Long-Term Outcomes in Patients With Treatment-Refractory Depression Receiving Intravenous Ketamine and Intranasal Esketamine:

An Observational Study

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Abstract

Objective: This study examines the durability (defined as time between treatments) of intravenous ketamine (IV-KET) and intranasal esketamine (IN-ESKET) for treatment-resistant depression (TRD), in a real-world clinical setting with repeated ketamine/esketamine maintenance therapy.

Methods: This was a single-center, observational study of adults with TRD who completed acute-phase treatment between August 17, 2017, and June 24, 2021, and received IV-KET (0.5 mg/kg) or IN-ESK (56/84 mg) maintenance therapy. Maintenance cycle duration was measured from the first treatment after the acute phase to the final treatment. Depressive symptoms were assessed using the Quick Inventory of Depressive Symptomatology before each treatment. Linear mixed-effects models and generalized linear mixed models (GLMM) evaluated treatment effects. The number of days between treatments (treatment intervals) was modeled using a negative binomial GLMM.

Results: Fifty-six maintenance cycles from 38 patients were included. The median baseline age was 46.2 years (78.9% female). Sixty-eight percent (n = 26) received IV-KET, and 32% (n = 12) received IN-ESKET. The median duration of the longest maintenance cycle was 61 weeks for IV-KET and 48 weeks for IN-ESKET, with 14 and 28 median treatments, respectively. IV-KET patients had longer intervals between treatments compared to IN-ESKET (incidence rate ratio: 1.75, $P < .001$). Mean treatment intervals were 18.9 days for IV-KET vs 10.8 days for IN-ESKET. Both treatments showed stable systolic blood pressure trajectories.

Conclusion: This study provides evidence regarding longer durability of IV-KET compared to IN-ESKET. These findings need to be replicated in larger prospective studies and confirmed in a randomized controlled trial comparing these two treatment interventions.

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Since the seminal study on intravenous ketamine (IV-KET) for treatment-resistant depression (TRD) by Berman et al[1] in 2000, multiple randomized controlled trials (RCTs) and open-label trials have explored its efficacy for depression.[2] Subsequently, intranasal esketamine (IN-ESKET) was developed and received US Food and Drug Administration (FDA) approval as an adjunct to oral antidepressants for TRD in 2019, for major depressive disorder (MDD) with suicidal ideations/behaviors in 2023 and as monotherapy for TRD in 2025.[3,4] Most patients with TRD who respond to IV-KET or IN-ESKET require maintenance treatment to sustain the antidepressant effects.[2,5] A pivotal RCT demonstrated a reduced risk of relapse with ongoing maintenance IN-ESKET use in patients with TRD who responded to IN-ESKET following an induction phase.[6] While limited studies have reported on maintenance IV-KET therapy for TRD,[7–10] no studies to date have compared IV-KET with IN-ESKET for maintenance treatment.

We previously assessed the efficacy and safety of IV-KET and IN-ESKET during the acute phase, demonstrating that IV-KET induces a more rapid antidepressant response.[11] Subsequently, additional

Clinical Points

- Intravenous (IV) ketamine and intranasal (IN) esketamine have shown efficacy as rapid-acting antidepressants for treatment-resistant depression (TRD).
- This study provides evidence of longer durability (defined as *time between treatments*) for IV ketamine compared to IN esketamine.
- The results suggest that patients with TRD who are on maintenance treatment require less frequent treatments with IV ketamine compared to IN esketamine.

studies have reported on the short-term comparisons of IV-KET and IN-ESKET across diverse populations.[12–14] A recent meta-analysis found comparable response and remission rates for both treatments, though IV-KET was associated with a faster acute response.[15] Nevertheless, data on the differences between IV-KET and IN-ESKET for maintenance treatment remain scarce. In the absence of RCTs, observational studies can offer valuable real-world insights, supporting clinicians in making more informed comparisons between these interventions to enhance patient care.

In this study, the primary aim was to compare the "durability" (defined as time between treatments) of IV-KET and IN-ESKET in a real-world setting among patients with TRD after they had completed the acute-phase treatment.

