Research paper

Cost-effectiveness of esketamine nasal spray compared to intravenous ketamine for patients with treatment-resistant depression in the US utilizing clinical trial efficacy and real-world effectiveness estimates

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ABSTRACT

Objective: The aim of this study was to estimate the cost-effectiveness of esketamine nasal spray relative to intravenous ketamine for patients with treatment-resistant depression (TRD) in the US.
Methods: We used a Markov model with a 1-month cycle length, and we estimated quality-adjusted life years (QALYs), costs (2020 USD), and incremental cost-effectiveness ratios (ICER) of esketamine relative to ketamine over a 3-year time horizon, from both the healthcare sector and patient perspectives. We ran the model using efficacy estimates from both clinical trial and real-world effectiveness (RWE) data. One-way and probabilistic sensitivity analyses (PSAs) were performed to evaluate the robustness of findings.
Results: Over a 3-year time horizon, the use of esketamine yielded 1.98 QALYs (RWE/clinical trial efficacy), and the use of ketamine yielded 2.03 QALYs (clinical trial efficacy) or 1.99 QALYs (RWE). Esketamine was dominated by ketamine using the healthcare perspective. ICERs were above $150,000/QALY threshold with the patient perspective. Under the healthcare perspective, PSA showed there are no scenarios where esketamine was cost-effective compared to ketamine. With the patient's perspective, the probability that esketamine was cost-effective compared to ketamine was 0.0055 (clinical trial efficacy) and 0.35 (RWE).
Limitations: The data utilized for efficacy have limitations. The time horizon may fail to capture longer-term costs and benefits.
Conclusions: In this decision analytic model evaluating esketamine versus ketamine for TRD, we found esketamine unlikely to be cost-effective under a healthcare sector perspective. Under a patient perspective, esketamine had similar effectiveness and was less costly than ketamine due to insurance coverage.

1. Introduction

Major depressive disorder (MDD) is one of the most common mental health disorders in the United States (US) and is a major cause of disability (Hough, 2019). In 2017, an estimated 17.3 million adults (7.1 % of adults) in the US had at least one major depressive episode (NIMH, 2019). Furthermore, MDD carries a significant cost burden near $210.5 billion in the US, with 45 % attributable to direct costs, 50 % to workplace costs, and 5 % to suicide-related costs (Amos et al., 2018; Greenberg et al., 2015). Treatment-resistant depression (TRD) is broadly defined as failure to achieve response or remission to at least two antidepressant medications with adequate dosing and duration (Hough,

2019; Ionescu et al., 2015). TRD patients account for approximately one third of MDD patients, and this population disproportionally accounts for the burden of disease caused by depression with twice the hospitalization rate and a 7-fold increase in suicide rate (Amos et al., 2018; Hough, 2019; Ionescu et al., 2015; Rush et al., 2006).

Current pharmacotherapy strategies for TRD include switching antidepressants, combining antidepressants, second-generation antipsychotics, and augmentation with lithium (Luan et al., 2017; NIMH, 2019). However, TRD patients may be at imminent risk of suicidal ideation or suicide attempt, and most antidepressants take several weeks to begin aiding with symptom improvement (Hasin et al., 2018; Jakuszkowiak-Wojten et al., 2019; Kim et al., 2019). Non-pharmacological treatments

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for TRD include somatic therapies such as transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), and deep brain stimulation (DBS). However, these therapies have limited data on efficacy and long-term benefits, are time consuming and costly, and may have severe side effects such as amnesia (Agboola et al., 2020; Cusin and Dougherty, 2012; Hough, 2019). Consequently, patients with TRD have a significant unmet need for a rapid acting antidepressant medication.

Ketamine was approved by the US Food and Drug Administration (FDA) in 1970 as an anesthetic and has been observed to improve symptoms of depression and other mood disorders at low doses (Bahji et al., 2021; Kim et al., 2019; Moghaddam, 2021). Ketamine is a noncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) glutamate receptors and a racemic mixture of two stereoisomers – the S-enantiomer and the R-enantiomer (Hough, 2019; Kim et al., 2019; Sanacora et al., 2017). There has been some evidence showing that the S-enantiomer, termed "esketamine," binds to the NMDA receptors with greater affinity (Agboola et al., 2020; Moghaddam, 2021). Racemic ketamine can be administered via intravenous (IV), intranasal (IN), oral, sublingual (SL), anal, subcutaneous (SQ) and IM routes; however, the majority of research to date has been on IV ketamine administration (Dore et al., 2019; Sanacora et al., 2017). Clinical trials, case reports, and psychiatric clinics that administer ketamine for the treatment of depression have reported using ketamine hydrochloride at a dose of 0.5 mg/kg to 1.0 mg/kg per 40 min IV (Novamind, 2021; Sanacora et al., 2017). While racemic ketamine is only prescribed for psychiatric disorders as an off-label indication, esketamine nasal spray (Spravato™) was developed by Janssen Pharmaceuticals and was approved by the FDA in March of 2019 as a rapid-acting treatment for TRD (Agboola et al., 2020; Kim et al., 2019). Esketamine has garnered interest for the treatment of TRD with its novel mechanism of action for depression pharmacotherapy and rapid reduction of depressive symptoms as early as 24 h post-administration.

