabilistic sensitivity analysis, there was >95% likelihood that esketamine's ICER would be above $150,000/QALY. At a cost-effectiveness

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threshold of \$150,000/QALY, esketamine's value-based price was approximately \$140/dose (versus a current price of \$240/dose).

Conclusions: Esketamine is unlikely to be cost-effective for management of treatment-resistant depression in the United States unless its price falls by more than 40%.

INTRODUCTION

Esketamine is an intranasally-dosed antidepressant that was approved by the Food and Drug Administration (FDA) in March 2019 for use in treatment-resistant major depressive disorder (1). Its approval has sparked intense interest for several reasons.

First, esketamine has a novel mechanism of action (NMDA receptor antagonism) as compared with prior antidepressants (monoamine neurotransmitter modulation) (2). Second, esketamine's rapid onset of effect has raised the potential for novel applications such as acute reduction of suicidality in emergency settings (3). Third, and the reason for its FDA approval, esketamine has demonstrated efficacy in patients with treatment-resistant depression (4) – that is, patients for whom 2 or more prior treatments have failed (5). Patients with treatment-resistant depression experience markedly reduced quality of life and increased healthcare costs (6) and have remission rates with further antidepressants as low as 10–15% (7). As a novel treatment option with demonstrated efficacy in this subpopulation, esketamine could thus have immense individual and societal benefits.

However, esketamine has drawbacks that may limit its use. Most notably, the FDA requires that patients be observed in a healthcare setting for 2 hours after each dose to monitor for dissociation and hypertension (1). Even without considering the costs of this monitoring, esketamine is substantially more expensive than other antidepressants. The first 2 months of esketamine treatment have been estimated to cost \$7,000–11,000 (8); in contrast, a recent assessment of national price databases revealed that commonly-used oral antidepressants cost <\$100 per year (9, 10). Amidst ongoing efforts to control the growth of healthcare spending in the United States (US), it's critical to ensure that such an expensive treatment provides a good health-economic value (11, 12).

To address this issue, we used a previously-developed decision-analytic model (13) integrating data from 4 recently-published phase III clinical trials (4, 14) to assess the value of esketamine. Our analysis has two main objectives: 1) to quantify the cost-effectiveness of esketamine nasal spray compared to usual care for patients with treatment-resistant depression in the US, and 2) to determine drug price thresholds at which esketamine would be considered cost-effective by commonly-applied criteria in the US.

METHODS

Overview

We used a decision-analytic model, parameterized with data from phase III clinical trials of esketamine, to simulate the clinical and economic consequences of the following two treatment strategies for adults with major depressive disorder who have failed two prior antidepressants: 1) *Esketamine*: initial treatment with esketamine nasal spray plus oral

antidepressants, followed by additional antidepressants and/or psychotherapy if depressive symptoms do not respond; 2) *Usual care*: initial treatment with oral antidepressants, followed by additional antidepressants and/or psychotherapy if depressive symptoms do not respond.

Over a five-year time horizon, we projected symptomatic outcomes, quality-adjusted life-years (QALYs), and costs, in 2015 United States dollars (USD), under each strategy. We chose this time horizon to ensure adequate time for longer-term costs and benefits to accrue without requiring excess extrapolation beyond available outcomes data (4, 15, 16); we varied the time horizon between 2 and 10 years in sensitivity analysis. Future costs and QALYs were discounted at an annual rate of 3% (17). We evaluated costs from both the healthcare sector perspective (incorporating those costs accrued within the medical system) and the societal perspective (including additional costs such as productivity losses, patient time, etc.) (table in online supplement) (17).

Using these outcomes, we calculated the incremental cost-effectiveness ratio (ICER) of esketamine as the ratio of its incremental cost to its incremental QALYs relative to usual care; a lower ICER indicates a better health-economic value. In the US, ICER thresholds between $50,000/QALY and $150,000/QALY have been advocated for designating health interventions as "cost-effective" (18, 19). To reflect this range of recommendations, we report results for distinct cost-effectiveness thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY. For each threshold, we calculated the value-based price of esketamine, defined as the per-dose price at which its ICER is equal to the threshold (20); this value represents the highest price at which esketamine would be deemed cost-effective for a given cost-effectiveness threshold.

In reporting our methodology and findings, we adhere to the 2013 Consolidated Health Economic Evaluation Reporting Standards guidelines (21). As this study used published literature without identifiable data, it was exempt from institutional review board regulation. The study was conducted between March 2019 and December 2019.

Model description

To simulate the effects of esketamine, we used a previously-developed state-transition model of depression treatment (10, 13). The model uses a 1-month cycle length. The model is implemented in Microsoft Excel; statistical analyses were performed OpenMetaAnalyst (22).

