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Effectiveness of intravenous ketamine in mood disorder patients with a history of neurostimulation

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Original Research

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Abstract

Background. Patients unsuccessfully treated by neurostimulation may represent a highly intractable subgroup of depression. While the efficacy of intravenous (IV) ketamine has been established in patients with treatment-resistant depression (TRD), there is an interest to evaluate its effectiveness in a subpopulation with a history of neurostimulation.

Methods. This retrospective, posthoc analysis compared the effects of four infusions of IV ketamine in 135 ($\bar{x} = 44 \pm 15.4$ years of age) neurostimulation-naïve patients to 103 ($\bar{x} = 47 \pm 13.9$ years of age) patients with a history of neurostimulation. The primary outcome evaluated changes in depression severity, measured by the Quick Inventory for Depression Symptomatology-Self Report 16-Item ($QIDS\text{-}SR_{16}$). Secondary outcomes evaluated suicidal ideation (SI), anxiety severity, measured by the Generalized Anxiety Disorder 7-Item (GAD-7), and consummatory anhedonia, measured by the Snaith–Hamilton Pleasure Scale (SHAPS).

Results. Following four infusions, both cohorts reported a significant reduction in $QIDS\text{-}SR_{16}$ Total Score ($F(4, 648) = 73.4$, $P < .001$), SI ($F(4, 642) = 28.6$, $P < .001$), GAD-7 ($F(2, 265) = 53.8$, $P < .001$), and SHAPS ($F(2, 302) = 45.9$, $P < .001$). No between-group differences emerged. Overall, the neurostimulation-naïve group had a mean reduction in $QIDS\text{-}SR_{16}$ Total Score of 6.4 (standard deviation [SD] = 5.3), whereas the history of neurostimulation patients reported a 4.3 (SD = 5.3) point reduction.

Conclusion. IV ketamine was effective in reducing symptoms of depression, SI, anxiety, and anhedonia in both cohorts in this large, well-characterized community-based sample of adults with TRD.

Introduction

Major depressive disorder (MDD) and bipolar depression (BD) continue to have high rates of treatment resistance (eg, treatment resistant depression [TRD]), with many mood disorder patients experiencing chronic and persistent depressive symptoms after numerous treatment trials. The Sequenced Treatment Alternatives to Relieve Depression Study demonstrated that only 60% of patients with MDD experienced full remission of symptoms, despite multiple intervention attempts.[1,2] Even higher rates of TRD are observed in BD, as indicated by the Systematic Treatment Enhancement Program for Bipolar Disorder Study.[3] As such, low remission rates and inadequate response to current treatment options are a major unmet need within mood disorder populations.

When pharmacological and psychological interventions provide inadequate antidepressant effects, neurostimulation options (ie, repetitive transcranial magnetic stimulation [rTMS] and electroconvulsive therapy [ECT]) may be explored as evidence-based alternatives for TRD.[4] Currently, ECT continues to be the gold standard and most effective treatment option for severe TRD. A recent meta-analysis by the Ontario government concluded that in trials directly comparing ECT with rTMS, there was a statistical and clinical benefit for ECT treatments.[5]

It is estimated that response rates for ECT are between 70% and 80%.[4,6] Converging lines of evidence suggest that a higher degree of treatment resistance is often predictive of poor treatment

outcomes.[2,7,8] Moreover, without maintenance treatment, relapses approximate 50%, even following successful ECT treatment.[9] Therefore, patients unsuccessfully treated with ECT treatments are left to try experimental neuromodulatory treatments such as deep brain stimulation or focused ultrasound, which requires further trials to characterize their effect on TRD.[10,11] Indeed, effective treatments for ECT-refractory depression are limited with minimal research and no consensus regarding optimal treatment after failing a course of ECT.[4]

