Comparison of Real-World Response and Remission Among Patients With Treatment-Resistant Depression Treated With Esketamine Nasal Spray or Antipsychotic Augmentation

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Introduction

- Esketamine nasal spray (ESK) and second-generation antipsychotic (SGA) augmentation are treatment options for treatment-resistant depression (TRD)[1,2]
- The ESCAPE-TRD clinical trial demonstrated superiority of ESK versus quetiapine (an SGA), both in combination with an antidepressant, with respect to remission at 8 weeks after treatment initiation[3]
- Real-world evidence regarding relative effectiveness of ESK versus SGA augmentation in TRD remains limited

Objective

- To compare real-world response and remission on ESK versus SGA augmentation among patients with TRD

Methods

Data source

- Open claims from the Komodo Research Database and Patient Health Questionnaire-9 (PHQ-9) scores from the Komodo Clinical Observations Database were used (01/2016-06/2023)
- Data were de-identified and complied with the Health Insurance Portability and Accountability Act

Study design

- A retrospective cohort study design was used
- The intake period spanned from 03/05/2019 to the end of data; the index date was the date of ESK or SGA augmentation initiation
- Patient clinical activity was defined based on the first and last patient record (e.g., any claim or clinical measure) observed in the data
- The baseline period included the 12 months of clinical activity before the index date; the follow-up period spanned the index date until the earliest of end of clinical activity or data availability

Sample selection

- Patients met the following selection criteria:
  - ≥1 Major Depressive Disorder diagnosis (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]: F32.X [excluding F32.A and F32.8], F33.X [excluding F33.8])
  - Initiation of index therapy during the intake period in the following order of priority: (1) ESK (ESK cohort), or (2) antidepressant and SGA augmentation agent, based on ≥1 overlapping day of supply (SGA cohort)
  - Evidence of TRD before the index date (i.e., ≥2 unique antidepressants of adequate dose and duration during the major depressive episode that includes the index date)
  - ≥18 years old on the index date
  - ≥12 months of clinical activity before the index date and ≥6 months of clinical activity after the index date
  - ≥1 PHQ-9 score during the baseline period or on index date and ≥1 PHQ-9 score while on treatment (i.e., from index date up to 30 days after the last ESK session or after the last day of antidepressant and SGA augmentation supply)
  - <2 claims on separate days during the baseline period with a diagnosis of psychosis, schizophrenia, schizo-affective disorder, and other non-mood psychotic disorders
  - For the SGA cohort: no claims for ESK before or after the index date

Outcomes measures

- Outcomes were measured while on treatment using PHQ-9 scores (range: 0-27, higher scores indicate higher severity), a patient-reported tool with a recall period of 2 weeks[4]
- Response was defined as ≥50% decrease in PHQ-9 score from baseline, and remission was defined as PHQ-9 score <5

Statistical analysis

- Patients in the ESK cohort were selected and matched 1:1 based on an exact matching factor (baseline PHQ-9 score) and propensity scores derived using baseline demographic characteristics, comorbidities, treatments, healthcare resource use, and healthcare costs
- Standardized differences were used to evaluate the balance between cohorts, with a value of ≤10 indicating balanced variables
- Time to response and remission were described using Kaplan-Meier survival analysis and compared between matched cohorts with Cox proportional hazard models adjusted for baseline electroconvulsive therapy and transcranial magnetic stimulation use; patients without an outcome were censored at the end of the on-treatment period

Results

Baseline characteristics

- Both cohorts included 254 patients after matching. Baseline characteristics of these patients are reported in **Table 1**
- In the SGA cohort, aripiprazole (56.3%), quetiapine (31.5%), and brexpiprazole (11.0%) were the most common SGA augmentation agents at index date

Response

- The probability of achieving response 12 months post-index while on-treatment was 49.6% in the ESK cohort and 41.7% in the SGA cohort
- During the 12 months post-index, patients treated with ESK had a statistically significant 45% higher chance of response compared to patients treated with SGA augmentation

Remission

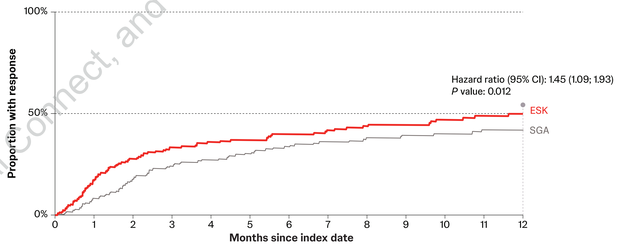
- The probability of achieving remission 12 months post-index while on treatment was 37.7% in the ESK cohort and 28.3% in the SGA cohort
- During the 12 months post-index, patients treated with ESK had a statistically significant 49% higher chance of remission compared to patients treated with SGA augmentation

