Ketamine Reduces Suicidality-Associated Emergency Department Utilization in Patients With Treatment-Resistant Depression:

A 6-Month Mirror-Image Study

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Abstract

Background: Short-term studies have demonstrated antisuicidal effects of ketamine/esketamine for patients with treatment-resistant depression (TRD). However, long-term data and their impact in reducing suicidality-related health care utilization are limited. This 6-month mirror-image study compares suicidality-associated emergency department (ED) visits before and after acute treatment with ketamine/esketamine in a TRD cohort.

Method: This study included adults with TRD evaluated at Mayo Clinic Depression Center (Rochester, Minnesota) from May 2018 to May 2024, who received an acute series of intravenous (IV) ketamine or intranasal (IN) esketamine treatments. The primary outcome measure was the number of suicidality-associated ED visits in the 6 months before and after treatment. Negative binomial mixed-effects model was utilized to analyze suicidality-associated ED visits per person, estimating incidence rate ratios (IRRs) and 95% confidence intervals for the change between pre- and posttreatment periods.

Results: Of 124 eligible individuals, 27 were excluded due to unavailable data, leaving 97 for analysis. The cohort was 69% female, with a median age of 48.9 years; 97% had major depressive disorder, and most (75%) received IV ketamine. After the acute treatment phase, ED visits for suicidal ideation decreased by 84% (IRR = 0.16, 95% CI, 0.06–0.46, $P = .001$), and total ED visits for suicidality decreased by 63% (IRR = 0.37, 95% CI, 0.18–0.77, $P = .007$).

Conclusions: Ketamine and esketamine reduced long-term ED visits for suicidality in individuals with TRD. Further longer-term follow-up research is encouraged to ascertain if these benefits on suicidality reduction are mood state dependent or reflect an independent mechanism.

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Depression affects over 300 million people globally[1] and accounted for $333.7 billion in costs in 2019, with 40% attributed to direct health care expenses.[2] Only 50% of individuals respond to the first antidepressant treatment, and approximately 35% of patients fail to respond to at least 2 antidepressant trials, a condition often classified as treatment-resistant depression (TRD).[2,3] Suicide and suicidal ideation (SI; with and without plan) and behavior (hereafter referred to as *suicidality*) are common outcomes in individuals with depression. During depressive episodes, over half of patients experience SI, and approximately 15% attempt suicide.[4,5] In patients with TRD, the rates of attempted and completed suicides are notably higher, underscoring treatment resistance as a significant risk factor for suicidality.[6] Suicide and self-harm significantly contribute to health care utilization in depression. Between 2006 and 2013, over 3.5 million emergency department (ED) visits in the US were related to suicidality, with 42% of these visits involving individuals diagnosed with a mood disorder.[7]

Unimodal antidepressants are foundational in the treatment of episodes of major depression, and observational studies indicate antidepressant use may reduce the overall risk of suicide attempts (SA) and completed suicide across various psychiatric disorders.[8]

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Clinical Points

- Ketamine and esketamine reduce depressive symptoms in short-term, but their long-term effect on suicidality-related health care utilization visits in treatment-resistant depression (TRD) is unclear.
- In patients with TRD, ketamine/esketamine may reduce suicidality-related emergency department visits over 6 months.

However, the time course for clinical impact is less clear. A recent network meta-analysis of 29 double-blind randomized trials found that selective serotonin reuptake inhibitors (SSRIs) exert a short-term effect on reducing SI, which diminishes by week 8[9]—a pattern also observed with amitriptyline and bupropion. It is during the same time frame that, in fact, a US Food and Drug Administration (FDA) black box warning exists for antidepressants in young adults (≤24 years of age), due to the potential risk of worsening SI.[10] However, there remains a need for fast-acting treatments to more rapidly address suicidality.

