Comparative Effects of Repeated Ketamine Infusion Versus Intranasal Esketamine in Patients With Treatment-Resistant Depression:

A Retrospective Chart Review

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Abstract

Objective: Both intravenous (IV) racemic ketamine and intranasal (IN) esketamine have emerged as rapid-acting antidepressants for treatment-resistant depression (TRD) and are increasingly used in clinical settings. Relatively few studies, however, have compared these interventions in larger, naturalistic cohorts. This study was conducted to assess the comparative efficacy and rapidity of response observed with repeated IV ketamine versus IN esketamine in a psychiatric neurotherapeutics specialty service. Through retrospective chart review, we conducted what is, to the best of our knowledge, among the larger such comparisons to date.

Methods: Data from 153 patients with severe TRD were reviewed (111 patients received IV ketamine and 42 patients received IN esketamine). In accordance with consensus criteria for TRD and validated objective criteria for illness severity, included patients failed a minimum of 2 adequate antidepressant treatment trials and demonstrated a preketamine treatment score of 16 or higher on the 16-item Quick Inventory of Depressive Symptomatology-Self-Report ($QIDS\text{-}SR_{16}$). Severity of depression was subsequently reassessed with the $QIDS\text{-}SR_{16}$ prior to each ketamine and esketamine administration. A 2-way analysis of variance was used to compare changes in $QIDS\text{-}SR_{16}$ scores between the IV ketamine and IN esketamine treatment groups.

Results: With equivalent depression severity measured by $QIDS\text{-}SR_{16}$ at pretreatment baseline, the IV ketamine treatment group showed significantly greater decreases in $QIDS\text{-}SR_{16}$ scores compared to the IN esketamine group, as measured immediately before each treatment from the third to the eighth session (all P values $< .05$). Patients who received IV ketamine infusions demonstrated a 49.22% reduction in $QIDS\text{-}SR_{16}$ scores by the eighth treatment, while patients who received IN esketamine over the same induction period showed a 39.55% reduction. As expected, both IV ketamine and IN esketamine treatments resulted in significant decreases in $QIDS\text{-}SR_{16}$ scores. In the IV ketamine group, the decrease in $QIDS\text{-}SR_{16}$ scores reached significance after 1 treatment, while in the IN esketamine treatment group, the decrease in $QIDS\text{-}SR_{16}$ scores reached significance after the second treatment.

Conclusion: In this naturalistic sample of patients with similarly severe TRD treated in a ketamine subspecialty service over a 4–5-week induction period, treatment with IV racemic ketamine was associated with a more rapid response and greater overall efficacy than treatment with IN esketamine.

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Major depressive disorder (MDD) is a common psychiatric condition affecting approximately 280 million individuals worldwide.[1] Approximately 30% of patients with MDD have treatment-resistant depression (TRD), often characterized as depression that fails to adequately respond to 2 or more antidepressant therapies.[2,3] The management of TRD is complex, typically involving multiple strategies including psychotherapy, medication augmentation with mood stabilizers or antipsychotics, and neurotherapeutic approaches like electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS).

Among the diverse treatment options for TRD, ketamine has emerged as a promising intervention for

Clinical Points

- Limited data compare intravenous (IV) ketamine and intranasal (IN) esketamine for treatment-resistant depression (TRD). This study provides real-world insights into their effectiveness.
- IV ketamine led to greater and faster symptom reduction than IN esketamine in patients with severe TRD. IV ketamine showed significant improvement after 1 treatment, while IN esketamine required at least 2 treatments.

carefully selected patients when delivered in treatment settings with adequate medical and psychiatric resources. In a landmark 2000 randomized double-blind trial, racemic ketamine—classically described as an *N*-methyl-D-aspartate (NMDA) receptor antagonist but with substantial receptor and signaling heterogeneity—demonstrated rapid antidepressant effects.[4] A single subanesthetic infusion of ketamine (0.5 mg/kg) produced rapid and substantial antidepressant effects in half of the patients, though these effects diminish by day 10 to day 14.[5–8] Subsequent work has shown that nonresponders to a single ketamine infusion may benefit from repeated administrations, while initial responders can maintain improvements through additional infusions.[9–11] Esketamine, the S-enantiomer in the racemate, has gained particular interest due to its higher affinity for NMDA receptors relative to the R-enantiomer.[12] The US Food and Drug Administration's 2019 approval of intranasal esketamine for adult TRD, together with additional and related approvals in 2020 and 2025, has garnered considerable attention, underscoring the demand for novel treatments in this challenging condition.

