Real-World Prescribing Patterns of Esketamine Monotherapy vs Adjunctive Therapy in Routine Psychiatric Care

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Introduction

- Esketamine nasal spray is an established treatment for treatment-resistant depression (TRD) with demonstrated efficacy.[1-4] On January 21, 2025, the FDA approved updated labeling permitting esketamine use without a concurrent oral antidepressant, creating a formal monotherapy indication[5]
- It is currently unknown which patient characteristics and preferences may influence the choice of esketamine as a monotherapy or adjunctive to oral antidepressant for TRD

Objectives

- **Primary objective:** Evaluate and characterize real-world clinical and demographic differences between patients prescribed esketamine monotherapy versus adjunctive therapy at treatment initiation.
- **Secondary objective:** Explore how prior pharmacological burden, psychiatric comorbidities, and geographic region are associated with treatment assignment

Methods

Patient selection criteria and data sourcing

- A retrospective analysis was conducted using de-identified electronic health record (EHR) data from outpatient psychiatric clinics utilizing the Osmind platform
- Patients were included if they were ≥18 years of age, carried a diagnosis of major depressive disorder (MDD) (ICD-10: F32/F33), and received at least 1 documented esketamine treatment during the study period
- Treatment choice was collected from the mandatory structured antidepressant question embedded directly in the Osmind clinical note, which captured whether esketamine was initiated with or without a concurrent oral antidepressant at the time of treatment. Patients who received esketamine on or after April 30, 2025 (when this structured field was implemented in the Osmind platform), were eligible for inclusion
- The index date was defined as the date of the first documented esketamine treatment administration

Statistical analysis

- Univariate logistic regression models estimated odds ratios (ORs) with 95% confidence intervals for each variable
- Independent *t* tests and chi-square tests evaluated continuous and categorical group differences, respectively.
- Sensitivity analyses were conducted in a subsample of patients who maintained consistent treatment patterns throughout their longitudinal care

Results

Cohorts

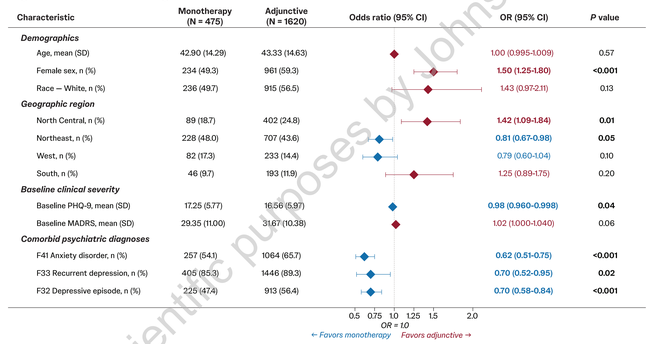
- Of the 2095 patients who initiated esketamine, 1620 received esketamine as adjunctive therapy and 475 as monotherapy

Demographics and clinical characteristics

- Female patients were significantly more likely to receive adjunctive esketamine therapy (odds ratio [OR]: 1.50, $P < 0.001$), while male patients were significantly more likely to receive esketamine monotherapy (OR: 0.67, $P < 0.001$) (**Figure 1**)
- Patients treated in the North Central geographic region were significantly more likely to receive adjunctive treatment (OR: 1.42, $P = 0.01$) (**Figure 1**)
- Baseline 9-item Patient Health Questionnaire (PHQ-9) scores were modestly higher in the monotherapy group (OR: 0.98, $P = 0.04$) (**Figure 1**)
- Comorbid anxiety disorders (F41), recurrent depressive disorder (F33), and depressive episode (F32) diagnoses were each associated with lower odds of patients starting on adjunctive treatment (OR: 0.62, $P < 0.001$; OR: 0.70, $P = 0.02$; OR: 0.70, $P < 0.001$, respectively) (**Figure 1**)

Figure 1: Baseline demographics and clinical characteristics

Characteristic	Monotherapy (N = 475)	Adjunctive (N = 1620)	OR (95% CI)	*P* value
Demographics				
Age, mean (SD)	42.90 (14.29)	43.33 (14.63)	1.00 (0.995-1.009)	0.57
Female sex, n (%)	234 (49.3)	961 (59.3)	**1.50 (1.25-1.80)**	**<0.001**
Race — White, n (%)	236 (49.7)	915 (56.5)	1.43 (0.97-2.11)	0.13
Geographic region				
North Central, n (%)	89 (18.7)	402 (24.8)	**1.42 (1.09-1.84)**	**0.01**
Northeast, n (%)	228 (48.0)	707 (43.6)	**0.81 (0.67-0.98)**	**0.05**
West, n (%)	82 (17.3)	233 (14.4)	0.79 (0.60-1.04)	0.10
South, n (%)	46 (9.7)	193 (11.9)	1.25 (0.89-1.75)	0.20
Baseline clinical severity				
Baseline PHQ-9, mean (SD)	17.25 (5.77)	16.56 (5.97)	**0.98 (0.960-0.998)**	**0.04**
Baseline MADRS, mean (SD)	29.35 (11.00)	31.67 (10.38)	1.02 (1.000-1.040)	0.06
Comorbid psychiatric diagnoses				
F41 Anxiety disorder, n (%)	257 (54.1)	1064 (65.7)	**0.62 (0.51-0.75)**	**<0.001**
F33 Recurrent depression, n (%)	405 (85.3)	1446 (89.3)	**0.70 (0.52-0.95)**	**0.02**
F32 Depressive episode, n (%)	225 (47.4)	913 (56.4)	**0.70 (0.58-0.84)**	**<0.001**

