Research Article

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US budget impact analysis of esketamine nasal spray in major depressive disorder with acute suicidal ideation/behavior

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Background: Esketamine nasal spray plus an oral antidepressant is approved in adults with major depressive disorder with acute suicidal ideation or behavior (MDSI). **Methods:** A budget impact analysis from a US payer perspective was performed with a hypothetical 1-million-member plan, using pharmacy and medical costs associated with adding esketamine plus an oral antidepressant to usual care. **Results:** Estimated annual total healthcare costs of managing patients with MDSI increased from $32,988,247 without esketamine to $34,161,188 in Year 3 with esketamine (primarily due to medical costs). The per-member-per-month incremental costs were $0.02, $0.06 and $0.10 in Years 1, 2 and 3, respectively. **Conclusion:** Incorporation of esketamine results in a modest estimated impact on the annual budget over a 3-year time horizon.

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Keywords: antidepressant • budget impact • esketamine • major depressive disorder • nasal spray

Background

Major depressive disorder (MDD) is a common mental disorder and the second leading cause of disability in the USA [1]. According to the most recent National Institute of Mental Health statistics (2019), the prevalence of MDD among adults in the USA was 7.8%, with over 19 million individuals affected [2]. Patients with MDD experience symptoms such as depressed mood, loss of pleasure, insomnia or hypersomnia, worthlessness and fatigue or loss of energy [3]. Some patients with MDD may also experience acute suicidal ideation (MDSI) or attempt suicide [2,4,5]. These patients often have more severe depressive symptoms and worse response to treatment compared with patients with MDD without suicidal ideation (SI) [6,7].

MDD is also associated with increased societal and healthcare-associated costs. The total economic burden of MDD in the USA was estimated as $326 billion in 2018; suicide-related costs contributed $13.4 billion, 4.1% of MDD-associated costs [8]. Patients with MDD and high SI have also been reported to have significantly higher burden compared with patients with MDD without SI; patients with high SI had lower mean SF-36 mental component summary scores, higher work productivity loss and greater per-patient-per-month hospitalization and emergency visits, as well as healthcare costs [9]. In a separate retrospective analysis of patients with MDSI and a hospital encounter, the rate of subsequent all-cause hospital encounters was 22.3%, and the rate of subsequent MDD-related hospital encounters was 12.0%. The costs for these encounters were $5136 ± $11,791 and $3722 ± $9621, respectively [10].

Usual care for patients with MDSI varies, but typically includes pharmacologic treatment as well as psychotherapy and other nonpharmacologic treatment [11]. Pharmacologic treatment with antidepressants is the mainstay of treatment for patients with MDSI; however, standard antidepressants require 4–6 weeks for full effectiveness, and patients may experience the burden of treatment-associated side effects [11].

Esketamine nasal spray, a noncompetitive N-methyl D-aspartate receptor antagonist, was approved by the US FDA in conjunction with an oral antidepressant, as a treatment for depressive symptoms in adults with MDSI in

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Table 1. Market share without and with esketamine.

Regimen	Current market scenario (without esketamine)	New market scenario (with esketamine)		
	Yearly (Years 1–3)	Year 1	Year 2	Year 3
	Patients (n) (proportion of market)	Patients (n) (proportion of market)	Patients (n) (proportion of market)	Patients (n) (proportion of market)
Esketamine + oral antidepressant	0	36 (1.0%)	109 (3.0%)	182 (5.0%)
Usual care	3637 (100.0%)	3601 (99.0%)	3528 (97.0%)	3455 (95%)
Total	3637 (100.0%)	3637 (100.0%)	3637 (100.0%)	3637 (100.0%)

July 2020, following its approval for the treatment of treatment-resistant depression (TRD) in adults in March 2019 [12]. In Phase III ASPIRE I and II studies, patients with MDSI who received esketamine nasal spray experienced robust reduction in depressive symptoms at 24 h, and as early as at 4 h after the first dose, fulfilling the unmet need for a rapid-acting antidepressant in patients with MDSI [13,14]. Furthermore, the percentage of patients who experienced remission at day 25 was 54% and 47% for patients who received esketamine, compared with 38% and 37% for standard of care at day 25 in the ASPIRE I and II studies, respectively.

A budget impact analysis may estimate the expected cost associated with reimbursing esketamine nasal spray and predicts the financial impact of esketamine adoption on the overall health plan over a certain time period. Because esketamine is a novel antidepressant with a rapid-acting indication administered under healthcare provider observation in a risk evaluation and mitigation strategy, it is important to estimate the expected budget impact for population health decision makers. The objective of this study is to evaluate the potential budgetary impact on a health plan in the USA of introducing esketamine plus an oral antidepressant as a therapy for the treatment of depressive symptoms in adult patients with MDSI.

Methods

We developed a budget impact model from a US healthcare payer perspective over a 3-year time horizon. The analysis followed guidance from the International Society for Pharmacoeconomics and Outcomes Research Budget Impact Analysis Good Practice Task Force [15].