METHODS

This preplanned secondary analysis of a previously published retrospective cohort study,[11] approved by the Mayo Clinic Institutional Review Board (IRB#20-012789), included adults (≥18 years) with TRD who provided consent and received either IV-KET infusions (0.5 mg/kg body weight, over 40 minutes) or IN-ESKET (56/84 mg) treatments between August 17, 2017, and June 24, 2021, and progressed to maintenance treatment at the Mayo Clinic Depression Center.[11] MDD and bipolar disorder diagnoses were made based on the *DSM-5* criteria. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Patients meeting criteria for TRD, defined as failure to respond to at least 2 adequate trials of depression treatments in the current episode of depression (antidepressants, mood stabilizers for bipolar depression, atypical antipsychotics, electroconvulsive therapy [ECT], or transcranial magnetic stimulation [TMS]), were included.[16,17] Patients with a 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 were excluded.

Demographics, baseline characteristics, current/past treatments (medications, ECT, TMS), psychiatric comorbidities, and clinical assessments were collected by trained Mood Psychiatrists/Mood Fellows from the electronic health records. Sixty-two adults with TRD who received ketamine/esketamine during the induction/acute phase (August 17, 2017, to June 24, 2021),[11] along with 1 patient whose first cycle acute phase was unavailable and received treatment solely as maintenance, were included. Subsequent infusions were organized into distinct cycles, each comprising an acute phase and a maintenance phase. Induction/acute phase data were not incorporated in the maintenance cycles. A new cycle was considered if more than 60 days had passed since the previous infusion. During the first cycle, the acute phase included up to 6 IV ketamine infusions or the first 8 IN-ESKET treatments.[11] In subsequent cycles, the acute phase was defined as 28 days immediately following the first treatment of the cycle. Only patients who progressed to maintenance treatment were included in the analysis. We further restricted the data to the maintenance phase, excluding any period after a switch from IV to IN or vice versa, which occurred in 3 cases.

Depression symptoms were assessed using the 16-Item Quick Inventory of Depressive Symptomatology–self-report (QIDS-SR)[18] scale before and 24 hours after ketamine/esketamine treatment. For maintenance treatment, we incorporated pretreatment QIDS-SR scores up to October 3, 2024. The number of days between treatments was tracked. QIDS-SR and vitals data (SpO_2, heart rate, respiratory rate, and blood pressure [BP]) were extracted electronically.[19]

Vital signs (SpO_2 and pulse) were measured approximately every 5 minutes for IV-KET and every 40–60 minutes for IN-ESKET. Blood pressure was recorded approximately every 5–20 minutes for IV-KET and every 40–60 minutes for IN-ESKET.

Overview of Treatment Allocation and Treatment Phases

The decision to allocate IV-KET or IN-ESKET would depend on patient preference or insurance coverage. IN-ESKET is FDA approved for TRD and would require prior authorization from most insurance providers. In our sample, all patients, except 1 receiving IV-KET, had their treatments covered by insurance. Mostly, it came down to patient preference. With IN-ESKET, we followed FDA's Risk Evaluation and Mitigation Strategy (REMS) requirements with 2-hour mandatory monitoring, whereas with IV-KET, monitoring after treatment typically lasted between 30 and 60 minutes. For both treatments, patients were discharged with a responsible adult and advised not to drive for the rest of the day.

In our clinic, we adhered to data from our research studies on IV-KET and FDA regulations for IN-ESKET.

During the acute phase, patients received up to 6 IV-KET or 8 IN-ESKET treatments. Maintenance treatment was considered for patients who showed at least a partial response (more than 25% reduction in QIDS from baseline) or subjectively reported significant improvement with clinical evaluation during acute phase.

After an initial positive response, most patients transitioned to the next phase, where they received 4 weekly treatments. If they maintained a positive response, we gradually attempted to reduce the frequency of treatments. The objective was to determine the optimal frequency to sustain the treatment response. Treatments were initially administered every 2 weeks, then extended to every 3, 4, and 5 to 6 weeks if a positive response was maintained. The frequency was adjusted as needed if the response was lost. Once a clinical response was established at an optimal frequency, patients continued receiving treatments at this determined frequency. Periodic reviews were conducted collaboratively to attempt reducing the frequency of treatments. If patients managed to maintain their response at 6-week intervals, discontinuation of treatment was considered after 2 cycles.