Ketamine is a glutamatergic agent that has shown rapid and robust antidepressive effects and reductions to suicidal ideation (SI).[12–16] There is, however, a paucity of data regarding the effectiveness of intravenous (IV) ketamine in patients with a history of receiving neurostimulation. One study compared 17 patients with TRD who did not respond to ECT to 23 patients who were ECT-naïve receiving a single dose of IV ketamine.[17] Overall, both groups exhibited a similar depressive symptom reduction with a trend toward favoring ECT-naïve patients that did not reach statistical significance. Given the small sample size, this study was likely underpowered to detect differences between response in ECT-refractory vs ECT-naïve patients. Herein, we aim to further extend these results by characterizing the overall antidepressant, antisuicidal, antianxiety, and antianhedonic effects of repeated-dose IV ketamine in a community sample of TRD patients that includes the largest clinical sample of patients receiving IV ketamine who had previously received neurostimulation (rTMS or ECT).

Methods

A total of 260 adult patients received repeated-dose IV ketamine infusions at the Canadian Rapid Treatment Center of Excellence (CRTCE) between July 2018 and April 2020. The CRTCE provided ketamine treatment, outside of a clinical trial, to adults, older than 18 years, with TRD (defined as Stage 2 treatment resistance or greater).[8] Retrospective data analysis was approved by a community institutional research ethics board (IRB#00000971) and registered on clinicaltrials.gov under the identifier NCT04209296. The treatment protocol and eligibility criteria have previously been characterized in detail.[14] Only measures pertinent to this study will be described herein.

Briefly, patients deemed eligible for treatment by the clinic psychiatrist and anesthesiologists, and provided written consent to the treatment, received infusions of IV ketamine hydrochloride, diluted in 0.9% saline solution, over 40 to 45 minutes. In total, four infusions were administered, over 7 to 14 days, depending on patient scheduling and availability. The first two infusions were administered at a dosage of 0.5 mg/kg based on patients' true body weight. Patients who did not experience clinical benefit (ie, ≤20% reduction in the total Quick Inventory for Depressive Symptomatology-Self Report 16-Item [QIDS-SR_{16} score]) following two infusions were eligible for a dose increase to 0.75 mg/kg, based on previous research suggesting that some patients require a higher dose of ketamine for full effects.[18] Eligibility for the dose increase was also based on patient preference and tolerance to the index dose. Following the four infusions, patients returned to the clinic for a follow-up visit with the treatment psychiatrist.

Assessments

History of ECT and rTMS treatments were ascertained from referral forms of patients. Following a chart review, patients who had received either treatment were grouped into the history of neurostimulation group, whereas patients who had not received ECT or rTMS were placed in the neurostimulation-naïve cohort.

Prior to each infusion, patients were administered a short self-report assessment battery to characterize severity of depression (ie, QIDS-SR_{16}), anxiety (ie, Generalized Anxiety Disorder 7-Item [GAD-7]), and consummatory anhedonia (ie, Snaith–Hamilton Pleasure Scale [SHAPS]).[19–21] Suicidal ideation was measured using the QIDS-SR 16-Item 12. The QIDS-SR_{16} assessment was completed at all five timepoints (ie, baseline, post-infusions 1 to 4). The GAD-7 and SHAPS scales were administered at baseline, post-infusion 3 and the post-initiation treatment visit.

Statistical analysis

Data were collected at point-of-care from patients using a tablet device and stored directly onto Research Electronic Data Capture.[22,23] Data were analyzed using Statistical Product and Service Solutions (SPSS version 23 for Mac; SPSS, Inc., Chicago, IL) and Graphpad Prism 8.0.

