Characteristics and Clinical Outcomes of Patients With Treatment-Resistant Depression Completing Esketamine Intranasal Spray Induction Phase in the Veterans Health Administration

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Introduction

- Major depressive disorder (MDD) is a common mental illness in the US veteran population¹
- Treatment-resistant depression (TRD), a difficult-to-treat form of MDD, is most commonly defined as inadequate response to two or more antidepressant (AD) courses of adequate dose and duration²
- While traditional AD therapies usually take several weeks to demonstrate effect, the novel esketamine nasal spray can provide MDD symptom relief as soon as 2 to 4 hours after the first dose³
- Esketamine is administered twice a week for 4 weeks during the induction phase, weekly during the first 4 weeks of the maintenance phase, and weekly or bimonthly thereafter⁴
- The number of completed esketamine treatment sessions has been correlated to the degree of clinical improvement in a real-world retrospective study, highlighting the importance of completing the induction phase⁵
- Given the high prevalence of MDD among veterans, there is a need to better understand effectiveness of esketamine among veterans with TRD completing the induction phase of treatment

Objective

 To describe patient characteristics and clinical outcomes among veterans with TRD who completed esketamine induction phase

Methods

Data source

- This study utilized the Veterans Health Administration (VHA) database from March 5, 2018 (esketamine approval date – 1 year), to January 17, 2025 (latest data; study period)
- VHA is the single largest integrated health system in the US, which provides comprehensive health services to >9 million enrolled veterans across the entire care continuum

Study design

- This was a retrospective observational cohort study
- The study population consisted of adult US veterans who were diagnosed with MDD
- Patients with evidence of TRD during the study period were identified:
- Having ≥3 distinct ADs and ≥1 MDD diagnosis within a 12-month period⁶
- Earliest date of the third qualified AD initiation was considered as the TRD date
- Patients with TRD receiving esketamine on or after March 5, 2019, were selected and indexed on the first esketamine session. All patients were required to have ≥8 sessions (induction phase) during the post-index period, ≥1 total score of the 9-item Patient Health Questionnaire (PHQ-9) within 60 days before or at esketamine initiation, and ≥1 PHQ-9 total score within 7 days of induction phase completion (Figure 1)
- PHQ-9 is a validated, multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression. The total score ranges from 0-27, was the date of TRD. with a higher score indicating more severe depression⁷

- Demographic and baseline clinical characteristics were evaluated in the 12-month baseline period for all
- MDD severity and symptoms assessed by PHQ-9 total and item-level scores were evaluated at esketamine initiation and at induction phase completion

Figure 1: Study design

With ≥1 diagnosis of MDD during the study period (Mar 5, 2018-Jan 17, 2025) N=2,292,045

With evidence of TRD within a 12-month period during the study period¹

With ≥1 esketamine session on or after the date of first evidence of TRD and during Mar 5, 2019-Oct 17, 2024; index date = first qualified esketamine session date

> With ≥12 months of baseline and ≥3 months of follow-up

Aged ≥18 years, resided in the US at index, and with no missing sex or VHA priority

Without evidence (≥2 diagnoses on separate days) of psychosis, schizophrenia, schizoaffective disorder, or other non-mood psychotic disorders anytime during baseline

> Without esketamine during the 12-month baseline period

With ≥8 sessions of esketamine (including the index session) during the ≥3-month follow-up

With ≥1 PHQ-9 score within 60 days before or at index and ≥1 PHQ-9 score within 7 days of induction phase (8th session) completion

Esketamine Cohort

AD, antidepressants; MDD, major depressive disorder; TRD, treatmentresistant depression: VHA, Veterans Health Administration, ^aEvidence of TRD was defined as having ≥1 MDD diagnosis and ≥3 distinct ADs (on GPI-10 level) that are ≥30 days apart within a 12-month period during the study period. The earliest date of the third distinct AD initiation within a 12-month period during the study period