Patient population

Published epidemiologic data were used to calculate the number of patients in a hypothetical health plan who are eligible for treatment with esketamine (Figure 1). This was extrapolated by estimating the proportion of adults in the plan with MDD and, of those, the proportion of patients with SI or behavior who sought professional treatment [16–18].

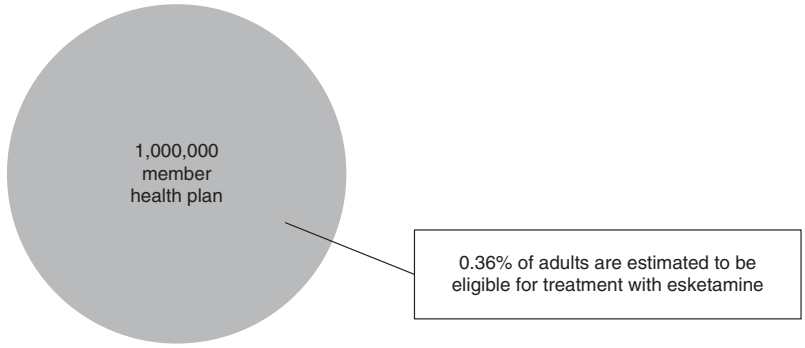
Market share without & with esketamine

The budget impact of adding esketamine plus an oral antidepressant to usual care was evaluated, assuming esketamine uptake during the first 3 years to be 1%, 3% and 5%, respectively (Table 1). These values were based on a general uptake curve with specialty products in a generic market. In the base case, usual care was defined as a mix of oral antidepressants alone or augmented with atypical antipsychotics.

Input data

Costs of esketamine

Drug cost inputs are summarized in Table 2, assuming that esketamine is covered as a medical benefit. As a high-end estimate of treatment costs, patients were assumed to have completed up to eight sessions (twice-weekly sessions for 4 weeks) with three devices (28 mg per device) per session (84 mg of esketamine) according to the FDA-approved label. The estimated cost of monitoring per session differs between the first and subsequent visits. The cost of the first esketamine visit was estimated based on evaluation and monitoring codes provided by a physician (99204: office or other outpatient visit for the evaluation and management of a new patient; 99354: a physician provides direct prolonged service in an inpatient or outpatient setting). The cost of subsequent visits was estimated based on services provided by a nonphysician (99213: office/outpatient visit, established patient; 99354: nonphysician other qualified healthcare professional provides direct prolonged service in an inpatient or outpatient setting).



	Epidemiologic data (%)	Calculation of number of patients
Plan membership rate	–	1,000,000
Patients in the plan who are adults (%)	77.6	1,000,000 × 77.6% = 776,000
Prevalence rate for MDD among adult patients	7.1	776,000 × 7.1% = 55,096
Patients with MDD who have acute suicidal ideation or behavior (%)	11.5	55,096 × 11.5% = 6336
Patients who saw or talked to a mental health professional about depression (%)	57.4	6336 × 57.4% = 3637

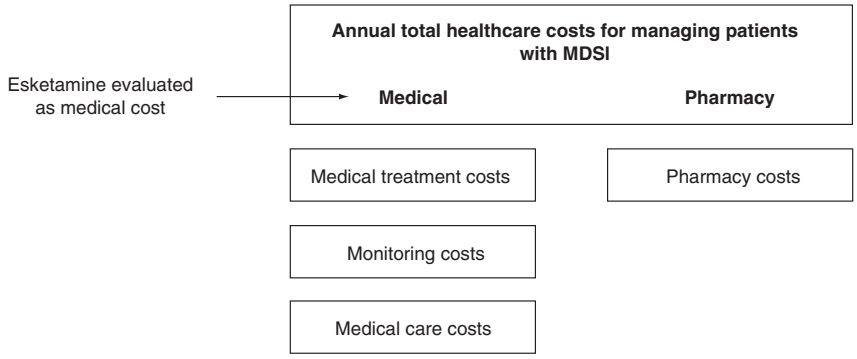


Figure 1. Patient population and esketamine treated as a medical cost in the current model.
MDD: Major depressive disorder; MDSI: Major depressive disorder with acute suicidal ideation or behavior.
Data taken from [16–18].

Table 2. Drug cost inputs (medical plan coverage of esketamine).

Regimen	Annual costs of medical treatment			Annual pharmacy costs	Ref.
	Treatment costs	Monitoring costs	Medical care costs		
Esketamine + oral antidepressant	$7427.04	$1502.64	$3957.95†	$2633.08	[19]
Usual care	0	0	$6437.38‡	$2633.08	[19]

†Calculation for esketamine medical costs: (IP visit probability × IP visit cost) + (ER visit probability × ER visit cost) + (OP visit probability × OP visit cost) = 0.48 × $7131 + 0.24 × $1773 + 0.28 × $391 = $3958.
‡Calculation for usual care medical costs: (IP visit probability × IP visit cost) + (ER visit probability × ER visit cost) + (OP visit probability × OP visit cost) = 0.6 × $9777 + 0.3 × $1773 + 0.1 × $391 = $6437.
ER: Emergency room; IP: Inpatient; OP: Outpatient.

