Factors Associated With Fulfillment of First Esketamine Prescription Among Patients With Treatment-Resistant Depression in the United States

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Background

- Esketamine nasal spray is an innovative outpatient therapy for treatment-resistant depression (TRD) approved in the United States (US) on March 5, 2019[1-3]
- Access to esketamine can be challenging due to insurance coverage limitations, availability of local treatment centers, transportation, and time necessary to receive treatment[4,5]
- Patient characteristics and factors contributing to primary nonadherence[6] - when patients prescribed esketamine do not start treatment within an acceptable time frame or at all - are not well understood
- The objective of this study was to quantify the fulfillment rate of the first esketamine prescription and identify factors associated with prescription fulfillment among patients with TRD in the US

Methods

Data source

- This study used HealthVerity® Veradigm® electronic medical record (EMR) data linked with Inovalon Insights Source 20 medical and pharmacy claims (January 1, 2016 to March 3, 2024)
- Data were de-identified and complied with the Health Insurance Portability and Accountability Act

Study design

- A retrospective observational study design was used
- The index date was the date of the first esketamine prescription
- The baseline period spanned 12 months before the index date and was used to describe patient characteristics
- The follow-up period spanned the index date until the end of health plan eligibility or data availability and was used to report time to fulfillment of the first esketamine prescription
- To identify characteristics associated with prescription fulfillment, patients were stratified into two groups based on fulfillment of the prescription during the first 90 days of the follow-up period (the landmark period)

Study sample

- All patients met the following criteria:
  - First prescription of esketamine in EMR data was on or after March 5, 2019 (index date), and no claims for esketamine occurred before this date
  - Evidence of TRD as of the index date (≥2 unique antidepressant therapies of adequate dose and duration within the same major depressive episode [MDE] as the index date); MDE was defined as no gaps of ≥180 days between antidepressant fills or major depressive disorder (MDD) diagnoses
  - ≥1 diagnosis of major depressive disorder during the same MDE as the index date (*International Classification of Diseases, Tenth Revision, Clinical Modification*: F32.X [excluding F32.A and F32.8], F33.X [excluding F33.8])
  - Aged ≥18 years as of the index date
  - ≥12 months of continuous insurance eligibility before the index date
- Patients in the analysis of characteristics associated with fulfillment of the first esketamine prescription met the following additional criteria:
  - ≥90 days of continuous eligibility after the index date
  - Known region of residence and insurance plan on the index date

Outcome measures

- Fulfillment of the first esketamine prescription was defined as ≥1 medical or pharmacy claim for esketamine on or after the date of the first prescription

Statistical analysis

- Kaplan-Meier survival analysis was used to describe time to prescription fulfillment from the index date; patients who did not fulfill the prescription were censored at the end of follow-up
- Modified Poisson regression models with robust error variance were used to evaluate patient characteristics associated with fulfillment of the first esketamine prescription within the first 90 days

Results

Patient characteristics

- A total of 473 patients were included in the study (patient characteristics are reported in **Table 1**)