Free-standing ketamine clinics have opened across the US to provide ketamine to patients for mood disorders, and patient cost per infusion can vary from $295 to $1000 (Novamind, 2021; Thielking, 2018). Ketamine treatment for depression is not covered by insurance since it is not an FDA approved indication (Thielking, 2018). Therefore, the entire cost of the treatment visit must be paid out-of-pocket by patients. Esketamine, on the other hand, may be covered by insurance under a medical or pharmacy benefit depending on the patient's insurance plan (Janssen, 2019a). However, at its current list price, esketamine is substantially more expensive than other antidepressants with an estimated cost between $590 and $895 per treatment visit (Janssen, 2019b; Ross and Soeteman, 2020). These costs do not take into account insurance coverage or price reductions through the manufacturer's copay assistance program for eligible commercially insured patients or state-sponsored prescription financial assistance programs (Agboola et al., 2020; Janssen, 2021; Ross and Soeteman, 2020). For example, patients with commercial insurance may enroll in the manufacturer's copay assistance program and pay $10 per treatment for esketamine medication cost (Janssen, 2020). Therefore, the cost of esketamine treatment from the patient's perspective in real-world practice may differ substantially from current estimates.

Two published cost-effectiveness analyses comparing esketamine to standard of care concluded that esketamine is not cost-effective according to commonly applied criteria in the US ($150,000/QALY) (Agboola et al., 2020; Ross and Soeteman, 2020). Importantly, these cost-effectiveness analyses did not consider the patient perspective and insurance coverage or manufacturer co-pay assistance for esketamine. Furthermore, there has not been a study utilizing patient-level data from a real-world healthcare setting administering esketamine or ketamine for TRD.

To assess the cost-effectiveness of esketamine compared to ketamine utilizing efficacy estimates from both clinical trial data and real-world effectiveness (RWE) data, we utilized data from clinical trials and from a private integrative psychiatric clinic that provides outpatient mental health treatment for both therapies. The clinic is a certified esketamine treatment center. Thus, with the goal of aiding decision making, the aim of our study is to estimate the incremental costs and cost-effectiveness of esketamine relative to ketamine for the treatment of TRD. We use both clinical trial efficacy and RWE estimates and assess the cost-effectiveness of these two strategies from both the healthcare sector and patient perspective in the US.

2. Methods

2.1. Overview of the analysis

We used a Markov model to assess the cost-effectiveness of esketamine relative to ketamine for adults with TRD. We estimated quality-adjusted life years (QALYs), costs (2020 USD), and incremental cost-effectiveness ratios (ICER) over a 3-year time horizon. This time horizon was used to allow for adequate time for costs and benefits of the two strategies to accrue without extrapolating beyond 2 years from available data (FDA, 2019; Marcantoni et al., 2020; Novamind, 2021). We varied the time horizon from 1 to 5 years in the sensitivity analysis. Future costs and QALYs were discounted at a rate of 3 % annually. The analysis was conducted using efficacy estimates derived from data of clinical trials of esketamine and IV ketamine as well as patient-level data from a private outpatient psychiatric clinic. We evaluated costs from the healthcare sector perspective (including costs accrued in the medical system) and the patient perspective (including additional costs of patient time and patient co-payments). The ICER value of esketamine relative to ketamine was calculated as a ratio of the incremental cost to the incremental benefit of esketamine compared to ketamine for each perspective.

We adhered to the 2013 Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines in reporting our methods and findings (Husereau et al., 2013). Because the study used de-identified and published data, it was exempt from institutional review board review. Meta-analyses of clinical trial data for the efficacy estimates were conducted in STATA version 16. Model creation and analyses were performed with TreeAge Pro Suite 2021.

2.2. Model description

To simulate the effects of esketamine compared to ketamine for TRD, we developed a Markov cohort model with a 1-month cycle length. Patients enter the model upon initiation of third-line antidepressant treatment, as this is the typical definition of TRD. Each strategy is modeled with four health states: TRD, non-response/relapse, response, and all-cause mortality. All patients start in the TRD health state after initiation of esketamine or ketamine treatment. Response is defined as partial resolution of depressive symptoms with a 50 % or greater improvement in the depression score on a validated symptom rating scale such as the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAM-D), or the Patient Health Questionnaire-9 (PHQ-9) (FDA, 2019; Marcantoni et al., 2020; Rush et al., 2006). Relapse is defined as a return of depressive symptoms after the patient had initially achieved response (Agboola et al., 2020; Ross and Soeteman, 2020).

2.3. Model input data

2.3.1. Demographics and mortality

We simulated a population with age of 40 (±13.2) years with 64.2 % females based on an analysis of insurance claims for patients with TRD (Amos et al., 2018). Patients were assumed to have commercial health insurance. We applied age and gender-specific mortality rates from US life tables as well as a mortality hazard ratio of 1.58 (95 % CI 1.47–1.70) for people with depression versus the general population (Cuijpers et al., 2014).

2.3.2. Esketamine – clinical trial efficacy data

The clinical trial data for esketamine was based on four phase 3 clinical trials that were included in a FDA Advisory Committee briefing document for esketamine (FDA, 2019). Change in depressive symptoms for all trials was evaluated with the MADRS (FDA, 2019). In three 4-week, placebo-controlled, parallel-group studies (TRANSFORM-1 and TRANSFORM-2 in adults 18 to 65 years of age; TRANSFORM-3 in patients 65 years or older) patients with MDD who had failed on two or more prior treatment lines were randomized to receive esketamine nasal spray versus placebo (FDA, 2019). We conducted a random-effects, restricted maximum likelihood meta-analysis on the 4-week intention-to-treat response rate (see Fig. 2 in online supplement). The estimated relative risk for esketamine versus placebo was 1.32 (95 % CI 1.10–1.58) for response. We converted this risk to a monthly probability of response.

We obtained relapse rates from the long-term withdrawal study (SUSTAIN-1) where patients who initially achieved response or remission when receiving esketamine were randomly assigned to continue esketamine or replace with a placebo (FDA, 2019). During the 89 week follow up, the relapse hazard ratio for esketamine versus placebo was 0.30 (95 % CI 0.16–0.55) for patients in response. We converted the hazard ratio to a monthly probability of relapse from response to use in our model.

