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Comparative Effectiveness of Intravenous Ketamine and Intranasal Esketamine in Clinical Practice Among Patients With Treatment-Refractory Depression: An Observational Study

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ABSTRACT

Objective: Ketamine has been redeveloped as a rapid-acting antidepressant for treatment-resistant depression (TRD). There is a paucity of literature comparing subanesthetic intravenous (IV) ketamine and US Food and Drug Administration (FDA)–approved intranasal (IN) esketamine for TRD in real-world clinical settings. We compared the efficacy and time to achieve remission/response with repeated ketamine and esketamine.

Methods: An observational study of adults with TRD received up to 6 IV ketamine (0.5 mg/kg over 40–100 minutes) or up to 8 IN esketamine (56- or 84-mg) treatments from August 17, 2017, to June 24, 2021. Depressive symptoms were measured utilizing the 16-item Quick Inventory of Depressive Symptomatology self-report (QIDS-SR) before and 24 hours after treatment. Cox proportional hazard models were used to evaluate associations between time to response (≥ 50% change in QIDS-SR score) and remission (QIDS-SR score ≤ 5).

Results: Sixty-two adults (median age = 50 years, 65% female) received IV ketamine (76%, n = 47) or IN esketamine (24%, n = 15). Neither baseline-to-endpoint change in QIDS-SR score nor response/remission rates were significantly different between groups. Time to remission, defined as number of treatments (adjusting for age, body mass index, sex, and baseline QIDS-SR score), was faster for IV versus IN treatment (HR = 5.0, *P* = .02).

Conclusions: Intravenous ketamine and intranasal esketamine showed similar rates of response and remission in TRD patients, but the number of treatments required to achieve remission was significantly lower with IV ketamine compared to IN esketamine. These findings need to be investigated in a randomized control trial comparing these two treatment interventions.

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Major depressive disorder (MDD) is highly prevalent in the US with a 12-month prevalence of 10%, or 1 in 10 Americans.[1] A cornerstone to initial management of moderate-to-severe MDD is antidepressant pharmacotherapy. However, conventional therapies for MDD have maintained their initial focus on drug development that enhances monoaminergic neurotransmission.[2] The therapeutic gap of the now more than 30 US Food and Drug Administration (FDA)–approved treatments for MDD is that only ≈ 50% of patients have an adequate response and ≈ 33% achieve remission. Furthermore, for those who respond, the time delay is several weeks to several months.[3] Patients with treatment-resistant depression (TRD) represent a significant proportion of the MDD burden on society.[4]

Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, has been redeveloped as a rapid-acting antidepressant for TRD.[5–9] Infusions of racemic ketamine and enantiomers, neurosteroids, and psychedelic-assisted therapies might eventually occupy a place along a continuum of FDA-approved antidepressant therapies that also includes psychotherapy, electroconvulsive therapy (ECT), and transcranial magnetic stimulation (TMS). The *S*-enantiomer of ketamine, esketamine, is FDA approved in adults for unipolar TRD (in conjunction with an oral antidepressant) and for MDD with suicidal ideations/behaviors.[10] Racemic intravenous (IV) ketamine is often not covered by insurance, while intranasal (IN) esketamine is expensive, although covered by insurance.[11]

Subanesthetic-dose IV ketamine (0.5 mg/kg infused over 40 minutes) produces a rapid and robust antidepressant response, which is typically short-lived.[8,9,11–13] Maintenance ketamine requiring repeated ketamine infusions twice or thrice weekly over 2 weeks, followed by once-weekly infusions for an additional 4 weeks, is provided to help maintain the antidepressant response for those with TRD.[7,13,14] Although IV ketamine use and IN esketamine use have been expanding rapidly,[15] there is a paucity of literature on efficacy data comparing subanesthetic IV ketamine and IN esketamine for TRD in real-world scenarios. In a recent review, Bahji et al[16] pooled data from randomized controlled trials (RCTs) in which IV ketamine or IN esketamine was used to treat TRD and, using meta-analytic techniques, found IV ketamine to be more efficacious and have lower dropout rates than IN esketamine. However, none of the RCTs compared IV ketamine to IN esketamine in a head-to-head trial.

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Clinical Points

- There is not a head-to-head randomized controlled trial comparing intravenous (IV) ketamine and intranasal (IN) esketamine, despite the fact that both have been used in clinical settings for patients with treatment-resistant depression (TRD).
- IV racemic ketamine and IN esketamine showed similar response/remission in TRD patients in an acute/induction phase.
- The number of treatments required to achieve remission was significantly lower with IV ketamine compared to IN esketamine.

In the absence of an RCT, an observational study in real-world settings can provide critical information to practicing clinicians and can help in hypothesis generation for future RCTs.

Thus, we conducted this study to compare the effectiveness of IV ketamine and IN esketamine in a real-world setting among patients with TRD. We also aimed to investigate the role of comorbidities in the efficacy of ketamine among TRD patients.