Ketamine, a rapid-acting antidepressant, has demonstrated effectiveness in reducing suicidality, though its effects are often transient.[11] Repeated doses of intravenous (IV) racemic ketamine have been shown to alleviate SI in up to 70% of individuals with TRD in the short term.[12] Esketamine is FDA-approved as a monotherapy for TRD and as an adjunctive therapy with an oral antidepressant for TRD and major depressive disorder (MDD) with acute SI or behavior. However, its efficacy in reducing suicidality remains limited.[13] Patients with TRD and SI require more treatments to achieve a response with ketamine or esketamine in the acute/induction phase.[14] There is limited evidence on the long-term effectiveness of IV ketamine and IN esketamine in reducing suicidality and in addressing health care utilization related to suicidality.

A large nationwide commercial database study among individuals with MDD reported that ketamine prescriptions were associated with a reduction in clinical encounters coded for SI compared to other antidepressants, with effects observed at various time points up to 270 days.[15] Another large commercial database study, which measured changes in all-cause health care utilization in individuals with MDD and suicidality after a 12-month period, compared esketamine with electroconvulsive therapy (ECT), antidepressant monotherapy, and augmentation with second-generation antipsychotics.[16] The study found that individuals with esketamine claims had the highest reduction in health care utilization compared to the other groups, with a 58% decrease from baseline.[16] Investigating long-term changes in suicidality after ketamine/esketamine treatment in real-world settings presents challenges, as standardized suicide assessment scales are not routinely used in clinical practice, making direct measurement difficult. A reasonable indirect measure is urgent health care utilization, particularly suicidality-associated ED visits.[17] Thus, we aimed to conduct a 6-month mirror-image study in a real-world clinical practice to investigate changes in suicidality-associated ED visits among patients with TRD receiving ketamine or esketamine.

METHODS

Study Design

This study was approved by the Mayo Clinic Institutional Review Board (20-012789), and all patients authorized the use of their clinical data. This mirror-image design was nested within a historical cohort of adult patients (≥18 years) with TRD evaluated at Mayo Clinic Depression Center (Rochester, Minnesota) from May 2018 to May 2024 who received at least 3 IV ketamine infusions or 8 IN esketamine treatments as per the clinic protocol.[18,19] Patients received IV ketamine at a dose of 0.5 mg/kg body weight infused over 40 minutes, while IN esketamine was administered at the FDA-approved doses of 56 or 84 mg. Patients may receive up to 6 IV ketamine infusions in the acute/induction phase. A mirror-image study design offers a distinctive approach to compare a prior treatment phase with a subsequent one.[20,21] This method proves valuable in assessing the effects of various treatment modalities or events, as the outcomes are measured for the same duration both before and after the intervention or event. By making each patient their own control, this approach minimizes individual variability and reduces potential confounding factors. This design allows for the reliable examination of outcomes over time, capturing changes in response to the intervention effectively and comprehensively. The index event was the completion of the acute phase of IV ketamine/IN esketamine treatment. Mirror periods were defined as the 6 months pre and post the index event. Patients without available electronic medical records (EMRs) for both mirror periods were excluded. Suicidality-associated ED visits were defined as visits to the ED in which the diagnosis included SI, SA, or intentional self-harm, and/or clinical documentation indicated the visit was due to SI (with or without a plan), SA, or self-harming behavior.

Data Extraction

We followed a standardized protocol for the extraction of information from the EMR. Data were collected by psychiatry resident physicians and psychiatrists undergoing mood fellowship under the

direct supervision of subspecialty psychiatrists in the Depression Center. The following data were extracted from the EMR: demographics, baseline clinic characteristics (primary mood diagnosis, medical and psychiatric comorbidities, psychotropic treatment), number of suicidality-associated ED visits during the 6 months prior to the IV ketamine/IN esketamine treatment, and number of suicidality-associated ED visits during the 6 months after the completion of the acute phase of IV ketamine/IN esketamine treatment. To identify suicidality-associated ED visits, we retrieved all ED visits for each individual in the cohort. We then reviewed the associated diagnoses and examined the clinical notes to determine the reason for the visit. All information was deidentified and secured in protected files.

