Impact of Duration of Esketamine Nasal Spray Treatment on Change in Depression Symptoms in Real-World Patients

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Background

- Major depressive disorder (MDD) is the leading cause of disability worldwide, with 21 million adults in the United States reporting at least 1 major depressive episode in 2021[1]
- As many as 30% of adults with MDD meet the criteria for treatment-resistant depression (TRD), generally defined as a failure to respond to at least 2 antidepressant trials (ADTs) of adequate dose and duration in a given major depressive episode (MDE)[2]
- Increased severity of depression is associated with incremental economic and productivity burden among employed patients with TRD[3]
- Esketamine nasal spray (ESK) was approved by the FDA for treatment of TRD in adults in 2019. However, there is still a paucity of data on the clinical effectiveness and impact of ESK treatment in real-world settings both acutely and over time

Objective

- To assess the real-world clinical effectiveness of ESK based on changes from baseline in a commonly used clinical scale for depressive symptoms, the 9-item Patient Health Questionnaire (PHQ-9)

Methods

Patient selection criteria

- Osmind makes an electronic health record (EHR) designed to capture structured data from routine mental health visits. Patients were included in the study (the "ESK all-comers" cohort) if they met the following searchable inclusion criteria in the Osmind EHR:
  - ≥18 years old as of the index date confirmed in the Osmind EHR.
  - A diagnosis of MDD, either as confirmed by the patient on the intake assessment, as recorded by a provider, or as provided in referrals or other medical history documentation
  - Received at least 1 ESK treatment (index treatment)
  - Date of the first documented ESK treatment ("index date") occurs on or after March 5, 2019 (ESK approval date for TRD in the United States), and on or before March 31, 2023. The date March 31, 2023, was chosen to allow a minimum period of 90 days between the index date and the end of follow-up period, which spanned until the data cutoff date of June 30, 2023
- Two subgroups for the analyses were then defined as follows:
  - Patients were included in the ESK-TRD cohort if medication source data indicated evidence of use of at least 2 unique ADTs occurring within 2 years (730 days) prior to the index date. Medication source data records included the EHR prescribing system, clinical note text, the patient's psychiatric treatment history recorded in the EHR, and/or the electronic psychiatric intake assessment
  - Induction was complete when ≥8 ESK treatment sessions within 42 days were administered. A 6-week cutoff for completion of the induction was arbitrarily selected, as opposed to the label definition of 28 days, given previous studies of ESK treatment patterns using claims data have shown that the majority of patients do not complete at least 8 treatments within 28 days (the mean number of days to completion was 85 in 1 study)[4]

Outcome measures

- The outcome measure was the change in the PHQ-9 score from baseline to the first PHQ-9 within 30 days of the first ESK treatment and all documented PHQ-9 scores that were obtained thereafter within 30 days of an ESK treatment. Baseline PHQ-9 scores were measured as the most recent documented PHQ-9 prior to the index date, no longer than 30 days prior to the index date

Statistical analysis

- 2 analyses were performed separately for the ESK all-comers and the ESK-TRD cohorts
- First, mixed-effects models were used to evaluate the change in PHQ-9 score from baseline as a function of the number of treatments
- Multiple parameterizations of time were tested to capture the optimal relationship between PHQ-9 scores and the number of ESK treatments and baseline covariates. Key model parameters were interpreted, and estimated marginal means of the model were used to evaluate change from baseline after incremental increases in the number of treatments. These models were also repeated for the induction completers within each cohort
- The time to initial response (50% reduction from baseline PHQ-9 score) was assessed using a survival analysis (Turnbull method)

Results

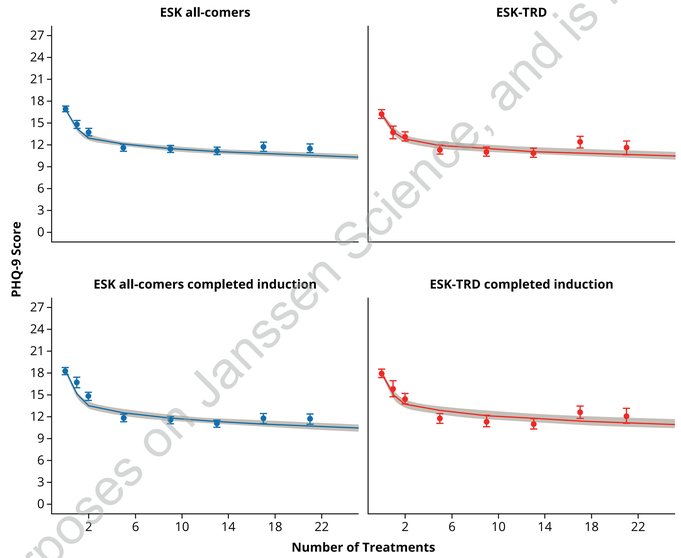
Patient sociodemographic characteristics

- The overall cohort included 664 patients treated with ESK, of which 361 were in the ESK-TRD cohort based on prior ADTs; patient characteristics are shown in **Table 1**
- Patient characteristics were largely consistent between the 2 cohorts with mean age of 45 years and a majority being female (~60%). For ESK-TRD, of the 240 patients with race reported, 95% were White in the ESK all-comers cohort, with a similar race distribution in the ESK-TRD cohort
- The number of ESK treatments were similar for both the ESK-TRD and the ESK all-comers cohorts (**Table 2**). The majority of ESK-TRD patients (~67%) continued to receive ESK beyond the 8-12 treatment induction phase