To date, racemate and S-enantiomer delivery through IV and IN routes, respectively, comprise the most common ketamine administration practices for TRD.[13,14] Relatively few studies, however, have compared these interventions in larger, naturalistic cohorts. In 2018, the clinical Ketamine Service at McLean Hospital began treating carefully selected patients with IV racemic ketamine. After esketamine received its first FDA approval, IN esketamine was introduced by the Service as an additional option for eligible patients struggling with TRD. Over the years, we have thus refined a serial infusion ketamine protocol based on evolving literature and our cumulative clinical experience, while operationalizing the esketamine protocol as insurance coverage has gradually broadened.

The goal of this study was to assess, through retrospective chart review, the comparative efficacy and rapidity of response observed with repeated IV ketamine versus IN esketamine during the induction phase of treatment. To the best of our knowledge, this is one of the largest such comparisons to date.

METHODS

Procedure and Patients

All patients met criteria for MDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, and had failed a minimum of 2 adequate antidepressant treatment trials. Inclusion criteria also required a pretreatment score of 16 or higher on the 16-item Quick Inventory of Depressive Symptomatology-Self-Report ($QIDS\text{-}SR_{16}$), indicating severe depression.[15] Cases in which treatment occurred while the patient was an inpatient in the hospital were excluded. As consistent with the Service's policies more generally, patients with a history of psychosis, concerning substance use, or relevant uncontrolled medical illnesses (ie, recent myocardial infarction, aneurysmal disease, arteriovenous malformations) were not considered eligible for treatment.

Depression symptom severity was evaluated using the $QIDS\text{-}SR_{16}$, which is scored on a scale of 0–27, with 0 representing a complete absence of depressive symptoms and 27 representing the most severe symptoms.[15] The $QIDS\text{-}SR_{16}$ was administered at baseline and at each subsequent visit.

Patients who completed the full induction course with IV racemic ketamine received 8 treatments, administered twice weekly, over 4–5 weeks. The initial dose was 0.5 mg/kg of ketamine over 40 minutes, with gradual and conservative dose escalation permitted up to 1.0 mg/kg. The details of the dosing strategy and frequency of treatments were illustrated in our previous publication.[16] Patients were monitored at the clinic for a minimum of 90 minutes after initiating each infusion. Similarly, participants who completed the full induction course with IN esketamine also received 8 treatments, administered twice weekly, over 4–5 weeks. Most participants received an initial dose of 56 mg of esketamine with prompt dose escalation to 84 mg.

During each treatment, blood pressure, heart rate, oxygen saturation, and respiration rate were monitored. Criteria for discharge included return to baseline mental status, absence of gait disturbance, and normalizing blood pressure. Driving was not permitted postadministration until the following day.

Statistical Analyses

In the present report, patients in our outpatient subspecialty setting with MDD who started ketamine treatment from September 2019 to May 2023 were included. This retrospective data analysis was approved by the Institutional Review Board of Mass General Brigham.

The Fisher exact test was used to assess differences in demographic, clinical, and medication variables between IV ketamine and IN esketamine groups. A 2-tailed Student *t* test compared differences in weights and ages between the groups. The Fisher exact test post χ^2 tests was also used to assess differences of dropout rate at the eighth treatment between IV ketamine and IN esketamine treatment groups.

The percentage of reduction of QIDS-SR_{16} was calculated using the following formula: (baseline QIDS-SR_{16} – posttreatment QIDS-SR_{16})/baseline QIDS-SR_{16} *100.

A 2-way analysis of variance was employed to compare changes in metric scores between IN esketamine and IV ketamine treatment groups. When a significant *F* value was found, post hoc analysis was performed using the Bonferroni test. All analyses were performed using IBM SPSS Statistics 21.0, and a *P* value of < .05 was considered statistically significant.

RESULTS

Patient Clinical and Demographic Characteristics

In this study, 153 eligible subjects aged 18–78 years who have been assessed for depression with QIDS-SR_{16} before the treatment and have received 2 or more administrations of either IV ketamine or IN esketamine were identified. Table 1, summarized below, presents the demographic characteristics of those patients with TRD in this study. There were no significant differences between the IV ketamine and IN esketamine groups in terms of age, body mass index (BMI), gender, marital status, race, education level, or current employment status. Similarly, no significant differences were found in clinical characteristics, including current concomitant psychiatric disorder or history of previous ketamine, ECT, or TMS. Regarding current concomitant medications, most patients continued antidepressants before starting ketamine or esketamine, with no significant differences in the use of antidepressants, mood stabilizers, stimulants, or benzodiazepines between the groups. However, a higher proportion of patients in the IV ketamine group were taking antipsychotics for antidepressant augmentation compared to the IN esketamine group (26.2% vs 51.4%, *P* < .05). This difference may suggest greater baseline illness severity in the IV ketamine group, which could have influenced treatment response.