METHODS

This was an observational (retrospective cohort) study, approved by the Mayo Clinic Institutional Review Board, in which we included adults (≥ 18 years) with TRD who provided consent and had received up to 6 IV ketamine infusions (0.5 mg/kg, infused over 40–100 minutes) or up to 8 IN esketamine (56- or 84-mg) treatments for TRD at the Mayo Clinic Depression Center (from August 17, 2017, to June 24, 2021). Data were collected by the trained mood psychiatrists (board certified psychiatrists)/mood fellows (Health Insurance Portability and Accountability Act [HIPAA]–compliant trained physicians/psychiatrists) from the electronic health records.

The Mayo Clinic Depression Center has a ketamine service within the Department of Psychiatry and Psychology. This clinic provides IV ketamine or IN esketamine for patients with MDD or bipolar disorder, with current TRD defined as failure to respond to at least 2 adequate trials of depression treatments (antidepressants, mood stabilizers, or atypical antipsychotic drugs with indication for bipolar depression; ECT; or TMS).[17] *DSM-5* criteria were used to make the diagnoses of MDD and bipolar disorder. Logistics and patient preference would often determine which treatment would eventually be prescribed. Our IV ketamine clinic was built first, with expectations that patients would pay out of pocket as insurance typically does not cover IV ketamine. After mid-2020 when our IN esketamine practice started, if the IV clinic was full, patients would be offered IN esketamine if it was covered by their insurance. For patients struggling with bipolar depression, insurance would not cover IN esketamine, so these patients would be offered IV ketamine when a slot was available. IN esketamine was provided in accordance with FDA labeling for use in patients with MDD with no upper age limit. Exclusion criteria include psychotic disorder, substance use disorder (except nicotine and caffeine) within 6 months, cognitive disorders, and any other primary psychiatric disorder that is not a mood disorder. Our ketamine clinic is based on our prior research studies[7,18] in which we offered IV ketamine to patients (18–65 years of age) with treatment-resistant unipolar or bipolar depression. Most patients completed the acute phase within 4–5 weeks; however, due to scheduling issues or patient's preference, some treatments were delayed. Thus, we included acute phase, up to 6 weeks of treatment, during which patients received their initial 6 IV ketamine infusions or 8 IN esketamine treatments.

Depression symptoms were measured utilizing the self-report 16-item Quick Inventory of Depressive Symptomatology scale (QIDS-SR)[19] before and 24 hours after ketamine/esketamine treatment. If the data were collected using the Montgomery-Asberg Depression Rating Scale (MADRS),[20] they were converted to QIDS-SR scores.[21]

Clinical treatments were provided generally twice or thrice per week. For each treatment, a patient recorded up to 2 posttreatment QIDS-SR scores: (1) 24 hours after treatment and (2) just prior to their next treatment. The QIDS-SR outcome is the change from baseline to the lower of these 2 scores. The number of days between treatments varied for each patient. The acute phase duration was defined as 44 days from baseline or approximately 6 weeks of treatments plus time for the last post treatment QIDS-SR. If a specific treatment occurred within 43 days of baseline but was missing a QIDS-SR outcome, the QIDS-SR outcome from the previous treatment was imputed and the time of evaluation was set as 1 day after the specific treatment. Remission and response were defined as QIDS-SR score ≤ 5 and ≥ 50% change in QIDS-SR score, respectively. The number of treatments to response and number to remission were noted for each patient. Thorough clinical history, including clinical assessments and psychiatric comorbidities, was collected from the HIPAA-compliant electronic health records by HIPAA-compliant trained physician researchers.

Statistical Analysis

Wilcoxon rank sum and Fisher exact tests were used to test for differences in demographic, clinical, and medication variables between IV and IN groups. Differences between treatment groups in changes in vital measurements and clinical assessments during sessions were assessed using repeated-measures analysis of variance (ANOVA). Similar univariate tests were conducted for differences by demographics and clinical measures between response/nonresponse and remission/non-remission groups. *P* values in results and figures are not adjusted for multiple comparisons to support hypothesis generation. Mixed-effects linear models were used to assess the percent change from baseline over treatment course adjusting for age, sex, body mass index (BMI), and baseline QIDS-SR score. A random intercept and AR(1) covariance structure were

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Table 1. Patient Characteristics by Ketamine Treatment Group and Overall[a]

