Real-World Safety Profile of Esketamine Nasal Spray: An Analysis of the Risk Evaluation and Mitigation Strategy Program Approximately 5 Years After Approval in the United States

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Introduction

- Major depressive disorder (MDD) is a chronic and life-threatening psychiatric disorder that affects an estimated 3.8% of the global population (approximately 280 million people).[1] A large proportion of patients with MDD (30%-55%) do not have a response to 2 or more antidepressant regimens and are considered to have treatment-resistant depression (TRD)[2-4]
- Esketamine nasal spray (ESK) is a noncompetitive N-methyl-D-aspartate receptor antagonist approved by the US Food and Drug Administration (FDA) for use in combination with an oral antidepressant (OAD) for the treatment of adults with TRD, as well as for depressive symptoms in adults with MDD with acute suicidal ideation or behavior[5]
- The recommended ESK dosing for TRD is twice per week for the first 4 weeks, once per week for the next 4 weeks, and weekly or every other week thereafter, starting at a dose of 56 mg with the option to increase to 84 mg after session 1, as needed to maintain response and as tolerated by the patient[5]
- Based on FDA requirements, Johnson & Johnson developed the Risk Evaluation and Mitigation Strategy (REMS) program at the time of ESK approval to mitigate the risks of serious adverse outcomes resulting from sedation, dissociation, and misuse and abuse, and to monitor changes in vital signs. The REMS program ensures that
  - Healthcare settings (HCSs) that treat patients with ESK and pharmacies that dispense ESK are REMS certified
  - ESK is only dispensed and administered to patients in a medically supervised HCS
  - Outpatients are enrolled in the REMS registry prior to treatment with ESK to further characterize risks and to support safe use of ESK
  - All patients are informed about the potential for serious adverse outcomes resulting from sedation and dissociation and the need for monitoring
  - Administration of ESK is performed under the direct observation of a healthcare provider, and patients are required to be monitored by a healthcare provider for at least 2 hours after dosing for sedation, dissociation, and changes in vital signs
  - ESK is never dispensed directly to patients for home use
- To comply with the REMS, certified pharmacies and HCSs must follow specific requirements to receive, dispense, and treat patients with TRD

Objective

- To examine real-world incidence of adverse events of special interest (AESIs), specifically, actively solicited events of sedation, dissociation, and increased blood pressure (BP), and serious adverse events (SAEs) associated with ESK

Methods

REMS data collection

- Data from REMS patient enrollment and monitoring forms (PMFs) were evaluated to describe and summarize patient demographics and key safety findings for the first 5 years (58 months) following product approval (March 5, 2019, to January 5, 2024)
- Outpatient HCSs were required to submit PMFs within 7 days following each ESK treatment session
- Sedation and dissociation were solicited via checkboxes on the PMF, and time to resolution in minutes was captured in a free-form text field by the healthcare provider
- BP increase, as measured at 40 minutes post-ESK administration, was defined as a post-administration BP increase of ≥20 mm Hg or a value ≥180 mm Hg for systolic, or ≥15 mm Hg or a value ≥105 mm Hg for diastolic, compared with values prior to administration
- An SAE was defined as any event that leads to hospitalization, disability or permanent damage, death, a life-threatening condition, or any event that may jeopardize the patient or may require intervention to prevent one of these outcomes

Data analyses

- Patient characteristics, ESK dosage patterns, and adverse events (AEs), including AESIs and SAEs, were summarized using descriptive statistics
- AEs were described both per session and cumulatively, and by the proportion of patients experiencing AEs or as the proportion of treatment sessions in which AEs were reported
- Treatment phases were defined as induction (sessions 1-8), early maintenance (sessions 9-12), and late maintenance (sessions ≥13)