Effect of Repeated Ketamine Infusions vs IN Esketamine Treatments on Depression as Measured by QIDS-SR_{16}

As shown in Figure 1, there was no significant difference in depression severity measured by QIDS-SR_{16} at baseline between the IV ketamine group and the IN esketamine group (*P* > .05). Interestingly, after the second treatment, the two treatment groups began to demonstrate a significant difference in QIDS-SR_{16} scores. From the third through the eighth treatment, QIDS-SR_{16} scores measured beforehand were significantly lower in the IV ketamine group, compared to the IN esketamine group (all *P* values < .05). The overall decrease in QIDS-SR_{16} scores from baseline to the eighth treatment was 49.82% in the IV ketamine group and 39.55% in the IN esketamine group. In the IV ketamine group, mean scores (±SE) decreased from 19.23 ± 0.23 at baseline to 9.65 ± 0.48 at the eighth treatment. In the IN esketamine group, scores decreased from 19.52 ± 0.39 at baseline to 11.80 ± 0.65 at the eighth treatment. By the eighth treatment, 88 of 111 patients in the IV ketamine group and 35 of 42 patients in the IN esketamine group completed the final induction treatment (the average final dose of IV ketamine was 0.67 mg/kg, and the average final dose of IN esketamine was 82.67 mg). Terminal dropout rates were comparable: 21% of patients in the IV ketamine group and 17% in the IN esketamine group discontinued treatment before completing the induction phase. Reasons for dropout included lack of efficacy, adverse effects, logistical barriers, and insurance coverage limitations. While dropout rates were not significantly different between groups (*P* = .654, Fisher exact test), the differences in long-term adherence could impact treatment outcomes and require further investigation in prospective studies.

As expected, QIDS-SR_{16} scores decreased significantly after IV ketamine and IN esketamine treatment, indicating significant improvement in depression. In the IN esketamine group, the decrease in QIDS-SR_{16} scores became significant after the second treatment (*P* values for each treatment compared to baseline were .342, .014, <.001, <.001, <.001, <.001, <.001, respectively). In the IV ketamine treatment group, the decrease in QIDS-SR_{16} scores became significant immediately following the first treatment (*P* values for each treatment compared to baseline were all <.001). Hence, the rapidity of the antidepressant response was greater in the IV group when compared to the IN esketamine group.

Overall, both treatments were generally well-tolerated and shared similar side-effect profiles (although this study was not designed to quantify or otherwise describe these effects). Among side effects reported, the most clinically salient for both treatments included transient dissociation, anxiety, nausea, dizziness, ability to tolerate oral intake, and increased blood pressure.

DISCUSSION

To the best of our knowledge, this study is among the largest naturalistic comparisons of IV ketamine and IN