Outcomes

Our primary outcome was the number of suicidality-associated ED visits between the mirror periods. Secondary outcomes were changes in psychotropic medications. We also compared outcomes between patients with and without a history of suicidality-associated ED visits before starting ketamine/esketamine.

Response to ketamine/esketamine was defined as a ≥50% reduction in the baseline Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR)[22] score at the completion of the acute phase. Partial response was defined as a 26%–49% reduction in the baseline QIDS-SR. In case of discrepancy regarding response status, at least two psychiatrists reached consensus based on clinical assessment, including changes in QIDS-SR scores and clinical response. Remission was defined as a QIDS-SR score ≤5.

Statistical Analysis

Descriptive statistics were used to summarize the data. Differences between participants with any preacute treatment suicidality-associated ED visit and those without were assessed using Fisher exact tests for categorical variables and Mann-Whitney *U* test for continuous variables. To examine the number of suicidality-associated ED visits per person, we used negative binomial mixed-effects models with random intercepts to account for within-subject correlation. These models estimate incidence rate ratios (IRRs) and 95% confidence intervals (CIs) to quantify changes between pre- and posttreatment periods. To enhance interpretability, we also calculated the number needed to treat (NNT) for binary outcomes (ie, the occurrence of any suicide-specific ED visit). NNT was derived from the absolute risk reduction between pre and post, defined as the inverse of the difference in the proportion of individuals experiencing at least 1 event in the post vs pre period. To evaluate pre and post changes in use of antidepressant medication classes, we used the McNemar test.

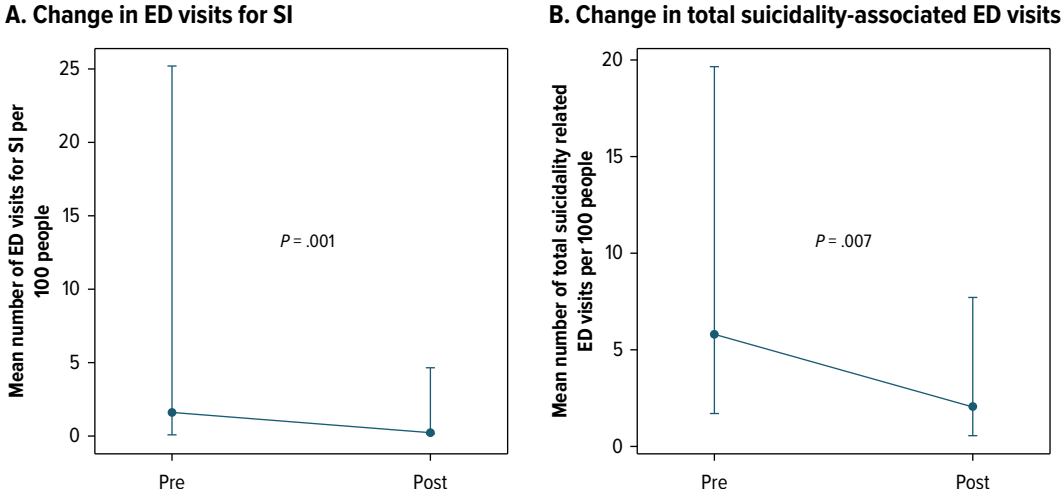
RESULTS

A total of 134 individuals were identified in the ketamine clinic during the study period. Of these, 124 met the inclusion criteria, and 27 were excluded due to unavailable medical records for the mirror periods. Consequently, 97 patients were included in the final analysis. Sixty-nine percent (n = 67) of patients were female, with a median age of 48.9 years (interquartile range 41.3–56.1). Regarding diagnosis, 96.9% (n = 94) had unipolar depression, with a median duration of the episode of 2.2 years, and the majority (n = 73; 75.3%) were treated with IV ketamine. Most patients who received esketamine (22/24; 91.7%) started at 56 mg, with the rest (2/24; 8.3%) beginning at 28 mg. By the end of the acute phase, 66.6% (16/24) were on 84 mg, while 33.3% (8/24) remained on 56 mg. During the maintenance phase, 6 of 8 patients transitioned to 84 mg, and 2 remained on 56 mg. The median number of psychotropic medications was 3.0, and the most frequently used psychotropics were benzodiazepines (37.1%), serotonin-norepinephrine reuptake inhibitors (SNRIs) (35.1%), and SSRIs (32.0%). Twenty-four percent of patients had failed ECT, and 19% had failed TMS prior to the trial of ketamine or esketamine for depression. Response rate was 56.7%, and remission rate was 29.9% at the end of the acute phase. Partial response was observed in 22.7% of individuals. Following the acute phase, 76.3% (n = 74) of individuals continued maintenance treatment.