Characteristic	IV (n = 47)	IN (n = 15)	Total (N = 62)	*P*
Demographic				
Age, median (Q1, Q3) [min, max], y	50.6 (39.9, 54.3) [19.9, 63.8]	46.8 (37.3, 61.8) [26.5, 68.4]	50.2 (39.9, 55.5) [19.9, 68.4]	.39*
Sex, n (%)				.13†
Male	14 (29.8)	8 (53.3)	22 (35.5)	
Female	33 (70.2)	7 (46.7)	40 (64.5)	
Body mass index, median (Q1, Q3) [min, max]	27.9 (24.0, 32.4) [20.8, 39.6]	32.0 (27.7, 36.3) [23.8, 50.9]	28.5 (24.8, 33.4) [20.8, 50.9]	**.049***
Employment, n (%)				1.00†
Unemployed	3 (6.4)	0 (0.0)	3 (4.8)	
Employed	25 (53.2)	8 (53.3)	33 (53.2)	
Disability due to depression	11 (23.4)	4 (26.7)	15 (24.2)	
Homemaker, retired, or student	8 (17.0)	3 (20.0)	11 (17.7)	
Clinical				
Diagnosis, n (%)				1.00†
MDD	44 (93.6)	15 (100.0)	59 (95.2)	
BD-I	1 (2.1)	0 (0.0)	1 (1.6)	
BD-II	2 (4.3)	0 (0.0)	2 (3.2)	
Depression episode duration, median (Q1, Q3) [min, max], y	2.3 (1.0, 5.0) [0.3, 20.0]	8.0 (2.0, 11.0) [0.5, 37.0]	3.0 (1.5, 8.0) [0.3, 37.0]	**.01***
PTSD, n (%)	6 (12.8)	0 (0.0)	6 (9.7)	.32†
Anxiety disorders, n (%)	29 (61.7)	10 (66.7)	39 (62.9)	1.00†
Fibromyalgia or chronic pain, n (%)	4 (8.5)	3 (20.0)	7 (11.3)	.34†
OCD, n (%)	2 (4.3)	0 (0.0)	2 (3.2)	1.00†
Eating disorder, n (%)	2 (4.3)	1 (6.7)	3 (4.8)	1.00†
Borderline personality disorder, n (%)	3 (6.4)	2 (13.3)	5 (8.1)	.59†
History of substance use disorder, n (%)	4 (8.5)	4 (26.7)	8 (12.9)	.09†
Study Variables				
Esketamine nasal dosage deficit relative to IV ketamine dosage, median (Q1, Q3) [min, max], mg[b]	NA	8.4 (5.5, 24.2) [0.6, 24.8]	NA	NA
Baseline QIDS-SR score, median (Q1, Q3) [min, max]	17 (15, 20) [9, 24]	19 (18, 20) [16, 23]	18 (15, 20) [9, 24]	.07*
No. of treatments, n (%)				**< .001**†
1 to 3	25 (53.2)	1 (6.7)	26 (41.9)	
4 to 6	22 (46.8)	0 (0.0)	22 (35.5)	
7 or 8	0 (0.0)	14 (93.3)	14 (22.6)	
No. of treatments per week, median (Q1, Q3) [min, max][c]	1.5 (1.0, 2.0) [0.7, 3.0]	2.0 (1.6, 2.0) [0.7, 2.0]	1.5 (1.2, 2.0) [0.7, 3.0]	.11
QIDS-SR score change from baseline to last treatment, median (Q1, Q3) [min, max]	−8 (−13, −4) [−21, 3]	−10 (−13, −4) [−16, −2]	−8 (−13, −4) [−21, 3]	.84†
QIDS-SR score percent change from baseline to last treatment, median (Q1, Q3) [min, max]	−53 (−77, −25) [−100, 20]	−55 (−69, −24) [−80, −10]	−54 (−75, −24) [−100, 20]	.65†
Response, n (%)	27 (57.4)	9 (60.0)	36 (58.1)	1.00†
Remission, n (%)	20 (42.6)	4 (26.7)	24 (38.7)	.37†
Oxygen saturation[d]				
Change at 40 min[e]	0.44 (0.42)	−0.34 (0.52)	0.13 (0.33)	.25‡
Change to endpoint[f]	0.25 (0.44)	−0.30 (0.54)	0.03 (0.34)	.43‡
Systolic BP[d]				
Change at 40 min[e]	8.66 (1.25)	0.97 (1.35)	5.41 (1.09)	**< .001**‡
Change to endpoint[f]	5.88 (1.38)	1.02 (1.67)	3.94 (1.12)	**.03**‡
Diastolic BP[d]				
Change at 40 min[e]	3.38 (0.96)	2.27 (0.94)	2.82 (0.67)	.42‡
Change to endpoint[f]	1.30 (1.00)	2.53 (1.03)	1.90 (0.71)	.40‡
Heart rate[d]				
Change at 40 min[e]	1.66 (0.88)	−3.12 (1.05)	−0.24 (0.76)	**.001**‡
Change to endpoint[f]	0.42 (0.98)	−2.80 (1.22)	−0.84 (0.80)	**.04**‡
CADSS score[d]	4.14 (1.24)	8.09 (1.66)	5.53 (1.02)	.06‡
Current Medications				
No. of psychotropics, median (Q1, Q3) [min, max]	3.0 (3.0, 5.0) [1, 6]	3.0 (3.0, 5.0) [2, 7]	3.0 (3.0, 5.0) [1, 7]	.83*
Individual psychotropic/class, n (%)				
SSRI	12 (25.5)	4 (26.7)	16 (25.8)	1.00†
SNRI	16 (34.0)	5 (33.3)	21 (33.9)	1.00†
TCA	6 (12.8)	2 (13.3)	8 (12.9)	1.00†
MAOI	0 (0.0)	2 (13.3)	2 (3.2)	.056†
Atypical antipsychotics	17 (36.2)	3 (20.0)	20 (32.3)	.35†
Mirtazapine	4 (8.5)	1 (6.7)	5 (8.1)	1.00†
Bupropion	14 (29.8)	2 (13.3)	16 (25.8)	.31†
Stimulants	13 (27.7)	1 (6.7)	14 (22.6)	.16†

