A Retrospective Study of Real-World Outcomes for Esketamine Nasal Spray Among Patients With Treatment-Resistant Depression

L. Alison McInnes,[1]* Kruti Joshi,[2] Gary Kane,[1] Matt Worley,[1] Lisa Harding[3]

[1]Osmind, San Francisco, CA; [2]Janssen Scientific Affairs, LLC, Titusville, NJ; [3]Depression MD, Milford, CT

*Presenting author

Background

- Randomized controlled trials of esketamine nasal spray (ESK) treatment for treatment-resistant depression (TRD) evaluated response rates at a specific 4-week time point after the induction regimen of 8 ESK treatments biweekly[1-8]
- Real-world data on cumulative response rates over time beyond the induction phase for ESK is crucial. However, clinicians in the real world often employ various depression scales for patient-reported outcomes (PROs) and administer them at different intervals, which can pose challenges for interpretation[9]
- Furthermore, it is important for clinicians to grasp the real-world clinical characteristics of patients seeking ESK treatment, as they may differ from those typically studied in experimental trials

Objectives

- Our primary objective was to assess the real-world clinical effectiveness of ESK using other clinical scales, including the Hamilton Rating Scale for Depression (HRSD), Beck's Depression Inventory II (BDI-II), Quick Inventory of Depressive Symptomatology – 16 (QIDS-SR16), and limited use of the Montgomery-Åsberg Depression Rating Scale (MADRS)
- Our secondary objective was to explore comorbid diagnoses and concomitant medications among patients treated with ESK

Methods

Patient selection criteria

Patients were included in the study (the "ESK all-comers" cohort) if they met the following inclusion criteria:

- ≥18 years old as of the index date confirmed in the Osmind electronic health record (EHR) database
- A diagnosis of major depressive disorder (MDD), either as reported by the patient on the intake assessment, as recorded by a provider, or as provided in referrals or other medical history documentation
- Received treatment with ESK on at least 1 instance
- Date of the first documented ESK treatment ("index date") occurred 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

Confirmed TRD subgroup for analysis

- Patients were included in the ESK-TRD cohort if medication source data indicated evidence of use of at least 2 unique antidepressant trials 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

Outcome measures

- The outcome measures reported included changes in the PHQ-9, HRSD, QIDS-SR16, BDI-II, and MADRS from baseline to post-index. Baseline scores were measured as the most recent documented PRO within 30 days prior to the index date. All documented PRO scores that were obtained after the index date and within 30 days of an ESK treatment were included

Statistical analysis

Two 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 PRO score from baseline as a function of the number of treatments
- Multiple parameterizations of time were tested, to capture the optimal relationship between PRO 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
- The time to initial response (50% reduction from baseline PHQ-9 score) was assessed using a survival analysis (Turnbull method)

Results

Summary of demographics

- Of our sample of real-world patients, collected from multiple different clinics across the United States, ~60% were female with a mean age of 45 years (percentages nearly identical for both cohorts). For ESK-TRD, of the 240 patients for whom we had data on race, 95% were White (% similar for ESK all-comers)

Esketamine outcomes analysis PHQ-9

- Patients in both cohorts had a mean baseline PHQ-9 score of 17
- Patients in both cohorts showed a significant, non-linear reduction in PHQ-9 scores that continued beyond the initial treatment phase (8-12 treatments). PHQ-9 scores rapidly declined during treatments 1-4 and continued to decline gradually and consistently during the remaining treatments[10]
- The median number of treatments to initial response was 12 for the ESK-TRD group and 10 for the ESK all-comer group (administered within a mean of ~70 days)
- The survival models predicted that 75% of the ESK-TRD group and 85% of the ESK all-comers group eventually achieved initial response (**Figure 1**)
- **Figure 2** shows the change in observed (in red) and modeled (in black) clinical response rates as assessed by additional depression rating scales. As with the PHQ-9 data, the probability of response increased beyond 12 treatments

FIGURE 1: Median number of treatments to attain response

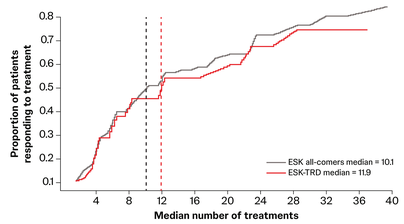
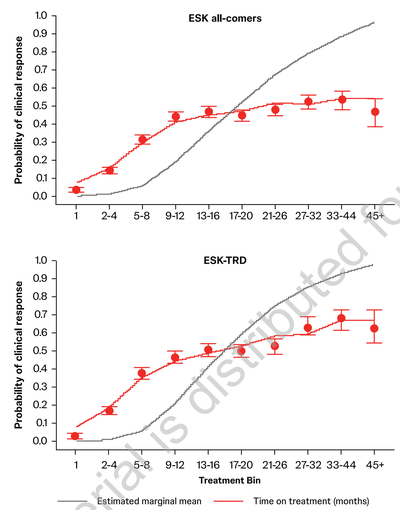


FIGURE 2: The probability of attaining clinical response



Comorbid psychiatric diagnoses in patients receiving ESK

- Anxiety (>70%) was the most common comorbid diagnosis present in three-quarters of the patients, followed by trauma and stressor-related disorders and neurodevelopmental disorders, each present in just under a third of patients (depicted in **Table 1**). Attention deficit disorders (>25%) constituted the majority of neurodevelopmental disorders. Sleep-wake disorders were also observed in a substantial fraction of patients depicted in **Table 1**