Patients enter the model upon initiation of 3rd-line antidepressant treatment and can progress through up to 9 total treatment lines (figure in online supplement). With the exception of esketamine, these treatment lines do not simulate specific medications, psychotherapy, or other treatments; they are instead intended to capture the aggregate costs and effectiveness of the range of therapies provided to patients with treatment-resistant depression (7, 9).

Each treatment line is modeled using the following 5 health states: 1) *Initiation*: the first month on a new treatment; 2) *Remission*: near-complete resolution of depressive symptoms, as determined by a validated symptom rating scale (e.g. Quick Inventory of Depressive

Symptomatology   5) (7); 3) *Response*: partial resolution of depressive symptoms, defined as
 50% reduction in score on a validated symptom rating scale (7, 14); 4) *Non-response*:
initial failure to achieve response or remission; 5) *Relapse*: recurrence of depressive
symptoms after initial response or remission.

Patients start each new treatment in the *initiation* state and then transition to *remission*,
response, or *non-response* in the next cycle based on efficacy estimates for that treatment.
Patients in *remission* and *response* are then subject to a monthly probability of relapse.
Patients in *relapse* or *non-response* will transition to *initiation* of the following treatment line
during the next cycle. Note that patients who never respond to a given treatment will receive
it for 8 weeks (1 month in *initiation*, 1 month in *non-response*), consistent with
recommendations for the duration of an adequate antidepressant trial (23, 24).

Finally, patients in all states are subject to a monthly all-cause mortality probability; for
simplicity, this probability is not shown in the model diagram (online supplement).

Model input data

Base case model input data, uncertainty analysis ranges, and sources are shown in Table 1.
Where possible, input data reflect US adults with treatment-resistant, nonpsychotic major
depressive disorder.

Demographics and mortality—Based on demographic data from an insurance claims
analysis of patients with treatment-resistant depression, we simulated a population with
mean age 40.5 years (SD 13.2), 64.2% female (25). We applied age/gender-specific
mortality rates from the 2013 US life tables (26), along with a mortality hazard ratio of 1.58
(95% CI 1.47–1.70) for people with depression versus the general population (27); this
yielded an overall annual mortality probability of 0.0040.

Esketamine efficacy—We based our estimates of esketamine's efficacy on the results of
4 phase III clinical trials which are presented in the FDA Advisory Committee briefing
document for esketamine (4).

In three short-term trials (TRANSFORM-1, TRANSFORM-2, and TRANSFORM-3),
patients with major depressive disorder who had failed two or more prior treatment lines
were randomized to esketamine nasal spray versus placebo; in addition, all patients received
a new oral antidepressant. TRANSFORM-1 and TRANSFORM-2 included patients aged
18–64; TRANSFORM-3 included patients aged   65. We performed random effects,
restricted maximum likelihood meta-analyses on four-week intention-to-treat remission and
response rates from these trials (figures in online supplement). Of 421 total patients
randomized to esketamine, 142 (33.7%) achieved remission and 199 (47.3%) achieved
response; of 289 randomized to placebo, 68 (23.5%) achieved remission and 102 (35.3%)
achieved response. Estimated relative risks for esketamine versus placebo were 1.39 (95%
CI 1.09–1.79) for remission and 1.32 (95% CI 1.10–1.58) for response.

In the long-term SUSTAIN-1 trial, patients who achieved initial remission or response on
esketamine were randomized to continuation of esketamine versus replacement with placebo

(4). During follow-up extending up to 89 weeks, relapse hazard ratios for esketamine versus placebo were 0.49 (95% CI 0.29–0.84) for patients in remission at randomization and 0.30 (95% CI 0.16–0.55) for patients in response. These results indicate that continuation of esketamine reduces relapse risk compared to withdrawal of esketamine among patients who initially responded to it; they do not indicate that patients who respond to esketamine have a lower relapse risk than patients who respond to oral antidepressants. Because of this, in the base case of our analysis we assumed equal relapse rates for esketamine and oral antidepressants; we varied this assumption in sensitivity analysis.

Usual care efficacy—Estimated rates of remission (30.6–13.0%) and response (28.5–16.3%) across multiple treatment lines under usual care were drawn from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (7). STAR*D was a pragmatic randomized trial in which outpatients with major depressive disorder were followed across four treatment "steps". Specific treatments included citalopram, bupropion, cognitive therapy, lithium augmentation, and others. Notably, remission and response rates in the first step of STAR*D (36.8% and 48.6%) were lower than observed in multiple meta-analyses of antidepressant efficacy (28, 29), possibly due to prior treatment experience among STAR*D participants; for this reason, we derived our estimates of 3rd-line treatment efficacy from step 2 of STAR*D.

Monthly relapse probabilities (5.1–17.8%) were derived from the long-term follow-up phase of STAR*D (7). Observed relapse rates were higher for patients in response than in remission, and for patients who had received more prior treatments.