continued

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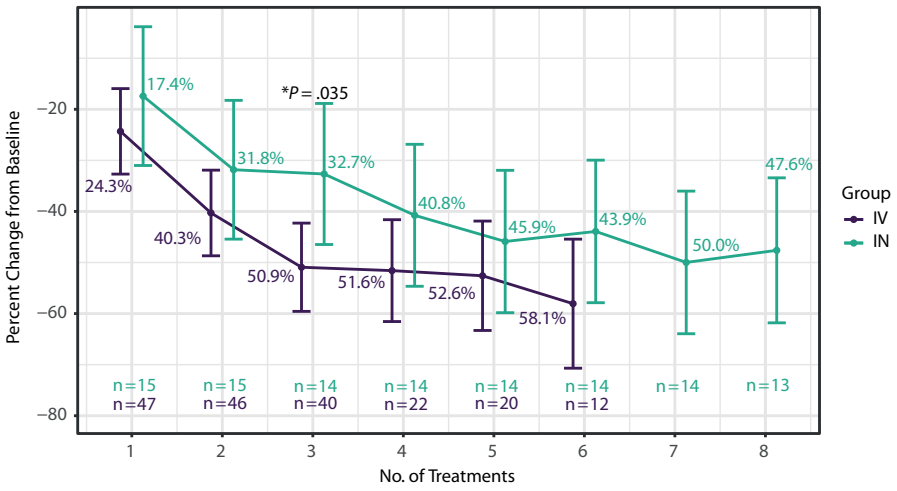
Table 1 (continued).

Characteristic	IV (n = 47)	IN (n = 15)	Total (N = 62)	*P*
Trazodone	16 (34.0)	3 (20.0)	19 (30.6)	.36†
Gabapentin	6 (12.8)	1 (6.7)	7 (11.3)	1.00†
Z-drugs	6 (12.8)	5 (33.3)	11 (17.7)	.12†
Benzodiazepines	20 (42.6)	8 (53.3)	28 (45.2)	.56†
Neuromodulation (tried in current episode), n (%)				
ECT	17 (36.2)	2 (13.3)	19 (30.6)	.12†
TMS	8 (17.0)	2 (13.3)	10 (16.1)	1.00†

[a]Boldface indicates statistical significance.
[b]Deficit calculated from dosage esketamine nasal patient would have received during IV ketamine treatment minus 45% of their maximum esketamine dose.
[c]Patient-averaged number of treatments per week.
[d]n = 32 to 34 for IV patients because data were missing for 13 to 15 patients. n = 14 for IN patients for CADSS because data were missing for 1 patient. Values are shown as mean (SE).
[e]The value closest to 40 minutes after the start of treatment was used.
[f]The value at the end of the session within 100 minutes was used.
*Wilcoxon rank sum *P* value; †Fisher exact *P* value; ‡repeated-measures ANOVA.
Abbreviations: ANOVA = analysis of variance, BD = bipolar disorder, BMI = body mass index, BP = blood pressure, CADSS = Clinician-Administered Dissociative States Scale, ECT = electroconvulsive therapy, IN = intranasal, IV = intravenous, MAOI = monoamine oxidase inhibitor, MDD = major depressive disorder, NA = not applicable, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, QIDS-SR = 16-item Quick Inventory of Depressive Symptomatology self-report, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TMS = transcranial magnetic stimulation.

Figure 1. Mean Percent Change From Baseline to Most Improved Posttreatment QIDS-SR Score by IV Ketamine and IN Esketamine Across Treatment Course[a]



[a]Error bars indicate 95% CIs.
Abbreviations: IN = intranasal, IV = intravenous, QIDS-SR = 16-item Quick Inventory of Depressive Symptomatology self-report.

used to account for correlation of repeated measures within patients.

Cox proportional hazard models were used to evaluate associations between the number of treatments to response and remission and treatment group, adjusting for age, sex, BMI,[17] and baseline QIDS-SR score. For number of treatments (primary outcome), patients without a response or a remission were censored at the last treatment within the acute phase.

In a pre-planned exploratory analysis, we assessed whether the 2 available doses (56 and 84 mg) of IN esketamine contributed to reduced efficacy for IN esketamine; this group of patients was split in half based on the difference between the potential dosage that would have been received during IV ketamine treatment and 45% of their maximum esketamine dose.[22,23] We assessed for effects of high-dosage (difference less than the median difference) versus low-dosage (difference above than the median difference) IN esketamine.

Analyses were performed in R version 4.0.3 (Vienna, Austria) and SAS Studio 3.81 (SAS Institute; Cary, North Carolina). *P* values < .05 were considered significant.