The monitoring cost for the first visit was $332 (i.e., the sum of $194 for 99204 and $138 for 99354), and the monitoring cost for subsequent visits was $190 (i.e., the sum of $76 for 99213 and $114 for 99354) based on the 2018 Commercial MarketScan data. Esketamine-related monitoring costs, when administered in the inpatient setting, were assumed to be included as part of the overall hospitalization cost.

Costs of usual care

The pharmacy cost of oral antidepressants was calculated as the weighted average cost of oral antidepressants alone and oral antidepressants augmented with atypical antipsychotics. The proportion of patients receiving oral

antidepressants alone (47%) was based on the ASPIRE I and II MDSI studies [13,14]; the remaining 53% of patients received augmentation regimens. In this model, augmentation was assumed to be with atypical antipsychotics. The average weekly pharmacy cost was $5.44 for oral antidepressants and $90.72 for augmentation regimens with atypical antipsychotics [19].

Costs of inpatient stays & outpatient visits

The model captured the cost of inpatient stays and outpatient visits, as well as the cost of a stay at an emergency room to account for medical care costs (Figure 2A). Based on real-world data, it was estimated that under usual care, 90% of patients with MDSI sought treatment from a professional present in a hospital. Specifically, 60% are admitted to the inpatient setting and 30% are seen at the emergency room and not ultimately admitted to the hospital [20]. It was conservatively assumed that 40% of the patients being treated in a hospital under usual care may be eligible for outpatient treatment. This input (40%) was derived from a study reporting that 40% of patients who present to the hospital with SI may be treated safely in an outpatient setting if their depression symptoms get better and/or resolve [21].

Including esketamine in the new market scenario presented herein adds a rapid-acting antidepressant to the formulary. Because expert consensus recommends that the provider should determine the least restrictive care setting for a suicidal patient [22,23], and due to the finding that perception of coercion into psychiatric hospitalization is associated with an increased risk of post-discharge suicide attempts [24], it was estimated that employing esketamine may result in more patients being treated in the outpatient setting rather than in the inpatient setting or emergency room. Given the estimate cited above for 40% of patients who may be eligible for outpatient treatment if depression symptoms improve, it was assumed that 40% of the patients being treated as inpatients under usual care may be comfortable switching to outpatient treatment with esketamine in the event of early symptom improvement (40% of 60% = 24% of patients who switch to outpatient). We used previously published conversions to apply patient health questionnaire-9 (PHQ-9) reductions to montgomery-asberg depression rating scale (MADRS) reductions [25]. It was estimated that 50% of these patients would experience symptom improvement and could adjust site of care: 50% of 24% = 12% of total patients. Finally, it was assumed that the proportion adjusting out of inpatient care to outpatient care (12% of 60%, or one in five) would be proportional in the emergency room setting (6% out of 30%, or one in five).

Length of stay estimates for esketamine were extrapolations based on data from US patients in the ASPIRE clinical trial program [13,14]. Based on real-world data, 41% of patients with MDSI receiving usual care have a short length of stay (defined as 1–3 days, mean 2.2 days), 27% have a medium/typical length of stay (defined as 4–5 days, mean 4.4 days) and 32% have a long length of stay (defined as ≥6 days; mean 9.7 days; Figure 2B) [10]. Based on a *post hoc* analysis of the ASPIRE studies, US patients on esketamine have a 40% shorter time to remission (MADRS <12) compared with those on placebo. Therefore, a 40% reduction in length of stay among the subset of patients with a long length of stay was estimated. This estimate reduced mean length of stay in the subset with long length of stay from 9.7 to 5.8 days, and consequently reduced overall length of stay with esketamine from 5.2 to 3.9 days.

Based on the length of stays, inpatient medical care costs ($1725 per day) were calculated to be $7131.15 for patients on esketamine (with oral antidepressant therapies) and $9777.30 for patients on usual care [10,20]. Outpatient cost per visit was $391, and emergency room cost per visit was $1773 [20].

Readmission was also included in the model. Based on the ASPIRE clinical program [13,14], the relative difference in readmission between esketamine and usual care was 33%. In real-world data, patients on usual care had a 9% 30-day readmission rate [10]. Using this observation in our model and the differences observed in the ASPIRE clinical program, patients on esketamine were estimated to have a 6% 30-day readmission rate.