Utility—Utility values for our model's depression health states were derived from a French study which used the Euro-Qol-5D questionnaire to assess quality of life among outpatients treated for major depressive disorder; utility estimates for remission, response, and non-response were 0.85, 0.72, and 0.58 (30).

Costs—Cost estimates are expressed in 2015 USD. We used the Medical Care Expenditure index from the Bureau of Labor Services to inflate costs from earlier years to 2015 (the most recent year for which this index is available) (31, 32). We deflated later costs to 2015 using the Personal Consumption Expenditure index from the Federal Reserve (33).

We derived estimates of the aggregate cost of depression treatment (including medications and outpatient, inpatient, and emergency department services) from a claims-based analysis of privately-insured patients with major depressive disorder in the US (25). Annual costs ranged from $12,047 to $18,667 for patients with 2 to 6+ prior treatments.

Our estimate of the total cost of esketamine provision includes costs of the medication itself, physician visits, and medical assistant observation during the two hours after each dose. We used a cost per 28 mg of esketamine of $240, drawn from the Veterans Affairs Federal Supply Schedule (34); of note, this database tends to provide a lower-bound estimate for a medication's cost (35). Per manufacturer recommendations, esketamine is given twice weekly for the first 4 weeks and weekly or every other week thereafter; the initial dose is 56 mg, with subsequent doses either 56 mg or 84 mg (4). We used observed dose and dose-

frequency data from the TRANSFORM-2 and SUSTAIN-1 trials (4) to estimate the number of doses patients would receive in the first month and subsequent months, depending on depression health state (table in online supplement); multiplying by the above unit cost yielded monthly medication costs ranging from $5,572 for month 1 to $1,699 for patients in remission after month 1.

We assumed that patients would see a physician at each presentation for esketamine dosing; we used a cost of $71 per visit, based on reimbursement from the 2019 Centers for Medicare and Medicaid Services Physician Fee Schedule for a 15-minute office visit (CPT code 99213) (36). Finally, we assumed a medical assistant would supervise 4 patients per 2-hour dosing/monitoring period, resulting in a per-patient cost of $8 for 30 minutes of medical assistant time (37).

When performing analyses from the societal perspective, we included additional non-medical costs. We used severity-dependent productivity losses of 8.4 hours/week, 4.2 hours/week, and 1.5 hours/week for patients in the non-response, response, and remission states, derived from a national survey-based study of American workers with depression (38). We applied a cost of $26/hour to these productivity losses, based on average hourly earnings in the US (39). Finally, we assumed each esketamine dose would require 3 hours of patient time (including dosing, monitoring, and travel) with a cost of $26/hour (39).

Uncertainty and sensitivity analyses

We performed several types of sensitivity analysis to quantify the impact of modeling assumptions and uncertainty in model input parameters on our results.

In one-way sensitivity analyses, we varied the values of individual model parameters (or groups of parameters) and assessed their effect on our results. All parameters in Table 1 were included in one-way sensitivity analyses except for discount rate, relapse rate with esketamine, and esketamine costs, which were assessed in separate sensitivity analyses.

In probabilistic sensitivity analyses, the model was run using parameter values drawn at random from distributions reflecting their uncertainty (Table 1). Model results were compiled across 10,000 repetitions of this process in order to quantify the aggregate uncertainty in results attributable to joint uncertainty in the model's input parameters.

Finally, in scenario sensitivity analyses, we assessed the effects of specific alternative modeling assumptions on our results. Scenarios included: excluding TRANSFORM-3 from our meta-analysis of esketamine efficacy due to the older patient population in this trial (figures in online supplement) (4); incorporating improved relapse rates with esketamine versus usual care, based on SUSTAIN-1, which reported relapse hazard ratios of 0.49 (remitters) and 0.30 (responders) (4); providing esketamine as 4th-line or 5th-line treatment, rather than 3rd-line; providing electroconvulsive therapy after failure of 3rd-line treatment (electroconvulsive therapy efficacy parameters were 50.9% remission, 66.6% response, and 3.0% relapse per month; monthly costs were $5,077 for the first month and $846 thereafter (13)); eliminating costs of physician visits, medical assistant time, and patient time from the total cost of esketamine to assess the effect of relaxing monitoring requirements.

RESULTS

Model validation

To assess the external validity of our model, we compared model output to independent estimates from the literature. We identified two relevant validation targets for clinical outcomes. In a treatment-resistant depression cohort in the United Kingdom followed prospectively for 8–84 months (mean 39 months), patients spent an average of 39.9% of time with uncontrolled symptoms (i.e. not in remission or response) (16); in contrast, in a US treatment-resistant depression cohort followed for 24 months, patients spent 87.8% of time with uncontrolled symptoms (15). Over 32 months of usual care, our model projected that patients spend 61.7% of time with uncontrolled symptoms.