A repeated measures linear mixed effects model was used to determine if there were between- or within-group differences in depression severity, suicidal ideation, anxiety severity, and anhedonic severity. Model terms were *group* (ie, history of neurostimulation vs neurostimulation-naïve), *infusion*, and *group by infusion.* A compound symmetry matrix was used, and the data were estimated using REML. The model was adjusted for any covariates that were significantly different between the two cohorts. The alpha was set to 0.05. Posthoc analyses were corrected for multiple comparisons using the Bonferroni method. Categorical outcomes for responders (ie, reduction of QIDS-SR_{16} Total Score ≥50% from baseline) and remitters (ie, QIDS-SR_{16} Total Score ≤ 5) were reported following each infusion. Subsequent analyses were completed comparing the effects of IV ketamine in patients with a history of rTMS to patients with a history of ECT. Patients who had received both modalities were included into the latter group, as ECT is the gold standard. Linear mixed effects models were used to determine between- and within-group effects in QIDS-SR_{16} Total Score, SI score, GAD-7, and SHAPS.

Results

Sample characteristics

Of the 260 patients, a total of 135 (57%) patients had never received ECT or rTMS prior to beginning ketamine infusions, while 103 (43%) patients received at least one of the modalities. Within the neurostimulation-history group, 65 (27%) patients had received rTMS only, 19 (8%) patients received ECT only, and 19 (8%) patients had received both modalities. Neurostimulation data were unavailable for 22 patients and were therefore excluded from subsequent analyses. Baseline demographics are described in Table 1. There were no significant differences in age, body mass index (BMI), concomitant medications, or baseline depression severity between groups. There was a significant statistical difference in sex (X^2 (1) = 4.95, P = .026), as there were less males in the history of neurostimulation group, and the total number of past antidepressant trials prior to infusion (U = 3811, P < .001). Sex and past antidepressant trials were controlled for in subsequent analyses.

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Table 1. Baseline Characteristics.

Characteristic at Baseline	Neurostimulation-Naive (n = 135)	History of Neurostimulation (n = 103)
Received ECT only	N/A	19
Received rTMS only	N/A	65
Received both ECT & rTMS	N/A	19
Sex n (% within cohort)[a]		
Male	68 (50.4)	37 (35.9)
Female	67 (49.6)	66 (64.1)
Mean age in years (SD)	44 (15.4)	47 (13.9)
BMI (kg/m^2) (SD)	28.0 (7.2)	28.9 (6.7)
Primary diagnosis n (% within cohort)		
MDD	118 (87)	80 (78)
BD	10 (8)	21 (20)
Post-Traumatic Stress Disorder	3 (2)	1 (1)
Obsessive Compulsive Disorder	4 (3)	1 (1)
Mean number of prior lifetime antidepressant trials (SD)[a]	5.04 (3.2)	7.99 (4.2)
Mean number of antidepressants at time of infusion (SD)	1.27 (1.28)	1.54 (1.67)

Abbreviations: BD, bipolar depression; ECT, electroconvulsive therapy; MDD, major depressive disorder; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation.
[a]A significant difference between the two cohorts (p < .05).

Table 2. Omnibus Statistical Tests Between the Neurostimulation and Neurostimulation-Naive Cohorts.

Clinical Outcome	*F* Statistic	*P* Value	Partial η^2
Main effect of infusion			
QIDS-SR$_{16}$ Total Score*	F (4, 648) = 73.4	P < .001	0.31
QIDS-SR$_{16}$ SI Score*	F (4, 642) = 28.6	P < .001	0.15
GAD-7 Total Score*	F (2, 265) = 53.8	P < .001	0.29
SHAPS Total Score*	F (2, 302) = 45.9	P < .001	0.23
Main effect of group			
QIDS-SR$_{16}$ Total Score	F (1, 224) = 1.2	P = .27	0.01
QIDS-SR$_{16}$ SI Score	F (1, 220) = 0.006	P = .94	<0.01
GAD-7 Total Score	F (1, 224) = 1.5	P = .22	0.01
SHAPS Total Score*	F (1, 223) = 4.3	P = .04	0.02
Group by infusion interaction			
QIDS-SR$_{16}$ Total Score	F (4, 648) = 2.1	P = .07	0.01
QIDS-SR$_{16}$ SI Score	F (4, 642) = 1.3	P = .28	0.01
GAD-7 Total Score	F (2, 265) = 2.0	P = .14	0.01
SHAPS Total Score	F (2, 302) = 0.19	P = .83	<0.01

Abbreviations: GAD-7, Generalized Anxiety Disorder 7-Item; QIDS-SR16, Quick Inventory for Depression Symptomatology-Self Report 16-Item; SHAPS, Snaith–Hamilton Pleasure Scale; SI, suicidal ideation.

