Factors Associated With Reaching Remission on Esketamine Among Patients With Treatment-Resistant Depression in the United States

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Introduction

- Esketamine nasal spray, an innovative therapy for treatment-resistant depression (TRD), was approved in the United States (US) in March 2019
- Its efficacy was demonstrated in multiple multicenter, randomized, phase 3 trials and in the real world[1-3]
- However, little is known about predictors of remission following esketamine initiation

Objective

- To evaluate predictors of remission defined based on the 9-item Patient Health Questionnaire (PHQ-9) scores among patients with TRD treated with esketamine

Methods

Data source

- Open claims from Komodo Research Database and PHQ-9 scores from Komodo Clinical Observations Database were used (January 2016 to June 2023)
- Data were de-identified and complied with the Health Insurance Portability and Accountability Act

Study design

- A retrospective cohort study design was used
- The intake period spanned from March 5, 2019, to the end of data; the index date was the date of esketamine initiation
- Patient clinical activity was defined based on the first and last claim or clinical measure observed in the data
- The baseline period included the 12 months of clinical activity before the index date; the follow-up period spanned the index date until the earliest of 1) clinical activity end, 2) data availability end, 3) on-treatment period end (i.e., up to 30 days after the last esketamine session)

Sample selection

- Patients met the following selection criteria:
  - Had ≥1 major depressive disorder diagnosis (*International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM]: F32.X [excluding F32.A and F32.8], F33.X [excluding F33.8])
  - Initiation of esketamine during the intake period
  - Evidence of TRD before the index date (i.e., ≥2 unique antidepressants of adequate dose and duration during the major depressive episode that includes the index date)
  - Aged ≥18 years on the index date
  - Had ≥12 months of clinical activity before the index date and ≥6 months of clinical activity after the index date
  - Baseline PHQ-9 score of ≥10 and ≥1 follow-up PHQ-9 score
  - No evidence of psychosis, schizophrenia, schizoaffective disorder, and other non-mood psychotic disorders during baseline period
  - Known insurance type at index date

Outcomes measures

- The PHQ-9 is a patient-reported measure with a 2-week recall period, scored from 0 to 27, with higher scores reflecting greater severity of symptoms[4]
- Remission was defined as a PHQ-9 score of <5 measured during the follow-up period

Statistical analysis

- Multivariate Cox proportional hazards model was used to evaluate factors associated with remission; patients who did not achieve remission during the follow-up period were censored at the end of follow-up

Results

Baseline characteristics

- A total of 184 patients were included in the study. Baseline characteristics of these patients are reported in **Table 1**
- Patients had an average baseline PHQ-9 score of 18.4, indicating moderately severe depression[5]

Table 1: Patients baseline characteristics

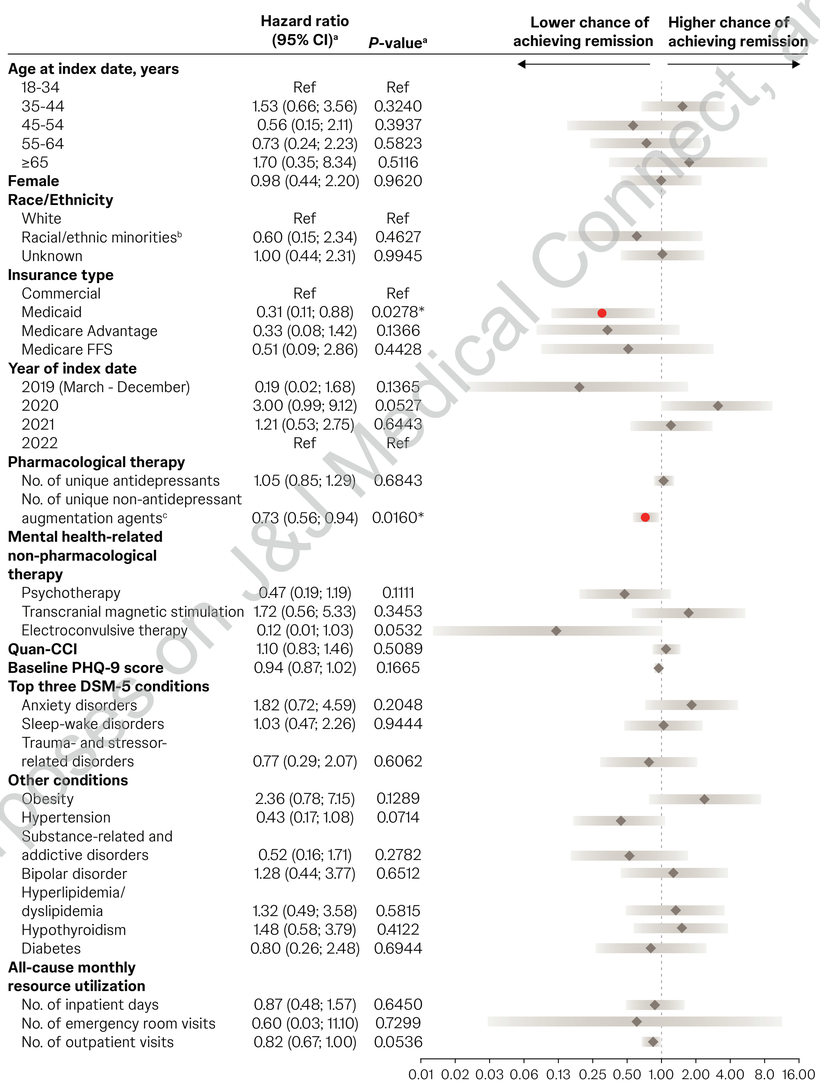
n (%) or mean ± SD [median]	Patients receiving esketamine N = 184
Age at index date, years	43.1 ± 14.3 [40.0]
18-34	62 (33.7)
35-44	48 (26.1)
45-54	26 (14.1)
55-64	32 (17.4)
≥65	16 (8.7)
Female	114 (62.0)
Race/Ethnicity	
White	102 (55.4)
Racial/ethnic minorities[a]	27 (14.7)
Unknown	55 (29.9)
Insurance type	
Commercial	116 (63.0)
Medicaid	41 (22.3)
Medicare Advantage	17 (9.2)
Medicare FFS	10 (5.4)
Year of index date	
2019 (March - December)	11 (6.0)
2020	24 (13.0)
2021	69 (37.5)
2022	80 (43.5)
Pharmacologic therapy	
Number of unique antidepressants	3.2 ± 1.8 [3.0]
Number of unique non-antidepressant augmentation agents[b]	2.4 ± 1.5 [2.0]
Augmentation with second-generation antipsychotics[c]	92 (50.0)
Mental health–related non-pharmacological therapy	
Psychotherapy	147 (79.9)
Transcranial magnetic stimulation	30 (16.3)
Electroconvulsive therapy	16 (8.7)
Quan-CCI	0.9 ± 1.7 [0.0]
Baseline PHQ-9 score	18.4 ± 4.6 [18.0]
Top three DSM-5 conditions	
Anxiety disorders	145 (78.8)
Sleep-wake disorders	85 (46.2)
Trauma- and stressor-related disorders	51 (27.7)
Other conditions	
Hyperlipidemia/dyslipidemia	58 (31.5)
Obesity	55 (29.9)
Hypertension	51 (27.7)
Hypothyroidism	35 (19.0)
Substance-related and addictive disorders	34 (18.5)
Diabetes	31 (16.8)
Bipolar disorder	29 (15.8)
All-cause monthly resource utilization	
Number of inpatient days	0.28 ± 1.16 [0.00]
Number of emergency room visits	0.12 ± 0.37 [0.00]
Number of outpatient visits	3.81 ± 2.74 [3.21]

DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; FFS, fee-for-service; PHQ-9, 9-item Patient Health Questionnaire; Quan-CCI, Quan-Charlson Comorbidity Index; SD, standard deviation.
[a]Racial/ethnic minorities include Asian, Black, Hispanic, and other racial/ethnic groups.
[b]Non-antidepressant augmentation agents included anticonvulsants, non-benzodiazepine anxiolytics, psychostimulants, second-generation antipsychotics and thyroid hormones, as well as lithium and atomoxetine.
[c]Second generation antipsychotics included aripiprazole, brexpiprazole, olanzapine with fluoxetine, and quetiapine.

Factors associated with reaching remission

- Holding everything else equal, age, sex, race, as well as baseline comorbidities had no impact on chances of reaching remission
- Medicaid relative to commercial insurance was associated with 69% lower chances of reaching remission
- Further, each additional non-antidepressant augmentation agent used during the baseline period was associated with 27% lower chances of reaching remission (**Figure 1**)

Figure 1: Factors associated with reaching remission



CI, confidence interval; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; FFS, fee-for-service; PHQ-9; 9-item Patient Health Questionnaire; Quan-CCI, Quan-Charlson Comorbidity Index.
*indicates statistical significance at 5%.
[a]Hazard ratios and *p*-values were generated using multivariable Cox proportional hazard models. Patients without remission are censored at the end of the follow-up period.
[b]Racial/ethnic minorities include Asian, Black, Hispanic, and other racial/ethnic groups.
[c]Non-antidepressant augmentation agents included anticonvulsants, non-benzodiazepine anxiolytics, psychostimulants, second-generation antipsychotics and thyroid hormones, as well as lithium and atomoxetine.

Limitations

- TRD was identified based on pharmacy claims; pharmacy claims do not guarantee that the medication dispensed was taken as prescribed
- In approximately one-third of patients, race was unknown, which does not allow for reliably estimating race as a predictor of remission
- PHQ-9 score is patient-reported and can be subject to recall bias
- Results could be subject to residual confounding due to unmeasured patient characteristics (e.g., socioeconomic status, family history)

Conclusions

- The results highlight esketamine's effectiveness in achieving remission across diverse patients, irrespective of their baseline comorbidities, age, or sex
- Medicaid insurance is linked to factors that may increase patient distress; implementing care coordination for scheduling and reminders, providing transportation assistance, and offering social support could help improve treatment outcomes in this vulnerable population
- Considering esketamine earlier in the treatment course, rather than after multiple failed augmentation strategies, may be beneficial for treatment outcomes

Disclosures

KC has served on an advisory board for Janssen Pharmaceuticals. MZ, AV, AT-S, FJ, 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. YD is an employee and stockholder of Johnson & Johnson.

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