Clinical Effectiveness of Intravenous Racemic Ketamine Infusions in a Large Community Sample of Patients With Treatment-Resistant Depression, Suicidal Ideation, and Generalized Anxiety Symptoms:

A Retrospective Chart Review

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ABSTRACT

Introduction: Few studies have been published to date exploring the effectiveness of ketamine for treatment-resistant depression (TRD) in large clinical samples. We report on the clinical outcomes of a large cohort treated with ketamine as part of clinical practice.

Methods: Deidentified electronic chart data were obtained from a multisite private ketamine infusion clinic for 424 patients with TRD seen from November 9, 2017, to May 4, 2021. Ketamine infusions were administered at a starting dose of 0.5 mg/kg/40 minutes for 6 infusions within 21 days. Maintenance infusions were offered based on clinical response. Changes in outcome measures (scores on the Patient Health Questionnaire-9 [PHQ-9] and Generalized Anxiety Disorder-7 [GAD-7]) within subjects were analyzed using longitudinal multilevel modeling with Kaplan-Meier estimates. Logistic regression was used to analyze for a priori theorized potential moderators of response.

Results: Significant improvements from baseline were observed over time on the main outcomes (all $P < .001$). Based on PHQ-9 self-report data, within 6 weeks of infusion initiation, a 50% response rate and 20% remission rate for depressive symptoms were observed. Response and remission rates were 72% and 38%, respectively, after 10 infusions, and there was a 50% reduction in self-harm/suicidal ideation (SI) symptom scores within 6 weeks. Half of patients with SI at baseline no longer had it after 6 infusions. A 30% reduction in anxiety symptoms (per the GAD-7) was observed.

Conclusions: Ketamine was effective at reducing symptoms of SI, depression, and anxiety. The high rates of response and remission were similar to those for interventional treatments in community samples of TRD. Comparative efficacy trials with other interventions and randomized controlled trials of racemic ketamine infusion as the primary treatment for SI are needed.

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Treatment-resistant depression (TRD), related suicidal ideation (SI), and co-occurring symptoms of generalized anxiety disorder (GAD) are major health problems both in the US and globally.[1] In 2015, self-harm was the second leading cause of death by injury in the world, and despite a slight decline in rates of suicide in the US since 2018, rates increased by 33% from 1999 to 2017.[2,3] In the US alone, approximately 12.2 million adults reported having serious thoughts of suicide and 1.2 million adults attempted suicide in 2020.[4] Additionally, in 2020, 45,979 suicide deaths were recorded by the US National Institutes of Mental Health (NIMH), of which 24,292 were by firearm.[5] Depression has been estimated to afflict more than 322 million people, or 4.4% of the world's population.[6] Of those with TRD, an estimated number as high as 30% might be expected to attempt suicide at least once in their lives.[7] With recent positive findings from meta-analyses of ketamine infusions[8] and intranasal ketamine[9–10] and pivotal trials of intranasal esketamine,[11–14] the early efficacy of ketamine treatment of both SI and TRD is well established; however, the clinical effectiveness of ketamine outside of controlled clinical trials is less clear.[15] Data on the clinical effectiveness of ketamine therapies in real-world community settings are needed to inform clinical practice.

No oral outpatient treatment of SI associated with mood disorders is approved by the US Food and Drug Administration (FDA). Traditional antidepressant medications (ie, selective serotonin reuptake inhibitors [SSRIs] and serotonin-norepinephrine reuptake inhibitors [SNRIs]) may take several months for a patient to see a significant change in their mood and have a failure rate of more than 30%.[16–18] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial demonstrated that standard pharmacotherapy alone with a single agent resulted in 37% response whereas trials of multiple agents resulted in 67%.[17] Response to treatment with pharmacotherapy appears to be reinforced and response maximized by concurrent administration of psychotherapy with response rates approaching 50%–60% in MDD.[19–21] Combination

Clinical Points

- There are very few reports on the effectiveness of intravenous racemic ketamine infusions for treatment-resistant depression (TRD) and suicidal ideation in the community, and thus it has been unclear how to prioritize or consider the treatment amongst others for TRD.
- Very favorable outcomes were achieved in a large proportion of patients treated with intravenous racemic ketamine, and many patients had a rapid reduction in suicidal ideation.
- For patients with TRD, with or without suicidal ideation, intravenous racemic ketamine infusions are a viable treatment consideration.

therapy may achieve remission rates of only roughly 50% overall after trialing multiple pharmacologic agents in major depressive disorder (MDD).[22] The remaining 50% of patients are said to have TRD.[1] Lithium has been shown to be protective against SI[23,24]; however, support for its use in patients already exhibiting symptoms with unipolar depression is less robust.[25]

