RESEARCH LETTER

Evaluation of the Trajectory of Depression Severity With Ketamine and Esketamine Treatment in a Clinical Setting

Although intravenous racemic ketamine has rapid antidepressant properties, it is not approved for depression treatment.[1] However, the US Food and Drug Administration has approved intranasal esketamine for treatment-resistant depression.[1]

Supplemental content

Correia-Melo et al[2] treated 63 participants with intravenous ketamine or esketamine and observed that esketamine was noninferior to ketamine. A recent meta-analysis suggested that intravenous ketamine was more effective,[3] but the only head-to-head trial included was from Correia-Melo et al,[2] rendering interpretation difficult. To our knowledge, no multidose, head-to-head comparisons of these treatments have been reported.

The Yale Interventional Psychiatry Service (IPS) provides both intravenous ketamine (0.5 mg/kg over 40 minutes) and intranasal esketamine (56 or 84 mg). Patients receive similar care with comparable protocols in the same physical space. We analyzed Yale IPS clinical data to evaluate these treatments in a clinical setting.

Methods | For this comparative analysis, we reviewed retrospective data for all Yale IPS patients receiving intravenous ketamine or intranasal esketamine between September 2016 and April 2021 (eMethods in the Supplement). The Yale Institutional Review Board approved this analysis of existing clinical data and waived informed consent per the Common Rule. The analysis followed the ISPOR reporting guideline.

Results | Of 210 included patients, 129 (61.4%) received intravenous ketamine and 81 (38.6%) received intranasal esketamine. There were no differences in baseline demographic factors (**Table**). The estimated group difference in Montgomery-Åsberg Depression Rating Scale (MADRS) score by treatment end (primary outcome) was 2.15 (95% CI, −0.06 to 4.37; $P = .06$). Estimated group differences in Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) scores after full treatment course and MADRS and QIDS-SR scores after the first 6 treatments (secondary outcomes) were 1.59 (95% CI, 0.24-2.94; $P = .02$), 2.49 (95% CI, 0.01-4.98; $P < .05$), and 1.64 (0.08-3.19; $P = .04$), respectively, all favoring intravenous ketamine (**Figure**). Other models produced similar results. There were no group differences in response rates (37.8% [95% CI, 30.0%-46.3%] vs 36.0% [95% CI, 25.9%-47.5%]) or remission (29.6% [95% CI, 22.5%-37.9%] vs 24.0% [95% CI, 15.6%-35.0%]) for ketamine vs esketamine, respectively.

Table. Clinical and Demographic Characteristics of Study Participants[a]

Characteristic	Treatment		Total (N = 210)	*P* value
	Ketamine (n = 129)	Esketamine (n = 81)		
Age, y, mean (SD)	49.9 (16.4)	46.7 (17.1)	48.7 (16.7)	.19
Sex[b]				
Male	46 (35.7)	38 (46.9)	84 (40.0)	.11
Female	83 (64.3)	43 (53.1)	126 (60.0)	
Race[c]				
American Indian or Alaska Native	0 (0.0)	1 (1.2)	1 (0.5)	.13
Asian	3 (2.3)	0 (0.0)	3 (1.4)	
Black or African American	1 (0.8)	3 (3.7)	4 (1.9)	
White	123 (95.4)	76 (93.8)	199 (94.8)	
Ethnicity[c]				
Hispanic or Latino	4 (3.1)	3 (3.7)	7 (3.3)	.84
Non-Hispanic	117 (90.7)	75 (92.6)	192 (91.4)	
Health insurance				
Private	96 (74.4)	59 (72.8)	155 (73.8)	.27
Public	17 (13.2)	16 (19.8)	33 (15.7)	
No. of acute sessions, mean (SD)	5.79 (1.49)	7.47 (1.46)	6.44 (1.69)	NA[d]
Completed prescribed acute course[e]	109 (84.5)	69 (85.2)	178 (84.8)	.89

Abbreviation: NA, not applicable.

[a] Data were collected at the Yale Interventional Psychiatry Service (IPS) of the Yale New Haven Health System from September 2016 to April 2021. Values are presented as the number (%) of participants unless indicated otherwise. There was a small amount of missing data for race (3 [1.4%]), ethnicity (11 [5.2%]), and health insurance (22 [10.5%]); including these data in an "unknown" category does not alter the χ^2 results, suggesting that these data were missing at random.

