The Association Between Adherence to Esketamine Nasal Spray Therapy Dosing Regimen and Changes in Depressive Symptoms Among Patients With Treatment-Resistant Depression in the United States

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Background

- Treatment-resistant depression (TRD) is commonly defined as inadequate response to ≥2 antidepressant treatment courses of adequate dose and duration in the current episode among patients with major depressive disorder (MDD)[1,2]
- Estimates of TRD prevalence among adults with MDD vary but typically range between 30% and as high as 55%[2,3]
- Esketamine nasal spray (ESK) was approved by the US Food and Drug Administration in 2019 for the treatment of TRD in conjunction with an oral antidepressant under the Risk Evaluation and Mitigation Strategy program
- The ESK label recommends treatment administration twice a week for a 4-week induction period. After this, weekly treatments are recommended until week 8, with the option to reduce frequency to biweekly depending on symptom improvement
- Studies have demonstrated reductions in depressive symptoms associated with ESK in patients with TRD[4,5]

Objective

- To assess the association between adherence to ESK dosing regimen during induction phase and change in depressive symptoms as measured by the PHQ-9 among patients with TRD in a real-world setting

Methods

Data source

- Data were sourced from the PremiOM™ MDD Dataset (OM1, Boston, MA), a continuously updated cohort of over 440,000 patients with MDD in the United States with linked claims and electronic medical record (EMR) data

Study design

- A retrospective observational cohort study of patients with TRD treated with ESK between March 2019 and June 2022 was conducted
- The index date was the date of the first ESK prescription (written or filled)
- The baseline period was the 6-month period prior to and including the index date, and the follow-up period was the 6-month period after index
- ESK therapy dates were identified using medical claims and review of relevant unstructured clinical notes from EMRs by expert abstractors
- Patients who completed 6 or more sessions within 30 days of the first ESK treatment (i.e., 75% of recommended doses during induction phase) were categorized as adherent

TRD definition

- Documented history of ≥2 unique antidepressants of adequate dose and duration at any time prior to the index date and within the same major depressive episode, defined as no clean period of ≥180 days without antidepressants and/or MDD diagnoses between either the 2 most recent unique antidepressants of adequate dose and duration and the most recent antidepressant of adequate dose and duration and the index date (**Figure 1**)

Inclusion criteria

- Initiated ESK on or after March 2019 with no prior indications of use (documented evidence of prescriptions written or filled)
- ≥18 years of age on the index date
- ≥1 diagnosis for MDD during the 6 months prior to or on the index date
- Met criteria for TRD
- Linked claims and EMR for at least 6 months before and at least 6 months after the index date
- At least one 9-Item Patient Health Questionnaire (PHQ-9) score during the 6 months before and at least one PHQ-9 score during the 6 months after the index date
- Information confirming at least one ESK treatment session in unstructured clinical notes within 30 days after index date

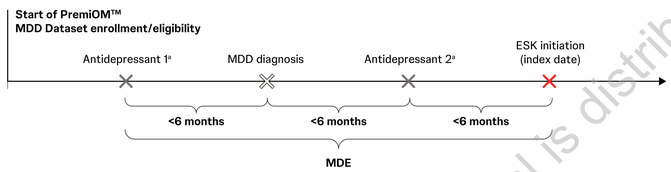
Outcome measure

- The PHQ-9 was used to measure depressive symptom severity[6]
- A machine learning model was used to estimate PHQ-9 scores for patient encounters using routinely recorded information from relevant clinical notes[7]
- Estimated scores were only used if observed scores were missing for the time window of interest
- The most recent PHQ-9 score in the 6 months prior to or on index date was used as the baseline score
- Baseline scores were compared to the most recent scores in the >0-3–month and >3-6–month windows after the index date
- For the adherence analysis, only PHQ-9 scores captured after the 30-day induction phase were used as follow-up scores
- Clinical significance of reductions in mean PHQ-9 scores by group were evaluated based on results from pooled clinical trial data assessing ESK among TRD patients with a clinically meaningful improvement defined as a 3-point reduction in mean PHQ-9 scores and a clinically substantial improvement defined as a 6-point reduction in mean PHQ-9 scores[8]