2.3.3. Esketamine – real-world effectiveness data

All adults 18 years or older with a diagnosis of MDD, recurrent without psychotic features (ICD-10 code F33.2) and a prescription order for esketamine from July 2019 to June 2021 were included in the analysis. Individuals who received any other form of ketamine, including intravenous, oral, sublingual, or intramuscular, at the outpatient psychiatric clinic prior or during the study timeframe were excluded. Data were collected retrospectively through customized reports in the psychiatric clinic's electronic health record (EHR) system and by medical chart review. Variables extracted electronically included treatment dates, demographics, adverse events, and PHQ-9 scores. The PHQ-9 scores were used for evaluating change in depressive symptoms. We included patients who had at least one month of treatment to calculate response rate. In this cohort, 29 (31 %) patients responded. The standard error of the response rate was calculated using the binomial distribution. We used clinical trial estimates for relapse from response.

2.3.4. Ketamine – clinical trial efficacy data

To approximate ketamine efficacy from the available data, we utilized the meta-analysis conducted by Marcantoni et al. (2020), as this study was limited to IV administration of ketamine, a patient population with TRD, and had efficacy estimates at 7 days post-infusion. We conducted a random-effects, restricted likelihood meta-analysis of the 7-day timepoint for response from the data reported by Marcantoni et al. (supplemental Fig. 3). We applied a continuity correction of 1.0 to account for zero cells inflating the results. The estimated relative risk for ketamine versus placebo was 2.79 (95 % CI 1.58–4.95) for response at the 7-day timepoint. We converted this risk to a monthly probability of response. We assumed equal relapse rates for ketamine and esketamine because there was not available data on relapse rates for ketamine in the literature.

2.3.5. Ketamine – real-world effectiveness data

The private outpatient psychiatric clinic we obtained data from mainly administers ketamine intramuscularly (IM); therefore, we assessed efficacy of patients receiving IM ketamine. We assumed IM ketamine efficacy estimates would be similar to IV ketamine efficacy, as the dose and dose frequency are similar for patients who received either strategy. All adults 18 years or older with a diagnosis of MDD, recurrent without psychotic features (ICD-10 code F33.2) and a clinical encounter for IM ketamine from January 2018 to June 2021 were included in the analysis. Individuals who received any other form of ketamine, including intravenous, oral, sublingual, or esketamine nasal spray at the outpatient psychiatric clinic prior or during the study timeframe were excluded from the analysis. Data were collected with the same methods as for patients receiving esketamine. We included patients who had at least one month of treatment to calculate response rate. In this cohort, 32 (33 %) of patients responded. The standard error of the response rate was calculated using the binomial distribution. We used clinical trial estimates for relapse from response.

2.3.6. Utility

We utilized utility values from a prospective cohort study that used the Euro—Qol-5D questionnaire to assess quality of life among outpatients treated for MDD with depression pharmacotherapy (Sapin et al., 2004). Utility estimates for response and non-response were 0.72 (95 % CI 0.65–0.79) and 0.58 (95 % CI 0.50–0.66), respectively (Sapin et al., 2004).

2.3.7. Esketamine administration costs

Our estimate for esketamine provision included cost of the medication, cost of the physician visit at each presentation of dosing, and cost of 2 h of observation by a medical assistant (MA) after each dose administration (Janssen, 2019c). For the cost of esketamine medication, we utilized RedBook's WAC price per 28 mg device ($324) (IBM, 2020). Dose and dose frequency of esketamine was based on the product's prescribing recommendations in the FDA-approved labeling (Janssen, 2019b). During the first month of treatment, esketamine was assumed to be given twice weekly at a starting dose of 56 mg, with subsequent doses either 56 mg or 84 mg thereafter. We assumed two starting doses at 56 mg for the base case analysis and varied this from one to four 56 mg doses for the upper and lower bounds of the sensitivity analysis. In the response health state, we assumed esketamine is given once weekly at 84 mg. In the non-response/relapse health state, we assumed esketamine is given twice weekly at 84 mg. For both response and non-response/relapse health states, we varied the esketamine medication cost by assuming one less dose and one additional dose for the upper and lower bounds of the sensitivity analysis.

We assumed patients would have a physician visit at each dosing session for esketamine. We used the Centers for Medicare and Medicaid Services Physician Fee Schedule for a 15-minute office visit, routine follow-up, (CPT code 99213) for the physician cost per visit ($78) (CMS, 2020). Additionally, we assumed a medical assistant performed 2 h of monitoring post dosing, as required by the Risk Evaluation and Mitigation Strategy (REMS) program (Janssen, 2019c). We obtained values for staff cost per hour ($18.5/h) and how many patients an MA monitors (4 patients per MA) from the outpatient psychiatric clinic, resulting in a per patient cost of $9.25 per 2 h of MA monitoring (Novamind, 2021).

For the patient perspective analysis, we included cost of patient time and replaced the cost of esketamine medication and cost of the physician visit with patient co-payments. We assumed that each visit for esketamine treatment would require 3 h of patient time, including travel, dosing, and monitoring. We obtained estimates for average hourly earnings of US adults in 2020 from the Bureau of Labor Statistics (BLS) ($29.37/h) (BLS, 2020). Esketamine medication co-payment was assumed to be $10/visit for the base case analysis, based on the manufacturer's copay assistance program for commercially insured patients (Janssen, 2021). We varied the medication co-payment using estimates for the average prescription drug co-payments for individuals with employer health benefits from a 2020 national survey by Kaiser Family Foundation (KFF). The 2020 KFF Employer Health Benefits Survey was also used to obtain estimates for average co-payment for a physician office visit ($42) (KFF, 2020).

