Response and Remission Following Esketamine Nasal Spray Initiation in Treatment-Resistant Depression: Real-World Evidence From a Multi-Site Practice

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Introduction

- Esketamine nasal spray (ESK) was approved for treatment-resistant depression (TRD) in the United States on March 5, 2019[1]
- Real-world evidence supports the effectiveness of ESK, and its use in routine clinical practice has expanded[2-5]
- However, long-term evidence in routine clinical practice remains limited
- The objective of this study was to describe time to response to ESK and remission of depressive symptoms up to 2 years after its initiation among patients with TRD at a large US multi-site psychiatric practice

Methods

Data source

- Retrospective electronic medical records data from Mindful Health Solutions (MHS) clinics (January 2018-August 2025)
  - Data include both patient-reported Patient Health Questionnaire-9 (PHQ-9) and clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS) scores
- Institutional review board exemption status under 45 CFR 46.104(d)(4) was granted prior to commencement of the study

Study design

- A retrospective observational design was used
- The intake period spanned from March 5, 2019, to data cutoff (i.e., August 4, 2025); the index date was the date of ESK initiation
  - The baseline period was the 12-month period prior to the index date
- The baseline PHQ-9 and MADRS scores were the most recent scores before or on the index date
- The follow-up period spanned from the index date through the earliest of ESK discontinuation, end of clinical activity, or end of data

Study population

- ≥1 record of ESK treatment session for TRD in MHS clinics on or after March 5, 2019
- ≥18 years old on the index date
- ≥1 assessment for PHQ-9 and ≥1 assessment for MADRS during baseline and follow-up periods

Outcomes

- PHQ-9[6]
  - Response: ≥50% reduction in PHQ-9 score from baseline
  - Remission: follow-up PHQ-9 score <5
- MADRS[7]
  - Response: ≥50% reduction in MADRS score from baseline
  - Remission: follow-up MADRS score ≤12

Statistical analyses

- Response and remission were evaluated separately based on PHQ-9 and MADRS scores and presented using Kaplan-Meier (KM) survival analysis among patients with moderate-to-severe depression at baseline (PHQ-9 ≥10; MADRS ≥28)
- Patients without an event were censored at the earliest of the last score prior to end of follow-up or end of data

Results

Patient characteristics

- 1201 patients were selected. Patient characteristics are reported in **Table 1**
  - Patients were predominantly commercially insured (84.1%) working-age adults (mean age, 44.5 years)
  - Mean depression severity at ESK initiation was high (MADRS: 35.7, severe range; PHQ-9: 16.9, moderately severe depression)
  - Anxiety was common, with a mean Generalized Anxiety Disorder-7 score of 12.7 (moderate anxiety)
  - Suicidal ideation or attempt was infrequent (0.6%)

Table 1: Patient characteristics

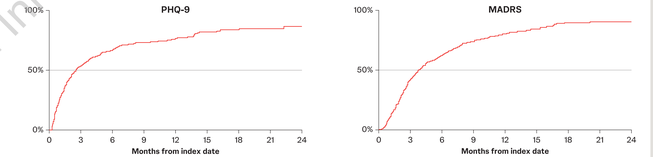
	N = 1201
Age, mean ± SD [median], years	44.5 ± 14.2 [43.0]
Female	700 (58.3)
Insurance	
Commercial	1010 (84.1)
Medicare or Medicare Advantage	142 (11.8)
Medicare	104 (8.7)
Medicare Advantage	38 (3.2)
Other (VA, TriCare, Self-pay, Unknown)	49 (4.1)
Year of index date	
2021	166 (13.8)
2022	316 (26.3)
2023	223 (18.6)
2024	298 (24.8)
2025	198 (16.5)
Selected comorbidities	1195 (100.0)
Neurodevelopmental disorders	194 (16.2)
Trauma- and stressor-related disorders	127 (10.6)
Suicidal ideation or probable attempt	7 (0.6)
Baseline PHQ-9 score (out of 27), mean ± SD [median]	16.9 ± 5.6 [17.0]
Days from baseline score to index date	5.5 ± 14.9 [0.0]
Baseline MADRS score (out of 60), mean ± SD [median]	35.7 ± 7.5 [36.0]
Days from baseline score to index date	32.2 ± 37.2 [24.0]
Baseline GAD-7 (out of 21), mean ± SD [median][a]	12.7 ± 5.5 [13.0]

GAD-7, Generalized Anxiety Disorder-7; MADRS, Montgomery-Åsberg Depression Rating Scale; PHQ-9, 9-item Patient Health Questionnaire; VA, Veterans Affairs.
[a]Among the 1055 patients with a GAD-7 score at baseline.
Data are n (%) unless otherwise specified.