RESULTS

The demographic characteristics (N = 62) are described in Table 1. The overall median age was 50 years (range, 20 to 68 years), more were female (64.5%), and most had a diagnosis of MDD (95.2%). Seventy-six percent (n = 47) and 24% (n = 15) received IV ketamine and IN esketamine,

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Table 2. Associations Between Clinical Outcomes With Demographics, Clinical Characteristics, and Comorbidities[a]

	Response			Remission		
Characteristic	No (n = 26)	Yes (n = 36)	*P*	No (n = 38)	Yes (n = 24)	*P*
Demographics						
Age, median (Q1, Q3) [min, max], y	49.1 (39.9, 55.1) [19.9, 68.4]	50.7 (40.5, 56.2) [23.2, 65.3]	0.66	50.3 (39.9, 55.5) [19.9, 68.4]	50.2 (40.5, 55.5) [23.2, 63.1]	.85
Male	12 (46.2%)	10 (27.8%)	0.18	13 (34.2%)	9 (37.5%)	.79
BMI, median (Q1, Q3) [min, max]	27.8 (24.3, 30.8) [21.8, 35.3]	29.3 (25.7, 36.1) [20.8, 50.9]	0.15	28.0 (24.3, 32.9 [20.8, 50.9]	28.8 (26.3, 35.6 [21.1, 40.9]	.39
Employment			0.61			.57
Unemployed	2 (7.7)	1 (2.8)		2 (5.3)	1 (4.2)	
Employed	12 (46.2)	21 (58.3)		21 (55.3)	12 (50.0)	
Disability due to depression	6 (23.1)	9 (25.0)		7 (18.4)	8 (33.3)	
Homemaker/retired/student	6 (23.1)	5 (13.9)		8 (21.1)	3 (12.5)	
IV	(n = 20)	(n = 27)		(n = 27)	(n = 20)	
Employment			0.12			.05
Unemployed	2 (10.0)	1 (3.7)		2 (7.4)	1 (5.0)	
Employed	9 (45.0)	16 (59.3)		15 (55.6)	10 (50.0)	
Disability due to depression	3 (15.0)	8 (29.6)		3 (11.1)	8 (40.0)	
Homemaker/retired/student	6 (30.0)	2 (7.4)		7 (25.9)	1 (5.0)	
IN	(n = 6)	(n = 9)		(n = 11)	(n = 4)	
Employment			0.24			.17
Unemployed	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Employed	3 (50.0)	5 (55.6)		6 (54.5)	2 (50.0)	
Disability due to depression	3 (50.0)	1 (11.1)		4 (36.4)	0 (0.0)	
Homemaker/retired/student	0 (0.0)	3 (33.3)		1 (9.1)	2 (50.0)	
Clinical						
Duration of depressive episode, median (Q1, Q3) [min, max], y	2.0 (1.0, 5.0) [0.4, 37.0]	4.3 (2.0, 9.0) [0.3, 16.0]	0.23	2.0 (1.0, 5.0) [0.4, 37.0]	5.0 (2.4, 9.0) [0.3, 16.0]	.08
Current no. of psychotropics, median (Q1, Q3) [min, max]	3.0 (3.0, 5.0) [1.0, 6.0]	3.0 (3.0, 5.0) [1.0, 7.0]	0.83	4.0 (3.0, 5.0) [1.0, 7.0]	3.0 (2.5, 5.0) [1.0, 6.0]	.16
Individual psychotropic/class						
SSRI	8 (30.8)	8 (22.2)	0.56	10 (26.3)	6 (25.0)	1.00
SNRI	8 (30.8)	13 (36.1)	0.79	16 (42.1)	5 (20.8)	.10
TCA	5 (19.2)	3 (8.3)	0.26	5 (13.2)	3 (12.5)	1.00
Atypical antipsychotics	9 (34.6)	11 (30.6)	0.79	12 (31.6)	8 (33.3)	1.00
Gabapentin	4 (15.4)	3 (8.3)	0.44	5 (13.2)	2 (8.3)	.69
Bupropion	5 (19.2)	11 (30.6)	0.39	10 (26.3)	6 (25.0)	1.00
Stimulant	4 (15.4)	10 (27.8)	0.36	9 (23.7)	5 (20.8)	1.00
Benzodiazepines	11 (42.3)	17 (47.2)	0.80	17 (44.7)	11 (45.8)	1.00
ECT	8 (30.8)	11 (30.6)	1.00	10 (26.3)	9 (37.5)	.40
TMS	6 (23.1)	4 (11.1)	0.30	7 (18.4)	3 (12.5)	.73
ECT or TMS	12 (46.2)	13 (36.1)	0.45	14 (36.8)	11 (45.8)	.60
Comorbidities						
PTSD	3 (11.5)	3 (8.3)	0.69	4 (10.5)	2 (8.3)	1.00
Anxiety disorders	19 (73.1)	20 (55.6)	0.19	26 (68.4)	13 (54.2)	.29
Fibromyalgia or chronic pain	0 (0.0)	7 (19.4)	**.035**	2 (5.3)	5 (20.8)	.098
OCD	2 (7.7)	0 (0.0)	0.17	2 (5.3)	0 (0.0)	.52
Eating disorder	1 (3.8)	2 (5.6)	1.00	2 (5.3)	1 (4.2)	1.00
Borderline personality disorder	2 (7.7)	3 (8.3)	1.00	4 (10.5)	1 (4.2)	.64
Substance use disorder	3 (11.5)	5 (13.9)	1.00	4 (10.5)	4 (16.7)	.70

[a]Values are shown as n (%) unless otherwise noted. *P* values are Wilcoxon rank sum or Fisher exact *P* value. Boldface indicates statistical significance.