Regarding economic outcomes, a 2018 systematic review identified 7 US-based studies on the costs of treatment-resistant depression; annual healthcare costs ranged from $12,000–19,000 (6). For comparison, over 24 months of usual care (the most common follow-up duration in the included studies), our model projected an annual healthcare cost of $15,949.

Five-year health and economic outcomes

Base case results are shown in Table 2. Over 5 years, esketamine was projected to increase the fraction of time patients are in remission from 25.3% to 31.1%; this translated to a gain of 0.07 QALYs. Total costs were projected to increase by $16,617 from the societal perspective and $16,995 from the healthcare sector perspective. This cost increase was driven largely by the cost of esketamine itself ($16,352), with smaller contributions from physician/medical assistant service costs ($2,062) and patient time costs ($2,074). Other healthcare costs and lost productivity costs both declined with esketamine.

Esketamine was not cost-effective under either perspective, with projected ICERs of $237,111/QALY (societal) and $242,496/QALY (healthcare sector).

Uncertainty and sensitivity analyses

In one-way sensitivity analyses, esketamine's ICER did not fall below $150,000/QALY with variation in any individual parameter (figure in online supplement). The lowest ICER attained with any parameter variation was $182,770/QALY (societal perspective), when applying the 95% CI upper limit estimates of relative risk of remission and response with esketamine versus usual care.

In probabilistic sensitivity analyses, the probability that esketamine is cost-effective was <0.01 at cost-effectiveness thresholds of $50,000/QALY and $100,000/QALY, regardless of perspective. At a threshold of $150,000/QALY, the probability that esketamine is cost-effective was 0.042 under a societal perspective and 0.021 under a healthcare sector perspective.

Value-based price estimates, along with confidence intervals based on probabilistic sensitivity analyses, are shown in Figure 1. To be cost-effective at a threshold of $150,000/QALY from the societal perspective, the per-dose price of esketamine would need to fall from its current value of $240 to a price of $144 or below (95% CI $24–253). From the

healthcare sector perspective, the per-dose price of esketamine would need to fall to $141 or below (95% CI $42–237).

In scenario sensitivity analyses (Figure 2), esketamine required price reductions to become cost-effective under all scenarios except one. At a cost-effectiveness threshold of $150,000/ QALY from the societal perspective, esketamine's value-based price was $244 when we simulated 50–70% reductions in relapse rate with esketamine versus usual care.

DISCUSSION

In this decision-analytic modeling analysis incorporating recently-released phase III clinical trial data (4), we found that esketamine nasal spray is unlikely to be a cost-effective treatment for patients with treatment-resistant depression in the United States at a cost of ~ $240 per dose. Our model projected base case ICERs of $237,111/QALY (societal perspective) and $242,496/QALY (healthcare sector perspective) for esketamine compared to usual care. In uncertainty analysis, we found a >95% likelihood that esketamine's ICER would fall above $150,000/QALY, a commonly applied upper bound for defining cost-effective medical interventions in the United States (18). To become cost-effective, we estimated that esketamine would require a price reduction of >40% from its current price of ~$240 per 28 mg dose (to ~$140 or less per dose) (34).

Our results were consistent across a wide range of deterministic and probabilistic sensitivity analyses. Of note, we did identify a single scenario under which esketamine's ICER was below $150,000/QALY: when we assumed 50–70% reductions in depression relapse rate with esketamine versus usual care. However, as described in our Methods section, this assumption represents an inappropriate application of findings from the SUSTAIN-1 trial (4) and was included only as an exploratory analysis. Under all other sensitivity analyses, including optimistic assumptions about esketamine's cost and efficacy, we found that esketamine cannot be considered cost-effective.

Two prior studies have evaluated the cost-effectiveness of esketamine. An evidence report released by the Institute for Clinical and Economic Review estimated esketamine's ICER to be $198,000/QALY (40), consistent with our finding that esketamine is unlikely to be cost-effective. In contrast, an industry-supported conference abstract reported an ICER below $100,000/QALY – a more precise value was not provided in the abstract (41).

From a health policy perspective, esketamine's current status – as a clinically effective medication that is priced well above its value-based price – is far from unique (11). For example, in a recent assessment of the 50 drugs accounting for the greatest New York state Medicaid spending, 5 had value-based price estimates; of these, 2 were priced at or below their value-based price, and the remaining 3 required discounts of up to 54% to reach their value-based price (12). Still, targeted efforts by payers and policymakers can be effective in reducing prices, even for drugs with market exclusivity. In the recent case of evolocumab and alirocumab, two novel lipid-lowering agents approved by the FDA in 2015 and initially priced at ~$14,000/year, insurers' efforts at limiting access via restrictive prior authorizations and copayment garnered 60% reductions in the medications' prices by 2018

(42). Subsequent analyses showed that the medications now meet cost-effectiveness criteria (42, 43). However, these price reductions came at the expense of curtailing use of these medications: prior to the price reductions, <1% of eligible patients received prescriptions for these medications (44), and a third of patients abandoned their prescriptions when confronted with the copay amount (45). In the case of esketamine, we're hopeful that policymakers and insurers can use positive incentives and proactive negotiation to establish fair prices without making the drug inaccessible to patients with treatment-resistant depression who could benefit from it (11, 12, 46, 47).