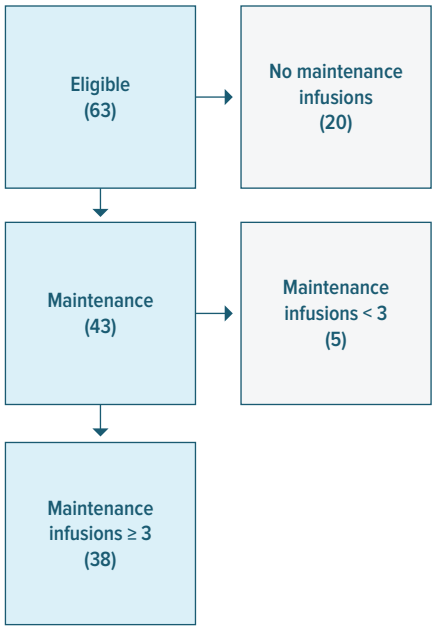
Loss of response status during maintenance phase. If a patient lost their positive response status after 2 consecutive maintenance phase treatments, a case review was conducted by at least 2 of the ketamine clinic clinicians to determine the appropriateness of continuing treatment. Should ongoing treatment have been deemed inappropriate, the patient did not receive further ketamine treatment under this clinical protocol and was referred back to their primary health care team. For patients considered appropriate for continued ketamine therapy, the dose and frequency of ongoing treatment, as well as the number of additional infusions before subsequent review, were collaboratively determined. In cases where the response was completely lost, a repeat acute series was offered, following the same procedural review process.

In summary, the frequency of maintenance treatment was personalized according to the patient's depressive symptoms. The intervals between IV-KET or IN-ESKET treatments were progressively extended as symptoms improved; however, if symptoms recurred, the frequency was adjusted to maintain symptom stability.

Statistical Analysis

Wilcoxon rank-sum and Fisher exact tests were used to test for differences between groups. Linear mixed-effects models (LMMs) and generalized linear mixed models (GLMMs) were used to evaluate the effects of treatment on various clinical outcomes. The longitudinal trajectory of pretreatment QIDS-SR scores over time was assessed using an LMM that adjusted for baseline body mass index, age, sex, treatment, and a restricted cubic spline for time in the maintenance phase. An interaction term between treatment and time captured differential trajectories, with random intercepts and slopes for time accounting for within-cycle correlation. The number of days between infusions was modeled using a negative binomial GLMM, while the probability of SpO_2 <92% was estimated with a binomial GLMM, modeling SpO_2 <92% as a proportion of total observations. Lastly, trajectories of the absolute value in changes from baseline to 40 minutes in systolic BP, diastolic BP, and pulse were assessed using a Tweedie GLMM, incorporating interaction terms between time and treatment. All models included random intercepts to account for within-cycle correlation. For all estimates, including those from LMMs and GLMMs, 95% confidence intervals (CIs) were reported. Estimates from GLMMs were back-transformed from the log scale to the original scale for interpretation, and differences between treatments were expressed as multiplicative effects (ratios) on the original scale. All analyses were performed in R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) using the lmer function from the lme4 package and the glmmTMB function from the glmmTMB package for mixed-effects modeling. *P* value < .05 was considered significant.

Figure 1.
Flowchart



RESULTS

Sixty-three subjects were eligible for the study, with 56 maintenance phase cycles from 38 patients included for analysis (Figure 1). Demographic and baseline characteristics are in Table 1. Sixty-eight percent

Table 1.