Regarding ED visits, 27 visits were identified in the preacute treatment period among 16 individuals, with 25 visits associated to SI and 2 to SA. No visits associated with self-harm behavior or completed suicide were identified during the study period. In the postacute treatment period, there were 10 visits among 8 individuals, with 8 associated with SI and 2 for SA. Using a negative binomial mixed-effects model, IV ketamine/IN esketamine treatment was associated with an 84% (IRR = 0.16, 95% CI, 0.06–0.46, $P = .001$) reduction in ED visits for SI (Figure 1A) and a 63% (IRR = 0.37, 95% CI, 0.18–0.77, $P = .007$) decrease in total (SI and SA) ED visits for suicidality (Figure 1B). Model-derived estimated means indicated that, per 100 individuals, the postacute phase was associated with 1.3 fewer ED visits associated to SI and 2.9 fewer total ED visits associated to suicidality compared to the preacute treatment period. When examining the occurrence of any ED visit (as a binary outcome), there were 9 fewer individuals with a SI-associated ED visit in the postacute treatment period, resulting in an NNT of 10.9 (ie, 97/9). Similarly, there were 8 fewer

Figure 1.

Change in Number of Suicidality-Associated ED Visits Comparing the 6 Months Pre- and Post-Acute Phase Treatment With IV Ketamine/IN Esketamine



Abbreviations: ED = emergency department, SI = suicidal ideation.

individuals with any suicidality-associated ED visit in the postacute treatment period, corresponding to an NNT of 12.1 (ie, 97/8). Patients with suicidality-associated ED visits during the preacute treatment period were significantly more likely to have at least 1 such visit in the postacute treatment period compared to those without preacute visits (31.5% vs 3.7%; $P = .003$). There were no significant differences in postacute suicidality-associated ED visits when comparing by treatment type (IV ketamine: 9.6% vs IN esketamine: 4.2%; $P = .68$), maintenance treatment (yes: 6.8% vs no: 13.0%; $P = .39$), or response status (responders: 3.6% vs nonresponders: 14.3%; $P = .07$). These differences became even less pronounced after adjusting for the presence of preacute suicidality-associated ED visits (all $P \geq .26$).

Regarding changes in psychotropic regimens following the acute treatment phase with IV ketamine/IN esketamine, the most notable modifications were changes in antidepressant (25.8%) and antidepressant discontinuation (25.8%). Additionally, 15% of individuals were started on an augmentation agent, and 11% initiated an anxiolytic. When comparing pre- and postacute treatment periods by medication class, a statistically significant change after the acute treatment with IV ketamine/IN esketamine was observed in SSRI use, with 10 individuals discontinuing their SSRI and 2 initiating 1 (McNemar test, $P = .04$). Among those who discontinued an SSRI, 5 transitioned to an SNRI, 2 to a monoamine oxidase inhibitor, 1 to a combination of bupropion and vortioxetine, 1 to vortioxetine alone, and 1 to vilazodone. No significant changes were found in the use of SNRIs, bupropion, or tricyclic antidepressants between the pre- and postindex event periods (all $P \geq .22$).