2.3.8. Ketamine administration costs

Our estimate for ketamine provision included cost of the medication, cost of physician visit at each presentation of dosing, and cost of 75 min

of observation by an MA after each dose. For cost of ketamine medication, we utilized RedBook's WAC price and the psychiatric clinic's invoice for 100 mg/1 mL of ketamine hydrochloride solution ($21) (Novamind, 2021). Dose and dose frequency were based on consultation with clinical experts. Each IV ketamine administration is typically given over 40 min, and we used gender and weight-based dosing to estimate the total milligrams of ketamine given per visit. For the first month of treatment, we assumed ketamine is given twice weekly at a starting dose of 0.5 mg/kg, with subsequent doses either 0.5 mg/kg or 1.0 mg/kg thereafter. We assumed two starting doses at 0.5 mg/kg for the base case analysis and varied this from one to four doses for the upper and lower bounds of the sensitivity analysis. In the response health state, we assumed ketamine is given once weekly at 1.0 mg/kg. In the non-response/relapse health state, we assumed ketamine is given twice weekly at 1.0 mg/kg. For both response and non-response/relapse health states, we varied the ketamine medication cost by assuming one less dose and one additional dose for the upper and lower bounds of the sensitivity analysis. We also included the cost of IV supplies ($12/administration) (Novamind, 2021).

We assumed patients would have a physician visit at each dosing session for ketamine, and this cost was the same as was used for esketamine provision. Additionally, we assumed a medical assistant performed 75 min of monitoring post dosing based on clinical expert consultation. Assuming one MA monitors four patients at a time, monitoring costs for ketamine administration were estimated at $5.78/patient (Novamind, 2021).

For the patient perspective analysis, we included cost of patient time and replaced the cost of the ketamine administration and physician visit with patient co-payments. We utilized a low estimate for IV ketamine administration based on clinics in the US that administer ketamine for depression ($295/administration), and we varied this estimate in the sensitivity analysis (Novamind, 2021; Thielking, 2018). Depression is not an FDA-approved indication for ketamine; thus, patients do not receive insurance coverage for ketamine treatment for TRD. We assumed that each visit for ketamine treatment would require 2 h 15 min of patient time, including travel, dosing, and monitoring. We used the same estimates for hourly wages of patients and for the physician visit co-payment for both esketamine and ketamine provision (BLS, 2020; KFF, 2020).

Table 1
Input data for the Markov model simulating the effects of esketamine nasal spray vs. intravenous ketamine for the treatment of treatment-resistant depression.

Parameters	Value	LCI	UCI	SE	Distribution	Reference
General and demographic						
Annual discount rate (%)	3					
Time horizon (years)	3	1	5			
Annual mortality probability	0.004	0.0038	0.0043	0.00013	Normal	Cuijpers et al. (2014)
Age	40.5			13.2		Amos et al. (2018)
Female (%)	64.2					Amos et al. (2018)
Utility by health state						
Nonresponse, relapse, initiation	0.58	0.50	0.66	0.04082	Beta	Sapin et al. (2004)
Response	0.72	0.65	0.79	0.03571	Beta	Sapin et al. (2004)
Effect of Interventions – Clinical Trial data						
Esketamine efficacy relative to usual care						
Response	0.2888	0.2529	0.3271	0.0189	Beta	FDA (2019)
Response to relapse	0.1083	0.0608	0.1821	0.0309	Beta	FDA (2019)
Ketamine efficacy relative to usual care						
Response	0.5347	0.3935	0.6709	0.0708	Beta	Marcantoni et al. (2020)
Response to relapse	0.1083	0.0608	0.1821	0.0309	Beta	FDA (2019)
Effect of Interventions – RWE data						
Esketamine efficacy relative to usual care						
Response	0.3085	0.2151	0.4019	0.0476	Beta	Novamind (2021)
Ketamine efficacy relative to usual care						
Response	0.3333	0.2390	0.4276	0.0481	Beta	Novamind (2021)
Costs (2020 $) - Healthcare sector perspective						
Cost per physician visit	78					CMS (2020)
Esketamine						
Cost per ESK device (28 mg)	324					IBM (2020)
Cost per 2 h MA monitoring	9					Novamind (2021)
Ketamine						
Cost per 100 mg/1 mL ketamine hydrochloride	21					IBM (2020); Novamind (2021)
Cost per 75 mins MA monitoring	6					Novamind (2021)
IV supply cost per administration[a]	12					Novamind (2021)
Costs (2020 $) - Patient perspective						
Co-payment per physician visit	42	37	53	4		KFF (2020)
Esketamine						
Medication co-payment per visit	10	0	116			Janssen (2020); KFF (2020)
Cost of patient time per visit (3 h)[b]	88					BLS (2020)
Ketamine						
Payment per visit	295	295	750	116		Novamind (2021)
Cost of patient time per visit (2 h 15 mins)[b]	66					BLS (2020)

Abbreviations: MA: medical assistant; IV: intravenous; mg: milligram; mins: minutes; h: hour; RWE: real-world effectiveness.
[a] Includes saline bag, IV administration set, IV start kit, needle, catheter, coban self-adherent wrap, pads, gloves, pillow case.
[b] Each visit includes dosing, monitoring, and travel.

2.3.9. Sensitivity and uncertainty analyses

We performed one-way and probabilistic sensitivity analyses (PSAs) to determine the impact of model parameter uncertainty and variability on our results. In one-way sensitivity analyses, we varied individual model parameter values and assessed their effect on our results. The model was determined to be sensitive to variables that quantitatively changed the results from the base case. In probabilistic sensitivity analyses, a second-order Monte Carlo simulation was performed ($n =$ 10,000) based on the distributions of variables (Table 1). Results of the PSA are presented graphically as incremental cost-effectiveness (ICE) and cost-effectiveness scatterplots.