Clinical outcomes

Omnibus statistical tests for all clinical outcomes are reported in Table 2. There was an overall significant main effect of infusion in the QIDS-SR$_{16}$ Total Score but the main effect of group and group by infusion interaction were not significant. Bonferroni corrected pairwise comparisons indicated that there was a significant reduction in QIDS-SR$_{16}$ Total Score from baseline to all subsequent timepoints (P < .001); from post-infusion 1 to post-infusion 3 (P < .001) and 4 (P < .001); and from post-infusion 2 to post-infusion 3 (P = .002) and 4 (P < .001) (Figure 1A). Overall, the neurostimulation-naïve patients had a mean reduction in QIDS-SR$_{16}$ Total Score of 6.4 (standard deviation (SD) = 5.3), whereas the history of neurostimulation patients reported a 4.3 (SD = 5.3) point reduction.

There was a significant main effect of infusion in the QIDS-SR$_{16}$ SI score. Pairwise comparison indicated a significant reduction in suicidal ideation from baseline to all subsequent timepoints (P < .001); and from post-infusion 1 to post-infusion 3 (P < .001) and 4 (P < .001) (Figure 1B). The neurostimulation-naïve cohort reported a 0.65 (SD = 0.89) mean score reduction on the QIDS-SR$_{16}$ Item 12. Patients who had received neurostimulation had a 0.41 (SD = 0.83) mean score reduction following infusions.

There was a significant main effect of infusion in anxiety severity total scores, but no main effect of group or group by infusion interaction. In addition, there was a significant reduction in anxiety symptom severity from baseline to post-infusion 3 and post-infusion 4 (P < .001) (Figure 1C). Overall, neurostimulation naïve patients reported a mead reduction of 5.28 (SD = 5.7) on the GAD-7 following four infusions, whereas the neurostimulation group reported a 3.1 (SD = 4.8) point reduction.

It was additionally observed that there was a significant main effect of infusion and a main effect of group in SHAPS total score. However, there was no significant group by infusion interaction. A significant reduction in anhedonic symptom severity from baseline to post-infusion 3 and post-infusion 4 was also observed (P < .001) (Figure 1D). Between-group differences in the estimated marginal means of patients who had received neurostimulation also emerged (Estimated Marginal Mean (EMM) = 7.65, standard error (SE) = 0.40) compared to those who did not (EMM = 6.51, SE = 0.35, P < .04). Overall, the neurostimulation-naïve patients reported a 2.8 (SD = 4.2) point reduction from baseline in SHAPS. Comparatively, patients who had received neurostimulation reported a 2.2 (SD = 3.9) point reduction.

A subsequent analysis was complete within the neurostimulation history group, wherein patients who received rTMS were compared to those who had received ECT or ECT and rTMS. There were significant main effects of infusion for QIDS-SR$_{16}$ Total Score (F (4, 297) = 23.5, P < .001), QIDS-SR$_{16}$ SI (F (4, 295) = 10.4, P < .001), GAD-7 (F (2, 111) = 14.3, P < .001), and SHAPS (F (2, 143) = 18.4, P < .001). Overall, depression severity significantly decreased from 18.4 (SE = 0.55) to 13.3 (SE = 1.1) and 18.7 (SE = 0.83) to 14.3 (SE = 1.3) in the TMS history and ECT history groups, respectively (Figure 2A). Mean SI severity scores reduced from 1.3 (SE = 0.11) to 1.1 (SE = 0.17) in the TMS history group and 1.7 (SE = 0.18) to 1.1 (SE = 0.28) in the ECT history group (Figure 2B). Similarly, GAD-7 scores reduced following IV ketamine from 13.8 (SE = 0.75) to 11.0 (SE = 1.1) in the TMS group and 12.5 (SE = 1.0) to 8.8 (SE = 1.4) in the ECT group (Figure 2C). Finally, SHAPS scores in the TMS group reduced from 9.1 (SE = 0.48) to 6.7 (SE = 0.74), while, in the ECT group, reduced from 10.0 (SE = 0.58) to 7.9 (SE = 1.2) (Figure 2D).