Analyses comparing individuals with and without suicidality-associated ED visits during the preacute treatment period revealed that use of trazodone (21% vs 50% $P = .03$), gabapentin (9.8% vs 31.2% $P = .04$), and prior exposure to ECT (18.5% vs 50% $P = .02$) were more prevalent among those with ED visits. Individuals with suicidality-associated ED visits in the pretreatment period had shorter depressive episode duration (1.0 vs 3.0 $P = .01$). Conversely, individuals without suicidality-associated ED visits in the pretreatment period showed higher response rates (61.7% vs 31.2% $P = .03$), greater reductions in QIDS-SR scores (58.4% vs 35.9% $P = .04$) during the acute phase, and a greater proportion transitioned to maintenance (81.5% vs 50.0% $P = .02$) treatment. No other statistically significant differences were observed among the 2 groups. Full description of sociodemographic and clinical characteristics are presented in Table 1.

DISCUSSION

Suicidality remains a major public health issue in the US, with nearly 50,000 deaths by suicide reported in 2022, more than 13 million adults experienced SI, and 1.6 million attempted suicide.[23] These numbers underscore the urgent need for developing novel treatments targeting suicidality. To the best of our

Table 1.

Patient Characteristics by Suicidality ED Visits Pretreatment and Overall

Characteristic	Median (Q1, Q3) [min, max] or N (%)			P[a]
	No ED visits pretreatment (N = 81)	ED visits pretreatment (N = 16)	Total (N = 97)	
Demographic				
Age, y	49.8 (41.5, 56.1) [23.2, 74.4]	45.6 (39.5, 56.0) [19.9, 61.2]	48.9 (41.3, 56.1) [19.9, 74.4]	.46
Sex				.25
Male	23 (28.4%)	7 (43.8%)	30 (30.9%)	
Female	58 (71.6%)	9 (56.2%)	67 (69.1%)	
Body mass index	28.9 (24.0, 33.2) [18.4, 50.9]	27.2 (24.9, 29.7) [23.8, 36.5]	28.3 (24.4, 32.4) [18.4, 50.9]	.49
Employment				.34
Unemployed	11 (13.6%)	2 (12.5%)	13 (13.4%)	
Employed	50 (61.7%)	8 (50.0%)	58 (59.8%)	
Disability due to depression	7 (8.6%)	4 (25.0%)	11 (11.3%)	
Homemaker, retired, or student	13 (16.0%)	2 (12.5%)	15 (15.5%)	
Clinical				
Diagnosis				1.00
MDD	78 (96.3%)	16 (100.0%)	94 (96.9%)	
BD-II	3 (3.7%)	0 (0.0%)	3 (3.1%)	
Duration of depressive episode, y	3.0 (1.0, 10.0) [0.2, 37.0]	1.0 (0.6, 2.0) [0.2, 16.0]	2.2 (1.0, 7.0) [0.2, 37.0]	**.01**
PTSD	17 (21.0%)	1 (6.2%)	18 (18.6%)	.29
Anxiety disorders	55 (67.9%)	13 (81.2%)	68 (70.1%)	.38
Fibromyalgia or chronic pain	14 (17.3%)	1 (6.2%)	15 (15.5%)	.45
OCD	3 (3.7%)	0 (0.0%)	3 (3.1%)	1.00
Eating disorder	3 (3.7%)	2 (12.5%)	5 (5.2%)	.19
Borderline personality disorder	5 (6.2%)	2 (12.5%)	7 (7.2%)	.33
History of substance use disorder	12 (14.8%)	2 (12.5%)	14 (14.4%)	1.00
Study variables				
Baseline QIDS-SR	18 (16, 20) [7, 24]	19 (16.8, 21.2) [11, 24]	18 (16, 20) [7, 24]	.24
Type of treatment				.34
IV ketamine	59 (72.8%)	14 (87.5%)	73 (75.3%)	
IN esketamine	22 (27.2%)	2 (12.5%)	24 (24.7%)	
No. of treatments	11 (8, 16) [3, 66]	6.5 (5, 14) [3, 30)	11 (7, 16) [3,66]	.07
QIDS-SR percent change from baseline to end acute phase (n = 96)	−58.4 (−70.4, −37.7) [−100.0, −13.6]	−35.9 (−50.6, −23.4) [−90.9, −20.0]	−52.7 (−69.0, −29.2) [−100, 20.0]	**.04**
Response	50 (61.7%)	5 (31.2%)	55 (56.7%)	**.03**
Partial response	17 (21.0%)	5 (31.2%)	22 (22.7%)	.35
Remission	27 (33.3%)	2 (12.5%)	29 (29.9%)	.14
Maintenance	66 (81.5%)	8 (50.0%)	74 (76.3%)	**.02**
Current medications				
No. of psychotropics	3.0 (3.0, 5.0) [0, 7]	3.0 (3.0, 5.0) [2, 7]	3.0 (3.0, 5.0) [0, 7]	.48
SSRI	24 (29.6%)	7 (43.8%)	31 (32.0%)	.38
SNRI	28 (34.6%)	6 (37.5%)	34 (35.1%)	1.00
TCA	6 (7.4%)	2 (12.5%)	8 (8.2%)	.62
MAOI	2 (2.5%)	0	2 (2.1%)	1.00
Atypical antipsychotic	21 (25.9%)	5 (31.2%)	26 (26.8%)	.76
Mirtazapine	5 (6.2%)	1 (6.2%)	6 (6.2%)	1.00
Bupropion	27 (33.3%)	4 (25.0%)	31 (32.0%)	.57
Stimulant	19 (23.5%)	1 (6.2%)	20 (20.6%)	.18
Trazodone	17 (21.0%)	8 (50.0%)	25 (25.8%)	**.03**
Gabapentin	8 (9.9%)	5 (31.2%)	13 (13.4%)	**.04**
Z-drug	19 (23.5%)	0	19 (19.6%)	**.04**
Benzodiazepine	27 (33.3%)	9 (56.2%)	36 (37.1%)	.10
Neuromodulation (tried in current episode)				
ECT	15 (18.5%)	8 (50.0%)	23 (23.7%)	**.02**
TMS	15 (18.5%)	3 (18.8%)	18 (18.6%)	1.00