3. Results

3.1. Base case – clinical trial efficacy data

The discounted costs, benefits, and cost-effectiveness of esketamine and ketamine treatment over a 3-year time horizon are presented in Table 2. For the analysis utilizing clinical trial efficacy estimates, the use of esketamine yielded 1.98 QALYs while the use of ketamine yielded 2.03 QALYs over the 3-year time horizon. Under the healthcare sector perspective, total costs of esketamine were $176,320 higher than for ketamine. This cost difference was largely driven by medication costs (esketamine: $179,204; ketamine: $2905). Thus, esketamine was dominated by ketamine. Under the patient perspective, total costs of esketamine were $42,532 lower than for ketamine. Again, this was largely driven by medication costs (esketamine: $1865; ketamine: $50,052). This resulted in an ICER of $867,606/QALY for ketamine compared to esketamine.

3.2. Base case – real-world effectiveness data

For the analysis utilizing RWE estimates, the use of esketamine yielded 1.98 QALYs and the use of ketamine yielded 1.99 QALYs over the 3-year time horizon. Under the healthcare sector perspective, total costs of esketamine were $172,919 higher than for ketamine. Again, this was driven by medication costs (esketamine: $177,369; ketamine: $3101). Thus, esketamine yielded 0.01 less QALYs and was more costly, so it was dominated by ketamine. Under the patient perspective, total costs of esketamine were $43,245 lower than for ketamine. This was also driven by medication costs (esketamine: $1844; ketamine: $45,090). This resulted in an ICER of $7,037,560/QALY for ketamine compared to esketamine.

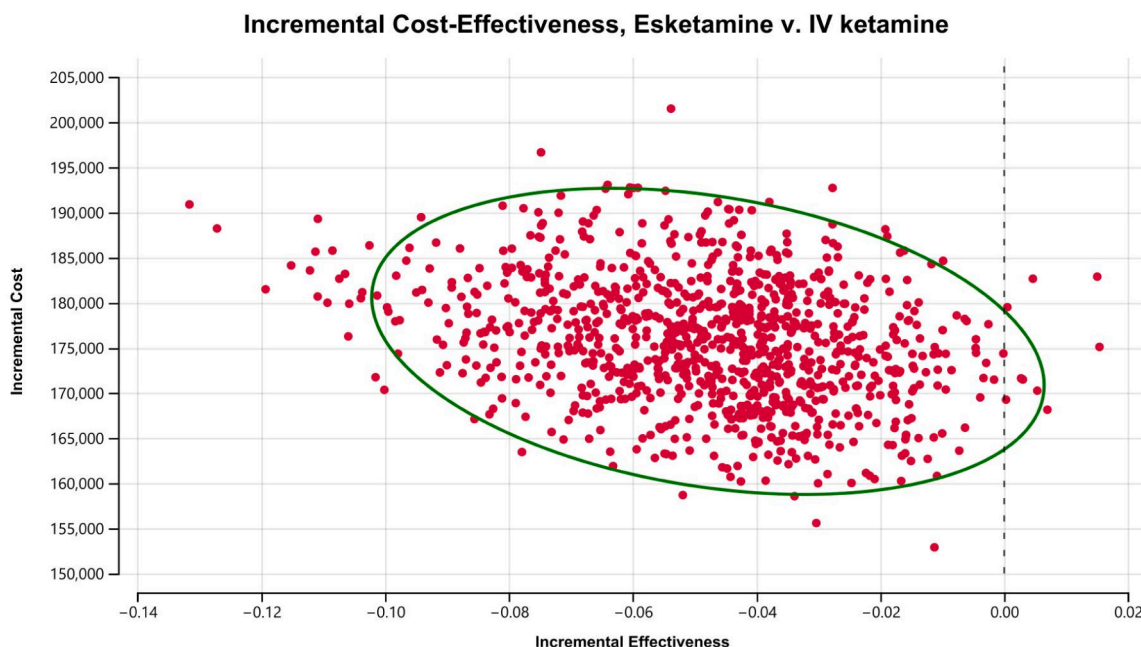#### 3.3. Sensitivity and uncertainty analyses

In one-way sensitivity analyses under the healthcare sector perspective, the ICER did not become positive with variation in any single individual parameter (see Figs. 4–5 in supplemental material). In one-way sensitivity analyses under the patient perspective with clinical trial efficacy estimates, the lowest ICER attained was $464,389/QALY when applying the lower limit of esketamine co-payment. In one-way sensitivity analyses under the patient perspective with RWE estimates, the lowest ICER attained with any parameter variation was $712,747/QALY when applying the upper limit of the probability of response to ketamine.