Additional analyses

Total medical cost offsets for esketamine were evaluated in an additional analysis. Medical costs were calculated as follows: (inpatient visit probability × inpatient visit cost) + (emergency room visit probability × emergency room visit cost) + (outpatient visit probability × outpatient visit cost). Total medical cost offsets were calculated as usual care medical costs – esketamine medical costs. Changes in inpatient resource use and associated costs were estimated only among the subset of patients that clinicians thought could be appropriate for outpatient treatment. No change in inpatient resource use was estimated among the larger subset of patients that clinicians deemed not to be appropriate for outpatient treatment. As noted above, changes in the length of stay and associated costs were

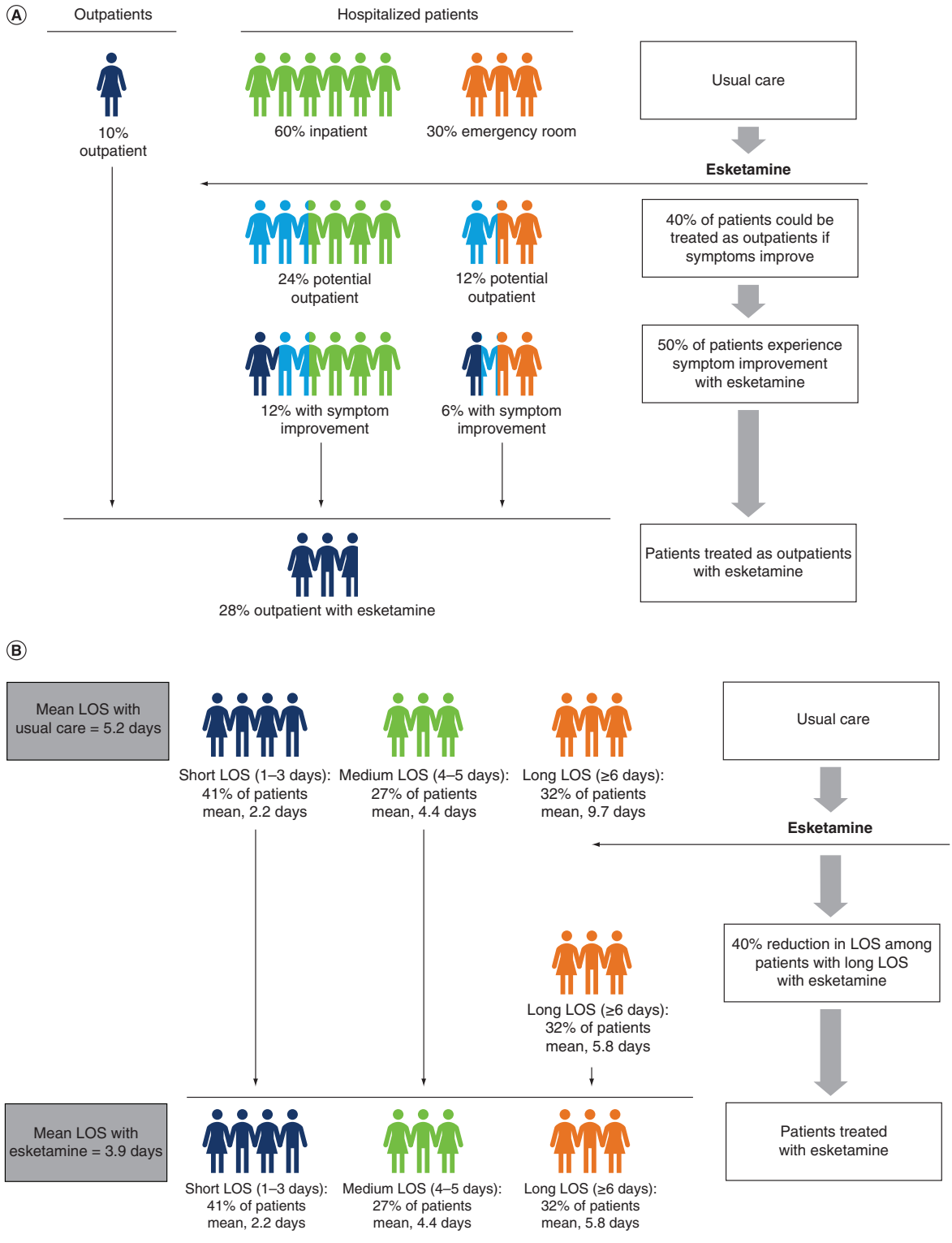


Figure 2. Total cost budget impact model. The introduction of esketamine may result in a change in **(A)** treatment setting and **(B)** mean LOS.
LOS: Length of stay.

Table 3. Total healthcare, medical and pharmacy costs without and with esketamine.

