# Concurrent SSRI, SNRI, or Other Antidepressant Use Not Associated With Differential Outcomes in Ketamine or Esketamine Treatment

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Ketamine and esketamine produce rapid antidepressant effects in treatment-resistant depression (TRD), offering a promising alternative to conventional therapies.[1,2] Few studies have examined whether the choice of oral antidepressant concurrent to ketamine/esketamine differentially affects clinical outcomes.[3] To investigate the relationship between concurrent antidepressant class and clinical outcomes in ketamine/esketamine treatment, we analyzed data from all patients with TRD treated with intravenous (IV) ketamine or intranasal (IN) esketamine at the Yale Interventional Psychiatry Service between March 2015 and August 2023.

## Methods

The treatment setting, clinical approach, and data collection of this

Table 1.

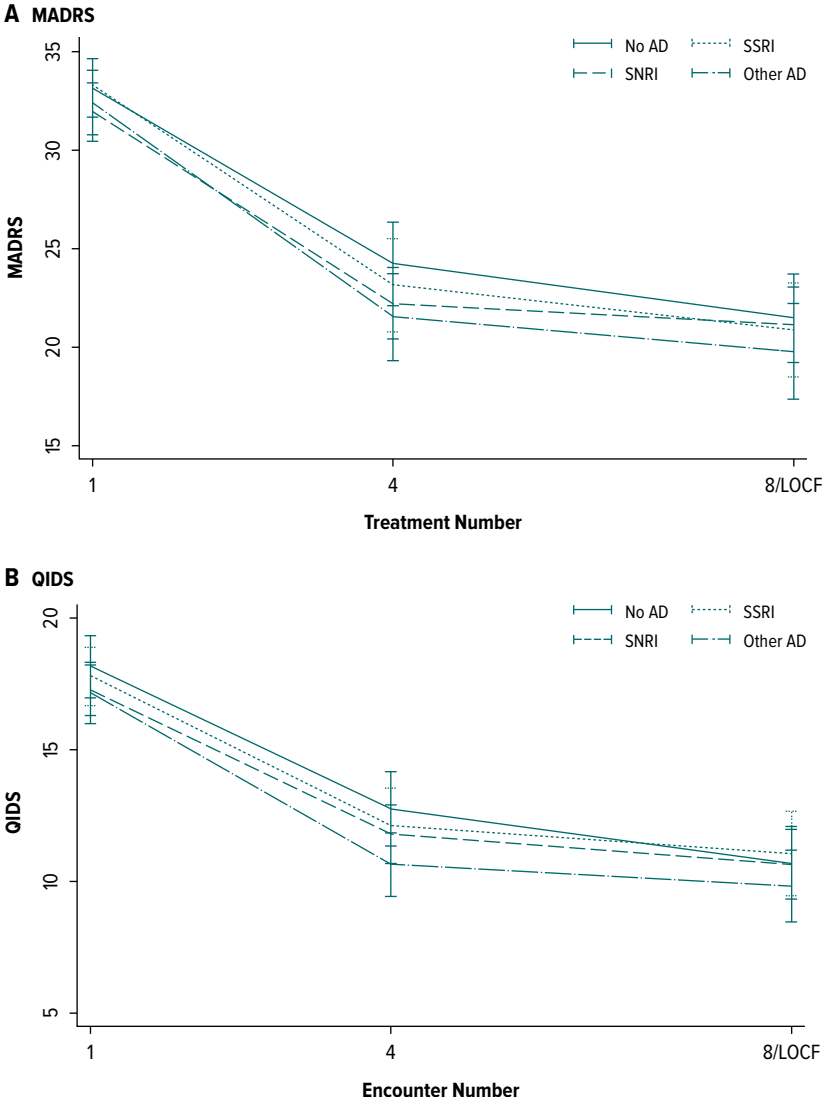
**Demographic and Clinical Characteristics of Patients at Baseline[a]**