Statistical analysis

- Paired t-tests were performed to test statistical significance of changes in PHQ-9 scores between the baseline and follow-up time windows of interest
- Effect sizes were estimated using Cohen's d

FIGURE 1: Definition of treatment-resistant depression



MDD, major depressive disorder; MDE, major depressive episode; ESK, esketamine nasal spray.
[a]Antidepressants 1 and 2 must be of adequate dose and duration.

Results

Patient characteristics

- A total of 64 patients met inclusion criteria, of whom 35 patients were adherent and 29 were not adherent
- Patients who were non-adherent were more likely to have received a diagnosis for anxiety disorder (75.9% among non-adherent patients and 48.6% among adherent patients), attention-deficit/hyperactivity disorder (34.5% among non-adherent patients vs 22.9% among adherent patients), bipolar disorder (24.1% among non-adherent patients and 11.4% among adherent patients), or hypertension (20.7% among non-adherent patients and 8.6% among adherent patients) in the 6 months prior to or on index compared to those who were adherent (**Table 1**)

Changes in PHQ-9 scores

- There were 46 patients treated with ESK with a PHQ-9 score at >0-3 months after index, of which 28 (60.9%) were adherent and 18 (39.1%) were non-adherent
  - The average (SD) PHQ-9 score at baseline was 18.0 (6.2) for adherent patients and 14.1 (6.8) for non-adherent patients
  - The average decrease in PHQ-9 scores among adherent patients was 6.6 (95% CI: 3.6, 9.6, $P < 0.001$, d = 0.85) compared to an average decrease of 3.6 (95% CI: −0.1, 7.2, $P = 0.057$, d = 0.48) among non-adherent patients
- There were 51 patients treated with ESK with a PHQ-9 score at >3-6 months after index, of which 28 (54.9%) were adherent and 23 (45.1%) were non-adherent
  - The average PHQ-9 score at baseline was 16.7 (6.4) among adherent patients and 13.2 (6.9) among non-adherent patients
  - The average (SD) decrease in PHQ-9 scores among the adherent patients was 7.1 (95% CI: 4.5, 9.8, $P < 0.001$, d = 1.05) compared to an average decrease of 4.1 (95% CI: 0.5, 7.8, $P = 0.029$, d = 0.49) among non-adherent patients

TABLE 1: Demographic characteristics of patients included in adherence analysis (N = 64)

	Adherent cohort n = 35	Non-adherent cohort n = 29
Age, years		
Mean (SD)	54.1 (13.9)	51.0 (14.8)
Median (Q1, Q3)	54 (44, 64)	50 (46, 62)
Sex, n (%)		
Female	17 (48.6%)	19 (65.5%)
Male	18 (51.4%)	10 (34.5%)
Race, n (%)		
Black	2 (5.7%)	0 (0.0%)
Caucasian	18 (51.4%)	19 (65.5%)
Unknown	15 (42.9%)	10 (34.5%)
Ethnicity, n (%)		
Hispanic/Latino	2 (5.7%)	0 (0.0%)
Non-Hispanic/Latino	14 (40.0%)	14 (48.3%)
Unknown	19 (54.3%)	15 (51.7%)
Comorbidities, n (%)		
Anxiety	17 (48.6%)	22 (75.9%)
Attention-deficit/ hyperactivity disorder	8 (22.9%)	10 (34.5%)
Bipolar disorder	4 (11.4%)	7 (24.1%)
Hypertension	3 (8.6%)	6 (20.7%)
Insurance, n (%)		
Commercial, Medicare, or Medicaid	20 (57.1%)	21 (72.4%)
US Census region, n (%)		
East North Central	0 (0.0%)	1 (3.4%)
East South Central	2 (5.7%)	0 (0.0%)
Middle Atlantic	2 (5.7%)	2 (6.9%)
Mountain	8 (22.9%)	10 (34.5%)
New England	3 (8.6%)	2 (6.9%)
Pacific	3 (8.6%)	2 (6.9%)
South Atlantic	4 (11.4%)	4 (13.8%)
West North Central	5 (14.3%)	1 (3.4%)
West South Central	8 (22.9%)	7 (24.1%)