The results of the PSAs are presented graphically in ICE scatterplots (Figs. 1-2) and cost-effectiveness scatterplots (see Figs. 6–7 in supplemental material). Over a 3-year time horizon, esketamine was consistently more expensive than ketamine under the healthcare sector perspective. However, under the patient perspective, ketamine was consistently more expensive than esketamine. Esketamine and ketamine had similar effectiveness under both perspectives and with clinical trial efficacy and RWE estimates. At a threshold of $150,000/QALY, there are no scenarios that esketamine is cost-effective compared to ketamine under the healthcare sector perspective. At the same threshold under the patient perspective, the probability that esketamine is superior compared to ketamine (quadrant IV in the ICE scatterplot) was 0.0055 with clinical trial efficacy estimates and 0.35 with RWE estimates. However, with increasing effectiveness esketamine becomes less costly compared to ketamine. When varying the time horizon from 1 to 5 years, esketamine was dominated by ketamine under the healthcare sector perspective. Under the patient perspective, the base-case ICERs projected with a 1-year or 5-year time horizon did not fall below $150,000/QALY (see Tables 1-2 in supplemental material).
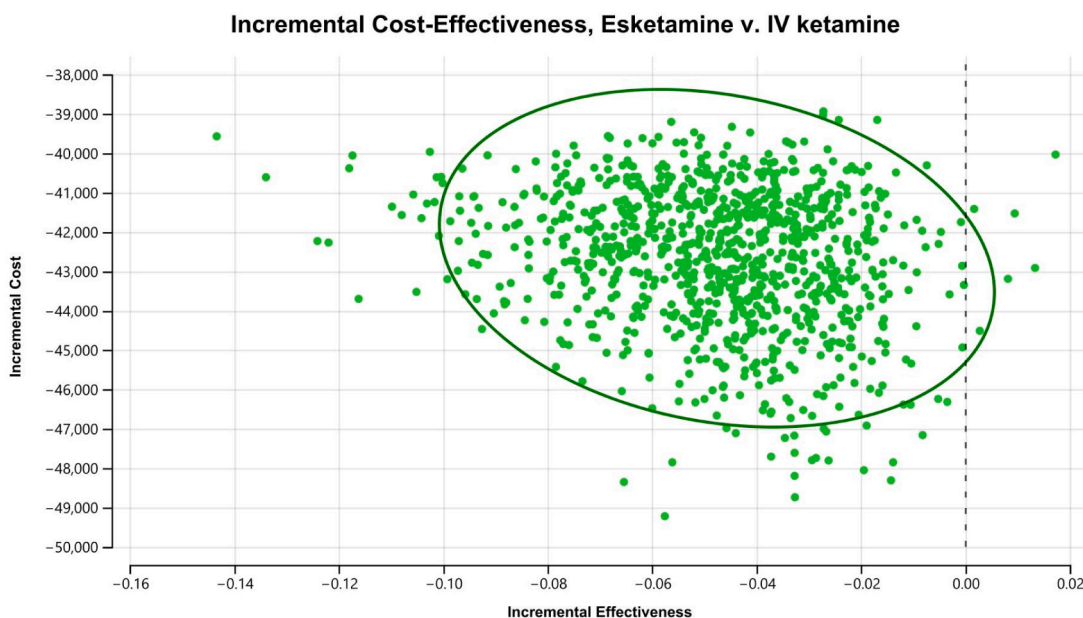
3.4. Discussion

In this decision analytic model evaluating esketamine nasal spray versus IV ketamine for the treatment of TRD, we found that esketamine is unlikely to be cost-effective compared to ketamine at $150,000/QALY, the typical upper bound for defining cost-effectiveness of health technology in the US (Anderson et al., 2014). Our model projected esketamine was dominated by ketamine under the healthcare sector perspective when utilizing either clinical trial efficacy or RWE. However, under the patient perspective, our model projected a base case ICER of $867,606/QALY (clinical trial data) and $7,037,560/QALY

Table 2
Base case results of a Markov model simulating the effects of esketamine nasal spray vs. intravenous ketamine treatment for treatment-resistant depression over a 3-year time horizon.

	Clinical trial efficacy data			Real-world effectiveness data		
	Esketamine	Ketamine	Difference	Esketamine	Ketamine	Difference
Quality-adjusted life years						
	1.98	2.03	0.05	1.98	1.99	0.01
Total costs (2020 $)						
Healthcare sector perspective	195,478	19,157	(176,320)	193,465	20,547	(172,919)
Patient perspective	23,143	65,675	42,532	22,891	70,497	47,606
Cost components (2020 $)						
Healthcare sector perspective						
Medication	179,204	2,905	(176,299)	177,369	3,101	(174,268)
Physician and medical assistant services	16,274	14,218	(2,056)	16,097	15,262	(834)
Supplies	N/A	2,034	2,034	N/A	2,184	2,184
Patient perspective						
Medication	1,865	50,052	48,187	1,844	45,090	43,245
Physician visit	4,848	4,411	(437)	4,796	4,735	(60)
Patient time	16,430	11,212	(5,219)	16,251	12,035	(4,217)
Incremental cost-effectiveness ratios ($/QALY)						
Esketamine vs. IV ketamine						
Healthcare sector perspective	Dominated			Dominated		
Patient perspective		867,606			7,037,560	

a. Healthcare sector perspective

Incremental Cost-Effectiveness, Esketamine v. IV ketamine

b. Patient perspective

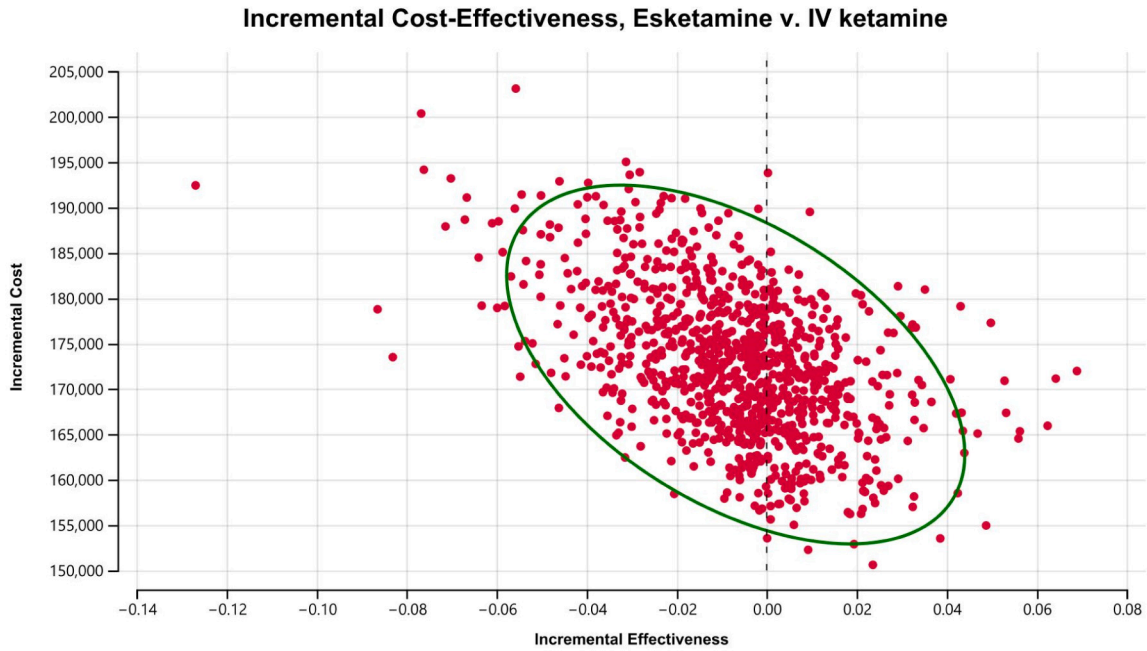**Incremental Cost-Effectiveness, Esketamine v. IV ketamine**

Fig. 1. Incremental cost-effectiveness scatterplots of esketamine vs. ketamine utilizing clinical trial efficacy estimates with a willingness to pay threshold of $150,000/QALY.