For individual patients and providers, the cost of esketamine (in terms of out-of-pocket expenses, patient time, or costs to the healthcare system as a whole) is likely to be an important component of shared decision-making (48). Fortunately, there are multiple alternative options for treatment-resistant depression that have been shown to be cost-effective. Until esketamine's price falls, we would recommend considering electroconvulsive therapy (13), antipsychotic augmentation (49), or cognitive-behavioral therapy (50, 51).

Our results should be interpreted in the context of several limitations. It's important to recognize that the data used to simulate esketamine reflect samples of a few hundred clinical trial participants (4); longer-term observational data or additional randomized trials could refine our cost-effectiveness estimates. In light of these limitations in input data, our model employs a 5-year time horizon, which may fail to capture relevant longer-term health-economic consequences; reassuringly though, cost-effectiveness outcomes were robust to variation in time horizon. Next, there are several limitations to the data drawn from other sources. In instances where inadequate data were available from patients with treatment-resistant depression, we have derived model inputs from the overall population with major depressive disorder; this may result in underestimating the degree of occupational impairment and mortality in treatment-resistant individuals (52, 53). Our utility estimates for remission, response, and non-response were drawn from a French study and thus may be less applicable to the United States (30); reassuringly, though, these utility estimates are consistent with those obtained from an international meta-analysis (54). And our estimates of depression severity-dependent productivity losses are not disaggregated by gender, which may lead to some inaccuracy given the overrepresentation of women among people with major depressive disorder (25, 38). Finally, in the absence of comparative outcomes data, we were unable to directly assess esketamine's cost-effectiveness versus alternatives such as electroconvulsive therapy or transcranial magnetic stimulation; however, indirect comparison in scenario sensitivity analysis revealed that our findings were unchanged when electroconvulsive therapy was included as a comparator.

Conclusions

In this decision-analytic modeling analysis, we found that esketamine is unlikely to be cost-effective for management of treatment-resistant depression at its current price of $240 per dose. Esketamine could become cost-effective by US standards if its price were to fall to $140 or less per dose. Achieving these price reductions while ensuring continued access for the patients who stand to benefit from esketamine will require careful and concerted efforts from payers and policymakers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- On the basis of several phase III randomized controlled trials demonstrating its efficacy, esketamine nasal spray was recently approved by the United States Food and Drug Administration for management of treatment-resistant depression.

- Using data from these trials and a decision analytic model, the authors estimated a greater than 95% likelihood that intranasal esketamine would not be cost-effective by commonly applied United States standards.