[b] Sex is based on categorization documented in the electronic medical records.

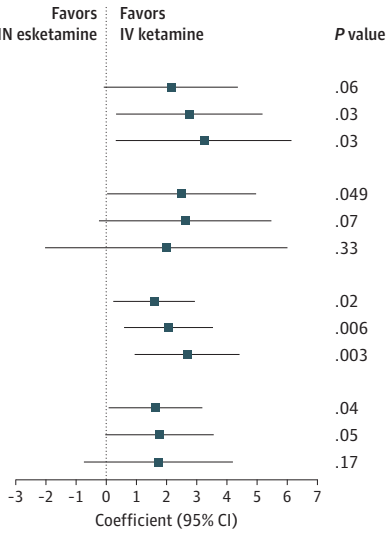
[c] Race and ethnicity are based on categorizations documented in the electronic medical records. These data were included because there was a notable difference in race and ethnicity compared with the population served by Yale IPS. Additional studies are needed to identify and address accessibility issues.

[d] For intravenous ketamine, the total number of treatments offered as part of the acute course has changed over the years included in the study, whereas esketamine always consisted of an 8-treatment course. As such, a comparison of the mean number of sessions completed is not appropriate.

[e] Defined as multiple treatments each 7 days apart or less.

Figure. Estimated Differences of Groups Treated With Intravenous Ketamine or Intranasal Esketamine

Source	Coefficient (95% CI)	*P* value
MADRS		
Log transformed	2.15 (-0.06 to 4.37)	.06
Square root transformed	2.76 (0.33 to 5.19)	.03
Linear (untransformed)	3.24 (0.32 to 6.15)	.03
MADRS, excluding the last 2 sessions		
Log transformed	2.49 (0.01 to 4.98)	.049
Square root transformed	2.62 (-0.24 to 5.48)	.07
Linear (untransformed)	1.99 (-2.03 to 6.02)	.33
QIDS		
Log transformed	1.59 (0.24 to 2.94)	.02
Square root transformed	2.07 (0.59 to 3.55)	.006
Linear (untransformed)	2.69 (0.95 to 4.43)	.003
QIDS, excluding the last 2 sessions		
Log transformed	1.64 (0.08 to 3.19)	.04
Square root transformed	1.78 (-0.01 to 3.57)	.05
Linear (untransformed)	1.74 (-0.74 to 4.21)	.17



Patients received intravenous (IV) ketamine (0.5 mg/kg over 40 minutes) or intranasal (IN) esketamine (56 or 84 mg) to treat depression. Their depression trajectories were assessed using scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR).

There were no group differences for intravenous ketamine vs intranasal esketamine in mean (SD) suicidal ideation scores on MADRS item 10 (3.03 [1.46] to 1.33 [1.11] vs 2.64 [1.26] to 1.26 [1.24]) and QIDS-SR item 12 (1.44 [0.93] to 0.50 [0.76] vs 1.23 [1.02] to 0.45 [0.74]). Subgroup analysis of 46 patients aged 65 years or older showed response and remission rates of 32.6% (95% CI, 19.5%-48.0%) and 30.4% (95% CI, 17.7%-45.8%), respectively, with no group differences.

Discussion | This comparative analysis evaluating the trajectory of depression severity with ketamine and esketamine yielded no significant differences between groups based on the primary outcome measure. However, secondary outcomes based on QIDS-SR scores after 8 treatments and MARDS and QIDS-SR scores comparing the first 6 treatments all favored intravenous ketamine. There were no differences in response or remission rates, although dichotomizing continuous outcomes inevitably reduces statistical power.[4] These findings suggest a trajectory of improvement in favor of intravenous ketamine, although this should be interpreted with utmost caution given the study limitations.

Response and remission rates, while within the range reported in the literature,[5,6] were lower than those of other reports. This could be because the Yale IPS functions as a tertiary referral center, resulting in a more severely ill, treatment-resistant patient population.

We did not detect significant between-group differences based on available demographic factors. However, the study demographics may not be representative of the general population, suggesting accessibility issues with these treatments. Identifying and addressing factors related to access is paramount and requires further attention.