(RWE) for esketamine vs. ketamine. Because esketamine and ketamine had similar effectiveness (clinical trial efficacy: +0.05 QALYs for ketamine vs. esketamine; RWE: +0.01 QALYs for ketamine vs. esketamine) and large differences in cost, the ICER values are inflated. In uncertainty analyses, esketamine was likely to be cost-effective compared to ketamine (i.e., ICER below $150,000/QALY) only under the patient perspective – clinical trial efficacy: 0.55 % of simulations; RWE: 35 % of simulations.

While there has been no studies published evaluating the cost-effectiveness of IV ketamine (or any other route of administration) for TRD, there have been three prior studies evaluating the cost-effectiveness of esketamine nasal spray compared to usual care for TRD (Agboola et al., 2020; Desai et al., 2021; Ross and Soeteman, 2020). The Institute for Clinical and Economic Review released an Evidence Report in 2019 evaluating esketamine for TRD where they compared the cost-effectiveness of esketamine to an oral antidepressant in patients with TRD (Agboola et al., 2020). With a base-case price of $295 per 28 mg intranasal device, they found that esketamine results in an ICER of

a. Healthcare sector perspective

Incremental Cost-Effectiveness, Esketamine v. IV ketamine

b. Patient perspective

Incremental Cost-Effectiveness, Esketamine v. IV ketamine
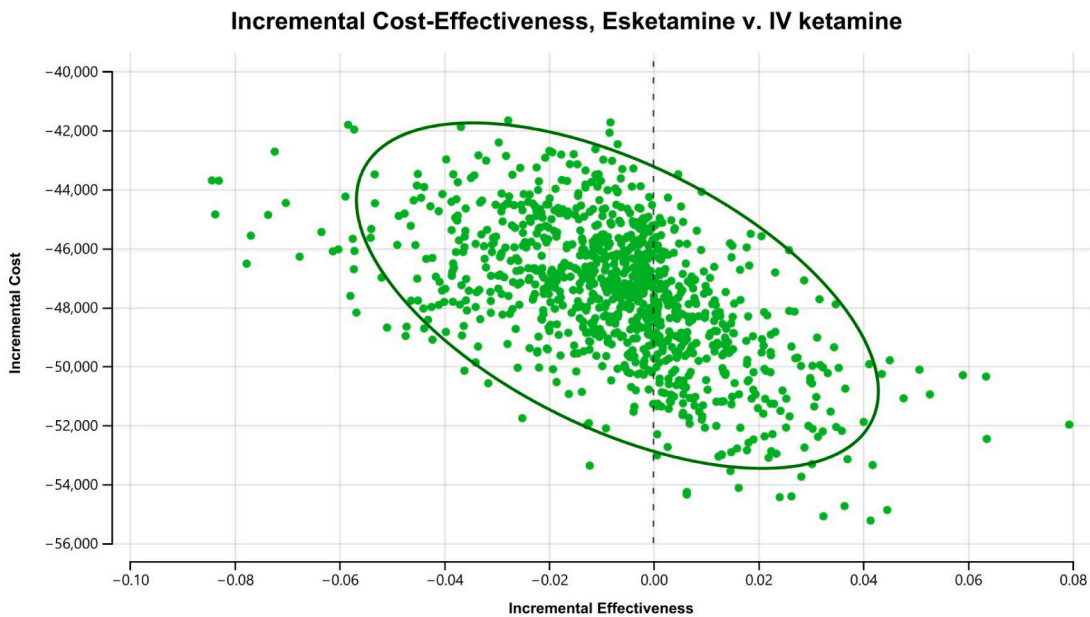
Fig. 2. Incremental cost-effectiveness scatterplots of esketamine vs. ketamine utilizing real-world effectiveness estimates with a willingness to pay threshold of $150,000/QALY.

$198,000/QALY compared to oral antidepressants using a healthcare sector perspective. An analysis by Ross et al. also found esketamine unlikely to be cost-effective compared to usual care utilizing a base-case price of $240 per 28 mg intranasal device. Ross et al. projected base-case ICERs of $242,496/QALY (healthcare sector perspective) and $237,111/QALY (societal perspective). These results are consistent with our findings that esketamine is unlikely to be cost-effective under a healthcare sector perspective with its current list price ranging from $240–$340/28 mg device. In comparison, an industry-sponsored study

assessed the annual per-patient direct costs associated with achieving remission (cost-per-remitter) with esketamine nasal spray plus an oral antidepressant compared to an oral antidepressant alone in treating patients with TRD (Desai et al., 2021). With a base-case time horizon of 7 months, this analysis found that treatment with esketamine resulted in significantly higher response/remission rates and lower relapse rates than oral antidepressants alone. The improved efficacy outcomes were associated with lower cost-per-remitter for esketamine compared to oral antidepressants, with differences in cost-per-remitter ranging from

$14,491 for commercial insurers to $38,842 for integrated delivery networks. The PSA found a cost-per-remitter advantage of esketamine across 54–68 % of input specifications, depending on insurance plan type. Thus, the authors concluded a dollar spent on esketamine nasal spray yields more clinical benefit than a dollar spent on an oral antidepressant (Desai et al., 2021).