Procedural treatments such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) provide substantial relief to this subgroup of patients but require greater expense as well as potential added risks. ECT also requires 2–3 treatments per week in the acute phase (totaling ~6–12 treatments, with some studies showing an average closer to 10 sessions for depression) and is frequently associated with severe side effects (eg, short- and long-term memory impairment, headache, nausea).[26–28] rTMS typically requires 4–6 weeks, approximately 30 hours of treatment, to achieve clinically sustained response[29] over 20–30 sessions and is generally less effective than ECT in treating depression.[30–32]

Over the past decade, an explosion of interest in treating SI/TRD with ketamine and esketamine occurred.[33] The majority of studies for racemic ketamine are relatively small, with one notable exception of a retrospective chart review of 231 patients.[34] Serial infusions of ketamine have been found to produce significant and lasting reductions in depressive symptoms in TRD.[35] Intranasal esketamine was approved by the FDA in 2019 for TRD. Intranasal esketamine rapidly improves Montgomery-Asberg Depression Rating Scale (MADRS) scores over placebo[9] in a dose-dependent manner.[36] A similar study of 346 TRD patients[37] had negative results, although the authors attributed this to dropout rates in the esketamine group and benefit of a novel antidepressant within the placebo group. Fu, et al,[38] found no difference between esketamine and comprehensive care versus placebo/comprehensive care groups in SI within 24 hours as measured by the Clinical Global Impression of Severity of Suicidality (CGI-SS); however, there was a significant reduction at 4 hours and 24 hours on the MADRS suicidal thoughts item.[39] No permanent effects of ketamine therapeutics on memory or cognitive decline have been noted[40]; a recent review[41] supports this conclusion more broadly as well, with no long-term side effects. No issues with long-term cognitive impairment were reported in the trials of esketamine.[42]

We report herein on a large sample of patients from the community with TRD and SI who were treated at a multisite racemic ketamine infusion practice. We sought to evaluate the clinical effectiveness and onset of benefit of ketamine infusions. We hypothesized that symptoms would significantly improve over the course of treatment and that response and remission rates would be similar to those reported for ECT and rTMS in community samples of TRD patients. We hypothesized that ketamine administration would result in rapid improvement of suicidal/self-harm ideation, depression, and anxiety.

METHODS

Context

This retrospective chart review analysis plan was given preliminary review by the Virginia Commonwealth University (VCU) Institutional Review Board (IRB) and was determined to be exempt from IRB review as it did not meet the criteria for human subject research. A deidentified data set without links to charts was received from 3 MindPeace Clinics locations in Arlington, Norfolk, and Richmond, Virginia (collectively, MindPeace Clinics; Richmond, VA).

Intervention

Participants were treated in the ambulatory setting among 3 clinics in the Commonwealth of Virginia and were seen from November 9, 2017, to May 4, 2021. These clinics specialize in providing ketamine infusion therapeutics for the treatment of SI, depression, and anxiety. All patients paid out-of-pocket for the infusions, with only a few receiving partial reimbursements from their insurers. Inclusion required a diagnosis of major depressive disorder or other mood disorder and receipt of at least one ketamine infusion. All patients who did not have a mood disorder diagnosis (eg, those receiving ketamine for chronic pain) or who declined ketamine infusion treatment after being deemed eligible by their treating physician were excluded from this analysis. Diagnoses were ascertained via clinical interview by treating physicians, and data were subsequently extracted from the electronic health record.

Ketamine was typically started at the dose of 0.5 mg/kg with an infusion time of 40 minutes. Patients were monitored for the symptoms of partial dissociation, and the dose was titrated to achieve this effect. Once the effect of partial disassociation based on the Clinician-Administered Dissociative States Scale (CADSS)[43] was reached, the dose generally remained stable for the remainder of treatment. Both clinics had a 2- to 3-week acute treatment phase (6 infusions, typically) followed by booster infusions as needed thereafter.

Outcome Measures and Assessments

During each clinic visit, patients filled out Patient Health Questionnaire-9 (PHQ-9)[44] as well as Generalized Anxiety

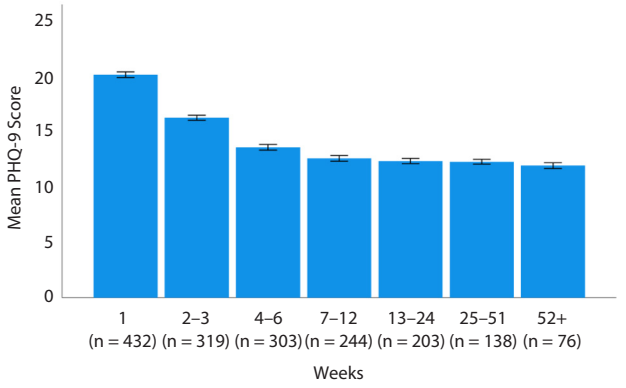
Disorder-7 (GAD-7)[45] electronic surveys prior to each treatment. The data were assessed using MoodMonitor (www.osmind.org), an internet-based application for tracking a patient's mood and treatments. This software program was specifically designed for ketamine infusion therapy. Scales were administered at the initial medical evaluation and before each infusion. Then, the monitoring program sent a link for survey completion every 2 weeks thereafter. The data were subsequently extracted and placed in a Microsoft Excel spreadsheet (Microsoft Corporation). PHQ-9 total scores were the primary outcome of interest. Item 9 (self-harm/SI) was extracted from the questionnaire and considered among the outcome measures. For those with a history or diagnosis of anxiety, GAD-7 total scores were included in the analysis as well. Using the PHQ-9 total score, "treatment response" was defined as >50% improvement and "depression remission" was defined as a score of less than 5.