TABLE 1: Patient sociodemographic characteristics

	ESK all-comers N = 664	ESK-TRD N = 361
Year of index date		
2020	4 (0.6%)	0 (0%)
2021	79 (12%)	37 (10%)
2022	361 (54%)	194 (54%)
2023	220 (33%)	130 (36%)
Age at index date, mean ± SD [median], years	45 ± 15 [43]	45 ± 15 [43]
Female, n (%)	405 (61%)	230 (64%)
Race, n (%)		
American Indian or Alaska Native	1 (0.2%)	1 (0.3%)
Asian	4 (0.6%)	2 (0.6%)
Black or African American	7 (1.1%)	4 (1.1%)
Mixed race	7 (1.1%)	4 (1.1%)
White	394 (59%)	229 (63%)
Unknown/Not documented	251 (38%)	121 (34%)
Ethnicity, n (%)		
Hispanic or Latino	12 (1.8%)	4 (1.1%)
Not Hispanic or Latino	186 (28%)	128 (35%)
Unknown/Not documented	466 (70%)	229 (63%)
Employment status, n (%)		
Employed (full-time)	168 (25%)	91 (25%)
Employed (part-time)	69 (10%)	42 (12%)
Employed and student	9 (1.4%)	3 (0.8%)
Retired	18 (2.7%)	11 (3.0%)
Student	27 (4.1%)	21 (5.8%)
Unemployed	188 (28%)	113 (31%)
Unknown/Not documented	185 (28%)	80 (22%)
Relationship status, n (%)		
Dating	40 (6.0%)	17 (4.7%)
Divorced	61 (9.2%)	35 (9.7%)
Married or partnership	267 (40%)	156 (43%)
Single	166 (25%)	98 (27%)
Widowed	7 (1.1%)	6 (1.7%)
Unknown/Not documented	123 (19%)	49 (14%)
Insurance type, n (%)		
Commercial	409 (62%)	226 (63%)
Medicaid	29 (4.4%)	18 (5.0%)
Medicare	77 (12%)	45 (12%)
Other	22 (3.3%)	10 (2.8%)
Unknown/Not documented	127 (19%)	62 (17%)

FIGURE 1: Change in PHQ-9 scores from baseline to post-ESK treatment



ESK treatment patterns

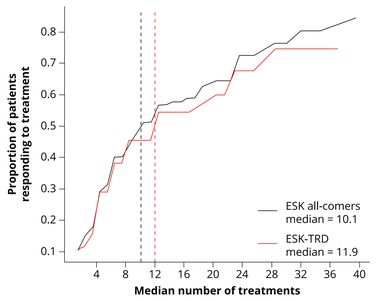
TABLE 2: ESK usage: number of treatments

Number of ESK treatments	ESK all-comers N = 664	ESK-TRD N = 361
1	30 (5%)	16 (4%)
2-4	50 (8%)	25 (7%)
5-8	61 (9%)	32 (9%)
9-12	82 (12%)	46 (13%)
13-16	80 (12%)	43 (12%)
17-20	77 (12%)	46 (13%)
21-26	83 (12%)	52 (14%)
27-32	61 (9%)	43 (12%)
33-44	69 (10%)	32 (9%)
45+	71 (11%)	26 (7%)

ESK outcomes analysis

- Patients in both cohorts had a mean baseline PHQ-9 score of 17.
- Statistically significant reductions from baseline PHQ-9 were observed after as few as 1 treatment, with estimated reductions exceeding 4 points after 5-8 treatments (b = −4.2/−4.9 for ESK-TRD and ESK-all-comers respectively) and larger clinically significant reductions after additional treatment (b = −5.1/−5.9 respectively after 13-16 treatments)[5] **(Figure 1)**
- As shown in the upper panel of **Figure 1**, we found similar patterns of change in PHQ-9 scores over time for the entire patient cohort compared with those patients completing the induction within 42 days (lower panel, completed induction)
- The median number of treatments to initial response was 12 for the ESK-TRD group and 10 for the ESK all-comers group, with response rates continuing to increase beyond those timepoints **(Figure 2)**. The equivalent temporal interval corresponded to a mean of 68 days and 70 days respectively (ESK-TRD/ESK all-comers)
- The survival models predicted that 75% of the ESK-TRD cohort and 85% of the ESK all-comers cohort achieved response to ESK treatment at some point **(Figure 2)**

FIGURE 2: Median number of treatments to attain response



Limitations

- Clinicians do not always report complete data in the EHR. These missing data may include variables such as race, insurance type, employment status, and details of prior medication trials
- Due to variability of medication documentation within the Osmind EHR, we could only confirm the use of 2 prior ADTs within the current episode for a subset of the patients (ESK-TRD); information on adequate dose and duration was not uniformly available

Conclusions

- Reductions in depression symptoms were observed with ESK treatment in real-world patients during the induction phase. Patients continued to improve during the ESK maintenance phase, consistent with a prior real-world treatment pattern study conducted in the United States[6]
- Most patients continue with ESK treatment after 8-12 treatments and clinically significant reductions in depressive symptoms were noted after 12 treatments in the maintenance phase
- More than 75% of the patients with TRD in the real-world setting achieved clinical response by being persistent on ESK, consistent with the SUSTAIN-2 results, in which 79.6% achieved sustained response[7]
- The findings of response rates continuing to increase beyond the induction phase suggests that continuing ESK treatment yields added benefit for patients with TRD

Acknowledgements
We would like to thank Jimmy J. Qian for advice and support.

Disclosures
LAM, MW, and GK are employees of Osmind. LAM is on the scientific advisory board of Clexio Biosciences Ltd.

Presented at the American Society of Clinical Psychopharmacology (ASCP) Annual Meeting; May 28-31, 2024; Miami Beach, Florida

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