- To become cost-effective, esketamine's price would need to fall to $140 or less per dose (a greater than 40% decline from its current price of approximately $240 per dose).
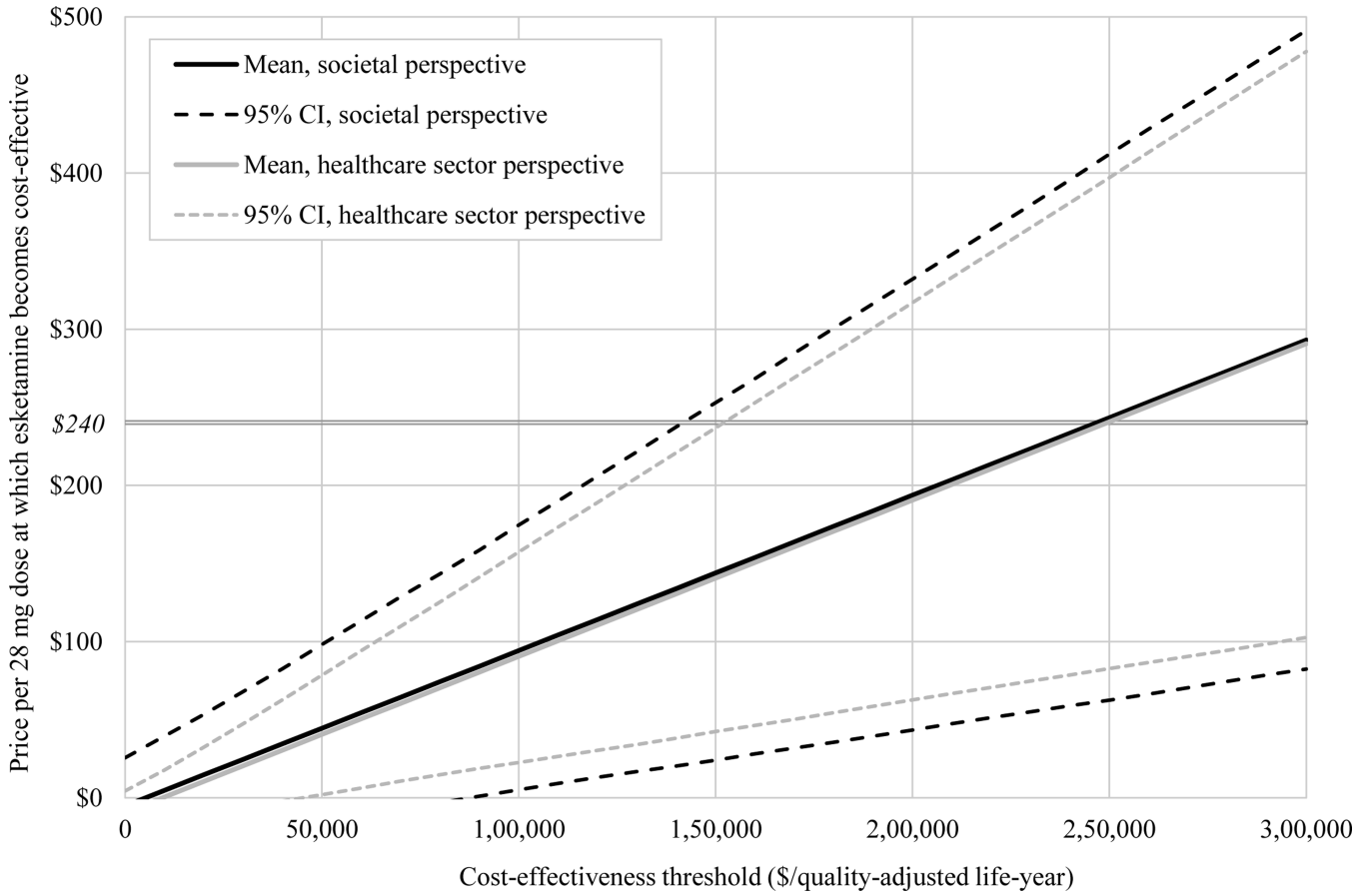
FIGURE 1. Value-based price estimates for esketamine[a]