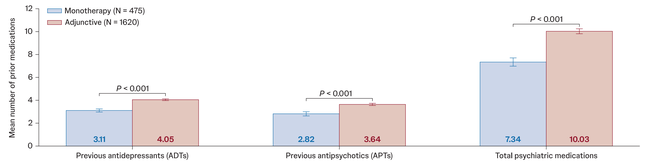


MADRS, Montgomery-Åsberg Depression Rating Scale; OR, odds ratio; PHQ-9, 9-item Patient Health Questionnaire.
CIs for continuous variables (age, PHQ-9, MADRS) represent per-unit ORs from logistic regression. Bold *P* values indicate statistical significance at $P \leq 0.05$.
Summarized patient profiles at the index date of esketamine initiation.

Prior pharmacological exposure profiles

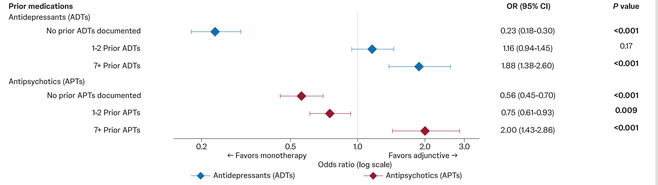
- Patients assigned to adjunctive esketamine had significantly greater historical exposure of antidepressants and antipsychotics compared to patients initiating monotherapy (**Figure 2**)
- Patients with no documented prior antidepressant use were more likely to initiate monotherapy ($P < 0.001$); prior use of 1-2 antidepressants showed no significant association with either treatment pathway ($P = 0.17$), whereas use of 7 or more prior antidepressants was associated with adjunctive treatment initiation ($P < 0.001$) (**Figure 3**)
- Similarly, patients with no documented prior antipsychotics and 1-2 prior antipsychotics were each associated with monotherapy initiation, and 7 or more prior antipsychotics was associated with adjunctive treatment initiation ($P < 0.001$) (**Figure 3**)

Figure 2: Mean prior pharmacological exposure



ADT, antidepressant; APT, antipsychotic; EHR, electronic health record.
Error bars represent ± SEM. All between-group differences *P* <0.001.
"No documented prior exposure" reflects absence of recorded medication history in the EHR prior to esketamine initiation and may include patients who were medication-naive, those whose prior treatment history was not captured in the Osmind platform, or patients referred without complete records.
Group-level comparisons of prior psychiatric medication burden at the index date.

Figure 3: Impact of medication burden extremes on treatment pathway assignment



ADT, antidepressant; APT, antipsychotic; OR, odds ratio.
Forest plot of odds ratios (log scale) with 95% confidence intervals.

Key Takeaways

This study provides the first real-world characterization of esketamine monotherapy versus adjunctive prescribing following the January 2025 FDA label update, revealing that among patients initiating esketamine in routine psychiatric care, 23% were prescribed monotherapy at treatment initiation

Prior medication burden, patient sex, psychiatric comorbidities, and geographic region each independently predict treatment pathway selection, highlighting that clinicians are integrating the new monotherapy indication in clinically differentiated ways

Limitations

Retrospective, observational design; unmeasured confounding cannot be excluded, and causality cannot be inferred from group differences

Concurrent oral antidepressant use was operationalized from EHR documentation, which may not fully capture active versus discontinued prescriptions at the time of esketamine initiation

Some relevant variables (race, ethnicity, Montgomery-Åsberg Depression Rating Scale score, insurance type, body mass index, etc) had missing data, limiting interpretation and generalizability for those subgroups

The sample is drawn from clinics using the Osmind platform, which may not be representative of all outpatient clinical practices in the US

Conclusions

Male patients were significantly more likely to receive esketamine nasal spray monotherapy, while female patients and those with comorbid anxiety or complex depressive disorder diagnoses (F32, F33) were more likely to receive adjunctive esketamine nasal spray therapy, highlighting different patient characteristics across treatment pathways

Patients in the North Central region were significantly more likely to receive adjunctive therapy, suggesting that local prescribing norms play a role alongside patient-level factors

Patients assigned to adjunctive therapy had significantly greater prior antidepressant and antipsychotic exposure, while patients with no documented prior antidepressant or antipsychotic exposure were strongly associated with monotherapy initiation. These sex differences in prior treatment exposures may be due in part to side effects, such as sexual dysfunction associated with antidepressants and antipsychotics, which impose a higher burden on males[6]

These findings provide an initial real-world characterization of how monotherapy and adjunctive esketamine nasal spray indications are being integrated into routine psychiatric care. Whether observed patterns reflect patient and clinician preferences cannot be determined from this observational design

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Disclosures
DM and BB are employees of Johnson & Johnson and may hold stock in the company.

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