Parameters	Current market scenario (without esketamine)	New market scenario (with esketamine)		
	Yearly (Years 1–3)	Year 1	Year 2	Year 3
Annual costs				
Total†	$32,988,247	$33,222,835	$33,692,012	$34,161,188
– Medical	$23,412,023	$23,646,612	$24,115,789	$24,584,965
– Pharmacy	$9,576,223	$9,576,223	$9,576,223	$9,576,223
PMPM				
Total†	$2.75	$2.77	$2.81	$2.85
– Medical	$1.95	$1.97	$2.01	$2.05
– Pharmacy	$0.80	$0.80	$0.80	$0.80
Budget impact				
Total†	–	$234,588	$703,765	$1,172,942
– Medical	–	$234,588	$703,765	$1,172,942
– Pharmacy	–	$0.00	$0.00	$0.00
PMPM				
Total†	–	$0.02	$0.06	$0.10
– Medical	–	$0.02	$0.06	$0.10
– Pharmacy	–	$0.00	$0.00	$0.00

†Total costs are the sum of medical and pharmacy costs.
PMPM: Per-member-per-month.

estimated only among the subset of patients with longer length of stay. No change in length of stay was estimated among the larger subset of patients with shorter length of stay. Changes in 30-day readmission rate and associated costs were based upon real-world treatment patterns and the ASPIRE clinical program. Size of effect in inpatient resource use changes, length of stay and readmission were extrapolated from real-world studies.

Results

Current market scenario (without esketamine) versus new market scenario (with esketamine)

For a health plan of 1 million members, the treatment-eligible population was estimated to be 3637 patients for each year (Years 1–3), representing 0.36% of the total member population (Figure 1). Annual total healthcare costs of managing patients with MDSI, including medical treatment costs, monitoring costs, medical care costs and pharmacy costs, increased from $32,988,247 without esketamine to $33,222,835 in Year 1, to $33,692,012 in Year 2 and $34,161,188 in Year 3 in the new market scenario with esketamine. The majority of the costs were medical (medical treatment and medical care), with a minority due to pharmacy costs.

The per-member-per-month (PMPM) total healthcare costs of managing patients with MDSI increased from $2.75 in the current market scenario without esketamine to $2.77 in Year 1, $2.81 in Year 2 and $2.85 in Year 3 in the new market scenario with esketamine (Table 3).

Budget impact of esketamine

The annual total healthcare budget impact of esketamine was $234,588 in Year 1, $703,765 in Year 2 and $1,172,942 in Year 3 (Table 3). The PMPM total healthcare budget impact of esketamine was $0.02 in Year 1, $0.06 in Year 2 and $0.10 in Year 3 (Table 3). In an alternate scenario analysis, when esketamine is covered as a pharmacy benefit, the net budget impact did not change, but the medical PMPM budget impact was $0.00, -$0.01 and -$0.01, and the pharmacy PMPM budget impact was $0.02, $0.07 and $0.11 over Years 1, 2 and 3, respectively.

In the exploratory analysis of total medical cost offsets, the mean length of stay was reduced by 25% with esketamine plus an oral antidepressant compared with usual care (5.2 days with usual care – 3.9 days with esketamine). The 30-day readmission rates were reduced by 33% with esketamine plus an oral antidepressant versus usual care (9% for usual care – 6% for esketamine). The total medical cost offsets with esketamine result in $2479 per patient per MDSI event versus usual care (usual care medical costs – esketamine medical costs = $6437 – $3958 = $2479; Table 2).