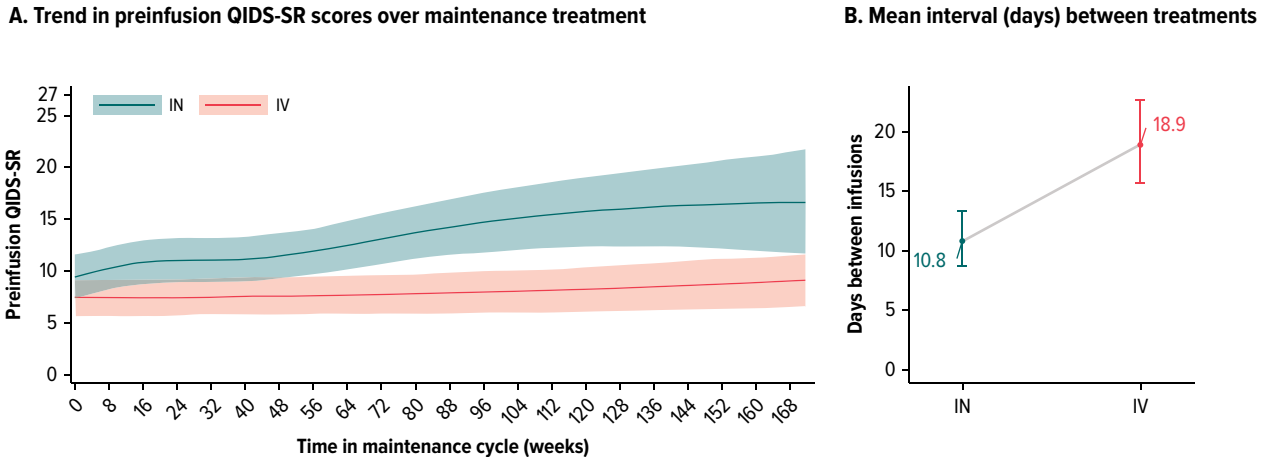
Patient Characteristics in the Maintenance Cycle by Ketamine Treatment Group and Overall

