Real-World Clinical Effectiveness of Esketamine Nasal Spray Based on the Montgomery-Åsberg Depression Rating Scale (MADRS) Among Patients With Treatment-Resistant Depression in the United States

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Introduction

- Clinical trials for esketamine nasal spray in treatment resistant depression (TRD) often assess efficacy using primary endpoints based on the Montgomery-Åsberg Depression Rating Scale (MADRS)[1-4]
- This analysis explored the real-world clinical effectiveness of esketamine using MADRS data from a large US group psychiatric practice and benchmarked findings against the clinical trial data

Methods

Data source

- Retrospective de-identified data including patient demographics, esketamine treatment information, and MADRS scores, were obtained from Mindful Health Solutions (MHS) clinics from 05/02/2018 to 01/15/2024
- Institutional review board exemption status under Exemption 45 CFR 46.104(d)(4) was granted prior to commencement of the study[5]

Study design

- A retrospective observational design was used
- The intake period spanned from 03/05/2019 to the end of data; the index date was the date of the first esketamine treatment session
- Adults who initiated esketamine for TRD in MHS clinics and had ≥1 baseline MADRS score (most recent score before or on the index date) were included in the overall cohort
  - Subgroup with baseline MADRS score ≥28 (moderate-to-severe depression) was identified separately (consistent with SUSTAIN-3 clinical trial inclusion criteria)[1]
- MADRS scores during the follow-up period, which spanned the index date to end of clinical activity or data, were obtained in 4-week intervals while on esketamine treatment; the most recent score in each 4-week interval was used

Outcomes

- MADRS is a clinician-rated measure of depression severity; scores range from 0 to 60 with higher scores indicating higher severity; it has a recall period of 7 days; however, 4-week intervals were used in this study to maximize sample size[6]
- Response and remission were assessed among patients with a MADRS score ≥28 and defined as below:
  - Response: MADRS score decrease from baseline by ≥50%[4]
  - Remission: MADRS score <12[4]

Statistical analysis

- Generalized estimating equations adjusted for repeated measurements were used to estimate mean change in follow-up MADRS scores from baseline; non-parametric bootstrap procedures were used to generate 95% confidence intervals (CIs) and *P* values
- Kaplan-Meier survival analysis was used to describe time from index date to response and remission; patients without an outcome were censored at the last MADRS score in the data

Results

Demographics and baseline characteristics

- 853 patients were included in the analysis, of which 727 (85.2%) had a baseline MADRS score ≥28; baseline characteristics are reported in **Table 1**

TABLE 1. Baseline demographic and clinical characteristics[a]

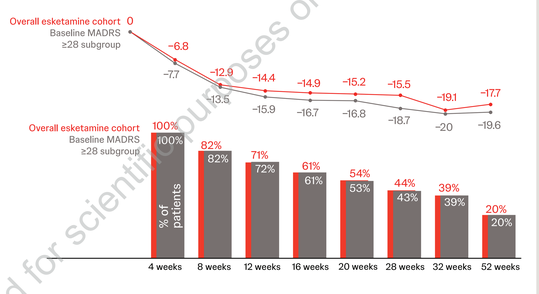
Mean ± SD [median] or n (%)	Overall esketamine cohort N = 853	Baseline MADRS ≥28 subgroup N = 727
Age at index date, years	43.8 ± 13.7 [42.0]	43.6 ± 13.8 [42.0]
Female	489 (57.3)	417 (57.4)
State		
California	838 (98.2)	713 (98.1)
Washington	15 (1.8)	14 (1.9)
Year of index date		
2021	182 (21.3)	134 (18.4)
2022	375 (44.0)	332 (45.7)
2023 and 2024	296 (34.7)	261 (35.9)
MADRS scores		
Baseline MADRS score (out of 60)	34.9 ± 7.9 [36.0]	37.4 ± 4.9 [37.0]
Time from baseline score to index date, days	34.8 ± 38.4 [27.0]	33.0 ± 34.9 [26.0]
Baseline depression levels		
Normal (0-6)	7 (0.8)	0 (0.0)
Mild (7-19)	31 (3.6)	0 (0.0)
Moderate (20-34)	304 (35.6)	216 (29.7)
Severe (35-60)	511 (59.9)	511 (70.3)
PHQ-9 scores		
Patients with a baseline PHQ-9 score	849 (99.5)	723 (99.4)
Baseline PHQ-9 score (out of 27)	16.8 ± 5.7 [17.0]	17.6 ± 5.3 [18.0]

MADRS, Montgomery-Åsberg Depression Rating Scale; PHQ-9, Patient Health Questionnaire 9; SD, standard deviation.