Table 1.
Clinical and Demographic Characteristics of the Patients

	IN (n = 42)	IV (n = 111)	*P*
Age, mean±SE, y	44.26 ± 2.34	40.45 ± 1.36	.15 (*t* test)
BMI, mean±SE	29.49 ± 0.99	27.64 ± 0.69	.15 (*t* test)
Gender, female, n (%)	26 (61.90%)	82 (73.87%)	.167 (FET)
Marital status, n (%)			.96 (FET)
Never married/divorced/widowed	26 (61.90%)	66 (59.46%)	
Married/partner	16 (38.10%)	43 (38.74%)	
Unknown	0 (0%)	2 (1.80%)	
Race, n (%)			.505 (FET)
White	36 (85.71%)	97 (87.39%)	
African American	2 (4.76%)	1 (0.90%)	
Hispanic	0 (0%)	2 (1.80%)	
Asian	3 (7.14%)	6 (5.41%)	
Unknown	1 (2.38%)	5 (4.50%)	
Education completed, n (%)			.345 (FET)
Grade 6–12 or graduated high school	13 (30.95%)	21 (18.92%)	
Graduated 4-year college	13 (30.95%)	44 (39.64%)	
Graduate/professional degree	9 (21.43%)	31 (27.93%)	
Unknown	7 (16.67%)	15 (13.51%)	
Current employment status, n (%)			.844 (FET)
Full time	12 (28.57%)	39 (35.14%)	
Part time	4 (9.52%)	11 (9.91%)	
On leave	3 (7.14%)	11 (9.91%)	
Retired	1 (2.38%)	4 (3.60 %)	
Student	5 (11.90%)	12 (10.81%)	
Unemployed	17 (40.48%)	31 (27.93%)	
Unknown	0 (0%)	3 (2.70%)	
Current concomitant psychiatric disorder, n (%)			
Anxiety	25 (59.52%)	69 (62.16%)	.853 (FET)
PTSD	10 (23.81%)	29 (26.13%)	.838 (FET)
OCD	4 (9.52%)	17 (15.32%)	.438 (FET)
Eating disorder	3 (7.14%)	12 (10.81%)	.761 (FET)
ADHD	14 (33.33%)	25 (22.52%)	.212 (FET)
ASD	2 (4.76%)	3 (2.70%)	.615 (FET)
Concomitant medications, n (%)			
Antidepressant drugs	37 (88.10%)	97 (87.39%)	1 (FET)
Mood stabilizers	11 (26.19%)	20 (18.02%)	.268 (FET)
Antipsychotics	11 (26.19%)	57 (51.35%)	.006 (FET)
Stimulants	17 (40.48%)	37 (33.33%)	.451 (FET)
Benzodiazepines	21 (50.00%)	58 (52.25%)	.857 (FET)
Treatment history of previous ketamine, n (%)	6 (14.29%)	6 (5.41%)	.051 (FET)
Treatment history of ECT, n (%)	10 (23.81%)	31 (27.93%)	.342 (FET)
Treatment history of TMS, n (%)	17 (40.48%)	34 (30.63%)	.109 (FET)

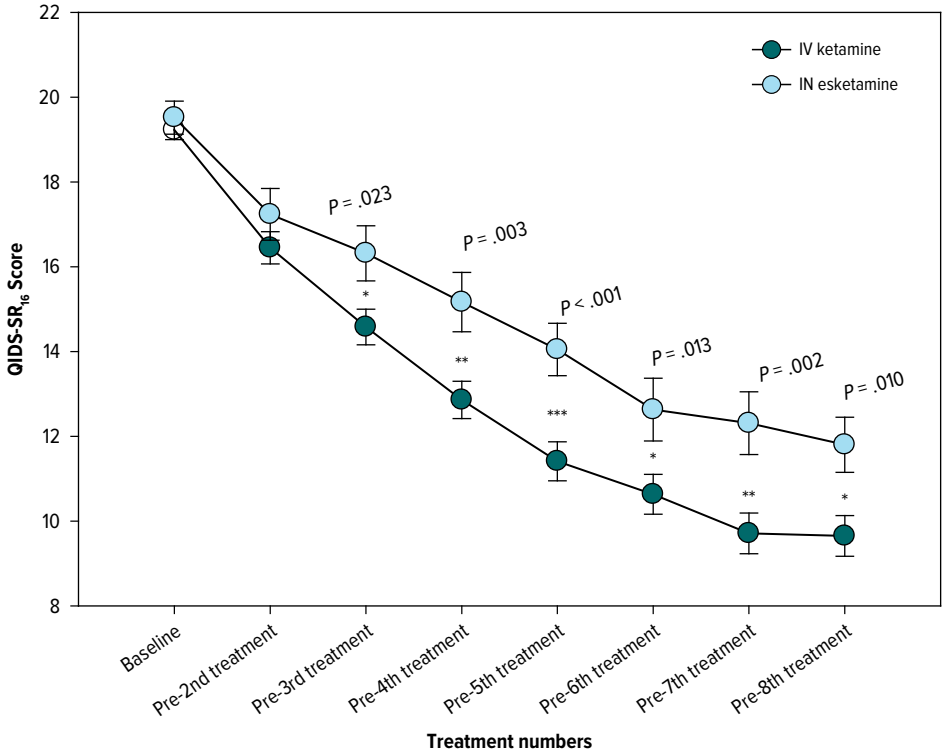
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, BMI = body mass index, ECT = electroconvulsive therapy, FET = Fisher exact test, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, TMS = transcranial magnetic stimulation.

esketamine conducted to date. With equivalent depression severity measured by QIDS-SR_{16} at pretreatment baseline, patients who received IV racemic ketamine demonstrated a 49.22% reduction in QIDS-SR_{16} by the end of induction. By comparison, patients who received IN esketamine demonstrated a 39.55% reduction. From the third through the eighth treatments, the IV ketamine group showed significantly lower QIDS-SR_{16} scores than the IN esketamine group. While both treatments generated significant improvement in depression, IV racemic ketamine achieved significant decreases in QIDS-SR_{16} immediately following the first treatment, whereas IN esketamine demonstrated significant decreases after the second treatment. IV racemic ketamine demonstrated greater antidepressant effect size, compared to IN esketamine.