Strengths

- Inclusion of medical and pharmacy claims and EMR data from multiple sources provides a rich real-world data source to assess patient outcomes
- Data captured in a real-world setting from multiple sources and a geographically diverse population provides valuable assessment of medication effectiveness

Limitations

- The sample size in this analysis is low. With a small sample size, there is an increased risk of chance effects influencing the results, as well as limitations in statistical power, potentially leading to difficulty in detecting meaningful associations or effects
- This analysis did not include a comparator group, which limits the ability to determine the extent to which the observed declines in PHQ-9 scores are attributable to ESK treatment
- Clinician notes may not fully represent the patient perspective; therefore, estimated PHQ-9 scores may differ from what a patient would have reported if the questionnaire was administered
- The multi-source nature of the data increases the observation time for each patient; however, at a given time, patient data may not be complete and the extent of missing data may vary over time

TABLE 2: Mean change in PHQ-9 scores at 3 and 6 months following initiation of esketamine among adherent and non-adherent users

Follow-up time interval	Adherence[a]	n	Mean (SD) at baseline	Mean (SD) at follow-up	Paired mean difference (SD)	95% CI	*P* value	Cohen's d
>0-3 months	Adherent	28	18.0 (6.2)	11.4 (8.2)	−6.6 (7.8)	−9.6, −3.6	<0.001	0.85
	Not Adherent	18	14.1 (6.8)	10.6 (6.0)	−3.6 (7.4)	−7.2, 0.1	0.057	0.48
>3-6 months	Adherent	28	16.7 (6.4)	9.6 (5.9)	−7.1 (6.8)	−9.8, −4.5	<0.001	1.05
	Not Adherent	23	13.2 (6.9)	9.0 (4.8)	−4.1 (8.5)	−7.8, −0.5	0.029	0.49

[a]Adherence is defined as completing at least 6 sessions within 30 days of the first ESK administration.

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Key takeaway

Decreases in depressive symptoms were observed among all patients with TRD treated with ESK. The largest decreases were observed among patients who were adherent to ESK dosing regimen during the induction phase

Conclusions

- In general, depressive symptoms decreased among patients with TRD treated with ESK
- The average decrease was greater among patients who were adherent compared to those who were non-adherent to the ESK dosing regimen during the induction phase
- Based on recent clinical trial data, the magnitude of mean change among adherent patients corresponded to "clinically substantial improvement," whereas mean change among non-adherent patients corresponded to "clinically meaningful improvement"[8]
- Patients who were non-adherent were more likely to have a comorbid psychiatric diagnosis and had lower PHQ-9 scores at baseline

Disclosures

SGS and CDM are employees of OM1, Inc. KJ is an employee of Janssen Scientific Affairs, LLC, a Johnson & Johnson company. MJ has received contract research grants from Neurocrine Bioscience, Navitor/Supernus and Janssen Research & Development; honorarium to serve as Section Editor of the Psychiatry & Behavioral Health Learning Network and as Guest Editor for Psychiatric Clinics of North America from Elsevier; consultant fees from Janssen Scientific Affairs and Boehringer Ingelheim; fees to serve on Data Safety and Monitoring Board for Worldwide Clinical Trials (Eliem and Inversargo), Vicore Pharma and IQVIA (Click); and honoraria for educational presentations from North American Center for Continuing Medical Education, Medscape/WebMD, Clinical Care Options, H.C. Wainwright & Co. and Global Medical Education.

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