Clinical Effectiveness of Esketamine for Treatment-Resistant Depression: A Real-World Study of Patients in Mindful Health Solutions Clinics

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Introduction

- Efficacy of esketamine nasal spray (ESK), approved in the United States (US) on March 5, 2019, for treatment-resistant depression (TRD), has been demonstrated in clinical trials[1,2]
- The 9-item Patient Health Questionnaire (PHQ-9) is a patient-reported measure of depression severity used to evaluate symptom changes in post-hoc analyses of ESK clinical trials[3,4]
- To evaluate real-world effectiveness of esketamine for TRD, PHQ-9 data from Mindful Health Solutions (MHS), a US group clinical practice specializing in ESK administration, was used

Methods

Data source

- Retrospective de-identified data including patient demographics, PHQ-9 scores, and ESK treatment information were obtained from MHS clinics from May 2, 2018, to January 15, 2024
- Institutional review board exemption status under Exemption 45 CFR 46.104(d)(4) was granted prior to commencement of the study

Study design

- Retrospective observational design was used
- The intake period spanned from March 5, 2019, to the end of data; the index date was the date of ESK initiation
- Adults who initiated ESK for TRD in MHS clinics during the intake period and had ≥1 baseline PHQ-9 score were included
- Baseline PHQ-9 score was the score closest to or on the index date; during the follow-up period, which spanned the index date to end of clinical activity or data, PHQ-9 scores within 2 weeks after treatment sessions were obtained

Subgroups

- 2 subgroups were analyzed separately:
  - Subgroup with comorbid anxiety (≥1 diagnosis of anxiety before or on the index date)
  - Subgroup with baseline PHQ-9 score ≥10 indicating moderate-to-severe depression; patients with baseline PHQ-9 score <10 may underreport symptoms

Outcome

- PHQ-9 is a patient-reported measure of depression severity with a recall period of 2 weeks; the score ranges from 0 to 27 with higher scores indicating higher severity[5]

Statistical analysis

- Mean change in PHQ-9 score from baseline and proportion of patients with PHQ-9 score ≥20 (severe depression) were described after ESK initiation and every 4 sessions thereafter
- Generalized estimating equation (GEE) models adjusted for repeated measurements were used to compare follow-up PHQ-9 scores to baseline and non-parametric bootstrap procedures were used to generate 95% confidence intervals (CIs) and *p* values for mean change in PHQ-9 scores

Results

TABLE 1: Patient baseline characteristics

Mean ± SD [median] or n (%)	ESK Cohort Overall N = 911	Subgroup With Comorbid Anxiety N = 624	Subgroup With Baseline PHQ-9 ≥10 N = 773
Age at index date, years	43.7 ± 13.7 [42.0]	43.8 ± 13.3 [43.0]	43.2 ± 13.4 [41.0]
Female	516 (56.6)	357 (57.2)	437 (56.5)
State			
California	892 (97.9)	611 (97.9)	758 (98.1)
Other	19 (2.1)	13 (2.1)	15 (1.9)
Year of index date			
2021	190 (20.9)	145 (23.2)	162 (21.0)
2022	394 (43.2)	265 (42.5)	349 (45.1)
2023	310 (34.0)	202 (32.4)	250 (32.3)
2024	17 (1.9)	12 (1.9)	12 (1.6)
Depression severity[3,4]			
Baseline PHQ-9 score (out of 27)	16.3 ± 6.1 [17.0]	16.3 ± 6.1 [17.0]	18.1 ± 4.5 [18.0]
Moderately severe depression (15-19)	297 (32.6)	205 (32.9)	297 (38.4)
Severe depression (20-27)	293 (32.2)	199 (31.9)	293 (37.9)
Days from baseline score to index date	3.6 ± 12.6 [0.0]	4.0 ± 14.2 [0.0]	3.4 ± 11.8 [0.0]
Baseline PHQ-9 <10 and has baseline MADRS score	102 (11.2)	66 (10.6)	-
Baseline MADRS score (out of 60)	27.8 ± 11.5 [31.5]	26.9 ± 11.7 [31.0]	-
Has baseline MADRS score	849 (93.2)	575 (92.1)	747 (96.6)
Baseline MADRS score (out of 60)[4]	34.9 ± 7.9 [36.0]	34.5 ± 8.2 [36.0]	35.8 ± 6.8 [36.0]

ESK, esketamine nasal spray; MADRS, Montgomery–Åsberg Depression Rating Scale; PHQ-9, 9-item Patient Health Questionnaire; SD, standard deviation.