[a]Boldface indicates statistical significance.

Abbreviations: BD = bipolar disorder, ECT = electroconvulsive therapy, ED = emergency department, GAD = generalized anxiety disorder, IV = intravenous, IN = intranasal, 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, SA = suicide attempt, SI = suicidal ideation, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, SUD = substance use disorder, TCA = tricyclic antidepressant, TMS = transcranial magnetic stimulation.

knowledge, this is one of the first real-world studies examining changes in suicidality-associated health care utilization in a clinical setting by assessing patients before and after initiation of ketamine/esketamine for TRD. Our findings show a decrease in suicidality-associated ED visits after the completion of ketamine/esketamine acute phase treatment.

Remission and response rates during the acute phase were consistent with those previously reported in our clinic.[19] Notably, individuals without suicidality-associated ED visits during the pretreatment period showed a trend toward better treatment outcomes including higher response rates, greater reductions in QIDS-SR scores, and fewer suicidality-associated ED visits in the posttreatment period. This might reflect that those with pretreatment suicidality-associated ED visits had more severe depression, which is consistent with the fact that half of them had undergone ECT during the current episode. However, baseline QIDS-SR scores did not differ significantly between groups, raising the question of whether standardized tools like the QIDS-SR are able to fully capture the severity of depression among individuals with TRD.

The observed reduction in ED visits for suicidality suggests that, while the effects of ketamine on suicidality scales appear short-lived, its impact on suicidal behavior may persist beyond what these measures capture. If replicated, these findings can have public health care implications. Our findings align with the preliminary insights from the commercial database studies by Harding et al.'s[16] and Pan et al.'s,[15] which evaluated longer-term suicidality outcomes based on esketamine claims, providing a limited view of treatment effects.[16] However, our study provides a more rigorous evaluation through intrasubject comparison and detailed clinical characterization of both the patient population and treatment course, allowing for a more precise assessment of ketamine/esketamine's impact on ED visits for suicidality.