Data for subjects with a diagnosis of TRD were specifically tabulated based on the number of previous medication trials. TRD was defined as a history of two failed medication over the past decade. The histories and diagnostic ascertainment were based on self-report to the treating clinician.

Statistical Analysis

We used a longitudinal multilevel modeling approach to examine clinical effectiveness of outcome measures in response and remission rates over time. All analyses were by intention to treat, a conservative approach that was aimed at avoiding an overestimation of the treatment effect and included all subjects who received infusion and provided mood data for at least 1 week. Descriptive statistics included means with standard deviations for quantitative variables and frequencies with percentages for qualitative variables. First, an exponential growth model, with random effects to allow differential rates in change between patients, was applied to PHQ-9 total score to model the overall trajectory of depression over time. This was followed by a linear mixed model in which weeks from inception of treatment were grouped into 7 distinct time periods (1 week, 2–3 weeks, 4–6 weeks, 7–12 weeks, 13–24 weeks, 25–51 weeks, 52+ weeks) to test for differences in depression (PHQ-9) and anxiety (GAD-7) levels across time periods. The models included pretreatment levels as a covariate to account for initial differences among patients. Comparisons between time periods were performed. The α was adjusted using Bonferroni correction for multiple comparisons. Demographic variables were entered in the model to test if change in scores across time periods varied across demographic characteristics. Missing data were not imputed. The frequency and percentage of treatment response and remission are reported by time period. For the analysis of PHQ-9 and GAD-7 scores, a linear mixed model was used that includes all observations and accounts for the correlation between scores across timepoints within the same patient. It uses maximum likelihood estimation and, assuming missing at random, gives valid estimates.

Figure 1. Mean PHQ-9 Total Score Across Weeks[a]



[a]Values are shown as mean ± standard error of the mean. Note that "week 1" is the PHQ-9 measurement completed by the patient at either the first office visit for the initial medical evaluation and consultation, or on the day of the first infusion, prior to infusion.
Abbreviation: PHQ-9 = Patient Health Questionnaire-9.

The Kaplan-Meier estimate was used to obtain median and mean time in days to treatment response and remission along with survival curves. We did not use imputation for missing data. The Kaplan-Meier estimates use information up to the last observation at which point the patient is considered censored if they still have not experienced the event of interest (eg, response, remission).

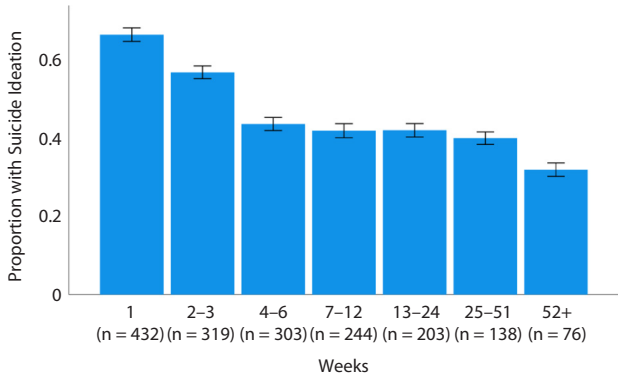
Univariate logistic regression was performed to test if any demographic variables were independently associated with treatment response or remission.

RESULTS

Initially the database consisted of 433 subjects, 9 of whom were excluded because they were primarily in treatment for chronic pain. The median ± SD dose administered following clinician titration was 0.93 ± 0.24 mg/kg/40 minutes. Supplementary Table 1 shows the summary of demographic characteristics of the 424 patients included in the analyses. The patient population considered in this study was 46% male and 54% female. A range of ages were represented from 15 to 65+ years with a mean ± SD of 41.7 ± 15.4 years. Though we have some demographic information, race was not included in the intake assessment. The main treatment course of at least 6 infusions was completed by 70% of the sample, with 30% stopping infusions prior to that point.