Characteristic	N (%) or Median (Q1, Q3) [range]			*P*
	IV (N = 26)	IN (N = 12)	Total (N = 38)	
Demographic				
Age	46.8 (39.6, 52.6) [23.1–63.8]	45.4 (36.4, 62.1) [26.4–65.3]	46.2 (37.8, 53.2) [23.1–65.3]	.706[a]
Sex				.081[b]
Male	3 (11.5%)	5 (41.7%)	8 (21.1%)	
Female	23 (88.5%)	7 (58.3%)	30 (78.9%)	
BMI	28.3 (24.3, 32.4) [21.1–39.6]	32.0 (27.6, 37.2) [23.8–50.9]	29.3 (25.2, 33.8) [21.1–50.9]	.116[a]
Employment—baseline				.694[b]
Unemployed	1 (3.8%)	0 (0.0%)	1 (2.6%)	
Employed	16 (61.5%)	6 (50.0%)	22 (57.9%)	
Disability due to depression	5 (19.2%)	2 (16.7%)	7 (18.4%)	
Homemaker/retired/student	4 (15.4%)	4 (33.3%)	8 (21.1%)	
Clinical				
Diagnosis				1.000[b]
MDD	25 (96.2%)	12 (100.0%)	37 (97.4%)	
BD-II	1 (3.8%)	0 (0.0%)	1 (2.6%)	
Depression episode duration, y	2.2 (1.0, 5.0) [0.3–13.0]	6.5 (2.0, 10.0) [0.5–16.0]	3.0 (1.1, 7.0) [0.3–16.0]	.086[a]
PTSD	3 (11.5%)	0 (0.0%)	3 (7.9%)	.538[b]
Anxiety disorders	15 (57.7%)	10 (83.3%)	25 (65.8%)	.158[b]
Fibromyalgia or chronic pain	2 (7.7%)	3 (25.0%)	5 (13.2%)	.301[b]
OCD	1 (3.8%)	0 (0.0%)	1 (2.6%)	1.000[b]
Eating disorder	1 (3.8%)	1 (8.3%)	2 (5.3%)	.538[b]
Borderline personality disorder	2 (7.7%)	2 (16.7%)	4 (10.5%)	.577[b]
History of substance use disorder	3 (11.5%)	1 (8.3%)	4 (10.5%)	1.000[b]
Study variables				
QIDS-SR[c]	8.7 (7.2, 11.7) [4.2–17.5]	11.1 (10.2, 13.2) [4.4–15.4]	9.6 (7.5, 12.5) [4.2–17.5]	.140[a]
Days between treatments[c]	21.0 (16.8, 28.1) [5.8–42.4]	10.2 (8.4, 13.9) [6.5–17.2]	16.8 (11.0, 23.5) [5.8–42.4]	**<.001**[a]
No. of cycles				.129[b]
1	14 (53.8%)	11 (91.7%)	25 (65.8%)	
2	8 (30.8%)	1 (8.3%)	9 (23.7%)	
3	3 (11.5%)	0 (0.0%)	3 (7.9%)	
4	1 (3.8%)	0 (0.0%)	1 (2.6%)	
No. of treatments[d]	14.0 (10.2, 52.0) [3.0–109.0]	28.0 (18.8, 41.0) [3.0–109.0]	22.5 (11.0, 48.2) [3.0–109.0]	.582[a]
Maintenance phase duration, weeks[d]	60.8 (25.2, 157.2) [3.1–280.9]	47.8 (21.7, 77.1) [1.9–172.0]	59.7 (22.7, 122.0) [1.9–280.9]	.258[a]
Baseline medications				
No. of psychotropics	3.0 (3.0, 5.0) [1.0–6.0]	3.5 (2.8, 5.0) [2.0–7.0]	3.0 (3.0, 5.0) [1.0–7.0]	.974[a]
Individual psychotropic/class				
SSRI	7 (26.9%)	4 (33.3%)	11 (28.9%)	.714[b]
SNRI	7 (26.9%)	4 (33.3%)	11 (28.9%)	.714[b]
TCA	3 (11.5%)	2 (16.7%)	5 (13.2%)	.643[b]
MAOI	0 (0.0%)	2 (16.7%)	2 (5.3%)	.094[b]
Atypical antipsychotics	8 (30.8%)	2 (16.7%)	10 (26.3%)	.453[b]
Mirtazapine	1 (3.8%)	1 (8.3%)	2 (5.3%)	.538[b]
Bupropion	9 (34.6%)	2 (16.7%)	11 (28.9%)	.444[b]
Stimulants	9 (34.6%)	1 (8.3%)	10 (26.3%)	.124[b]
Trazodone	11 (42.3%)	3 (25.0%)	14 (36.8%)	.472[b]
Gabapentin	3 (11.5%)	1 (8.3%)	4 (10.5%)	1.000[b]
Benzodiazepines	10 (38.5%)	8 (66.7%)	18 (47.4%)	.164[b]
Lamotrigine	5 (19.2%)	1 (8.3%)	6 (15.8%)	.643[b]
Lithium	1 (3.8%)	1 (8.3%)	2 (5.3%)	.538[b]
Melatonin	0 (0.0%)	0 (0.0%)	0 (0.0%)	.538[b]
Buspirone	3 (11.5%)	2 (16.7%)	5 (13.2%)	.643[b]
Vortioxetine	3 (11.5%)	2 (16.7%)	5 (13.2%)	.643[b]
Hydroxyzine	5 (19.2%)	0 (0.0%)	5 (13.2%)	.158[b]
Neuromodulation (tried in current episode)				
ECT	8 (30.8%)	1 (8.3%)	9 (23.7%)	.223[b]
TMS	3 (11.5%)	2 (16.7%)	5 (13.2%)	.643[b]

[a]Wilcoxon rank sum test. [b]Fisher exact test. [c]Patient-averaged from the patient's longest cycle in terms of duration. [d]From the patient's longest cycle in terms of duration.
Abbreviations: BD-II = bipolar II disorder, BMI = body mass index, ECT = electroconvulsive treatment, MAOI = monoamine oxidase inhibitor, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report, SNRI = serotonin and norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TMS = transcranial magnetic stimulation.

Figure 2.