Results

Patient population

- As of the 58-month cutoff on January 5, 2024, 58,483 patients had received at least 1 ESK treatment (**Table 1**)
- The median age was 42 years, and the mean age was 43.4 years with a standard deviation of ±14.7 years, indicating a wide age distribution (**Table 1**)
- Of patients who initiated ESK, 75.1% received 9 or more treatment sessions (early maintenance) and 60.3% received 13 or more treatment sessions (late maintenance) (**Table 1**)
- The mean (SD) number of treatment sessions per patient was 25.4 (±29.7 [range 1-420]), indicating high variability among patients. The median number of treatment sessions was 16, suggesting a skewed distribution in which many patients received fewer sessions or had started treatment more recently (**Table 1**)

TABLE 1. Sex, age, and treatment summary of patients with ≥1 ESK treatment session (March 5, 2019, to January 5, 2024)

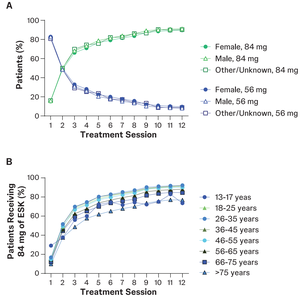
	Patients with ≥1 ESK treatment session N = 58,483
Sex, n (%)	
Male	22,300 (38.1)
Female	35,762 (61.1)
Other/Unknown	421 (0.7)
Age at enrollment, years	
Mean (SD)	43.4 (14.7)
Median	42
Range	12.0, 93.0
Age category (years), n (%)[a,b]	
≤12	1 (<0.1)
13 to 17	55 (0.1)
18 to 25	7453 (12.7)
26 to 35	12,078 (20.7)
36 to 45	13,914 (23.8)
46 to 55	11,589 (19.8)
56 to 65	8741 (14.9)
66 to 74	3720 (6.4)
≥75	932 (1.6)
Patients in each treatment phase, n (%)[c]	
Induction, ≥1 session during sessions 1-8[d]	58,471 (>99.9)
Early maintenance, ≥1 session during sessions 9-12	43,908 (75.1)
Late maintenance, ≥1 session after session 12	35,257 (60.3)
Number of treatment sessions per patient	
Mean (SD)	25.4 (29.7)
Median	16

ESK, esketamine nasal spray; HCS, health care setting; PMF, patient monitoring form; REMS, Risk Evaluation and Mitigation Strategy.
[a]ESK is not approved for the treatment of patients less than 18 years of age.
[b]Patient age at ESK treatment initiation.
[c]Data derived from outpatient PMFs only. However, treatments before September 18, 2020, may include those at inpatient settings enrolled before REMS distinguished between inpatient and outpatient care.
[d]There are 12 fewer patients reported here who received 8 or more treatment sessions in an inpatient HCS.

Esketamine nasal spray dosage

- Over 80% of patients received a 56-mg dose of ESK at their first treatment. At treatment session 2, the proportion of patients receiving 56 mg and 84 mg was similar between dosage groups, and by treatment session 6, most patients (≥80%) were receiving 84 mg (**Figure 1A**)
- A similar proportion of males and females received an 84-mg dose of ESK (**Figure 1A**)
- Compared with younger age groups, patients aged >75 years received an 84-mg dose at the lowest frequency (**Figure 1B**)

FIGURE 1. Summary of (A) ESK dose by sex and treatment session and (B) percentage of patients receiving an 84-mg dose of ESK by age and treatment session



ESK, esketamine nasal spray.

Adverse events

- AESIs (i.e, sedation, dissociation, increased BP) were reported in 76.8% of patients, and 51.4% of treatment sessions (**Table 2**)
- Sedation, dissociation, and increased BP were reported in 61.9%, 65.7%, and 11.7% of patients, respectively, and in 34.7%, 41.0%, and 0.9% of overall treatment sessions, respectively (**Table 2**)
- SAEs were reported in 1.6% of patients and in <0.1% of treatment sessions (**Table 2**)

TABLE 2. AESIs and SAEs as reported as cases on the REMS PMF (March 5, 2019, to January 5, 2024)