TABLE 1: Comorbid Diagnoses

Psychiatric diagnosis	All-comers N = 664	ESK-TRD N = 361
Anxiety disorders	467 (70.3%)	267 (74%)
Trauma- and stressor-related disorders	194 (29.2%)	106 (29.4%)
Neurodevelopmental disorders	192 (28.9%)	101 (28%)
Attention-deficit hyperactivity disorders	181 (27.3%)	92 (25.5%)
Other conditions that may be a focus of clinical attention	155 (23.3%)	108 (29.9%)
Sleep-wake disorders	141 (21.2%)	93 (25.8%)
Bipolar and related disorders	78 (11.7%)	48 (13.3%)
Substance-related and addictive disorders	64 (9.6%)	39 (10.8%)
Obsessive-compulsive and related disorders	58 (8.7%)	40 (11.1%)
Feeding and eating disorders	53 (8%)	37 (10.2%)
Personality disorders	41 (6.2%)	27 (7.5%)
Schizophrenia spectrum and other psychotic disorders	9 (1.4%)	4 (1.1%)
Sexual dysfunctions	6 (0.9%)	6 (1.7%)
Neurocognitive disorders	5 (0.8%)	4 (1.1%)
Medication-induced movement disorders and other adverse effects of medication	4 (0.6%)	2 (0.6%)
Elimination disorders	3 (0.5%)	3 (0.8%)
Somatic symptom and related disorders	3 (0.5%)	2 (0.6%)
Disruptive, impulse-control, and conduct disorders	1 (0.2%)	1 (0.3%)
Paraphilic disorders	1 (0.2%)	1 (0.3%)

Concomitant medications in patients receiving ESK

- Concomitant medications taken during ESK treatment are listed in **Tables 2** and **3** and are summarized in the following bullet points. These percentages may be underreported given missing data noted for each class of medication
- ~85% of ESK-TRD and 77% of ESK all-comers cohorts were taking 1 or more concomitant antidepressants (**Table 2**)
- ~65% of both ESK-TRD and ESK all-comers cohorts were taking an augmentation agent during ESK treatment (**Table 3**)
- ~40% ESK-TRD and ~50% of ESK-all comers cohorts were taking an additional psychiatric medication other than above (data not shown). The most common class of additional concomitant psychiatric medication was benzodiazepines, reported for 45% of ESK-TRD and 42% of ESK-all-comers cohorts

TABLE 2: Concomitant antidepressants

Antidepressant use during ESK	ESK all-comers N = 664	ESK-TRD N = 361
Unique antidepressants		
N	512	304
Mean (SD)	2 (1)	2 (1)
Median (IQR)	1 (1, 2)	2 (1, 2)
Range	1, 7	1, 7
N not documented (%)	152 (23%)	57 (16%)
Unique antidepressants (categorical), N (%)		
Not documented	152 (23%)	57 (16%)
1	258 (39%)	100 (28%)
2	188 (28%)	144 (40%)
3	51 (7.7%)	47 (13%)
4	10 (1.5%)	10 (2.8%)
5	4 (0.6%)	2 (0.6%)
6+	1 (0.2%)	1 (0.3%)

TABLE 3: Augmentation agent use during ESK

Augmentation agent use during ESK	ESK all-comers N = 664	ESK-TRD N = 361
Unique augmentation agents		
N	425	243
Mean (SD)	2 (1)	2 (1)
Median (IQR)	2 (1, 2)	2 (1, 2)
Range	1, 5	1, 5
N not documented (%)	239 (36%)	118 (33%)
Unique augmentation agents (categorical), N (%)		
Not documented	239 (36%)	118 (33%)
1	212 (32%)	120 (33%)
2	114 (17%)	63 (17%)
3	70 (11%)	40 (11%)
4	23 (3.5%)	16 (4.4%)
5	6 (0.9%)	4 (1.1%)
6+	0 (0%)	0 (0%)

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 antidepressants within the current episode for a subset of the patients (ESK-TRD); information on adequate dose and duration was not uniformly available

Conclusions

The analysis demonstrated that staying on ESK treatment results in improvement in depression, irrespective of the type of outcome assessment used

Over 75% of patients eventually respond to treatment, despite the presence of multiple comorbidities and polypharmacy, factors typically associated with poorer treatment response

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

References

1.Piojcova V et al. *Am J Psychiatry*. 2019;176(6):428-438. **2.** Fedgchin M et al. *Int J Neuropsychopharmacol*. 2019;22(10):616-630. **3.** Ochs-Ross R et al. *Am J Geriatr Psychiatry*. 2020;28(2):121-141. **4.** Reif A et al. Presented at DGPPN 2022; Berlin, Germany; November 23-26, 2022. **5.** Daly EJ et al. *JAMA Psychiatry*. 2019;76(9):893-903. **6.** Waje E et al. *J Clin Psychiatry*. 2020;81(3):19mt12891. **7.** Zaki N et al. Poster presented at 2021 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP), June 2, 2021, Virtual. **8.** A Study to Evaluate the Efficacy, Pharmacokinetics, Safety and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Participants With Treatment-resistant Depression. ClinicalTrials.gov Identifier: NCT03434041. https://beta.clinicaltrials.gov/study/NCT03434041. Accessed March 6, 2023. **9.** Yule AM et al. *J Clin Psychol*. January 17, 2024. doi: 10.1002/jclp.23639. **10.** McInnes LA et al. Poster presented at 2024 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP), May 28-31, 2024.

Novel Pathways in Depression

Scan the QR code

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Supported by Janssen Scientific Affairs, LLC, a Johnson & Johnson company