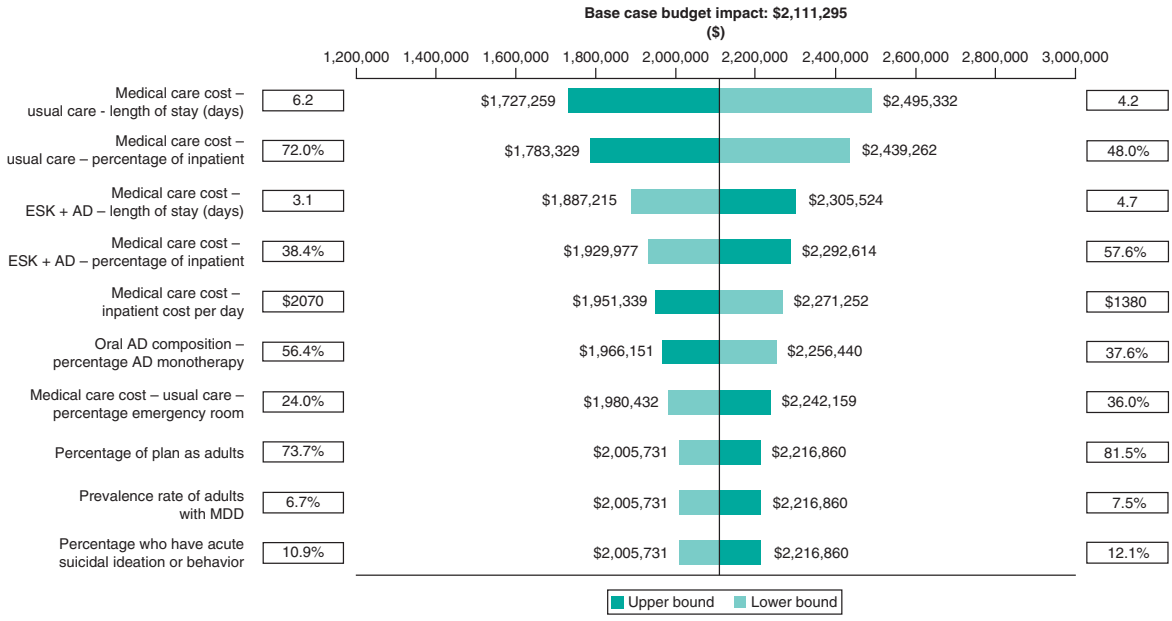


Figure 3. Tornado diagram for the ten most influential inputs on the 3-year total budget impact.
AD: Antidepressant; ESK + AD: Esketamine nasal spray in conjunction with an oral antidepressant; MDD: Major depressive disorder.

One-way sensitivity analysis

The 3-year total budget impact was most sensitive to changes in parameters affecting the medical care costs: length of stay and proportion of patients presenting as inpatients for both esketamine (with oral antidepressant therapies) and usual care, and the inpatient cost per day (Figure 3A & B). Inputs related to esketamine treatment (i.e., number of sessions and number of devices) were varied based on observed trial data (base case was based on treatment protocol). Epidemiologic inputs (e.g., percent of adults in the plan and percentage of patients with MDD) have been relatively stable over time and hence were varied by 5% of their mean value; other inputs (e.g., medical care cost per day) were varied by ±20% of their mean value.

Discussion

Esketamine was recently approved for use in conjunction with an oral antidepressant for the treatment of depressive symptoms in adults with MDSI [12]. This budget impact analysis from the US payer perspective resulted in modest budgetary impact on total healthcare costs and pharmacy costs PMPM over a 3-year time horizon. With this predicted shift in market shares, the overall PMPM cost for esketamine would increase from $0.02 in Year 1 to $0.10 in Year 3. Additionally, this model projected potential reductions in healthcare resource utilization and costs associated with esketamine compared with usual care: 20% lower use of inpatient resources, 25% reduction in mean length of stay and a 33% reduction in 30-day hospital readmission rate. The SPRAVATO US prescribing information indicates that the use of esketamine nasal spray does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose [12]. Therefore, the estimated change in inpatient resource use only included the subset of patients who could benefit from this switch and the reduction in length of stay was only estimated among the subset of patients with a long length of stay.

Suicide and SI represent an important public health challenge in the USA [2]. SI in patients with MDD has been associated with increased direct and indirect healthcare costs compared with patients with MDD without SI due to higher rates of hospitalization and ER visits [9]. In this patient population, immediate and sustained relief is critical [11]. Given that standard of care antidepressants take 4–6 weeks to reach full effect [26], esketamine nasal spray may fill an important unmet need by providing rapid improvement in depressive symptoms within hours of administration [13,14].

The medical care costs included in the analysis use real-world data to reflect the care pathways of patients with MDSI, a key strength of this analysis. Furthermore, the analysis incorporates estimated changes in the current and

future treatment landscape and disease-related costs. Specific pharmacy and medical budget responsibilities can be assessed. This analysis is specific to the on-label use of esketamine in this patient population. It should also be noted that budget impact estimates from this model are likely on the upper end of the budget impact because changes in inpatient resource use and associated costs were only estimated among the subset of patients who clinicians identified could be appropriate for outpatient treatment; changes in lengths of stay and associated costs were only estimated among the subset of patients with longer lengths of stay; and changes in 30-day readmission rate and associated costs were based on real-world treatment patterns and esketamine nasal spray clinical trial data. Although the model may not include all currently available billing codes, it does include those available at the time the model was built. Additionally, the most commonly used observation and monitoring service codes by healthcare providers (i.e., 99213, 99214, 99215, 99417, G2212) are generally reimbursed in the range between $175 and $500 per SPRAVATO treatment session. This current range of monitoring cost is consistent with the model input for the first and subsequent visits.

Limitations

Although every effort has been made to identify appropriate sources for the required data inputs and to support the required assumptions, the analysis faced several limitations. First, the model does not account for the potential of esketamine to displace electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS). Displacement of these treatments instead of pharmacotherapy would decrease the esketamine budget impact. Second, the model does not account for overlap with the TRD population; at equivalent market shares, accounting for any overlap would slightly lower the incremental budget impact of MDSI in a plan that already covers esketamine for TRD. Third, the model assumes patients receive a total of eight doses of esketamine; greater or fewer doses would change the estimated budget impact. Fourth, the budget impact model does not account for the possibility of patients decreasing the dose to 56 mg/session, which would decrease the estimated budget impact. Fifth, in the ASPIRE studies, hospitalization was funded, and in some regions, there were differences in the recommended duration of initial hospitalization which might have impacted the length of stay. Sixth, the inputs on the percentage of patients admitted to the ER or as inpatients may have been subject to bias given the nature of the study methodology, required coding of SI/suicide attempt, and stigma or implication of suicidality on clinical practice. Hence, our estimates may not include patients who may have SI but did not go to the ER or were inpatients. Seventh, the model does not include statutory or discretionary rebates, discounts or price reductions over time. Eighth, this was a payer perspective model, so only direct costs were evaluated. The true value of adding esketamine will also include benefits to the individual, healthcare providers and society holistically, and will be evaluated in future studies. Finally, because esketamine was only recently approved by the FDA for use in this population at the time of analysis, real-world estimates of esketamine use were not available to inform assumptions of medical care cost offsets. Accordingly, the PMPM may have been overestimated given that the expected shares of esketamine did not account for additional factors such as concomitant drug or alcohol use, comorbidities or insurance limitations. Thus, estimates were derived from the literature and extrapolation from clinical trials, using standard economic modeling procedures.