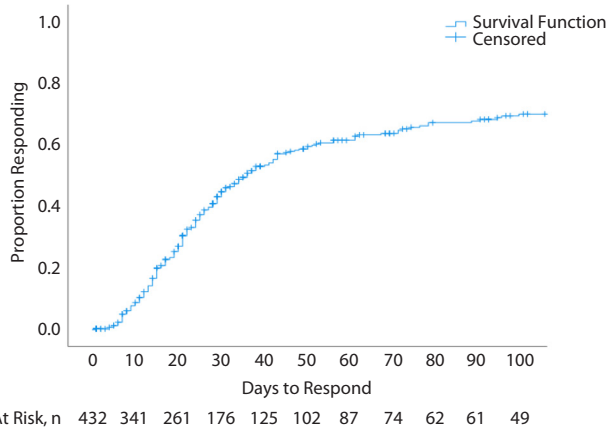
Figure 1 shows the mean ± SD PHQ-9 total score by week. Pairwise comparisons between time periods revealed a significant difference between week 1 and all later time periods (all P values <.001) and between weeks 2 and 3 and all later periods (all P values <.001) and no significant difference between the remaining 5 time periods. For the PHQ-9 question regarding self-harm/SI, there was a similar decrease in score across time points with week 1 significantly differing from the later time periods (all P values <.001) and weeks 2 and 3 significantly differing from all later time periods (all P values <.01) but no difference between the

Figure 2. Mean Proportion With Suicidal Ideation Over Time[a]



[a]Values are shown as proportion ± standard error of the mean. Note that "week 1" is the PHQ-9 item 9 measurement completed by the patient at either the first office visit for the initial medical evaluation and consultation or on the day of the first infusion, prior to infusion. Note also that the prevalence of SI reported in Supplementary Table 1 from baseline includes information about suicidal ideation asked by providers and recorded in the chart at the initial medical evaluation, not just the PHQ-9 item 9 score, and SI was reported at a higher rate by direct interview compared to initial PHQ-9 item 9 ratings.
Abbreviations: PHQ-9 = Patient Health Questionnaire-9, SI = suicidal ideation.

Figure 3. Time to Response[a]



[a]Kaplan-Meier estimates for the proportion of subjects meeting response criteria as a function of days to respond. Number at risk shown below the x-axis. Note that when transposed based on the number of subsequent infusions rather than time, after 3 infusions 14% responded, and after 10 infusions 72% responded. Among responders, the median number of infusions to remission and response was 6, with 25% of subjects reaching response and remission after 4 infusions.

remaining time periods (Figure 2). The mean ± standard error of the mean GAD-7 anxiety score by time period is shown in Supplementary Figure 1. Anxiety was highest at week 1 and was significantly lower at all later time periods (all P values < .05), but there were no significant differences between the remaining time periods. The model estimate of PHQ-9 score over time is shown in Supplementary Figure 2.

The Kaplan-Meier curve for the overall group of the cumulative proportion responding by days in treatment is shown in Figure 3. After 7 days, 5% responded, and by 14 days, 17% responded. The median time to response (ie, 50% have responded) was 36 days, and the mean time to response was 149 days. Figure 4 shows the survival curve for time to remission. After 7 days, 3.5% were in remission, and after 30 days, 20% were in remission. The median time to remission was 392 days, and mean time to remission was 489 days. When transposed based on the number of subsequent infusions rather than time, after 3 infusions, 14% responded and 7% were in remission, and after 10 infusions, 72% responded and 38% were in remission. Among responders, the median number of infusions to remission and response was 6, with 25% of subjects reaching response and remission after 4 infusions.

Figure 5 shows the Kaplan-Meier curve for the subgroup of patients who reported SI at treatment initiation on the PHQ-9 and the time to initial cessation of SI. After 3 infusions, 22% no longer reported SI, and by 6 infusions, 50% did not have SI. By 10 infusions, 75% no longer reported SI, and by 15 infusions, 85% no longer reported SI.

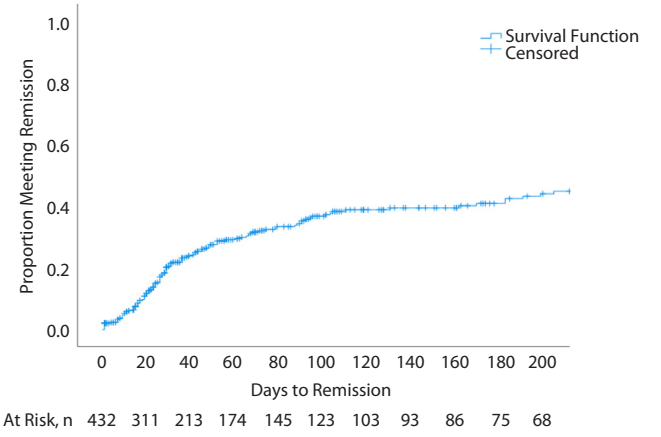
The logistic regression results for tests of patient characteristics predicting treatment response and remission are shown in Supplementary Table 2. There were no statistically significant predictors for either response or remission. However, history of psychosis (OR = 2.75, P = .086) and suicide planning (OR = 1.82, P = .083) trended toward higher response rates.