Changes in Clinical Measures During Maintenance Treatment With Intranasal (IN) or Intravenous (IV) Administration[a]



[a]Error bars and shaded regions represent 95% confidence intervals.
Abbreviation: QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report.

(n = 26) received IV-KET for maintenance, while 32% (n = 12) received IN-ESKET. The median duration of longest maintenance phase cycle was 61 weeks for IV-KET and 48 weeks for IN-ESKET, with median treatments of 14 and 28, respectively.

Pretreatment QIDS-SR scores for IN-ESKET showed an upward trend, suggesting worsening symptoms over time, especially notable after 1 year (Figure 2A). The trajectory for IV-KET was flatter, indicating more stable symptoms. At maintenance phase baseline, there was no significant difference between IN-ESKET and IV-KET ($P = .18$). At year 1, the difference was larger, with mean QIDS-SR of 7.6 (95% CI, 5.7–9.6) for IV-KET and 11.7 (95% CI, 9.3–14.0) for IN-ESKET ($P = .01$).

Patients receiving IV-KET treatment had significantly longer intervals between treatments compared to those receiving IN-ESKET, with an incidence rate ratio of 1.8 (95% CI, 1.3–2.3, $P < .001$) and mean treatment intervals of 18.9 days (95% CI, 15.7–22.7) vs 10.8 days (95% CI, 8.7–13.4) (Figure 2B).

The probability of low oxygen saturation ($SpO_2 < 92\%$) was near zero for both groups (0.007 for IV and 0.003 for IN, $P = .25$) (Figure 3A). Figure 3B–D illustrates the trajectories of the absolute vitals change from baseline to the value closest to 40 minutes over time. Both treatments showed relatively stable trajectories for systolic BP, with no significant trends observed. Diastolic BP demonstrated a slight downward trend in both groups. Pulse rate changes showed a gradual increase over time in the IV-KET, with a significant difference between treatments during the baseline maintenance phase. The mean change in pulse was 4.4 for IV-KET and 5.9 for IN-ESKET (ratio = 0.74; 95% CI, 0.58–0.96; $P = .02$).

During maintenance treatment, 3 patients attempted suicide while on IV-KET. Two of these patients had a history of prior suicide attempts before commencing ketamine treatments. Ketamine therapy was continued briefly for 1 patient who experienced difficulty in maintaining her safety but was eventually ceased. The other 2 patients, who had previously responded well to IV-KET, continued treatment after carefully weighing the benefits against the risks.

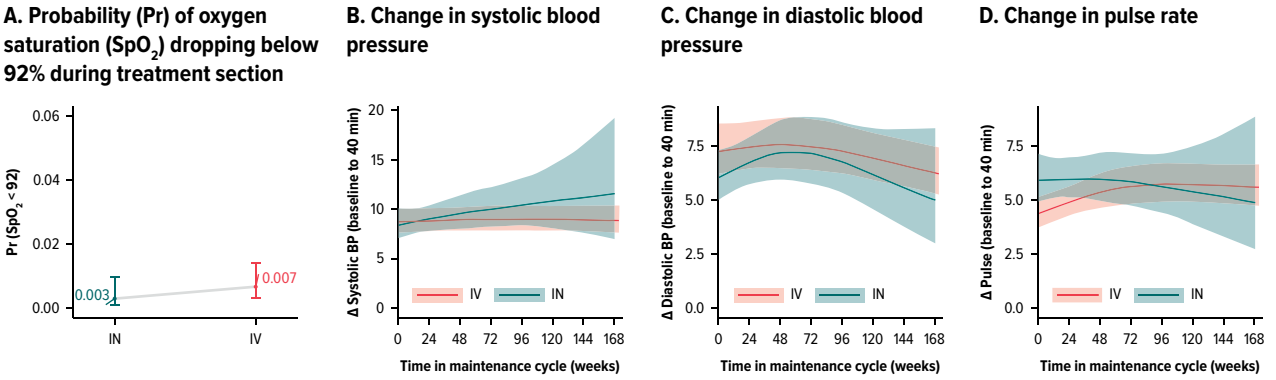
DISCUSSION

This is the first observational study assessing the durability of IV-KET and IN-ESKET in a single site, real-world setting among patients with TRD. Our main finding was that the mean time between treatments is significantly longer with IV-KET compared to IN-ESKET, with similar changes observed in vitals.