Conclusion

The results of this study suggest that including esketamine to treat depressive symptoms in adult patients with MDSI was estimated to have a modest impact on the annual budget of a health plan over a 3-year time horizon. The modest budget impact indicates that esketamine is an affordable treatment for this population with high unmet need. Further, this model did not account for esketamine displacing ECT or TMS. Assuming equivalent overall uptake, if esketamine displaced ECT or TMS, the budget impact of esketamine would decrease.

Author contributions

All authors contributed to the conception and design of the study or to the acquisition, analysis or interpretation of the data. All authors drafted the manuscript, revised the manuscript critically for important intellectual content, approved the final version for publication and agree to be accountable for all aspects of the work.

Financial & competing interests disclosure

This study was sponsored by Janssen Scientific Affairs, LLC. JJ Sheehan, HH Le, J Voelker and K Joshi are employees of Janssen Scientific Affairs, LLC, and may be stockholders in Johnson & Johnson. H Toro-Diaz and S Li are employees of Evidera and were

contracted to provide services for Janssen Scientific Affairs, LLC. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

This economic model is not considered human subjects research under the US Code of Federal Regulations.

Data sharing statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency.

Summary points

- Esketamine nasal spray in conjunction with an oral antidepressant was approved by the US FDA in July 2020 to treat depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior (MDSI).
- A budget impact analysis helps healthcare decision makers to understand the budget consequences of adopting esketamine nasal spray in their treatment settings.
- We conducted a budget impact analysis from a US payer perspective with a hypothetical 1 million-member plan using pharmacy and medical costs to evaluate adding esketamine plus an oral antidepressant to usual care.
- Esketamine has the potential to increase medication costs but also reduce medical costs, with changes in site-of-care use and decreases in the length of stay and readmission risk.
- Esketamine resulted in an estimated 20% reduction in inpatient and emergency department resource use, 25% reduction in the length of stay among those treated in the inpatient setting and 33% reduction in readmission risk.
- Annual total healthcare costs of managing patients with MDSI, including medical treatment costs, monitoring costs, medical care costs and pharmacy costs, increased from $32,988,247 without esketamine to $33,222,835 in Year 1, $33,692,012 in Year 2 and $34,161,188 in Year 3 in the new market scenario with esketamine.
- The per-member-per-month total healthcare costs of managing patients with MDSI increased from $2.75 in the current market scenario without esketamine to $2.77 in Year 1, $2.81 in Year 2 and $2.85 in Year 3 in the new market scenario with esketamine.
- The per-member-per-month incremental costs were $0.02, $0.06 and $0.10 in Years 1, 2 and 3, respectively.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. US Burden of Disease Collaborators. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA* 310(6), 591–608 (2013).
2. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2019 National Survey on Drug Use and Health (HHS Publication No. PEP20-07-01-001, NSDUH Series H-55) (2020). https://www.samhsa.gov/data/sites/default/files/reports/rpt29393/2019NSDUHFFRPDFWHTML/2019NSDUHFFR090120.htm
3. American Psychiatric Association. Major depressive disorder. In: *Diagnostic and Statistical Manual of Mental Disorders (5th Edition).* American Psychiatric Publishing, VA, USA, 160–168 (2013).
4. Hasin DS, Sarvet AL, Meyers JL *et al.* Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry* 75(4), 336–346 (2018).
5. Holma KM, Melartin TK, Haukka J, Holma IA, Sokero TP, Isometsa ET. Incidence and predictors of suicide attempts in DSM-IV major depressive disorder: a five-year prospective study. *Am. J. Psychiatry* 167(7), 801–808 (2010).
6. Sokero TP, Melartin TK, Rytsala HJ, Leskela US, Lestela-Mielonen PS, Isometsa ET. Suicidal ideation and attempts among psychiatric patients with major depressive disorder. *J. Clin. Psychiatry* 64(9), 1094–1100 (2003).
7. Lopez-Castroman J, Jaussent I, Gorwood P, Courtet P. Suicidal depressed patients respond less well to antidepressants in the short term. *Depress. Anxiety* 33(6), 483–494 (2016).
8. Greenberg PE, Fournier A-A, Sisitsky T *et al.* The economic burden of adults with major depressive disorder in the United States. *Pharmacoeconomics* 39(6), 653–665 (2021).