Abbreviations: BMI = body mass index, BP = bipolar disorder, ECT = electroconvulsive therapy, IN = intranasal, IV = intravenous, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TMS = transcranial magnetic stimulation.

respectively. BMI was higher in the IN esketamine treatment group (median 32.0 vs 27.9; $P = .049$), and the median duration of current depressive episode was longer in the IN esketamine treatment group (8.0 vs 2.3 years; $P = .01$). The median patient-averaged number of treatments per week was 1.5 for IV ketamine patients and 2.0 for IN esketamine patients. For 14 IV ketamine patients (29.8%) and 4 IN esketamine patients (26.7%), we found a 1-week period when no treatment was delivered. The remaining patients all had treatments delivered at least once per week across their treatment duration. Overall median (IQR) change in QIDS-SR score at the end of acute phase was −8 (−13 to −4) ($P < .001$), a significant reduction (improvement) from baseline (median [IQR] = 18 [15 to 20]). Overall remission and response rates were 38.7% and 58.1%, respectively. Response (57.4% vs 60.0%) and remission rates (42.6% vs 26.7%) were similar among patients who received IV ketamine or IN esketamine, respectively ($P > .05$). Changes from baseline to 40 minutes and to end of treatment in systolic blood pressure and heart rate were higher in IV

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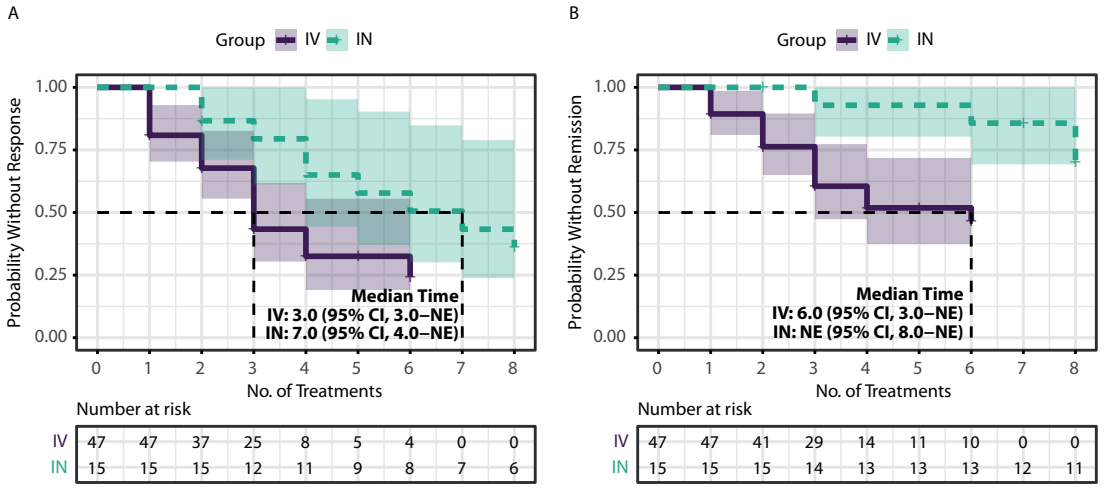
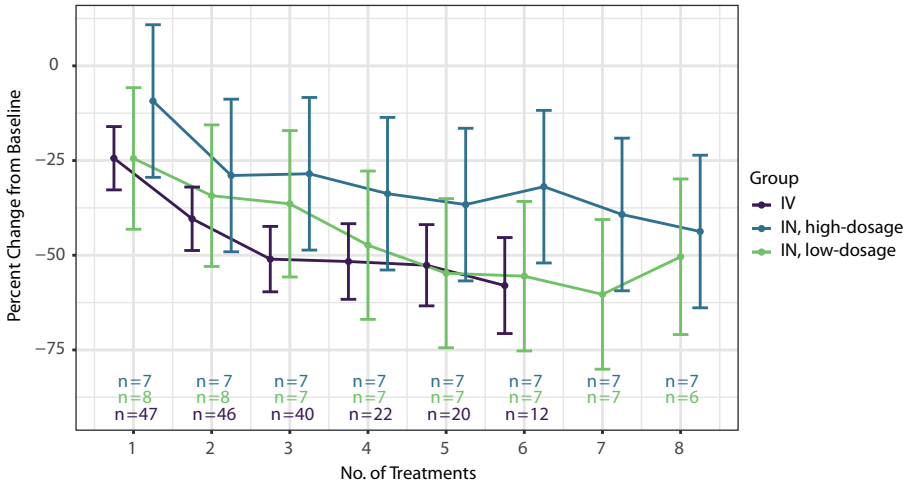
Figure 2. Probability Without (A) Response and (B) Remission in the Ketamine Treatment Groups[a]



[a]Shaded areas indicate 95% CIs.
Abbreviations: IN = intranasal, IV = intravenous, NE = not estimable.