In addition to the CEA of esketamine versus oral antidepressants, The Institute for Clinical and Economic Review conducted a cost-analysis to assess expected direct treatment costs for esketamine or ketamine (Agboola et al., 2020). The authors stated they did not use ketamine as a comparator to esketamine in their cost-effectiveness model because the quality of ketamine trials leads to non-comparable efficacy of ketamine and esketamine. However, we were able to use ketamine as a comparator because of available published ketamine clinical trials conducted in patients with TRD specifically, and we had access to real-world, patient-level data for patients treated with either esketamine or ketamine therapy. This ensured that we could assess the robustness of our results by comparing the model run with either clinical trial efficacy estimates or RWE estimates. The RWE data showed that ketamine's effectiveness was closer to esketamine's effectiveness compared to the clinical trial estimates (clinical trial efficacy: +0.05 QALYs; RWE: +0.01 QALYs). This difference is likely due to the short time frame in the ketamine clinical trials (1 week) compared to the esketamine clinical trials (28 days). Thus, the RWE estimates are likely more representative of ketamine's and esketamine's efficacy in clinical practice. Additionally, our model projected higher costs incurred for ketamine treatment with RWE estimates vs. clinical trial efficacy estimates under the healthcare sector perspective (clinical trial efficacy: $30,236; RWE: $32,354) and under the patient perspective (clinical trial efficacy: $103,592; RWE: $110,906). This is due to patients spending less time in response with RWE response rates compared to clinical trial response rate estimates for ketamine; thus, our model projected additional visits and administration of the medication. That being said, the cost analysis by The Institute for Clinical and Economic Review is consistent with our findings that esketamine is more expensive than ketamine under the healthcare sector perspective for treatment of TRD patients. The evidence report showed esketamine to be $32,900 more expensive than ketamine in terms of direct medical costs per year. Our study found esketamine to be $176,320 (clinical trial efficacy) or $172,919 (RWE) more expensive per year than ketamine under a healthcare sector perspective. When using a modified societal perspective and adding indirect costs associated with patient time (i.e., lost time from work, travel to clinic), the evidence report found esketamine to be $34,100 more expensive than ketamine. This is different from our patient perspective estimate of esketamine being $42,532 (clinical trial data) or $47,606 (RWE data) less expensive per year than ketamine. This difference is likely because the evidence report utilized WAC prices for both esketamine and ketamine. However, in our patient perspective analysis assessing patients with commercial insurance, we estimated the total net out-of-pocket payments for medications as the drug cost measurement, as recommended by the ISPOR Drug Cost Task Force when conducting analyses from the patient/consumer perspective (Hay et al., 2010).

Esketamine and ketamine are effective medications for the treatment of TRD. The cost-effectiveness of either medication depends on the perspective utilized. From a healthcare sector perspective, effort will be required by payers and policy makers to reduce esketamine's price to reach a value-based price. With similar effectiveness, ketamine may be the preferred choice to treat patients in a cost-effective manner. However, when considering the patient perspective, esketamine may be preferred since TRD is an FDA-approved indication, thus patients can receive insurance coverage for the medication. Additionally, patients can enroll in the manufacturer's copay assistance program or patient assistance program for low-income adults (Janssen, 2020). Insurance coverage in combination with these positive incentives provided by the manufacturer makes esketamine treatment accessible to patients with TRD. This is important in comparison to ketamine treatment, which can

range from $295–$1000 for IV ketamine infusion at free-standing ketamine clinics throughout the US. Because ketamine does not have an FDA-approved indication for mood disorders, the entire cost of the treatment must be paid out-of-pocket by patients. Shared decision-making with patients and providers will be an important element in determining which treatment patients can afford, access, and most benefit from.

4. Limitations

The results of this study must be interpreted in the context of its limitations. The data utilized for efficacy estimates of esketamine and ketamine have several limitations. The esketamine trials were conducted with a few hundred participants and the IV ketamine trials were conducted in a total of 118 patients. Additionally, longer-term (i.e., more than two months of treatment) observational or clinical trial data was not available. The model utilized a 3-year time horizon because of the availability of data, and this time horizon may fail to capture longer-term costs and benefits of utilizing these treatments for TRD. However, the results were robust when varying the time horizon to 5 years. Additionally, the analysis excludes potentially important benefits to families of patients with TRD and to the broader society. Effective treatment for depression may reduce the risk of substance use and improve productivity of patients, leading to long term benefits and reduced costs to the healthcare system. Lastly, it was assumed patients follow a similar and consistent pattern of treatment following relapse, which may not represent actual treatment patterns.

5. Conclusions

In this decision analytic model evaluating esketamine nasal spray versus IV ketamine for the treatment of TRD, we found that esketamine is unlikely to be cost-effective compared to ketamine under a healthcare sector perspective. Under a patient perspective, esketamine has similar effectiveness and becomes substantially less costly compared to ketamine due to insurance coverage and manufacturer assistance programs that make esketamine treatment accessible to patients with TRD. Shared decision-making with patients and providers will be necessary to determine which treatment patients can access and afford.

CRediT authorship contribution statement

All the authors have equal contribution towards conceptualizing and designing the study. MB developed the model completed the manuscript writeup. PT, RR, and DM reviewed the model and critically reviewed/revised the manuscript writeup. All authors have read and approved the final article.

Conflict of interest

Dr. Reid Robison is employed by Numinus Wellness and is an equity holder in the company. Dr. Reid Robison is on the Janssen Speakers Bureau for esketamine. Janssen Pharmaceuticals did not financially support this research.

Statement of ethics

These data do not contain any information that could identify subjects. Informed consent was not required for this study.

Role of funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.09.083.

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