[a]CI, confidence interval. The horizontal axis indicates the cost-effectiveness threshold used to classify an intervention as cost-effective or not. Plotted curves show the price per 28-mg dose at which esketamine would achieve an incremental cost-effectiveness ratio equal to the threshold (that is, the value-based price) along with confidence intervals estimated via probabilistic sensitivity analysis. The horizontal line indicates the current price per 28-mg dose of esketamine ($240).
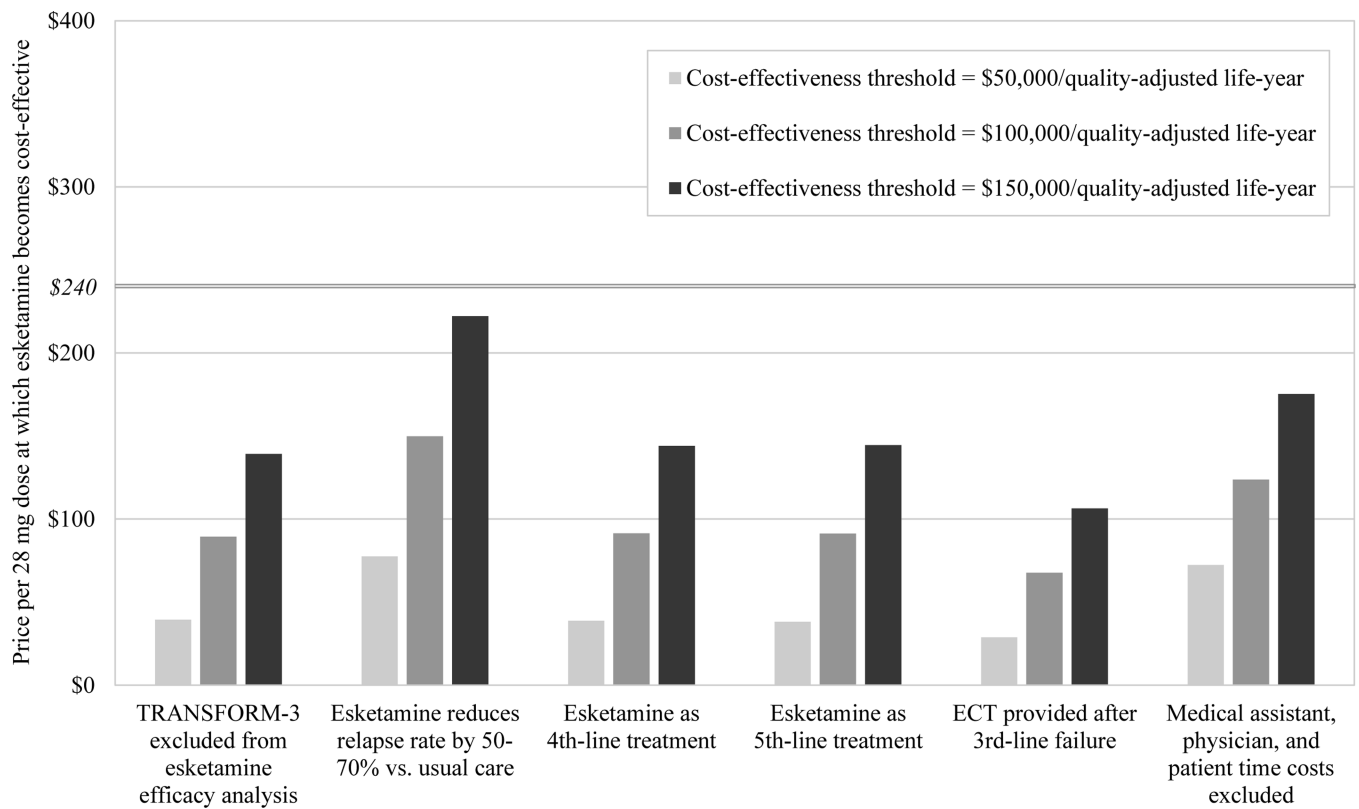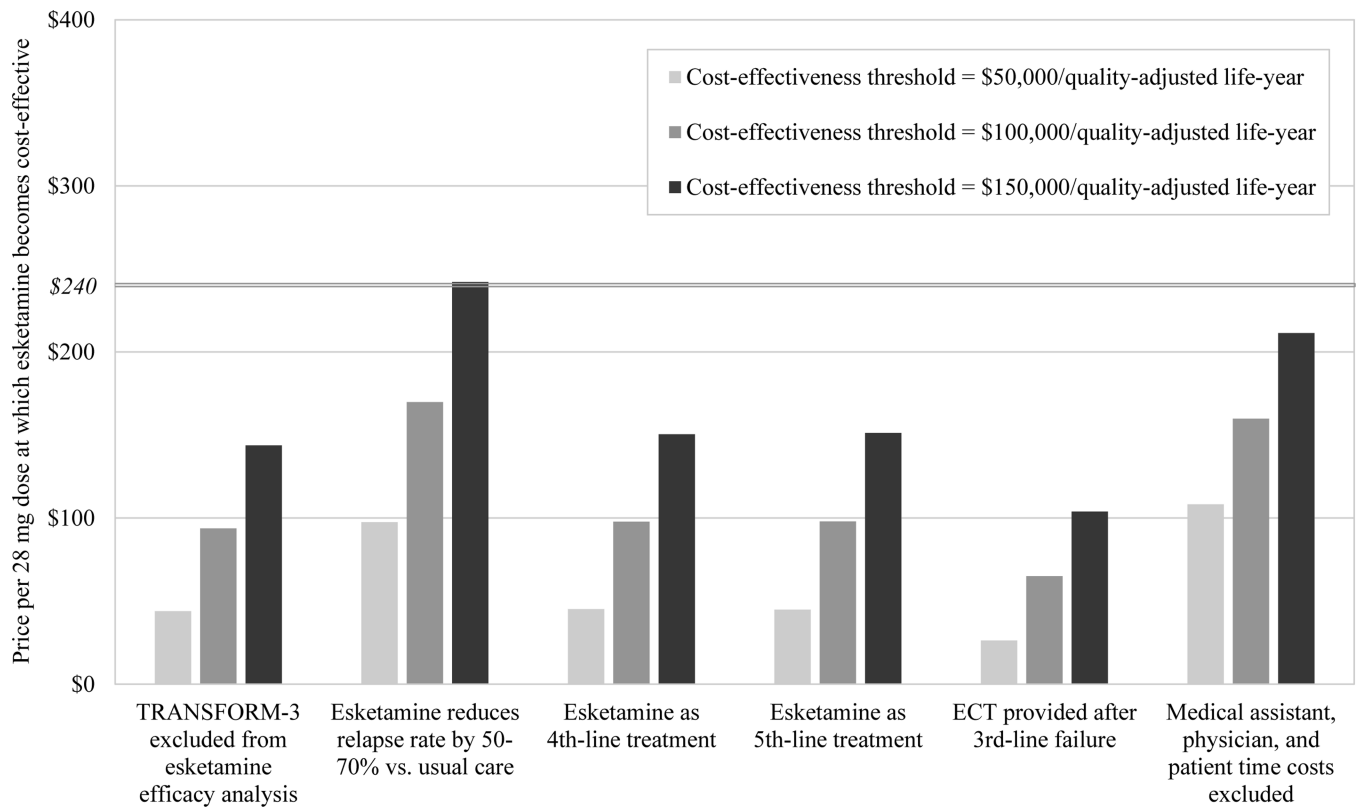
FIGURE 2. Scenario sensitivity analyses for the value-based price of esketamine, from (A) the societal perspective and (B) the health care sector perspective[a]

[a]ECT, electroconvulsive therapy. The vertical axis indicates the value-based price of esketamine, that is, the price per 28-mg dose below which esketamine would be deemed cost-effective at a given cost-effectiveness threshold. Bars indicate value-based prices at three alternative cost-effectiveness thresholds. For comparison, the horizontal line indicates the current price per 28-mg dose of esketamine ($240). The horizontal axis shows six scenarios simulated in sensitivity analysis, consisting of alternative modeling and input parameter assumptions related to treatment efficacy, treatment costs, and alternative treatments.