Table 1: Demographic and baseline clinical characteristics

Characteristic	Esketamine cohort (N=80)
Age, years	
Mean (SD)	47.2 (12.9)
Median (Q1-Q3)	44 (37-56)
Male, n (%)	66 (82.5)
Race, n (%)	
White	57 (71.3)
Black or African American	6 (7.5)
Hispanic	8 (10.0)
Asian/Other/Unknown/Missing	9 (11.3)
Geographic region, n (%)	
Northeast	19 (23.8)
Midwest	32 (40.0)
South	9 (11.3)
West	20 (25.0)
Marital status, n (%)	
Married	35 (43.8)
Divorced/separated	22 (27.5)
Widowed	0 (0.0)
Never married	23 (28.8)
MDD severity, n (%) ^a	
Severe	33 (41.3)
Moderate	21 (26.3)
Mild	3 (3.8)
In remission/Unknown	4 (5.0)
Unspecified	19 (23.8)
Quan-Charlson Comorbidity Index	· · · · · · · · · · · · · · · · · · ·
Mean (SD)	0.8 (1.5)
Median (Q1-Q3)	0 (0-1)
Selected non-mental health comorbidities, n (%)b	
Hyperlipidemia	33 (41.3)
Hypertension	27 (33.8)
Obesity	17 (21.3)
Diabetes	17 (21.3)
Osteoarthritis	16 (20.0)
Selected mental health comorbidities, n (%)b	
PTSD	62 (77.5)
Sleep-wake disorder	52 (65.0)
Anxiety disorder	51 (63.8)
Substance use disorder	28 (35.0)

^aObserved MDD severity based on the ICD-10-CM diagnosis code prior to and closest to the

category with <3 patients based on the Veteran Health Admininstration data reporting rule.

bComorbidities were identified by ≥1 outpatient or ≥1 inpatient diagnosis during baseline;

only the most common comorbidities are presented in the table.

index date. The categories of "In remission" and "Unknown" were combined to avoid reporting any

Results

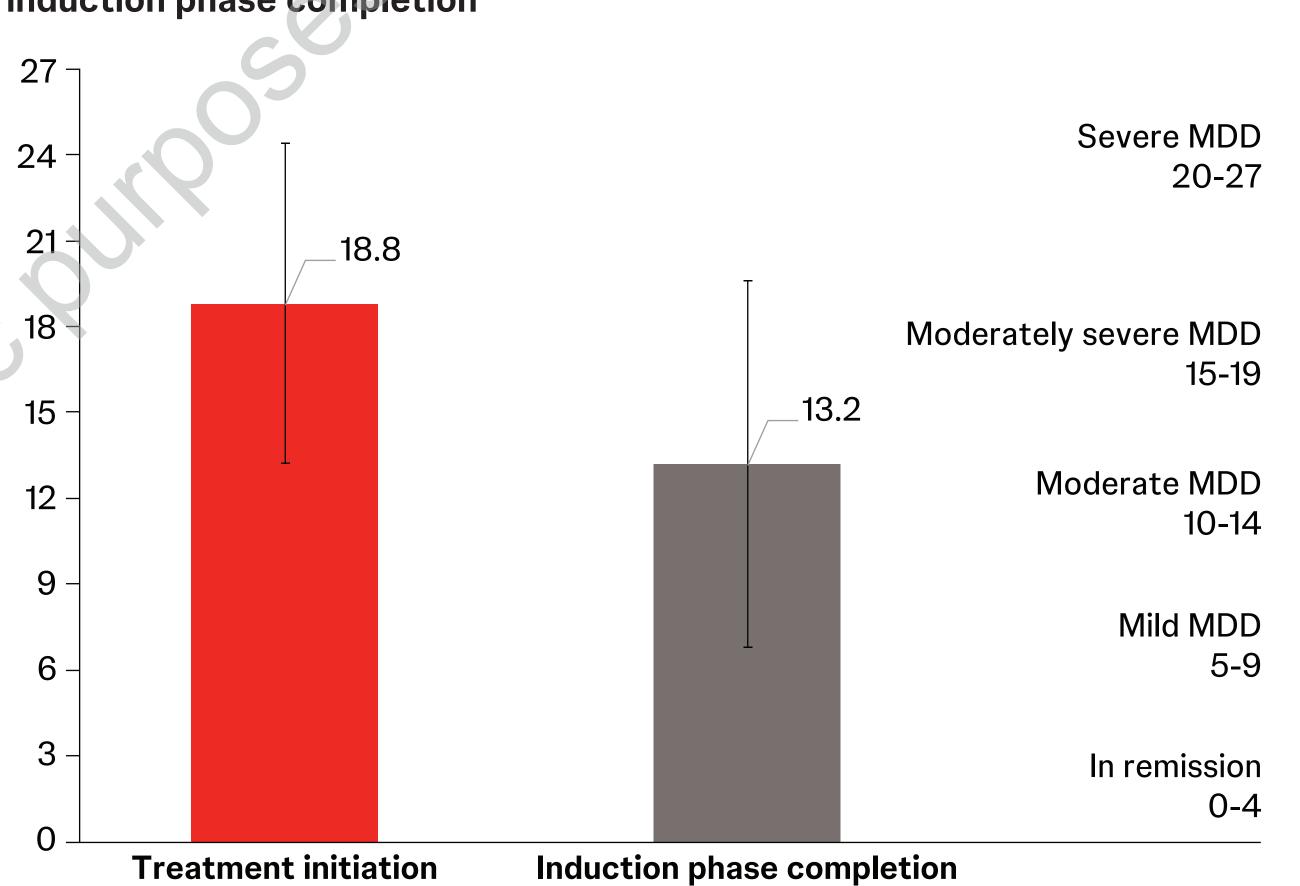
Patient characteristics (Table 1)