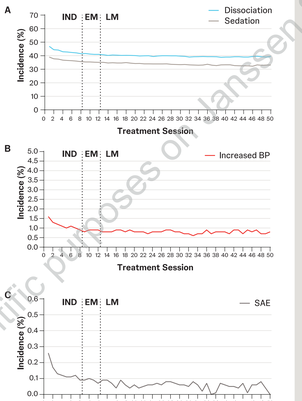
n (%)	Patients[a] N = 58,483	Treatment sessions[a] N = 1,486,213
≥1 AESI[b]	44,908 (76.8)	764,600 (51.4)
Sedation	36,190 (61.9)	515,367 (34.7)
Dissociation	38,410 (65.7)	608,746 (41.0)
Increased BP	6818 (11.7)	13,510 (0.9)
≥1 SAE	932 (1.6)	1184 (<0.1)

AE, adverse event; AESI, adverse event of special interest; BP, blood pressure; PMF, patient monitoring form; REMS, Risk Evaluation and Mitigation Strategy; SAE, serious adverse event.
[a]A patient could have had >1 treatment session and/or experienced >1 event within the same treatment session. A case was defined as a record of AEs during 1 treatment session for 1 patient; 1 case may contain >1 AE.
[b]AESI is defined as an actively solicited event of sedation, dissociation, or increased BP.

Adverse events by treatment session

- The incidence rates of sedation and dissociation decreased during the induction phase (sessions 1-8), but remained relatively consistent during the early (sessions 9-12) and late (sessions ≥13) maintenance phases (**Figure 2A**)
- The incidence rate of increased BP decreased from 1.6% during the first session to below 1% by the end of induction phase (**Figure 2B**)
- The incidence rate of SAEs dropped sharply after the first session, decreasing from 0.26% in the first session to below 0.1% by the end of the induction phase (**Figure 2C**)
- This trend was observed even though over 80% of patients were administered a lower initial dosage of 56 mg

FIGURE 2. Incidence of AEs of interest (A) sedation and dissociation, (B) increased BP, and (C) SAEs by treatment session

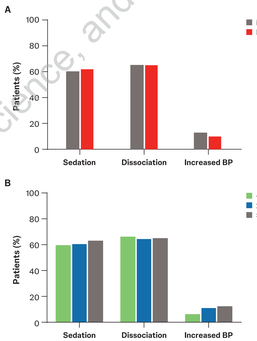


AE, adverse event; BP, blood pressure; EM, early maintenance; IND, induction; LM, late maintenance; SAE, serious adverse event.

Adverse events by sex and age

- No differences were observed in the proportion of patients that experienced 1 or more AESIs by sex (men, 76.9%; women, 76.8%)
- Males experienced increased BP at a slightly higher rate compared with females (13.4% vs 10.6%), while sedation and dissociation were each experienced at similar proportions for each sex (**Figure 3**)
- Patients aged 25-55 years and >55 years experienced increased BP at a higher rate (11.7% and 12.9%, respectively) than patients aged <25 years (6.8%), while sedation and dissociation were experienced at similar frequencies across age subgroups (**Figure 3**)
- SAEs occurred at similar proportions for males and females (1.5% vs 1.6%, respectively)
- Patients aged <25 years experienced SAEs at a slightly lower rate (1.1%) compared with patients aged 25-55 years (1.5%) and >55 years (1.9%)

FIGURE 3. Incidence of AESIs by sex and age as reported as cases[a] on the REMS PMF (March 5, 2019, to January 5, 2024)



AE, adverse event; AESI, adverse event of special interest; BP, blood pressure; PMF, patient monitoring form; REMS, Risk Evaluation and Mitigation Strategy.
[a]A patient could have had >1 treatment session and/or experienced >1 event within the same treatment session. A case was defined as a record of AEs during 1 treatment session for 1 patient; 1 case may contain >1 AE.