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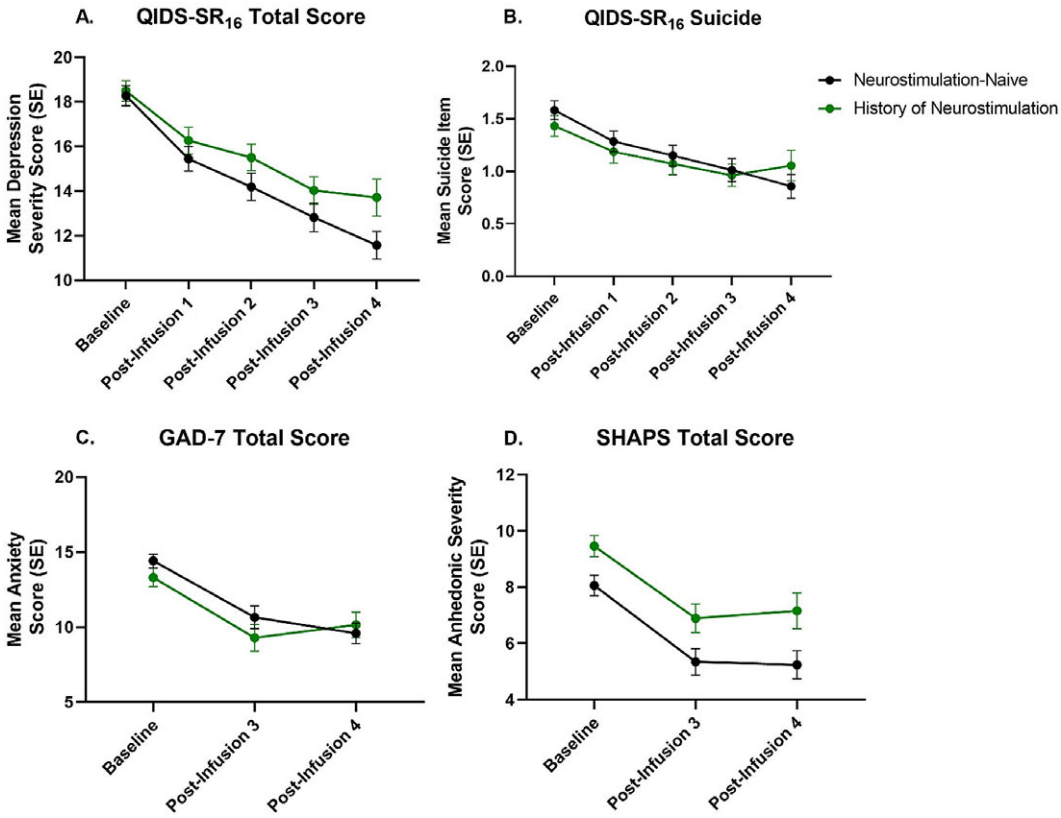

Figure 1. Comparison between the neurostimulation-naïve and history of neurostimulation groups across four IV ketamine infusions examining changes in (A). Mean Total Quick Inventory for Depression Symptomatology-Self Report 16-Item (QIDS-SR_{16}) Total Score, (B) Mean score of the QIDS-SR_{16} Suicide Item, (C) Generalized Anxiety Disorder 7-Item (GAD-7) Total Score, and (D) Snaith–Hamilton Pleasure Scale (SHAPS) Total Score.