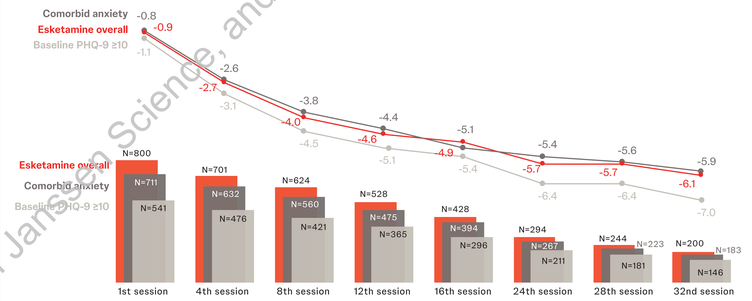
Demographics and baseline characteristics

- Of 911 patients included, 624 (68.5%) patients had comorbid anxiety and 773 (84.9%) had a baseline PHQ-9 score ≥10. Baseline characteristics of these patients are reported in **Table 1**
- Mean duration of follow-up period was 12.8 months in the overall ESK cohort (comorbid anxiety subgroup: 13.8 months; baseline PHQ-9 score ≥10 subgroup: 12.9 months)

Change in depression severity (Figures 1 and 2)

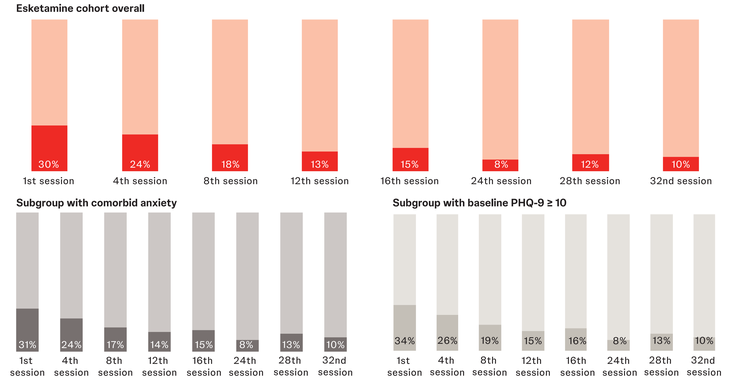
- Mean number of ESK sessions completed was 24.9 in the overall ESK cohort (comorbid anxiety subgroup: 26.2; baseline PHQ-9 score ≥10 subgroup: 26.3)
- After 8 sessions (induction completion):
  - Mean PHQ-9 score decreased by 4.0 points (95% CI: -4.4 to -3.5; $p<0.001$) in the overall ESK cohort
  - Mean PHQ-9 score decreased by 3.8 points (95% CI: -4.3 to -3.4; $p<0.001$) in the comorbid anxiety subgroup
  - Mean PHQ-9 score decreased by 4.5 points (95% CI: -4.9 to -4.0; $p<0.001$) in the baseline PHQ-9 score ≥10 subgroup
  - 17.5% of patients reported severe depression in the overall ESK cohort (comorbid anxiety subgroup: 17.3%; baseline PHQ-9 score ≥10 subgroup: 19.3%)
- After 32 sessions:
  - Mean PHQ-9 score decreased by 6.1 points (95% CI: -6.9 to -5.2; $p<0.001$) in the overall ESK cohort
  - Mean PHQ-9 score decreased by 5.9 points (95% CI: -7.1 to -4.8; $p<0.001$) in the comorbid anxiety subgroup
  - Mean PHQ-9 score decreased by 7.0 points (95% CI: -7.8 to -6.1; $p<0.001$) in the baseline PHQ-9 score ≥10 subgroup
  - 9.5% of patients reported severe depression in the overall ESK cohort (comorbid anxiety subgroup: 10.3%; baseline PHQ-9 score ≥10 subgroup: 9.8%)

FIGURE 1: Mean change in PHQ-9 score from baseline by number of ESK sessions completed[a]



ESK, esketamine nasal spray; PHQ-9, 9-item Patient Health Questionnaire.
[a]All mean changes were statistically significant at the 0.05 level.

FIGURE 2: Proportions of patients with severe depression by number of ESK sessions completed



ESK, esketamine nasal spray; PHQ-9, 9-item Patient Health Questionnaire.

Limitations

- PHQ-9 scores are patient-reported and subject to bias
- Results may not be generalizable to patients receiving ESK in non-MHS clinics, from states other than California, with public insurance or the uninsured

Conclusions

- ESK treatment was associated with clinically meaningful reduction in depressive symptoms (≥3 points on PHQ-9 score)[6] by induction completion
- Improvement in depressive symptoms continued to increase by the 32nd session
- Findings support effectiveness of sustained ESK treatment in TRD

Disclosures
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