Response

- Based on PHQ-9, the KM probabilities of response were 53.3%, 76.6%, and 86.4% at 3, 12, and 24 months, respectively
- Based on MADRS, the KM probabilities of response were 41.8%, 80.1%, and 90.3% at 3, 12, and 24 months, respectively

Figure 1: Time to response



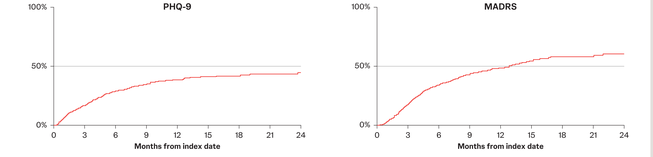
	PHQ-9				MADRS			
	3 months	6 months	12 months	24 months	3 months	6 months	12 months	24 months
N (%) at risk	343 (35.1)	162 (16.5)	50 (5.1)	6 (0.6)	386 (39.6)	182 (18.7)	44 (4.5)	7 (0.7)
KM rates (95% CI)	53.3% (50.0, 56.7)	66.7% (63.2, 70.1)	76.6% (72.8, 80.2)	86.4% (80.8, 91.1)	41.8% (38.4, 45.3)	61.8% (58.2, 65.7)	80.1% (76.1, 83.9)	90.3% (85.8, 93.9)

KM, Kaplan-Meier; MADRS, Montgomery-Åsberg Depression Rating Scale; PHQ-9, 9-item Patient Health Questionnaire.

Remission

- Based on PHQ-9, the KM probabilities of remission were 16.9%, 38.4%, 44.6% at 3, 12, and 24 months, respectively
- Based on MADRS, the KM probabilities of remission were 17.5%, 48.5%, 60.4% at 3, 12, and 24 months, respectively

Figure 2: Time to remission



	PHQ-9				MADRS			
	3 months	6 months	12 months	24 months	3 months	6 months	12 months	24 months
N (%) at risk	615 (63.0)	367 (37.6)	146 (15.0)	46 (4.7)	519 (53.3)	297 (30.5)	109 (11.2)	28 (2.9)
KM rates (95% CI)	16.9% (14.6, 19.6)	28.8% (25.6, 32.2)	38.4% (34.5, 42.6)	44.6% (39.4, 50.1)	17.5% (14.9, 20.4)	34.0% (30.4, 38.0)	48.5% (43.9, 53.3)	60.4% (54.1, 66.8)

KM, Kaplan-Meier; MADRS, Montgomery-Åsberg Depression Rating Scale; PHQ-9, 9-item Patient Health Questionnaire.

Key Takeaways

- ESK treatment shows early improvement with continued gains over time in real-world settings
- Consistent improvements were observed across patient- and clinician-reported measures

Limitations

- A limited number of patients remained at risk at 24 months, particularly for response analyses, due to either rapid response, discontinuation, or end of follow-up; findings should be interpreted with caution
- Results of this study may not be generalizable to patients who receive ESK treatment in non-MHS clinics, the uninsured, or patients covered under Medicaid insurance

Conclusions

- In a real-world setting, most patients with TRD achieved response, and a substantial proportion achieved remission within 2 years of esketamine nasal spray initiation
- Outcomes were consistent across clinician- and patient-reported instruments, supporting the robustness of findings
- These findings provide real-world evidence supporting the long-term effectiveness of esketamine nasal spray in routine clinical practice, as its use continues to expand

Acknowledgments
The authors thank Lynn Brown, PhD, CMPP (ApotheCom, Yardley, PA), for editorial and writing assistance, which was funded by Johnson & Johnson.

Disclosures
TM is an employee and stockholder of Mindful Health Solutions, as well as an honorarium speaker for Johnson & Johnson. DM, YD, and BB are employees of Johnson & Johnson and hold stock in the company. MZ, AV, AT-S, LO, and DP are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Johnson & Johnson, which funded the development and conduct of this study.

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This study was funded by Johnson & Johnson.

Presented at Psych Congress Elevate; June 3-6, 2026; Las Vegas, Nevada, USA

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