DISCUSSION

The findings of this retrospective chart-based study demonstrate the robust effectiveness of ketamine in a real-world TRD sample. Response and remission rates were substantial and promising for this emerging treatment, though it should be noted that the sample was not uniformly a hospitalized sample, and most were paying for therapy "out of pocket." Thus, although there are meaningful differences between our sample and those in other studies that prevent direct comparison of these data (ie, our sample may not have been as severely ill, and there was substantial attrition over time), estimates of response rates after the initial treatment phase were similar to the published usual rates for rTMS (40%–60% depending on the modality)[46] and oral medication for TRD (~50%). Similarly, remission rates were at least on par with rTMS rates from clinical practice (20%–30%)[46] and similar to published rates of community-based ECT samples,[47,48] although not as robust as ECT rates based on optimized clinical trial protocols.[49] After the initial 6 infusions (ie, within 2–3 weeks of treatment initiation), greater than 50% of subjects who had SI to begin with no longer had SI. Symptoms of generalized anxiety were also improved substantially.

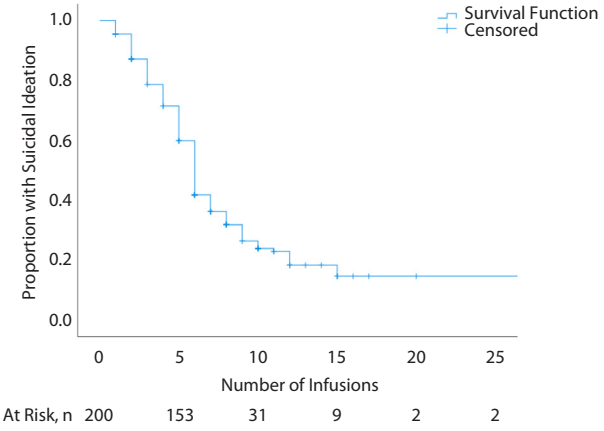
The most substantial improvements in SI were within the first 2–3 weeks, during which almost half the improvement of the entire treatment period was observed, and this corresponds roughly to the acute phase of treatment. Elimination of SI was robust in the acute phase of treatment (the first 6 infusions) with estimates of > 50% of subjects

Figure 4. Time to Remission[a]



[a]Kaplan-Meier estimates for the proportion of subjects meeting remission criteria as a function of the number of days to respond. Number at risk shown below the x-axis. When transposed based on the number of subsequent infusions rather than time, after 3 infusions 7% were in remission, and after 10 infusions 38% were in remission. Among responders, the median number of infusions to remission and response was 6, with 25% of subjects reaching response and remission after 4 infusions.

Figure 5. Cessation of Suicide Ideation by Number of Infusions[a]



[a]Kaplan-Meier estimates for the proportion of subjects (using only those with SI at baseline) who still had SI as a function of the number of ketamine infusions: time to initial cessation of SI. Number at risk shown below the x-axis.
Abbreviation: SI = suicidal ideation.

who initially had SI no longer reporting SI after the initial treatment series. Perhaps this could reflect greater improvement when compared to rTMS, which can achieve reduction in SI in 3–6 weeks, although a meaningful direct comparison cannot be made between these samples.[50,51] Our results show a similar proportion but slightly slower rate of response in terms of cessation of SI compared to Calabrese,[34] who noted cessation in 59% of subjects within 5 infusions. With continued infusions, we achieved higher estimated rates of SI cessation compared to Calabrese,[34] with 85% cessation by 15 infusions. There was no indication that SI predicted response or remission in this cohort. Admission of suicide plan at the time of initiating treatment, however, trended ($P = .083$) for response to treatment, perhaps pointing to a more depressed and more symptomatic subgroup of the patient population who were more responsive to treatment and benefitted more than other less symptomatic patients. Psychotic symptoms may provide another indicator of severity of symptomatology; in a similar fashion, this variable trended toward better response to treatment ($P = .086$) but not remission.

Sex and age did not predict response or remission, nor did any other demographic characteristics, with the exception of the aforementioned trends. A previous suicide attempt was observed as a significant predictor of a more robust response to ketamine in a smaller study by Niciu et al,[52] who also observed a significantly better response in those who had a positive family history of alcoholism. We did not find previous suicide attempts to predict response in this cohort, and we do not have data on family history of alcoholism. It is notable that a history of substance use disorders or treatment did not adversely affect treatment response in our study.

The response to treatment with ketamine is robust and improves with length of treatment. Overall, PHQ-9 total scores declined by 50% throughout the course of treatment, with much of the improvement achieved within 4–6 weeks. Given that an estimated ~25% of responders had responded and remitted by 4 infusions and 50% by 6 infusions, this finding suggests that many subjects have a very rapid response occurring within the first 3 weeks of treatment. Some subjects continued to show response to treatment over the next few weeks, with additional response and remission occurring with up to 10 infusions. After 10 infusions, relatively few subjects improved to a clinically significant endpoint. For the responders, this is a rapid and substantial improvement that indicates a need for side-by-side comparison with rTMS and ECT. Reduction in anxiety symptoms as measured on the GAD-7 was also considerable, with roughly a 30% reduction in score throughout the course of treatment and, again, the majority of response by 4–6 weeks. To our knowledge, this study is one of the few to report reduction in anxiety symptoms during treatment with ketamine.