Our findings are generally consistent with Bahji and colleagues' meta-analysis[17] in which IV ketamine demonstrated greater overall antidepressant effect relative to IN esketamine. They are likewise similar to Nikayin et al's work,[18] which demonstrated significant group differences favoring IV ketamine over IN esketamine in QIDS-SR scores after the full treatment course, as well as in MADRS and QIDS-SR scores after the first 6 treatments. By contrast, Sing et al,[19] in an important study of IN esketamine vs IV ketamine among

Figure 1.

Effect of Repeated Ketamine Infusions vs IN Esketamine Treatments on Depression Measured by QIDS-SR$_{16}$[a]



[a]Data are expressed as mean+SEM. Significance of difference: *P < .05, **P < .01, ***P < .001 (2-way ANOVA followed by a post hoc Bonferroni test).

Abbreviations: IN = intranasal, IV = intravenous, QIDS-SR$_{16}$ = 16-item Quick Inventory of Depressive Symptomatology-Self-Report Scale.

patients with TRD, did *not* see a statistically significant different in QIDS-SR between treatments across a 6 infusion series (though, similar to our work above, the response velocity was likewise greater with IV ketamine). The discrepancy observed across the 2 studies may be explained by several methodologic or treatment differences, including time of objective assessment relative to treatment, number of treatments, and dose received by patients undergoing IV ketamine therapy.

While IV ketamine provided a faster response in our analysis, with significant symptom reduction after 1 treatment compared to 2 IN esketamine treatments, the substantive value of this early difference may depend on clinical context. In acutely ill patients at high-risk for suicide, for example, the apparent difference in rapidity may constitute meaningful risk mitigation and high-stakes crisis stabilization. For most patients, however, the comparative temporal advantage may have less practical impact—especially given the overall antidepressant benefits observed with both treatments, and the abundance of logistical considerations that may influence feasibility. Similarly, the average difference in symptom reduction is statistically significant, though the degree to which this difference translates into meaningful improvements in daily functioning, quality of life, and long-term treatment trajectories remains uncertain. A reduction of this magnitude could comprise a perceptible benefit in some patients but may not necessarily alter clinical decision-making in cases when real-world logistics (eg, accessibility, cost, and degree of insurance coverage) influence treatment plausibility. Nonetheless, these findings highlight that IV ketamine, despite its status as an off-label treatment,[20,21] is at least as effective as the FDA-approved IN esketamine, if not more so.

This study has several limitations. First, as a retrospective chart review, it is inherently constrained by its observational nature, lack of randomization, and absence of a well-controlled comparison group. Without random assignment, treatment selection may have been influenced by selection bias and confounding variables, such as differences in patients' socioeconomic status (In our experience, insurance coverage can be highly variable across treatments and between insurance companies; in some cases, insurance alone dictates which treatment can realistically be considered for a given patient). Future

randomized controlled trials are needed to confirm the comparative efficacy of IV ketamine and IN esketamine in TRD. To our knowledge, an ongoing multisite randomized clinical trial sponsored by Patient-Centered Outcomes Research Institute is investigating this comparison. Second, patients from both treatment groups were allowed to continue or modify antidepressants and psychotherapy regimens according to recommendations from their treating psychiatrist. Potential confounding effects due to natural changes or other treatments cannot be ruled out. Third, our IV protocol was not limited to fixed dosing. Instead, it permitted conservative, sequential dose adjustments across a limited dose range. Hence, direct comparisons between the 2 treatments are thus complicated by different dosing approaches. Fourth, our study includes a larger number of patients receiving IV ketamine than intranasal esketamine (111 vs 42). This discrepancy reflects real-world clinical practice; IV ketamine may be more familiar to many providers and some patients because of its long history. While this imbalance is a limitation, on demographic comparison, no significant differences between the IV ketamine and IN esketamine groups in terms of age, BMI, gender, marital status, race, education level, or current employment status were found.

CONCLUSION

In this naturalistic sample of severely ill patients with TRD treated in a ketamine subspecialty service, repeated IV ketamine infusions yielded higher efficacy and response velocity than IN esketamine during the induction phase.

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