This study's limitations include the nonrandomized nature of treatment allocation and the retrospective nature of the analysis. Ratings were unblinded and conducted in a clinical rather than research setting. Furthermore, the acute course duration for intravenous ketamine was not the same during the entire course of the study. Although both treatments reduce symptoms, these findings signal a potential difference that could be attributable to many factors, including dosing, delivery mechanism, role of arketamine, or patient expectations. A randomized trial is needed to determine the comparative efficacy of these treatments.

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Conflict of Interest Disclosures: Dr Sanacora reported receiving personal fees and serving as a consultant to Allergan, Alkermes, AstraZeneca, Avanier Pharmaceuticals, Axsome Therapeutics, Biogen, Biohaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Cowen,

EMA Wellness, Engrail Therapeutics, Clexio, Denovo Biopharma, Gilgamesh, Hoffmann La-Roche, Intra-Cellular Therapies, Janssen Pharmaceuticals, Levo, Lundbeck, Merck, Navitor Pharmaceuticals, Neurocrine, Novartis, Noven Pharmaceuticals, Otsuka, Perception Neuroscience, Praxis Therapeutics, Sage Pharmaceuticals, Servier Pharmaceuticals, Seelos Pharmaceuticals, Taisho Pharmaceuticals, Teva, Valeant, Vistagen Therapeutics, and XW Labs. Dr Sanacora also reported receiving research contracts from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, and Usona over the past 36 months. Dr. Sanacora holds equity in Biohaven Pharmaceuticals and is a co-inventor on a US patent (8,778,979) held by Yale University and a co-inventor on US Provisional Patent Application 047162-7177P1 (00754) filed on August 20, 2018, by the Yale University Office of Cooperative Research. Yale University has a financial relationship with Janssen Pharmaceuticals and may in the future receive financial benefits from this relationship. The university has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest office. Dr Wilkinson reported receiving contract funding from Janssen Pharmaceuticals, Sage Therapeutics, and Oui Therapeutics for the conduct of clinical trials administered through Yale University as well as consulting fees from Biohaven Pharmaceuticals, Sage Therapeutics, Janssen Pharmaceuticals, and Oui Therapeutics. No other disclosures were reported.

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COMMENT & RESPONSE

Associating Violence With Schizophrenia—Risks and Biases

To the Editor Whiting et al[1] tested the meta-analytic association of schizophrenia spectrum disorder diagnosis with the social behavior of perpetrating violent outcomes. We believe the methods and their interpretations are flawed, and their uncritical dissemination risks fueling misunderstandings and stigmatization, potentially leading to violence against people with psychosis, as feared by our coauthor with lived experience of psychosis.

The representativeness of the data set is questionable, encompassing 4 decades of incomparable mental health care settings, obsolete diagnostic criteria (eg, *International Classification of Diseases, Eighth Revision*, or *DSM-III*) that have been dismissed because of their limited validity, unselective focus on psychotic disorders other than schizophrenia spectrum ("we chose schizophrenia spectrum disorders where possible"[1]), and mixing heterogeneous clinical stages without addressing timing of treatments.[2] Indeed, the authors acknowledged that only a few studies met the highest-quality selection criteria.[1]

The outcome of violence was itself spuriously operationalized using culturally sensitive and time-sensitive loose criteria (eg, "broad interpersonal violence perpetration" and "serious trouble with the law"[1]), including self-rated measures that were neither internationally validated nor shared across disciplines outside the academic arena, despite the moral and social bearing of such criteria. Not surprisingly, the study found substantial heterogeneity, contradicting the statement that the study provides "more precision for risk estimates."[1] Meta-regression and subgroup analyses could not address this heterogeneity because they were largely underpowered by the small meta-analytic data set. For example, Figure 3[1] reports an extreme meta-analytic odds ratio of perpetrating homicide in female individuals with psychosis of 43.2 (95% CI, 17.1-109.2). Such an extreme value is actually based on a small study (n = 29 patients), which did not even acknowledge the specific diagnostic codes of psychosis considered.

We are deeply troubled by the way associations have been analyzed without attention to confounding by social determinants of psychosis or reverse causality, leading to the conclusion that "the risk of perpetrating violent outcomes was increased in individuals with schizophrenia spectrum disorders."[1] Confounding by social class and violence inflicted on people with psychoses are well documented.[3,4] Pairwise meta-analyses cannot adequately address confounders (and the abstract does not acknowledge reporting unadjusted odds ratios). We call for an open debate rebutting these findings to ensure that the headline messages are not used to undo decades of work by human rights advocates and antistigma campaigners.

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