These findings have significant social and economic implications. Patients receiving IV-KET require fewer treatments to maintain response compared to IN-ESKET. Logistics and convenience are crucial, as patients have to take time off and arrange transportation due to posttreatment restrictions. Fewer treatments mean less disruption to daily life. Economically, fewer treatments reduce costs. Although IV-KET is off-label for TRD, insurance carriers might reconsider coverage due to the higher cost[20] and frequency of IN-ESKET treatments. In our sample, all patients, except 1 patient receiving IV-KET, had their treatments covered by insurance. Most patients

Figure 3.

Changes in Physiological Measures During Maintenance Treatment With Intranasal or Intravenous Administration



received clinical treatments with IV-KET every 2 to 3 weeks or longer, while on average, patients received IN-ESKET every 1 to 2 weeks. Maintenance treatment frequency was individualized based on the patient's depression symptoms. We gradually reduced the frequency of ketamine/esketamine treatments as symptoms improved, but if symptoms relapsed, we adjusted the frequency to maintain symptom stability. The start time for infusions and observation frequencies varied between treatments.

Various biological factors and potential placebo responses might play a role.[21] For instance, IV-KET may demonstrate greater efficacy due to the stronger placebo effect associated with its administration method, which includes IV access and cardiac monitoring, in contrast to the simpler IN-ESKET spray. Conversely, patients receiving IN-ESKET treatments required more frequent administrations despite the potential behavioral activation and supportive nursing interactions, suggesting evidence against the placebo hypothesis. IV-KET is dosed based on patient weight, whereas esketamine is administered as a fixed dose. Additionally, there are differences in bioavailability, with IV-KET having higher bioavailability compared to IN-ESKET. This factor could be significant for consideration in future studies. Furthermore, animal studies indicate that arketamine may exhibit longer-lasting antidepressant effects than esketamine, potentially enhancing the overall effectiveness of IV-KET.[22] These hypotheses require further investigation.

Strengths of this study include the single-site clinical setting, where patients receiving either IV-KET or IN-ESKET had nearly identical inclusion criteria, resulting in a more homogeneous sample. We employed a consistent real-world treatment protocol that compared ketamine and esketamine. Our primary limitation is the small sample size, particularly in the IN-ESKET group. Patients continued or adjusted/modified their psychotropic medications or psychotherapy as part of their usual treatment, so it is unclear if there was any particular interaction between ketamine and their psychotropics. However, currently, no specific antidepressant has been shown to enhance the efficacy of ketamine/esketamine in the RCTs. We did not conduct any ketamine-assisted psychotherapy, although patients may have continued their regular psychotherapy. For IV-KET, patients had continuous heart rate and respiratory monitoring with recordings every 5 minutes, while BP was recorded every 15 minutes. In contrast, for IN-ESKET, vital signs were recorded every 45 minutes. Given the more frequent monitoring for IV-KET, there was increased opportunity to find abnormal vital signs, and it is difficult to know how these results would compare if the vital signs for IN-ESKET were measured and recorded with that same increased frequency. To ensure consistency in these analyses, we standardized the two treatments by comparing baseline measurements with the observations recorded closest to 40 minutes. Lastly, these findings are not generalizable to patients without TRD.

CONCLUSION

This study suggests IV ketamine has greater durability with maintaining antidepressant response compared to IN esketamine. This is an important consideration for clinicians and patients when weighing the social and financial implications of starting treatment. These findings need to be investigated in an RCT comparing the two treatment interventions or validated in large longitudinal cohort studies.