Figure 3. Mean Percent Change From Baseline to Most Improved Posttreatment QIDS-SR Score by IV Ketamine and High-Dosage and Low-Dosage IN Esketamine Across Treatment Course[a]



[a]Error bars indicate 95% CIs.
Abbreviations: IN = intranasal, IV = intravenous, QIDS-SR = 16-item Quick Inventory of Depressive Symptomatology self-report.

patients compared to IN patients (all $P \leq .04$). No differences were found in oxygen saturation, diastolic blood pressure, or Clinician-Administered Dissociative States Scale (CADSS)[24] score (all $P \geq .06$). Unadjusted analyses of percent change from baseline to lowest QIDS-SR score after their last treatment was not significantly different between the two treatment groups ($P = .65$) (Table 1). Adjusting for baseline QIDS-SR score, age, sex, and BMI, the overall interaction for treatment group and treatment number on percent change in QIDS-SR was not significant ($P = .43$). Figure 1 shows the mean percent change from baseline to most improved posttreatment QIDS-SR score by IV ketamine and IN esketamine across treatment course.

Unadjusted analyses of response and remission were not significantly different between the two treatment groups (both $P \geq .37$) (Table 1). Adjusting for baseline QIDS-SR, age, sex, and BMI also did not show a difference between treatment groups (both $P \geq .38$). We found fibromyalgia or chronic pain to be more prevalent among patients who had a response (19.4% vs 0.0%; $P = .035$) or a remission (but not significantly for the latter: 20.8% vs 5.3%; $P = .098$). There were no other significant associations between response and remission with overall comorbidities or employment status, both overall and within treatment groups, or with other demographic or clinical characteristics overall (all $P > .05$) (Table 2).

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The median (IQR) number of treatments received to achieve response (2.0 [1.0–3.0] vs 4 [3.0–6.0]) and remission (2.0 [1.75–3.0] vs 7.0 [5.3–8.0]) was significantly lower among patients who received IV ketamine versus IN esketamine ($P \leq .01$). After adjusting for age, sex, BMI, and baseline QIDS-SR score, defining time as the number of treatments, there was trend for a faster response for IV ketamine (HR = 2.61; 95% CI, 1.0–7.1; $P = .05$), and time to remission was faster for IV ketamine (HR = 5.0; 95% CI, 1.0–24.3; $P = .02$) (Figure 2).

For those receiving IN esketamine, the median difference in dosage between what they would have received during IV ketamine treatment and 45% of their nasal esketamine dosage was 8.4 mg. Percent change in QIDS-SR score among high-dose IN esketamine (difference = less than 8.4 mg), low-dose esketamine (difference = 8.4 mg or more), and IV ketamine groups did not show a significant interaction with treatment number ($P = .75$), and no significant differences were found among the 3 groups at any treatment number (all $P > .05$) (Figure 3).

DISCUSSION

This observational study assessed the comparative effectiveness of IV ketamine and IN esketamine in a single-site real-world setting among patients with TRD. Within the acute induction phase, we found similar response and remission rates. Our main finding was that the number of treatments required to achieve remission was significantly lower (and thus the time accelerated) with IV ketamine as compared to IN esketamine (Figure 2).

As ketamine/esketamine use becomes more widespread,[15,25] patients are often considering both treatment options with questions regarding efficacy and cost. These findings suggest that a patient receiving IV ketamine will require fewer treatments to determine whether or not they are a responder/remitter to ketamine, which can be one factor in the cost equation. These findings have pharmacoeconomic implications, with significant cost savings for patients receiving IV ketamine. Insurance coverage is a significant cost variable, which is specific to each individual patient. As more data comparing IV ketamine to IN esketamine emerge in the field, insurance carriers may also want to reevaluate coverage options, especially with the much higher cost of IN esketamine. In post hoc analysis, we observed higher transient systolic blood pressure and heart rate elevation in the IV ketamine group compared to IN patients (all $P \leq .04$). None of the patients had to discontinue treatment during the cardiac monitoring. Concomitant medications (23% were on stimulants) in addition to the inherent sympathomimetic action of ketamine could have contributed to elevated blood pressure and heart rate.[26] The dissociative effects were similar between ketamine and esketamine during the monitoring. In the review by Bahji et al,[16] there were lower dropout rates with IV ketamine compared to IN esketamine. We did not observe a difference in dropout rates between the two groups, despite differences in systolic blood pressure and heart rate. Thus, more data are needed to better understand and compare tolerability between the treatment modalities.

To further investigate the difference in efficacy, we explored whether the two available doses (56 or 84 mg) of IN esketamine, which were not based on weight, contributed to reduced efficacy, because IV ketamine is tailored to the patient's weight. However, the dose change deficit did not show a significant interaction with the treatment. Recent animal data suggest that *R*-ketamine is more potent and has a potential for the longer-lasting antidepressant effects,[27,28] which could have theoretically contributed to the accelerated response with racemic IV ketamine compared to IN esketamine. However, the animal data do not easily extrapolate to humans, especially in TRD. Even though initial human data with IV *R*-ketamine look promising,[29] this issue would need to be further investigated.