Table 1: Patient baseline characteristics

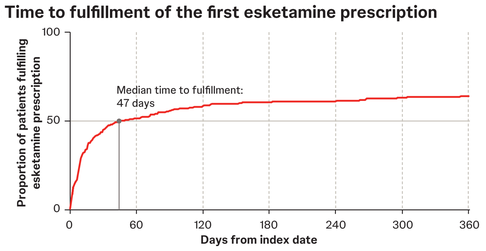
Mean ± SD [median] or n (%)	Esketamine cohort N = 473
Age, years	42.4 ± 13.1 [42.0]
(Min | Q1 | IQR | Q3 | Max)	18 | 32 | 21 | 53 | 76
Age categories	
18-34	146 (30.9)
35-44	129 (27.3)
45-54	93 (19.7)
55-64	89 (18.8)
Above 65	16 (3.4)
Female	290 (61.3)
Race/ethnicity	
White	218 (46.1)
Hispanic	25 (5.3)
Asian	19 (4.0)
Black	5 (1.1)
Other	14 (3.0)
Unknown or missing	192 (40.6)
Geographic region	
West	173 (36.6)
South	150 (31.7)
Northeast	79 (16.7)
North central	70 (14.8)
Unknown	1 (0.2)
Type of insurance plan	
Commercial	285 (60.3)
Medicaid	166 (35.1)
Medicare Advantage	18 (3.8)
Unknown	4 (0.8)
Year of index date	
2019	77 (16.3)
2020	64 (13.5)
2021	69 (14.6)
2022	124 (26.2)
2023	118 (24.9)
2024	21 (4.4)
Comorbid conditions	
Anxiety disorders	409 (86.5)
Sleep-wake disorders	208 (44.0)
Neurodevelopment disorders	172 (36.4)
Hypertension	148 (31.3)
Obesity	136 (28.8)
Drug abuse	113 (23.9)
Antidepressant use	
Number of unique antidepressants received	
SSRI	2.9 ± 1.3 [3.0]
SNRI	256 (54.1)
SMOD	254 (53.7)
NDRI	247 (52.2)
Mental health–related resource utilization (PPPM)	224 (47.4)
Number of inpatient days	1.6 ± 4.9 [0.0]
Number of emergency department visits	0.1 ± 0.2 [0.0]
Number of outpatient visits	3.7 ± 4.5 [2.4]

IQR, interquartile range; max, maximum; min, minimum; NDRI, norepinephrine-dopamine reuptake inhibitor; PPPM, per-patient-per-month; Q1, first quartile; Q3, third quartile; SD, standard deviation; SMOD, serotonin modulator; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Time to fulfillment of the first esketamine prescription

- Median time to fulfillment of the first esketamine prescription was 47 days (**Figure 1**); 55.7% of patients filled the prescription within 90 days, and 60.5% of patients filled it within 180 days (typically, a prescription is valid for 6 months[7])

Figure 1: Time to fulfillment of the first esketamine prescription



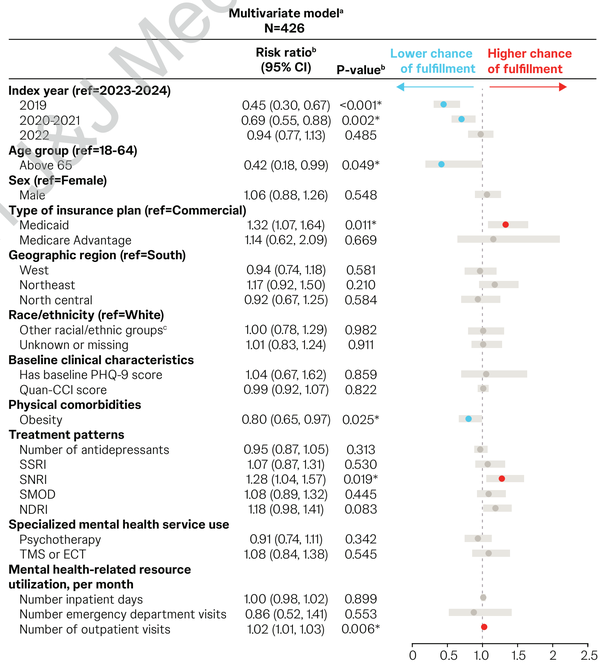
	30 days	60 days	90 days	180 days	360 days
KM rate (95% CI), %	45.3 (40.9, 49.9)	51.5 (47.0, 56.1)	55.7 (51.2, 60.3)	60.5 (56.0, 65.0)	63.9 (59.4, 68.4)
Patients at risk, n (%)	252 (53.3)	212 (44.8)	188 (39.8)	152 (32.1)	117 (24.7)
Patients censored, n (%)	10 (2.1)	20 (4.2)	26 (5.5)	42 (8.9)	65 (13.7)

CI, confidence interval; KM, Kaplan-Meier.