Mean change from baseline MADRS score

- Mean duration of follow-up was 12.9 months in the overall cohort and 12.3 months in baseline MADRS score ≥28 subgroup
- Mean number of esketamine sessions completed was 26.2 in the overall cohort and 26.4 in the baseline MADRS score ≥28 subgroup
- Mean change in MADRS scores from baseline, in the overall cohort and the subgroup, respectively, was as follows (**Figure 1**):
  - After 4 weeks, the score decreased by 6.8 points (95% CI: −7.7 to −6.0; *P* < 0.001) and 7.7 points (95% CI: −8.7 to −6.7; *P* < 0.001)
  - After 8 weeks, the score decreased by 12.9 points (95% CI: −13.8 to −11.9; *P* < 0.001) and 13.5 points (95% CI: −14.6 to −12.5; *P* < 0.001)
  - After 28 weeks, the score decreased by 15.5 points (95% CI: −17.4 to −13.3; *P* < 0.001) and 18.7 points (95% CI: −20.5 to −17.0; *P* < 0.001)
  - After 52 weeks, the score decreased by 17.7 points (95% CI: −20.3 to −15.4; *P* < 0.001) and 19.6 points (95% CI: −22.3 to −17.1; *P* < 0.001)

FIGURE 1. Mean change in MADRS score from baseline

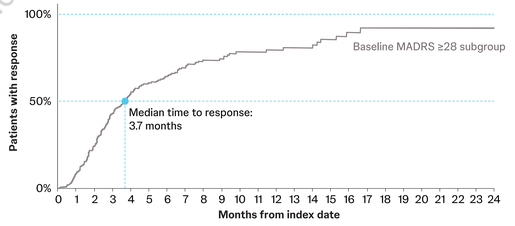


MADRS, Montgomery-Åsberg Depression Rating Scale.

Time to response and remission among the subgroup with baseline MADRS score ≥28

- At 12 months after the index date, the probability of response was 79.4%; the median time to response was 3.7 months (**Figure 2**)
- At 12 months after the index date, the probability of remission was 52.7%; the median time to remission was 10.2 months (**Figure 3**)

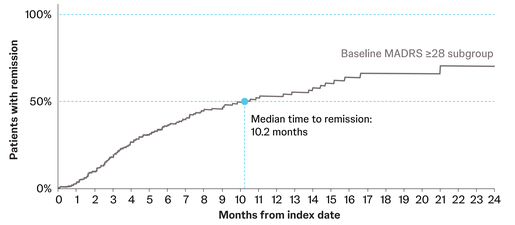
FIGURE 2. Time to response (baseline MADRS score decrease by ≥50%)



	3 months	6 months	9 months	12 months
Patients at risk, n (%)	193 (37.3)	83 (16.0)	34 (6.6)	17 (3.3)
Censored patients, n (%)	146 (28.2)	194 (37.5)	223 (43.1)	234 (45.2)
Kaplan-Meier rates, % (95% CI)	43.1% (38.4; 48.2)	64.7% (59.5; 69.9)	74.2% (68.8; 79.4)	79.4% (73.4; 84.7)

CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale.

FIGURE 3. Time to remission (MADRS score ≤12)



	3 months	6 months	9 months	12 months
Patients at risk, n (%)	269 (51.9)	146 (28.2)	77 (14.9)	47 (9.1)
Censored patients, n (%)	178 (34.4)	251 (48.5)	301 (58.1)	322 (62.2)
Kaplan-Meier rates, % (95% CI)	17.7% (14.2; 21.8)	35.9% (30.9; 41.6)	45.5% (39.6; 51.9)	52.7% (46.0; 59.7)

CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale.

Limitations

Results may not be generalizable to patients receiving esketamine in non-MHS clinics, from states other than California and Washington, with public insurance, or the uninsured

Conclusions

Clinically meaningful reduction in depressive symptoms (≥6 points on the MADRS scale)[7] was observed within 4 weeks of initiating esketamine and was maintained throughout the year

Over three-quarters achieved treatment response and over half achieved remission within a year of esketamine initiation

Findings are consistent with esketamine clinical trials and support the real-world effectiveness of esketamine[3,4]

Disclosures

TM and OE are employees and stockholders of Mindful Health Solutions, as well as honorarium speakers for Janssen Scientific Affairs, LLC, a Johnson & Johnson company. MZ, AS, BM, 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. KJ is an employee and stockholder of Johnson & Johnson.

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