Serious adverse events

- The number and proportion of patients and treatment sessions in which SAEs resulted in death, disability or permanent damage, hospitalization, a life-threatening event, or an important medical event are summarized in **Table 3**
- Of the 2096 reported SAEs, the most common were vomiting (n = 157), increased BP (n = 142), nausea (n = 141), dizziness (n = 103), unevaluable events (n = 85), and dissociation (n = 83) (**Table 4**)

TABLE 3. Summary of SAE outcomes as reported on the REMS PMF (March 5, 2019, to January 5, 2024)

n (%)	Patients[a] N = 58,483	Treatment sessions[b] N = 1,486,213
Death	2 (<0.1)	2 (<0.1)
Disability or permanent damage	1 (<0.1)	2 (<0.1)
Hospitalization	200 (0.3)	449 (<0.1)
Life-threatening	19 (<0.1)	28 (<0.1)
Important medical event	494 (0.8)	1014 (<0.1)
Not specified	296 (0.5)	704 (<0.1)

PMF, patient monitoring form; REMS, Risk Evaluation and Mitigation Strategy; SAE, serious adverse event.
[a]A patient could have had >1 treatment session and/or experienced >1 event within the same treatment session. A case was defined as a record of AEs during 1 treatment session for 1 patient; 1 case may contain >1 AE.
[b]Total number of events reported. In case of multiple treatment sessions reporting a death of an individual, only the first treatment session is counted.

TABLE 4. Summary of most common SAEs as reported on the REMS PMF (March 5, 2019, to January 5, 2024)

n (%)	SAEs[a,b] N = 2096
Vomiting	157 (7.5)
Increased BP	142 (6.8)
Nausea	141 (6.7)
Dizziness	103 (4.9)
Unevaluable event	85 (4.1)
Dissociation	83 (4.0)
Hypertension	80 (3.8)
Suicidal ideation	76 (3.6)
Anxiety	48 (2.3)
Headache	38 (1.8)
Panic attack	35 (1.7)
Dyspnea	30 (1.4)
Hypoaesthesia	28 (1.3)
Unresponsive to stimuli	27 (1.3)
Sedation	26 (1.2)
Chest pain	25 (1.2)
Seizure	23 (1.1)
Hyperhidrosis	23 (1.1)
Feeling abnormal	22 (1.0)
Feeling drunk	16 (0.8)
Loss of consciousness	16 (0.8)

BP, blood pressure; MedDRA, Medical Dictionary for Regulatory Activities; PMF, patient monitoring form; REMS, Risk Evaluation and Mitigation Strategy; SAE, serious adverse event.
[a]Total number of events reported.
[b]SAEs are coded using MedDRA version 22.0.

Limitations

- The data collected in the REMS registry through PMFs were analyzed in their original form, as submitted by health care providers. Data collected do not include indication. The data may contain errors since they represent real-world conditions and are not subjected to rigorous verification protocols
- Time between treatment sessions can vary widely in individual patients, so the timing of specific treatment sessions may differ (e.g., treatment session 20 might have been reported in the fourth or sixth month of treatment in different patients)
- It is unknown if the observed decrease in incidence rates of AEs over successive treatment sessions was related to the discontinuation of patients experiencing more frequent or severe AEs
- Sedation and dissociation were solicited via checkboxes on the PMFs based on the healthcare provider's clinical judgement. However, during clinical trials, these AEs were reported based on unsolicited treatment-emergent AEs and assessed using standardized tools like the Modified Observer's Assessment of Alertness/Sedation scale and the Clinician-Administered Dissociative States Scale. The variation in measurement methods might explain the reported differences in the proportion of sedation and dissociation events between the 2 types of investigations
- Reports of SAEs were made by healthcare providers who may not be fully trained in the Good Clinical Practice guidelines for SAE reporting
- There are no efficacy measures attached to the REMS program, so it is not possible to provide information on treatment efficacy
- Patients who initiated treatment close to the data-lock date (January 5, 2024) may not have completed their full course of treatment, which may have skewed summary statistics

Key Takeaway

Results from this real-world analysis of approximately 5 years of post-approval data from ESK treatment in patients with TRD is consistent with the established safety profile of ESK and no new signals were identified

Conclusions

- Incidence of AESIs (i.e., sedation, dissociation, and increased BP) and SAEs decreased throughout the induction phase and remained relatively stable in the early and late maintenance phases of ESK treatment
- While incidence of sedation and dissociation were similar regardless of sex or age, the incidence of increased BP trended higher in males compared with females, and with increasing age
- Incidence of SAEs remained low overall

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Disclosures

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