Our findings suggest that additional new response after 10 infusions is unlikely, but there appears to be substantial response after the traditional 6-infusion acute course. A moderate increase in the remission rate after 10 infusions may suggest that those who are responding at 10 infusions but that have not yet remitted should continue treatments. Additionally, in order to see if the frequency of infusions influenced treatment response, we included site as a proxy variable (of infusion frequency) in the main analysis, but this was not a significant moderator (data not shown).

The major limitations of this study are its retrospective nature and the lack of a control group and lack of blinding applied for the purpose of determining the effect. The sample is from a stand-alone referral-based infusion practice, and those who elect not to do infusions are not followed; thus, it is not possible to have even a chart-based control. Also, hospitalization was not a requirement as it was

with the ASPIRE trials of esketamine,[38,53] and participants were not randomized; thus, direct comparison between these studies is not possible. Another limitation was the primary dependence of the analysis and statistics on the self-report PHQ-9, which lacks a clinician assessment component. Furthermore, the self-harm/SI question of the PHQ-9 is often interpreted as including SI, but it does not literally ask about "suicidal" thoughts, but rather "thoughts that you would be better off dead, or of hurting yourself in some way," although studies have shown that it predicts suicidal behavior.[54] Another limitation is that we did not have systematic assessment of adverse events and side effects. Nurses routinely placed follow-up calls after treatment to assess the well-being of patients, and 2 suicide attempts (without completion) were reported during or shortly after ketamine treatment. The lack of detailed demographic information (eg, race, income level, years of education) leaves some potential question of the study findings' generalizability. Lastly, the attrition of subjects lost to follow-up over time limits the firmness of conclusions for observations made farther out in time. Patients may have left treatment for a variety of reasons, including feeling better and that additional treatments were not worth the expense, a lack of response, and side effects.

CONCLUSIONS

To our knowledge, the present study includes one of the largest real-world patient populations reported in the literature assessing ketamine infusions for the treatment of racemic ketamine in SI, TRD, and GAD. Ketamine was found to be associated with clinical improvements in patients with TRD, with excellent rates of response and remission. Substantial improvement in thoughts of self-harm/SI were noted. Symptoms of generalized anxiety were improved, with 30% reduction in GAD-7 scores after 6 infusions. With the exception of the study by Calabrese,[34] most studies of racemic ketamine infusion have included 20–50 patients, which may not be sufficient to rigorously assess the benefit in treating TRD with ketamine. Our findings are highly consistent with those of a recent similarly large (N = 537) study of community ketamine infusion clinics[55] that was published while the manuscript for the present study was under review. Racemic ketamine infusions cost less than esketamine and other procedural options for TRD, although currently they are not covered by health insurances and so must be paid for out of pocket, while ECT, rTMS, and, sometimes esketamine, are covered. Thus, there is a potential for cost savings if racemic ketamine infusions become covered by insurers. With the low risks and the potential low cost compared to other procedural interventions for TRD, racemic ketamine infusions appear to be an effective option for treatment. Given the present analysis and large cohort size and the extant literature on this topic, we conclude that ketamine infusion therapy should be considered as a treatment option for suicidal patients and patients with TRD. Further studies are needed for this treatment to routinely be considered prior to rTMS. Though ECT remains the gold-standard for treatment of TRD, the relative lower risks of side effects, accessibility, potential cost savings, and similar magnitude of improvement with racemic ketamine infusion may yet make it an option to consider for ECT-averse patients diagnosed with TRD. We anticipate prospective comparator trials currently underway to validate the findings of this study and further clarify the role of ketamine infusions in the treatment of TRD and SI.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.

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Supplementary Material

Article Title: Clinical Effectiveness of Intravenous Racemic Ketamine Infusions in a Large Community Sample of Patients With Treatment-Resistant Depression, Suicidal Ideation, and Generalized Anxiety Symptoms: A Retrospective Chart Review

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Supplementary Table 1: Demographic Characteristics of Patients

Demographics	Frequency	Percentage %
Age		
15-21	39	9.3
22-30	80	19.0
31-45	142	33.8
46-64	120	28.6
65+	39	9.3
Mean±SD	41.7±15.4	
Sex		
Female	226	53.9
Male	193	46.1
BMI		
Underweight	10	3.3
Normal	124	40.4
Overweight	88	28.7
Obese	85	27.7
Mean±SD	27.2 ± 6.5	
Substance Use		
Tobacco	89	21.3
Alcohol	161	38.3
Illegal Drugs	118	28.0
Previous Treatments		
ECT	36	9.0
TMS	103	24.8
Prior Ketamine	49	22.0
Addiction Treatment	36	8.3
Failed Two Antidepressants	348	80.3
Failed Three Antidepressants	286	66.0
Currently on Antidepressant	349	81
Psychological		
Psychosis	29	7.9
Personality Disorder	18	5.0
Suicide Attempt	118	28.3
Suicide Plan	50	11.9
Suicide Ideation	207	49.5
Taking Benzodiazepines	177	43.8

Note that not all variables were available for all subjects and the reported percentage is from the number from which data were available for that specific variable. For substance use not have detailed data on whether the substance use history was active, recent, or a past history as that was not systematically collected with a structured interview. Patients were recorded as having a substance use history if they reported significant past, recent, or current use of illicit drugs, alcohol, or tobacco/nicotine.