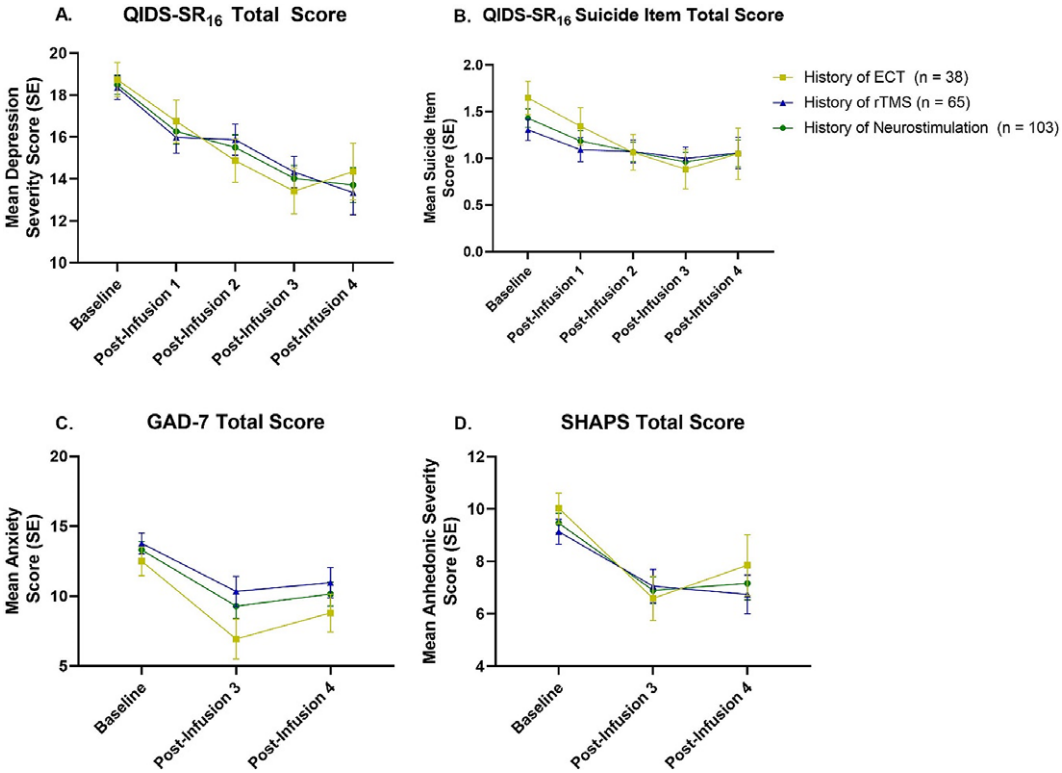

Figure 2. (A) Mean Total Quick Inventory for Depression Symptomatology-Self Report 16-Item (QIDS-SR_{16}) Total Score, (B) Mean score of the QIDS-SR_{16} Suicide Item, (C) Generalized Anxiety Disorder 7-Item (GAD-7) Total Score, and (D) Snaith–Hamilton Pleasure Scale (SHAPS) Total Score of patients who only received rTMS compared to those who received electroconvulsive therapy (ECT).

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Discussion

The analysis presented herein aimed to determine if patients with TRD who did not respond to neurostimulation (ie, rTMS or ECT) had differential outcomes to repeated doses of IV ketamine than patients who had never undergone neurostimulation. Overall, both patient groups exhibited a nonsignificant differential reduction in depression severity, suicidal ideation, anxiety severity, and anhedonic severity from baseline to post-infusion 4. There was a large effect size across infusions for depressive symptoms and anxiety symptoms, and a medium effect size for suicidal ideation and anhedonic severity reduction. These findings comport and extend initial reports that a moderate effect size in depressive symptom reduction was associated with ECT-resistant patients (n = 17) who received a single infusion of IV ketamine.[17] In addition, following four infusions, approximately 20% of patients with a history of neurostimulation responded to IV ketamine treatment (ie, reduction of QIDS-SR_{16} ≥50% from baseline) and 11% achieved remission (ie, QIDS-SR_{16} ≤ 5). In comparison, 32% of neurostimulation-naïve patients responded and 16% reached remission (Table 3).