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Data Availability: The datasets generated during 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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References

1. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47(4):351–354.
2. Singh B. Ketamine and esketamine for depression in daily practice: opportunities and challenges. *J Clin Psychopharmacol*. 2024;44(5):451–455.
3. Kim J, Farchione T, Potter A, et al. Esketamine for treatment-resistant depression - first FDA-Approved antidepressant in a new class. *N Engl J Med*. 2019;381(1):1–4.
4. SPRAVATO® (esketamine) approved in the U.S. as the first and only monotherapy for adults with treatment-resistant depression. Accessed January 22, 2025. https://www.jnj.com/media-center/press-releases/spravato-esketamine-approved-in-the-u-s-as-the-first-and-only-monotherapy-for-adults-with-treatment-resistant-depression
5. Singh B, Vande VJL, Frye MA, et al. Can ketamine be a safe option for treatment-resistant bipolar depression? *Expert Opin Drug Saf*. 2022;21(6):717–720.
6. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2019;76(9): 893–903.
7. Sakurai H, Jain F, Foster S, et al. Long-term outcome in outpatients with depression treated with acute and maintenance intravenous ketamine: a retrospective chart review. *J Affect Disord*. 2020;276:660–666.
8. Wilkinson ST, Katz RB, Toprak M, et al. Acute and longer-term outcomes using ketamine as a clinical treatment at the Yale Psychiatric Hospital. *J Clin Psychiatry*. 2018;79(4):17m11731.
9. Archer S, Chrenek C, Swainson J. Maintenance ketamine therapy for treatment-resistant depression. *J Clin Psychopharmacol*. 2018;38(4):380–384.
10. Li W, Zhou Y, Liu W, et al. Long-term outcomes of repeated ketamine infusions in patients with unipolar and bipolar depression: a naturalistic follow-up study. *J Affect Disord*. 2022;300:172–178.
11. Singh B, Kung S, Pazdernik V, et al. Comparative effectiveness of intravenous ketamine and intranasal esketamine in clinical practice among patients with treatment-refractory depression: an observational Study. *J Clin Psychiatry*. 2023;84(2):22m14548.
12. d'Andrea G, Pettorruso M, Di Lorenzo G, et al. The rapid antidepressant effectiveness of repeated dose of intravenous ketamine and intranasal esketamine: a post-hoc analysis of pooled real-world data. *J Affect Disord*. 2024; 348:314–322.
13. Gutierrez G, Swainson J, Ravindran N, et al. IN Esketamine and IV Ketamine: results of a multi-site observational study assessing the effectiveness and tolerability of two novel therapies for treatment-resistant depression. *Psychiatry Res*. 2024;340:116125.
14. Nikayin S, Rhee TG, Cunningham ME, et al. Evaluation of the trajectory of depression severity with ketamine and esketamine treatment in a clinical setting. *JAMA Psychiatry*. 2022;79(7):736–738.
15. Singh B, Kung S, Vande Voort JL. Intravenous (IV) ketamine versus intranasal esketamine for depression—advantage IV ketamine? *J Affect Disord*. 2024;356: 564–567.
16. Singh B, Bobo WV, Rasmussen KG, et al. The association between body mass index and remission rates in patients with treatment-resistant depression who received intravenous ketamine. *J Clin Psychiatry*. 2019;80(6):19l12852.
17. Vande Voort JL, Morgan RJ, Kung S, et al. Continuation phase intravenous ketamine in adults with treatment-resistant depression. *J Affect Disord*. 2016;206:300–304.
18. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.
19. Kumar R, LeMahieu AM, Stan MN, et al. The association between thyroid stimulating hormone and depression: a historical cohort study. *Mayo Clin Proc*. 2023;98(7):1009–1020.
20. Niciu MJ, Meisner RC, Carr BR, et al. National Network of Depression Centers position statement: insurance coverage for intravenous ketamine in treatment-resistant major depressive disorder. *J Affect Disord*. 2024;346:221–222.
21. Wilkowska A, Cubała WJ. The downstaging concept in treatment-resistant depression: spotlight on ketamine. *Int J Mol Sci*. 2022;23(23):14605.
22. Wei Y, Chang L, Hashimoto K. Molecular mechanisms underlying the antidepressant actions of arketamine: beyond the NMDA receptor. *Mol Psychiatry*. 2022;27(1):559–573.