Table 1:

Model input data

Parameter	Base case value	Uncertainty analysis range	Distribution	Sources
General and demographic				
Annual discount rate, percent	3	–	–	17
Time horizon, years	5	2–10[a]	–	–
Annual mortality probability, percent	0.40	0.38–0.43	Normal	25–27
Esketamine efficacy relative to usual care				
Response, relative risk	1.32	1.10–1.58	Log-normal	4
Remission, relative risk	1.39	1.09–1.79	Log-normal	4
Relapse, hazard ratio	1	–	–	4
Usual care efficacy by treatment line				
Remission probability, percent				
Line 3	30.6	28.2–33.0	Beta	7
Line 4	13.7	10.4–17.2	Beta	7
Lines 5+	13.0	7.7–19.5	Beta	7
Response probability, percent				
Line 3	28.5	26.2–30.9	Beta	7
Line 4	16.8	13.4–20.8	Beta	7
Lines 5+	16.3	10.3–23.2	Beta	7
Monthly relapse probability, percent				
In remission, line 3	7.8	6.6–9.1	Beta	7
In remission, line 4	7.7	4.1–12.6	Beta	7
In remission, lines 5+	8.6	3.7–16.4	Beta	7
In response, line 3	13.6	11.4–16.1	Beta	7
In response, line 4	17.8	12.9–24.2	Beta	7
In response, lines 5+	17.3	11.0–27.4	Beta	7
Utility by health state				
Non-response/relapse/initiation	0.58	0.50–0.66	Normal	30
Response	0.72	0.65–0.79	Normal	30
Remission	0.85	0.83–0.87	Normal	30
Costs, 2015 USD				
Annual direct healthcare cost by treatment line				
Line 3	12,047	9,666–14,428	Normal	25
Line 4	14,699	11,441–17,957	Normal	25
Line 5	15,073	13,053–17,093	Normal	25
Line 6	16,699	13,939–19,459	Normal	25
Lines 7+	18,667	17,089–20,245	Normal	25
Annual lost productivity cost by health state				
Non-response/relapse/initiation	11,573	8,063–15,083	Normal	38, 39
Response	5,757	3,445–8,070	Normal	38, 39

Parameter	Base case value	Uncertainty analysis range	Distribution	Sources
Remission	2,067	1,338–2,796	Normal	38, 39
Monthly costs of esketamine treatment				
Medication costs				
Month 1	5,572	–	–	4, 34
Months 2+, response	2,244	–	–	4, 34
Months 2+, remission	1,699	–	–	4, 34
Months 2+, non-response/relapse	1,966	–	–	4, 34
Physician and medical assistant services				
Month 1	685	–	–	4, 36, 37
Months 2+, response	275	–	–	4, 36, 37
Months 2+, remission	218	–	–	4, 36, 37
Months 2+, non-response/relapse	246	–	–	4, 36, 37
Patient time				
Month 1	689	–	–	4, 39
Months 2+, response	276	–	–	4, 39
Months 2+, remission	219	–	–	4, 39
Months 2+, non-response/relapse	248	–	–	4, 39

USD, United States dollars

[a] Time horizon is varied between 2 years and 10 years in one-way sensitivity analyses but held constant at 5 years in probabilistic sensitivity analyses.

Table 2:

Base case results

	Usual care	Esketamine	*Difference*
Fraction of time spent in health state, percent			
Initiation/non-response/relapse	72.3	66.9	−5.4
Response	2.4	2.0	−0.4
Remission	25.3	31.1	5.7
Quality-adjusted life-years	3.00	3.07	0.07
Costs, 2015 USD			
Total cost, societal perspective	121,073	137,690	16,617
Total cost, healthcare sector perspective	79,786	96,781	16,995
Cost components			
Esketamine treatment costs			
Medication cost	–	16,352	16,352
Physician and medical assistant services	–	2,062	2,062
Patient time	–	2,074	2,074
Other healthcare costs	79,786	78,367	−1,419
Lost productivity costs	41,287	38,836	−2,451
Incremental cost-effectiveness ratios, $/QALY			
Societal perspective	–	–	237,111
Healthcare sector perspective	–	–	242,496

USD, United States dollars; QALY, quality-adjusted life-year