Table 1: Patient baseline characteristics

Mean ± SD [median] or n (%)	Matched		
	ESK cohort N = 254	SGA cohort N = 254	Standardized difference %
Age at index date, years	44.2 ± 14.2 [42.0]	44.3 ± 15.1 [43.0]	0.7
Female	161 (63.4)	155 (61.0)	4.9
Race/Ethnicity			
White	147 (57.9)	147 (57.9)	0.0
Racial minorities[a]	33 (13.0)	35 (13.8)	2.3
Unknown	74 (29.1)	72 (28.3)	1.7
Payer insurance medical plan at index date			
Commercial	155 (61.0)	152 (59.8)	2.4
Medicaid	45 (17.7)	40 (15.7)	5.3
Medicare	45 (17.7)	51 (20.1)	6.0
Missing	9 (3.5)	11 (4.3)	4.1
Top 3 DSM-5 comorbidities			
Anxiety disorders	205 (80.7)	197 (77.6)	7.8
Sleep-wake disorders	114 (44.9)	105 (41.3)	7.2
Trauma- and stressor-related disorders	73 (28.7)	66 (26.0)	6.2
Quan-CCI[b]	1.0 ± 1.7 [0.0]	1.1 ± 1.9 [0.0]	3.9
Pharmacotherapy			
Number of unique antidepressant agents	3.1 ± 1.7 [3.0]	3.1 ± 1.5 [3.0]	0.0
Number of unique non-antidepressant augmentation agents	2.4 ± 1.5 [2.0]	2.5 ± 1.8 [2.0]	2.4
SGA augmentation use	129 (50.8)	120 (47.2)	7.1
SGA augmentation at index date[c]			
Aripiprazole	-	143 (56.3)	-
Quetiapine		80 (31.5)	-
Brexpiprazole		28 (11.0)	-
Olanzapine	-	7 (2.8)	-
Olanzapine-fluoxetine	-	1 (0.4)	-
Non-pharmacological therapy			
Psychotherapy	202 (79.5)	201 (79.1)	1.0
TMS	37 (14.6)	10 (3.9)	37.3†
ECT	21 (8.3)	9 (3.5)	20.1†
PHQ-9 score	14.9 ± 7.3 [16.0]	14.6 ± 7.2 [15.0]	3.2
Minimal (0-4)	29 (11.4)	29 (11.4)	0.0
Mild (5-9)	33 (13.0)	33 (13.0)	0.0
Moderate (10-14)	54 (21.3)	54 (21.3)	0.0
Moderately severe (15-19)	60 (23.6)	60 (23.6)	0.0
Severe (20-27)	78 (30.7)	78 (30.7)	0.0

DSM-5, *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition; ECT, electroconvulsive therapy; ESK, esketamine nasal spray; PHQ-9, Patient Health Questionnaire-9; Quan-CCI, Quan-Charlson Comorbidity Index; SD, standard deviation; SGA, second-generation antipsychotic; TMS, transcranial magnetic stimulation.
† denotes a standardized difference >10. [a]Racial minorities include Asian, Black, Hispanic, and other racial groups. [b]Quan H, Sundararajan V, Halfon P et al. Coding algorithms for defining comorbidities in ICD-10-CM administrative data. *Med Care*. 2005;43:1130-1139. [c]The SGA augmentation agents are not mutually exclusive since patients treated with SGA augmentation could have more than 1 antidepressant and SGA combinations at index date.

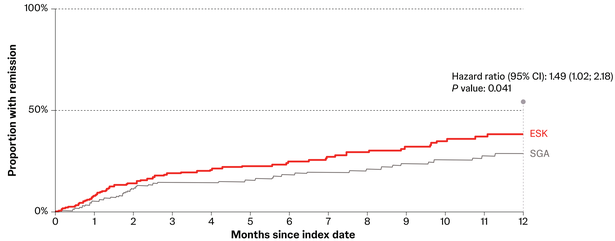
Figure 1: Time to response (PHQ-9 score decrease ≥50% from baseline)



Patients at risk, n (%)	3 months	6 months	9 months	12 months
ESK	135 (53.2)	102 (40.2)	71 (28.0)	46 (18.1)
SGA augmentation	160 (63.0)	115 (45.3)	85 (33.5)	61 (24.0)
Kaplan-Meier rates, % (95% CI)				
ESK	33.1 (27.5; 39.5)	39.6 (33.5; 46.4)	44.3 (37.8; 51.3)	49.6 (42.5; 57.2)
SGA augmentation	24.1 (19.2; 30.1)	33.5 (27.7; 40.2)	39.2 (32.8; 46.3)	41.7 (35.0; 49.1)

CI, confidence interval; ESK, esketamine nasal spray; PHQ-9, Patient Health Questionnaire-9; SGA, second-generation antipsychotic.

Figure 2: Time to remission (PHQ-9 score <5)



Patients at risk, n (%)	3 months	6 months	9 months	12 months
ESK	141 (62.7)	108 (48.0)	74 (32.9)	47 (20.9)
SGA augmentation	156 (69.3)	122 (54.2)	91 (40.4)	59 (26.2)
Kaplan-Meier rates, % (95% CI)				
ESK	18.5 (13.9; 24.5)	24.4 (18.8; 31.2)	31.6 (25.0; 39.3)	37.7 (30.2; 46.3)
SGA augmentation	14.0 (10.0; 19.5)	17.9 (13.2; 24.0)	23.2 (17.6; 30.3)	28.3 (21.7; 36.4)

CI, confidence interval; ESK, esketamine nasal spray; PHQ-9, Patient Health Questionnaire-9; SGA, second-generation antipsychotic.

Limitations

- TRD was identified based on pharmacy claims; pharmacy claims do not guarantee that the medication dispensed was taken as prescribed
- PHQ-9 score is patient-reported and can be subject to recall bias; additionally, patients in the ESK cohort had more frequent measurements, likely due to the nature of ESK administration and monitoring
- The ESK cohort was prioritized over the SGA augmentation cohort in sample selection to maximize its size; while matching was used to adjust for potential confounders, the ESK cohort could be more severe due to residual unmeasured confounders

Conclusions

- Patients with TRD treated with ESK had significantly higher chances of response and remission 12 months after treatment initiation compared to SGA augmentation
- Results complement ESCAPE-TRD clinical trial evidence suggesting that ESK is more effective than augmentation with SGAs in general, beyond augmentation with quetiapine only

Disclosures
KC has served on an advisory board for Janssen Pharmaceuticals. MZ, DP, AV, ATS, and FJ 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. YD and KJ are employees and stockholders of Johnson & Johnson.

Previous presentation
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