- A total of 80 patients initiated esketamine, completed the induction phase, and had PHQ-9 assessments at treatment initiation and induction phase completion (mean±SD age, 47.2±12.9 years). Patients were predominately male (82.5%), White (71.3%), married (43.8%), and resided in the Midwest (40.0%)
- At index, 41.3% of patients had a diagnosis of severe MDD
- During the 12-month baseline period, patients had a mean±SD Quan-Charlson Comorbidity Index score of 0.8±1.5; hyperlipidemia (41.3%) and post-traumatic stress disorder (77.5%) were the most prevalent physical and mental health comorbidity, respectively

MDD severity and symptoms at treatment initiation and induction phase

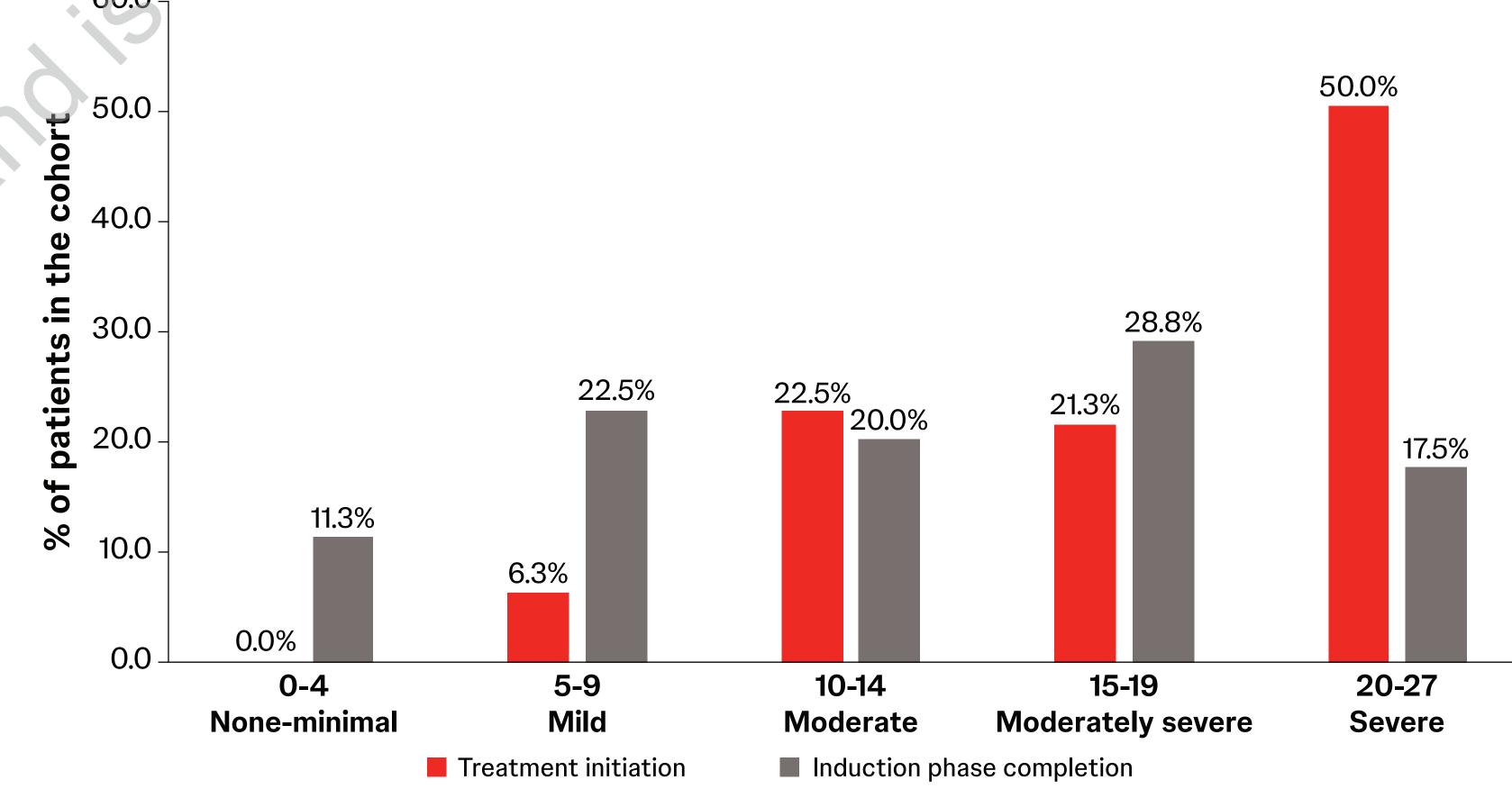
- The mean±SD total PHQ-9 score was 18.8±5.6 at treatment initiation and 13.2±6.4 within a week of induction phase completion, indicating a clinically meaningful reduction (>5 points⁸) in the total PHQ-9 score (**Figure 2**)
- The proportion of patients in remission was 11.3% at induction phase completion, whereas the proportion of patients with severe MDD (PHQ-9 ≥20) was 50.0% at treatment initiation and 17.5% at induction phase completion (Figure 3)
- Across the nine PHQ-9 items (Figure 4), the suicide ideation item had the largest change in mean scores from treatment initiation to induction phase completion (-42.2%), followed by the items indicating psychomotor retardation (-40.2%), feeling bad about yourself (-33.5%), feeling depressed/hopeless (-32.0%), anhedonia (-27.6%), insomnia (-26.3%), trouble concentrating (-26.3%), feeling tired (–25.9%), and poor appetite or overeating (–22.7%)

Figure 2: Mean total PHQ-9 scores at esketamine initiation and at induction phase completion