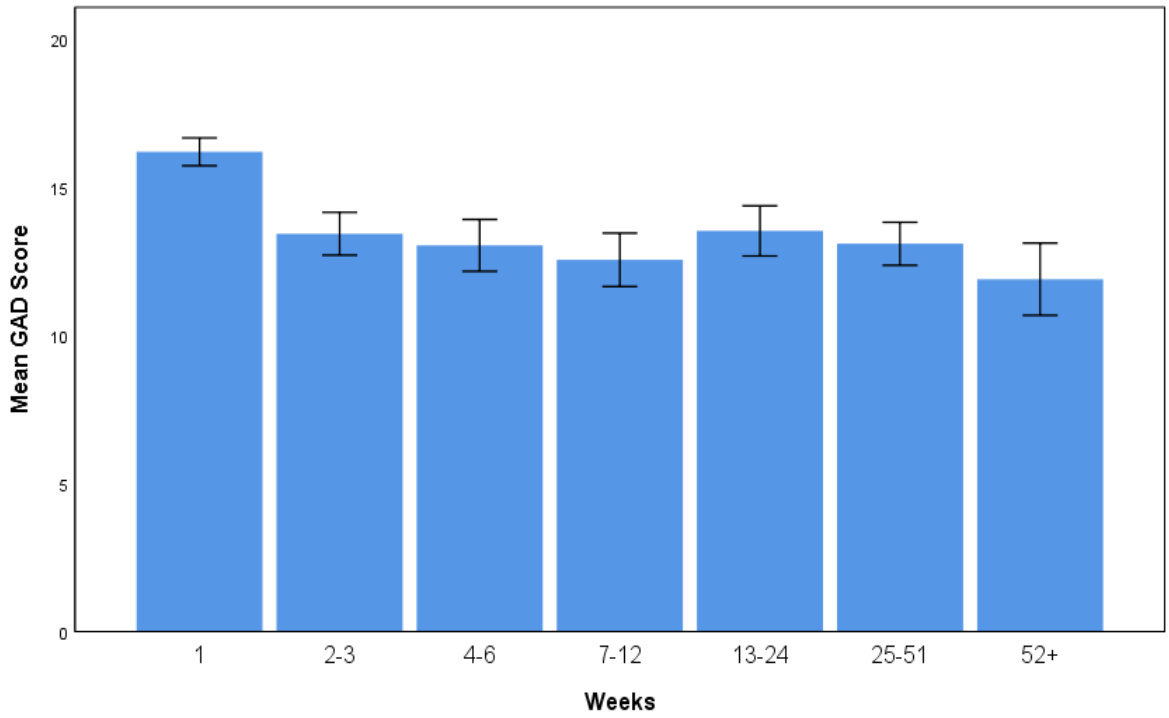
Supplementary Table 2:

Predictors of Treatment Response and Remission Odds Ratio (95% CI)

Demographics	Response		Remission	
	OR	P-Value	OR	P-Value
Age				
15-21 (39)	reference		reference	
22-30 (80)	1.12 (0.49-2.59)	.785	1.45 (0.52-4.05)	.480
31-45 (142)	0.78 (0.36-1.70)	.533	2.42 (0.93-6.27)	.070
46-64 (120)	0.74 (0.38-1.62)	.448	2.43 (0.93-6.36)	.071
65+ (39)	1.06 (0.41-2.76)	.903	2.72 (0.91-8.19)	.075
Sex				
Female (226)	reference		reference	
Male (193)	1.01 (0.68-1.49)	.967	0.89 (0.59-1.36)	.602
Psychosis				
No (33)	reference		reference	
Yes (29)	2.75 (0.87-8.71)	.086	1.52 (0.49-4.76)	.470
Denies (307)	1.09 (0.52-2.28)	.830	1.39 (0.60-3.21)	.446
Suicidal Ideation				
No (86)	reference		reference	
Yes (200)	0.84 (0.50-1.40)	.501	0.75 (0.43-1.29)	.290
Denies (109)	1.10 (0.61-1.95)	.759	1.01 (0.56-1.84)	.974
Suicide Plan				
No (151)	reference		reference	
Yes (48)	1.82 (0.92-3.60)	.083	1.29 (0.65-2.57)	.465
Denies (197)	1.36 (0.89-2.09)	.158	1.03 (0.65-1.64)	.895
Suicide Attempt				
No (114)	reference		reference	
Yes (113)	1.31 (0.76-2.22)	.313	0.76 (0.43-1.33)	.335
Denies (167)	1.34 (0.83-2.17)	.229	0.93 (0.56-1.55)	.930
History of Substance Use Problem (self-reported)				
No (59)	reference		reference	
Yes (36)	1.19 (0.51-2.79)	.693	0.55 (0.21-1.44)	.220
Denies (46)	1.20 (0.54-2.67)	.654	0.54 (0.22-1.33)	.182

Note that "denies" was used when the chart specifically stated that the patient denies that historical variable, but it was also not recorded as a clear "yes" or "no". Group size in parentheses in the leftmost column.