9. Benson C, Singer D, Carpinella CM, Shawi M, Alphs L. The health-related quality of life, work productivity, healthcare resource utilization, and economic burden associated with levels of suicidal ideation among patients self-reporting moderately severe or severe major depressive disorder in a national survey. *Neuropsych. Dis. Treat.* 17(2), 111–123 (2021).
10. Neslusan C, Voelker J, Lingohr-Smith M, Lin J. Characteristics of hospital encounters and associated economic burden of patients with major depressive disorder and acute suicidal ideation or behavior. *Hosp. Pract.* 49(3), 176–183 (2021).

•• **Retrospective analysis of hospital encounters among US patients with MDSI in the USA showed heterogeneity in care and high rates of costly subsequent hospital encounters.**

11. Jacobs DG, Baldessarini RJ, Conwell Y *et al.* Assessment and treatment of patients with suicidal behaviors. In: *APA Practice Guidelines*. 1–183 (2010).
12. Spravato. SPRAVATO® (esketamine) nasal spray, CIII [package insert]. Janssen Pharmaceuticals, Inc., NJ, USA (2020).
13. Ionescu DF, Fu DJ, Qiu X *et al.* Esketamine nasal spray for rapid reduction of depressive symptoms in patients with major depressive disorder who have active suicide ideation with intent: results of a Phase III, double-blind, randomized study (ASPIRE II). *Int. J. Neuropsychopharmacol.* 24(1), 22–31 (2021).

• **Phase III study (ASPIRE II), designed identically to ASPIRE I, showed esketamine plus comprehensive standard of care rapidly improved depressive symptoms in patients with MDSI.**

14. Fu DJ, Ionescu DF, Li X *et al.* Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients who have active suicidal ideation with intent: double-blind, randomized study (ASPIRE I). *J. Clin. Psychiatry* 81(3), doi:10.4088/JCP.19m13191 (2020) (Epub ahead of print).

• **Phase III study (ASPIRE I) showed esketamine nasal spray + standard of care was effective in rapidly improving depressive symptoms in patients with MDSI compared with placebo + standard of care.**

15. Sullivan SD, Mauskopf JA, Augustovski F *et al.* Budget impact analysis – principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health* 17(1), 5–14 (2014).
16. 2017 National population projections tables. https://www.census.gov/data/tables/2017/demo/popproj/2017-summary-tables.htm
17. Substacne Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53) (2019). https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.pdf
18. Kuvadia H, Wang K, Daly E *et al.* National trends in the prevalence of major depressive disorder with suicidal ideation among adults using the National Survey on Drug Use and Health. Presented at: *32nd Annual Psych Congress.* CA, USA, 3–9 October 2019.

• **Retrospective analysis of national trends in incidence of major depressive disorder and MDSI among adults in the USA showed increased prevalence of major depressive disorder and MDSI from 2009 to 2017, with trends in prevalence of MDSI varying by sociodemographic characteristics.**

19. Red Book Pricing. HIS global pricing and reimbursement: AnalySource drug pricing resource (2018). https://www.analysource.com/
20. Zhdanava M, Voelker J, Pilon D *et al.* Cluster analysis of care pathways in adults with major depressive disorder with acute suicidal ideation or behavior in the USA. *Pharmacoeconomics* 39(6), 707–720 (2021).

• **Cluster analysis of patients with MDSI before and after a suicide-related event found exposure to the healthcare system prior to the event to be a key differentiator of postindex care across clusters.**

21. Kroll DS, Karno J, Mullen B, Shah SB, Pallin DJ, Gitlin DF. Clinical severity alone does not determine disposition decisions for patients in the emergency department with suicide risk. *Psychosomatics* 59(4), 388–393 (2018).
22. Gelenberg AJ, Freeman MP, Markowitz JC *et al.* Practice guideline for the treatment of patients with major depressive disorder third edition. *Am. J. Psychiatry* 167(10), 1 (2010).
23. Zero Suicide Institute. Toolkit (2021). https://zerosuicide.edc.org/toolkit/treat
24. Jordan JT, Mcniel DE. Perceived coercion during admission into psychiatric hospitalization increases risk of suicide attempts after discharge. *Suicide Life-threatening Behav.* 50(1), 180–188 (2020).
25. Hawley CJ, Gale TM, Smith PS *et al.* Equations for converting scores between depression scales (MADRS, SRS, PHQ-9 and BDI-II): good statistical, but weak idiographic, validity. *Hum. Psychopharmacol.* 28(6), 544–551 (2013).
26. Santarsieri D, Schwartz TL. Antidepressant efficacy and side-effect burden: a quick guide for clinicians. *Drugs Context* 4, 212290 (2015).