The mechanisms through which ketamine/esketamine exerts its effects on suicidality remain poorly understood.[24,25] There is insufficient clarity regarding the relationship between the effects of ketamine and esketamine on glutamatergic transmission, opioid system modulation, and brain-derived neurotrophic factor release and the observed reduction in SI following their administration.[26] Clinically, its impact in suicidality appears to be, at least partially, associated to its effects on anhedonia and improvements in depressive symptoms.[27–29] Interestingly, in our study, the reduction in suicidality-associated ED visits occurred independently of whether response criteria were met during the acute-phase, suggesting that ketamine may reduce suicidality-associated urgent health care utilization, even in individuals who continue to experience depressive symptoms. This is consistent with prior observations of a reduction in suicidality following a single dose of IV ketamine, independent of changes in depressive symptoms.[30]

With interventions such as ketamine/esketamine, where frequent contact with the treatment team is required, visits occur regularly to receive the medication, and treatment may extent over the long term[31], there are contextual factors that can influence outcomes.[32] For instance, interaction between patients and clinic staff, particularly the nurses during the treatment, may provide elements of psychoeducation and behavioral activation. Furthermore, when patients transition to maintenance therapy, the expectation of continued care from empathetic clinicians who make them feel heard may contribute to a reduced need for emergency services. Finally, expectancy effects may also play a role, as the patient knows they are receiving the latest avant-garde treatment in psychiatry, which can positively influence their perception of improvement.

It is important to consider that other interventions, particularly psychotherapies, have shown positive effects on health care utilization for suicidality.[33,34] However, for individuals with TRD, severe symptoms often hinder full engagement in psychotherapeutic interventions. Symptom reduction may enhance receptivity and willingness to engage in psychotherapy, highlighting the importance of exploring additional therapies such as ketamine, which can facilitate symptom improvement.

In terms of changes in antidepressant regimens, the only statistically significant shift in psychotropic prescribing following acute ketamine/esketamine treatment was a reduction in SSRI use, with half of those who discontinued (5 of 10) transitioning to an SNRI potentially reflecting a clinical perception that dual agents may better maintaining the improvement achieved with glutamatergic interventions, a notion supported by recent evidence associating the combination of esketamine with an SNRI with improved clinical outcomes in individuals with TRD.[35]

Limitations

The use of an indirect measure for suicidality limited our ability to identify individuals who did not seek care in the ED and instead presented to other health care settings. The requirement for EMRs covering a period exceeding 1 year, rather than just the duration of treatment, restricted our sample. This extended timeframe posed a challenge for patients from out of state, whose records were often unavailable, and for those receiving care in private clinics. A limitation of this study is the lack of a comparator group to account for the impact of increased clinical contact during (es)ketamine treatment. Patients spend 1 to 2 hours with a nurse during treatment, and regular visits for their treatment could further provide behavioral activation. This may have contributed to the reduction in suicide-related

visits, even among nonresponders. However, in this study, we can only comment on suicidality-related ED visits, and no conclusions can be drawn about the absence of differences in antisuicide effects between responders and nonresponders. Lastly, our sample size and the low number of ED visits constrained our ability to conduct analyses adjusting for potential confounders. Response and remission status were reported largely based on the QIDS-SR score at the end of the acute series. However, it is possible that some patients may have met the response criteria before the last infusion in the acute phase or later during the maintenance phase.

CONCLUSION

In our cohort, ketamine/esketamine reduced long-term suicidality-associated ED visits among patients with TRD, regardless of treatment response or whether they are on maintenance treatment. Suicidality is a major contributor to the economic burden of TRD, and no pharmacologic interventions are currently approved to specifically target it. Although the antisuicidal effects of IV ketamine and IN esketamine, as measured by clinical scales, are transient, emerging evidence suggests potential long-term benefits in reducing the suicidality-associated urgent care visits. Larger, well-powered studies are needed to validate these findings.

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Ethics Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Mayo Clinic Institutional Review Board (IRB-20-012789, approval date: January 5, 2021). Patients who provided consent for the use of their medical records for research were included.

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