Patient characteristics associated with fulfillment of the first esketamine prescription within 90 days

- A total of 426 patients were included in this analysis
- Controlling for other factors, sex, region, behavioral comorbidities, and baseline psychotherapy, electroconvulsive therapy, or transcranial magnetic stimulation use did not significantly impact fulfillment of the first esketamine prescription (**Figure 2**)
- While race was included in the model, 40.1% of patients had unknown or missing race; therefore, no definitive statement can be made about race as a factor associated with fulfillment of the first esketamine prescription
- Factors associated with lower chances of fulfillment of the first esketamine prescription included:
  - Age over 65 years (57.6% lower chances)
  - Obesity (20.2% lower chances)
  - Being prescribed with esketamine early after US Food and Drug Administration approval, specifically in 2019 and 2020-2021 relative to 2023 and early 2024 (55.0% and 30.5% lower chances, respectively)
- Factors associated with higher chances of fulfillment of the first esketamine prescription included:
  - Medicaid insurance coverage (32.3% higher chances relative to commercial coverage)
  - Baseline use of serotonin-norepinephrine reuptake inhibitors (SNRIs) (27.8% higher chances)
  - Each additional mental health-related outpatient visit during the baseline period (2.0% higher chances)

Figure 2: Patient characteristics associated with fulfillment of the first esketamine prescription within 90 days



ECT, electroconvulsive therapy; NDRI, norepinephrine-dopamine reuptake inhibitor; PHQ-9, 9-item Patient Health Questionnaire; Quan-CCI, Quan-Charlson Comorbidity Index; SMOD, serotonin modulator; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TMS, transcranial magnetic stimulation.
Asterisks (*) denote statistical significance at the 5% level.
[a]Additional nonsignificant covariates included in the model but not shown in the figure were behavioral comorbidities (anxiety disorders, sleep-wake disorders, neurodevelopmental disorders, attention-deficit hyperactivity disorders, trauma- and stressor-related disorders, bipolar and related disorders, suicidal ideation or probable attempt, personality disorders, substance-related and addictive disorders) and physical comorbidities (hyperlipidemia/dyslipidemia, hypertension, insomnia, hypothyroidism, chronic pulmonary disease, asthma, fluid and electrolyte disorders, diabetes, other neurological disorders).
[b]Risk ratios and P values were generated using modified Poisson regression with robust error variance.
[c]Includes Asian, Black, Hispanic, and other racial/ethnic minorities.

Limitations

- Analyses were limited to insured adults in the US; therefore, results may not be generalizable to uninsured patients
- Pharmacy claims were used to identify evidence of TRD and do not guarantee that the medication dispensed was taken as prescribed or capture medications provided either over the counter or as samples
- Race was unknown in a substantial proportion of patients; results could also be subject to residual confounding due to other unmeasured characteristics (e.g., depression severity, socioeconomic status, distance to nearest treatment center, availability of own transportation, marital status, or caregiver availability)

Conclusions

- Fulfillment of the first esketamine prescription occured within 3 months for the majority of patients
- The rates of fulfillment of the first esketamine prescription improved historically, which may reflect growing awareness and accessibility of esketamine therapy; however, barriers such as older age and obesity suggest a need for targeted interventions to improve access
- Positive association of baseline SNRI use with esketamine prescription fulfillment confirms that the therapy is reserved for patients with previous treatment failure
- Higher rates of fulfillment of the first esketamine prescription among Medicaid beneficiaries and patients actively engaged in mental health care emphasize the critical role of affordability and consistent outpatient support among this patient population

Disclosures
TH is a contracted scientific advisor for Janssen Scientific Affairs, LLC. He is also a sub-investigator for the PCORI EQUIVALENCE and OBSERVE clinical trials and a practicing psychiatrist with the Mood Institute.
YD and BKB are employees and stockholders of Johnson & Johnson. MZ, AS, BL, ZC, and DP are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Janssen Scientific Affairs, LLC., a Johnson & Johnson company, which funded the development and conduction of this study.

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