| Characteristic | No antidepressant (n = 73) | SSRI (n = 84) | SNRI (n = 99) | Other antidepressant (n = 77) | Total (n = 332) | *P* value |
|---|---|---|---|---|---|---|
| **Treatment modality** | | | | | | .61 |
| IN esketamine | 36 (49.0%) | 50 (60.0%) | 53 (54.0%) | 44 (57.0%) | 183 (55.0%) | |
| IV ketamine | 37 (51.0%) | 34 (40.0%) | 45 (46.0%) | 33 (43.0%) | 149 (45.0%) | |
| **Number of sessions, mean (SD)** | 7.0 (1.4) | 7.3 (1.3) | 7.0 (1.4) | 7.1 (1.3) | 7.1 (1.3) | .7 |
| **Age, mean (SD), y** | 45.5 (16.2) | 42.6 (16.9) | 47.3 (16.7) | 45.9 (17.1) | 45.4 (16.7) | .31 |
| **Sex** | | | | | | .4 |
| Male | 36 (49.0%) | 33 (39.0%) | 39 (40.0%) | 28 (36.0%) | 136 (41.0%) | |
| Female | 37 (51.0%) | 51 (61.0%) | 59 (60.0%) | 49 (64.0%) | 196 (59.0%) | |
| **Race and ethnicity** | | | | | | .31 |
| Non-Hispanic white | 64 (88.0%) | 68 (81.0%) | 87 (89.0%) | 64 (83.0%) | 283 (85.2%) | |
| Non-Hispanic black | 1 (1.0%) | 3 (4.0%) | 1 (1.0%) | 4 (5.0%) | 9 (2.7%) | |
| Hispanic/Latino, any race | 1 (1.0%) | 5 (6.0%) | 7 (7.0%) | 4 (5.0%) | 17 (5.1%) | |
| Other/unknown | 7 (10.0%) | 8 (10.0%) | 3 (3.0%) | 5 (6.0%) | 23 (6.9%) | |
| **Marital status** | | | | | | .52 |
| Married | 29 (40.0%) | 28 (33.0%) | 39 (40.0%) | 33 (43.0%) | 129 (39.0%) | |
| Unmarried | 43 (58.9%) | 54 (64.3%) | 59 (60.2%) | 44 (57.1%) | 200 (60.0%) | |
| Other/unknown | 1 (1.0%) | 2 (2.0%) | 0 (0.0%) | 0 (0.0%) | 3 (1.0%) | |
| **Concurrent benzodiazepines** | 33 (45.0%) | 43 (51.0%) | 47 (48.0%) | 38 (49.0%) | 161 (49.0%) | .9 |
| **Concurrent antipsychotics** | 28 (38.0%) | 36 (43.0%) | 37 (38.0%) | 33 (43.0%) | 134 (40.0%) | .85 |
| **Baseline MADRS score, mean (SD)** | 32.8 (6.8) | 33.8(8.0) | 32.3 (7.43) | 32.5 (7.2) | 32.9 (7.4) | .57 |
| **History of psychiatric hospitalization** | 28 (38.0%) | 48 (57.0%) | 57 (58.0%) | 38 (49.0%) | 171 (52.0%) | .046 |
| **History of ECT** | 17 (23.0%) | 24 (29.0%) | 31 (32.0%) | 18 (23.0%) | 90 (27.0%) | .53 |
| **PTSD** | 8 (11.0%) | 10 (12.0%) | 17 (17.0%) | 10 (13.0%) | 45 (14.0%) | .61 |
| **SUD** | 1 (1.0%) | 9 (11.0%) | 6 (6.0%) | 11 (14.0%) | 27 (8.0%) | .022 |
| **Insurance[b]** | | | | | | .53 |
| Public | 15 (21.0%) | 22 (26.0%) | 17 (17.0%) | 19 (25.0%) | 73 (22.0%) | |
| Private | 57 (78.0%) | 61 (73.0%) | 78 (80.0%) | 58 (75.0%) | 254 (77.0%) | |
| Uninsured/unknown | 1 (1.0%) | 1 (1.0%) | 3 (3.0%) | 0 (0.0%) | 5 (2.0%) | |

[a]Baseline characteristics were assessed at first treatment with intravenous ketamine or intranasal esketamine, based on documentation in the electronic medical record. Number and percent are reported for count variables; mean and SD for continuous variables.
[b]Public insurance includes beneficiaries or Medicare, Medicaid, or both. Private insurance includes all other privately provided insurance plans.
Abbreviations: ECT = electroconvulsive therapy, IN = intranasal, IV = intravenous, MADRS = Montgomery-Asberg Depression Rating Scale, PTSD = posttraumatic stress disorder, SUD = substance use disorder.