Supplementary Figure 1: Mean GAD Total Score Across Weeks



"GAD" = GAD-7 Generalized Anxiety Disorder-7 scale.

Supplementary Figure 2: Multilevel Longitudinal Model estimate of Mean PHQ-9 Total Score Across Time

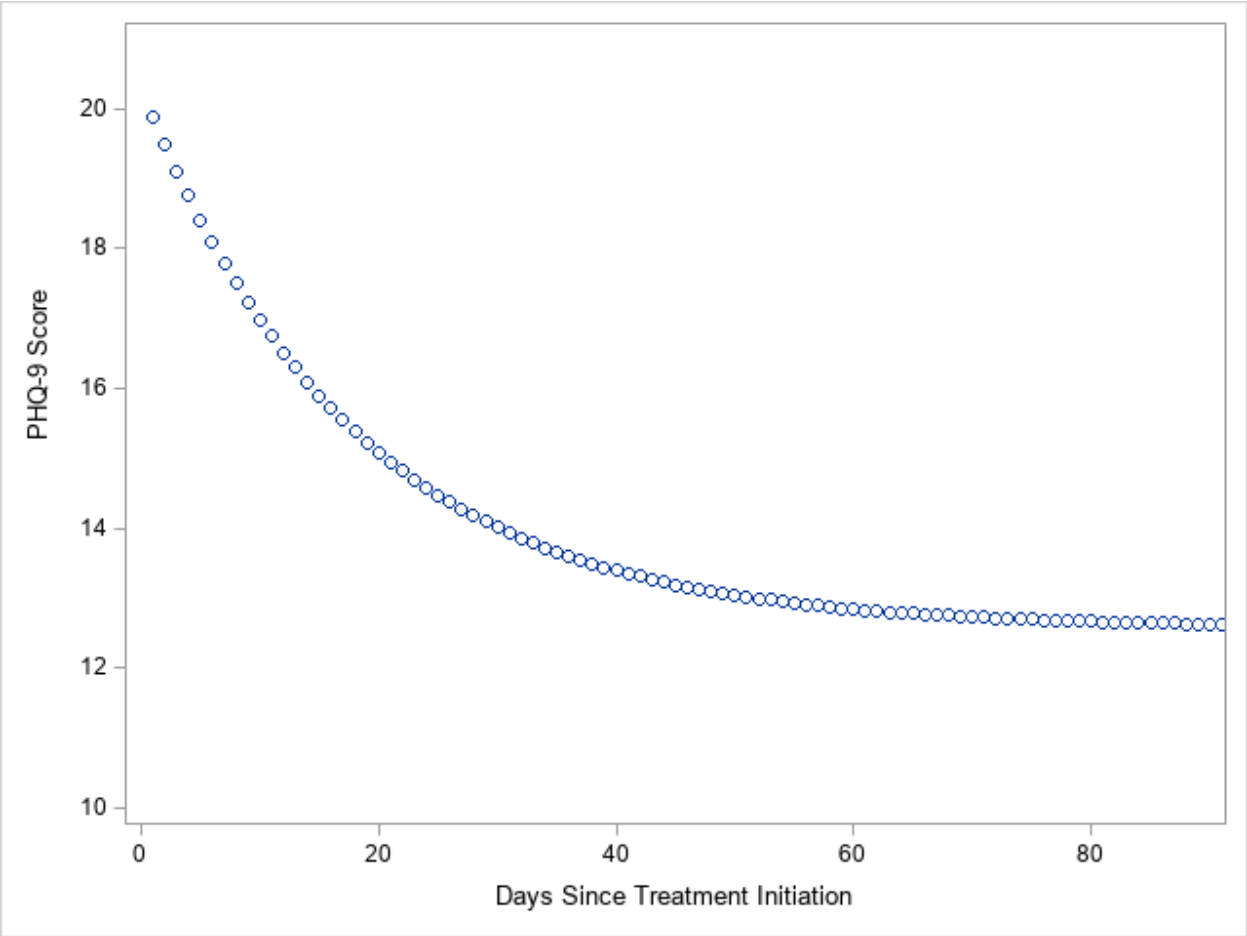


Figure shows the trajectory of PHQ-9 total score over time. The estimated intercept at day 0 was 20.3, the estimated amount of change was 7.7 points resulting in a lower asymptote of 12.5. The exponential rate parameter was -0.056 ($p<0.001$), which resulted in an estimated total score of 17.7 at day 7, 14.0 at day 30 and 12.6 by day 90.