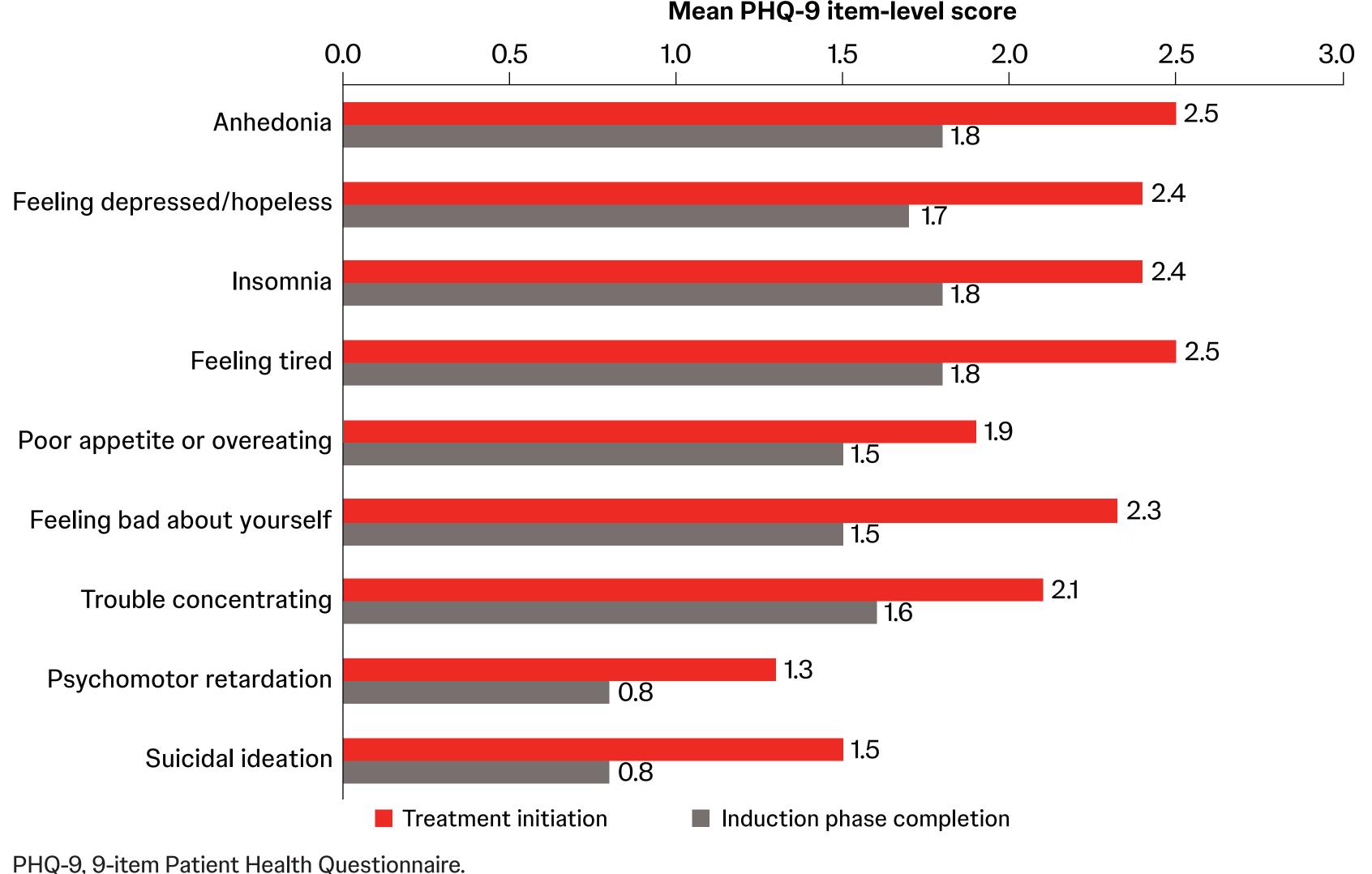
PHQ-9, 9-item Patient Health Questionnaire.

Figure 3: PHQ-9 score categories at esketamine initiation and at induction phase completion



PHQ-9, 9-item Patient Health Questionnaire

Figure 4: Mean item-level PHQ-9 scores at esketamine initiation and at induction phase completion Mean PHQ-9 item-level score



Limitations

- The requirement for patients to have PHQ-9 assessments at treatment initiation may have been biased toward patients with better mental health management
- As the study population consisted of veterans obtaining health care through the VHA system (predominantly White males), study findings may not be generalizable to the general US population,

• Although a published treatment-based proxy was used to identify TRD patients in the study,⁶ there is potential for misclassification of TRD

No statistical comparisons nor adjusted analyses were conducted due to the small sample size of the study cohort

- females, or racial minority groups

References

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Key Takeaways

This analysis using electronic health records from the Veterans Health Administration described depression severity and symptoms based on the 9-item Patient Health Questionnaire scores among US veterans with TRD before and after completing esketamine intranasal spray induction phase



Among the small cohort of veterans with complete questionnaire data, there were substantial improvements in overall depression severity and symptom burden following completion of the esketamine nasal spray induction phase

Conclusions



More than 40% of veterans completing esketamine nasal spray induction therapy and PHQ-9 assessments displayed severe MDD at esketamine initiation



Overall depression severity and symptoms were notably improved following completion of induction phase



In this study, a small cohort of veterans with TRD who initiated esketamine experienced a reduction of the MDD symptoms during the induction phase of treatment, suggesting that veterans might benefit from treatment with esketamine. Future studies with a larger sample size and adjusted analyses are warranted to confirm these findings

Disclosures

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Novel Pathways in Depression





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