There is not a head-to-head RCT comparing IV ketamine and IN esketamine, despite use of both in clinical settings for patients with TRD. There are obvious differences in the mode of ketamine and esketamine delivery (IV versus IN), thus hindering head-to-head comparison of the two. We did not notice a difference in response or remission rates between the groups. This finding is consistent with those of a recently published retrospective study.[30] However, that study reported secondary outcomes (group differences in depression scores) favoring IV ketamine. These findings need further investigation in longitudinal studies. In our study, patients with comorbid fibromyalgia or chronic pain had a higher response rate. In fibromyalgia, there is an imbalance between the hyperexcitatory and inhibitory neuronal pathways, resulting in altered nociceptive processing. The nociceptive hypersensitivity has been proposed to be dependent on the NMDA receptors. Due to its NMDA-antagonistic activity, ketamine has been proposed as a treatment to reduce the excessive central sensitization.[31] This higher response could be due to potential antinociceptive effect of ketamine. These hypothesis-generating findings could be tested in future studies investigating the role of ketamine in patients with fibromyalgia.[32]

For IV ketamine, most clinicians recommend trying up to 6 infusions to determine response,[15] while for IN esketamine, the manufacturer recommends 8 treatments. Our data suggest a plateauing effect at about 3 infusions (Figure 1), which is consistent with our earlier studies.[7] Our earlier research experience with IV ketamine found that after one treatment, approximately 32% of patients would respond, after the second-third treatment, about 68% would respond, and we were not seeing much more improved response after that.[7,17,18] Furthermore, in our clinical practice, we often advise patients that if there is absolutely no response after 3 or 4 infusions, the likelihood of response is minimal. For patients receiving IN esketamine, they know they have 8 treatments to achieve response if we are to continue with maintenance. Thus, a faster response in our study with IV ketamine could be due to patient expectations. There are also other factors that have not been formally explored in the literature regarding the differences between these two

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treatment modalities, for example, whether IV ketamine is more efficacious because of the greater placebo effect of being given a treatment that requires IV access and cardiac monitoring compared to a simpler IN spray.

Strengths of this study include the single-site clinical setting, where patients receiving either IV ketamine or IN esketamine had almost the same inclusion criteria. Other studies comparing IV and IN have been literature reviews, and conclusions are limited because of the heterogeneity of the studies.[33,34] We also utilized a real-world repeated-treatment protocol, as opposed to single-infusion studies that have compared ketamine and esketamine (IV route for both) and found them similar.[35] Additionally, we requested the patient complete a depression self-rating scale 24 hours after each infusion, which is thought to be an ideal time to capture improvement from the treatment, and obtained these data for 77.3% of treatments.

Limitations

Our major limitation is the small sample size, especially with the IN group, which can affect the statistical analysis. Although we saw nominally higher remission rates with IV ketamine, the difference was not statistically significant. This study was not powered to detect a minimal clinically meaningful difference in remission rates. A larger sample size in an RCT comparing IV ketamine and IN esketamine would be able to detect clinically meaningful differences between the two groups. This study was an observational study, and the groups were not randomized and thus predisposed to a higher risk of bias. There is a potential for referral bias, as Mayo Clinic is a tertiary referral center and is likely to receive patients with higher levels of TRD. However, the included study patients are reflective of real-world settings with significant treatment refractiveness. We collected data in a systematic way in a pre-designed Excel sheet after checking the research authorization and included patients with unipolar or bipolar TRD. Each patient completed the QIDS-SR or other depression scale before infusion and was provided a copy of the scale to be completed at 24 hours post-infusion. Despite our best efforts in collecting systematic data, not all patients completed a QIDS-SR form 24 hours post-infusion at each treatment, and this reflects a limitation in our study. Patients continued their other medications during the ketamine/esketamine treatment. Concomitant medications could be adjusted as clinically indicated, and there was not a limit to these changes. However, most patients were on stable medications prior to starting ketamine. We required only that patients be on ≤ 4 mg of lorazepam equivalents prior to starting ketamine based on our earlier research study.[36] This requirement could have impacted ketamine's efficacy, although at this moment there are no robust data suggesting a pharmacotherapeutic agent enhances efficacy for ketamine.[37] Results of the study are not generalizable to patients without TRD. Only a small subset of our population (4.8%) had bipolar depression. Prior studies have shown shorter duration of response in patients with treatment-resistant bipolar depression (TRBD).[13,38] All of the patients with TRBD received IV ketamine, as IN esketamine would be considered off-label for bipolar depression and not covered by insurance, making the treatment extremely expensive. Thus, we could not compare the efficacy of IV ketamine with IN esketamine in patients with TRBD. This is an area that needs urgent investigation, as ketamine/esketamine are being used more freely throughout the country, especially in non–FDA-approved indications, which may further increase as IN esketamine becomes off-patent in years to come.

CONCLUSION

Intravenous ketamine and intranasal esketamine led to similar response and remission in patients with TRD, but the number of treatments required to achieve remission was significantly lower with IV ketamine compared to IN esketamine. These findings need to be investigated in a randomized controlled trial comparing these two treatment interventions.

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Additional information: The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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