Figure 1.

**Trajectories of Depressive Symptoms Over Time, by Antidepressant Class**




Abbreviations: AD = antidepressant; SSRI = selective serotonin reuptake inhibitor; SNRI = selective serotonin–norepinephrine reuptake inhibitor; MADRS = Montgomery-Asberg Depression Rating Scale; QIDS = Quick Inventory of Depressive Symptomatology; LOCF = last observation carried forward.

report have been described elsewhere.[4,5] The Yale Institutional Review Board waived informed consent per the Common Rule. The primary exposure variable was antidepressant class (selective serotonin reuptake inhibitor [SSRI], serotonin–norepinephrine reuptake inhibitor [SNRI], or another oral antidepressant [AD]), relative to no antidepressant. Outcomes included mean changes in the Montgomery-Asberg Depression Rating Scale (MADRS) and Quick Inventory of Depressive Symptomatology (QIDS) scales, response (≥50% improvement on MADRS) and remission (≤10 on MADRS). Outcomes were assessed at first treatment, treatment 4, and final treatment (treatment 8 or last treatment carried forward). Linear mixed models were used to assess change in MADRS and QIDS over time; logistic regressions were used for remission and response and were adjusted for age, sex, race/ethnicity, concomitant benzodiazepine or antipsychotic use, history of electroconvulsive therapy or psychiatric hospitalization, comorbid psychiatric disorders, insurance type (public vs private), and treatment modality (IV ketamine vs IN esketamine). Analyses were conducted using Stata version 19/MP (StataCorp).

## Results

Overall, 332 patients were included in the analysis, of whom 149 received ketamine and 183 received esketamine. At the time of treatment, 84 were prescribed an SSRI, 98 an SNRI, 77 another AD, and 73 no AD. The groups were similar at baseline (Table 1). Using linear mixed-effects models, the mean adjusted MADRS score significantly decreased across visits but did not differ by AD class (SSRI: unstandardized coefficient (*b*), 0.19 [95% CI, −2.10 to 2.49]; $P = .87$; SNRI: *b*, −1.21 [−3.32 to 0.91]; $P = .26$; other AD: *b*, −0.74 [−2.97 to 1.49]; $P = .52$). Results for QIDS were similar (SSRI: *b*, −0.37 [−1.95 to 1.22]; $P = .65$; SNRI: *b*, −0.90 [−2.42 to 0.63]; $P = .25$; other AD: *b*, −1.00 [−2.67 to 0.67]; $P = .24$) (Figure 1).

The adjusted odds of response and remission also did not differ significantly by AD class. For response, odds ratios were 1.29 (95% CI, 0.64–2.58; $P = .31$) for SSRI, 0.79 (0.40–1.57; $P = .52$) for SNRI, and 1.74 (0.64–2.65; $P = .15$) for other AD. For remission, odds ratios were 2.00 (0.83–4.83; $P = .12$), 1.06 (0.45–2.51; $P = .89$), and 1.43 (0.56–3.61; $P = .45$), respectively. A subgroup analysis was conducted in which regressions were repeated within esketamine or ketamine subgroups; results were not meaningfully different.

## Discussion

This analysis did not detect group differences between concurrent oral antidepressant class and clinical outcomes among patients treated with IV ketamine or IN esketamine. This finding was consistent across different outcome measures assessed and models employed. The result suggests that concurrent antidepressant use does not meaningfully alter initial treatment outcomes from ketamine/esketamine. This may be due to ketamine/esketamine's unique mechanism of action that acts independently from oral antidepressants. Alternatively, the substantial nonspecific effects inherent in ketamine/esketamine treatment may mask subtle differential effects from oral antidepressants.[6]

Limitations of this study are the observational study design, the short follow-up period, and the lack of formal assessment for treatment resistance. This last weakness is mitigated in part by the fact that third-party payers generally require 2 failed antidepressant trials prior to authorizing treatment; the vast majority of patients at our clinic receive insurance coverage for both ketamine and esketamine. Longer-term, randomized trials are needed to confirm whether oral antidepressant class differentially affects efficacy and durability of response to ketamine/esketamine treatment. If confirmed, such findings have relevant clinical implications: concurrent prescribing during ketamine/esketamine treatment may be guided more by tolerability than clinical expectations of differential efficacy.

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