It should be noted that patients within the neurostimulation group presented with a high degree of treatment resistance to psychotropic medication (ie, average of eight unsuccessful past medication trials). Extant literature has indicated that higher degrees of treatment resistance portends a poorer likelihood to recover.[2,7] It is therefore notable that after adjusting for the differences in treatment resistance between the two groups, patients unsuccessfully treated by neurostimulation exhibited significant symptomatic improvement. Moreover, given that approximately 20% of patients do not exhibit symptomatic improvement with ECT treatment, these findings indicate that ketamine provides a reliable alternative therapy for patients.[6] These results comport with Lu et al,[24] who reported that patients unable to receive ECT treatment due to medical risk may benefit from ketamine as a safe and effective treatment alternative.[24]

Growing evidence suggests that ketamine's antidepressant effects may be mediated through similar neural structures and functional networks targeted by neurostimulation modalities in refractory depression.[25,26] Similarly, proton magnetic resonance spectroscopy in murine models suggests that ECT may elevate Gamma aminobutyric acid (GABA) and glutamate concentration.[27] To this end, there has been significant interest in combination therapy of ECT and ketamine as a viable treatment in TRD. Indeed, a meta-analysis of 346 patients receiving ketamine-ECT treatment demonstrated moderate antidepressant effects.[28] However, the cardiovascular side effect profile was significantly worse compared to controls.[28] Novel research paradigms will look to investigate whether nonresponders to ECT or ketamine can cross-over into the other modality for treatment.[29]

Notably, it has been demonstrated that depression can be subdivided into neurophysiological subtypes based on distinct patterns of functional magnetic resonance imaging brain activity, and some biotypes show widely differential responses to rTMS.[30] Future clinical research may investigate patient response to neurostimulation vs response to ketamine as a function of depression biotype with possible implications for prognostication and increasingly targeted treatment of depression.

Importantly, this study should be evaluated under a number of methodological limitations. Primarily, this is a posthoc analysis of retrospective, naturalistic, and open-label data. There is no control group to serve as a comparator, and therefore we are unable to rule

Table 3. Responder and Remitter Analysis following Individual Infusions

	Post-Infusion 1		Post-Infusion 2		Post-Infusion 3		Post-Infusion 4	
	Neurostimulation-Naive	History of Neurostimulation	Neurostimulation-Naïve	History of Neurostimulation	Neurostimulation-Naive	History of Neurostimulation	Neurostimulation-Naive	History of Neurostimulation
Sample size	109	86	101	85	89	78	65	55
Responders n (%)	9 (8.3)	8 (9.3)	17 (16.8)	8 (9.4)	21 (23.5)	12 (15.4)	21 (32.3)	11 (20)
Remitters	4 (3.6)	3 (3.5)	9 (8.9)	2 (2.4)	11 (12.4)	5 (6.4)	11 (15.7)	6 (10.9)

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out expectancy effects. It should be further noted that there is a large amount of missing data at post-infusion 4 due to patient dropout and patients who were followed-up over telehealth did not complete the scales. Notwithstanding these limitations, the study included a large, real-world, community sample of patients with TRD.

Conclusion

The data presented suggests that repeated doses of IV ketamine produced similar reductions in depression severity, SI, anxiety severity, and anhedonic severity in patients who had received neurostimulation when compared to patients who had not. These findings suggest that ketamine may offer an alternative treatment strategy for patients with unsuccessful ECT and rTMS therapy. Future studies should conduct controlled trials with neurostimulation-resistant patients to parse the benefits of treatment targeting the glutamatergic system within this subpopulation of mood disorder patients.

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Kevin Kratiuk is the Vice President of Operations at the Canadian Rapid Treatment Center of Excellence (CRTCE). He is a shareholder of Champignon Brands, which acquired the CRTCE in May 2020.

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