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Research paper

The effectiveness of repeated intravenous ketamine on depressive symptoms, suicidal ideation and functional disability in adults with major depressive disorder and bipolar disorder: Results from the Canadian Rapid Treatment Center of Excellence

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A B S T R A C T

Background: The effectiveness, tolerability, and safety of intravenous (IV) ketamine in adults with treatment resistant depression (TRD) receiving care in real-word settings is insufficiently characterized. Herein, results from a naturalistic, retrospective study are presented from a Canadian outpatient IV ketamine clinic.
Methods: Adults (N = 213; M_{age} = 45) with Major Depressive Disorder or Bipolar Disorder, with a minimum of Stage 2 antidepressant resistance, received IV ketamine at a community-based multi-disciplinary clinic. The primary outcome measure was change from baseline to post-infusion 4 on the Quick Inventory for Depression Symptomatology-Self Report-16 (QIDS-SR_{16}; n = 190). Secondary measures included QIDS-SR_{16}-measured response and remission rates, changes from baseline to endpoint in Generalized Anxiety Disorder-7 Scale (GAD-7; n = 188) and the Sheehan Disability Scale (SDS; n = 168).
Results: Significant improvement in total depressive symptoms severity ($p < 0.0001$) was observed after four infusions of IV ketamine 0.5–0.75 mg/kg. Moreover, the response rate (QIDS-SR_{16} total score change ≥ 50%) was 27% and remission (QIDS-SR_{16} total score ≤5) rate was 13%. Patients receiving IV ketamine exhibited anxiolytic effects ($p < 0.0001$,), improved overall psychosocial function ($p < 0.0001$), and reduced suicidal ideation ($p < 0.0001$). Compared to the baseline infusion, dissociation severity significantly reduced in subsequent infusions.
Limitations: This was a naturalistic, retrospective study, without a control group.
Conclusions: IV ketamine was safe, well-tolerated, and effective at improving depressive, anxiety, and functional impairment symptoms in a well-characterized cohort of adults with TRD.

1. Introduction

The majority of adults with major depressive disorder (MDD) fail to exhibit sufficient syndromal and functional recovery with available monoamine-based antidepressants. Moreover, sequential failure with monoamine-based antidepressants is associated with higher risk of relapse, intolerability, and suicidality (Rush et al., 2006). In addition, treatment options for patients with bipolar disorder (BD) also remain insufficient and poorly tolerated, yielding high rates of treatment resistance (Gitlin, 2006). Pharmacoeconomic analysis indicates that treatment resistant depression (TRD) disproportionately accounts for total costs associated with MDD (Olfson et al., 2018).

Although ketamine, an N-methyl-D-aspartate receptor antagonist, is not FDA-approved for any mental disorder, the isomer, esketamine, is the first FDA-approved non-monoamine-based psychotropic agent for adults with TRD. The FDA approval of the intranasal esketamine was based on results from replicated, randomized, double-blind, placebo-controlled trials (Kim et al., 2019). In addition to the proven efficacy of esketamine, the short-term efficacy of intravenous (IV) ketamine is established (Berman et al., 2000; Coyle and Laws, 2015; Daly et al., 2019; Kraus et al., 2017; Newport et al., 2016; Phillips et al., 2019; Popova et al., 2018; Singh et al., 2016; Wilkinson et al., 2018).

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Notwithstanding the demonstrated efficacy, safety, and tolerability of ketamine in rigorous controlled studies, there remains a need to assess the effectiveness (rather than efficacy) of ketamine in carefully assessed patients with treatment-resistant mood disorders (Zorumski and Conway, 2017). It has been previously observed that significant, and often clinically relevant, differences exist between results obtained (both symptomatic as well as tolerability and safety) in rigorously controlled studies (i.e., efficacy studies) when compared to more real-world naturalistic studies (i.e., effectiveness studies). The discrepancy (i.e. the efficacy-effectiveness gap) can be attributed to the observation that individuals in clinical trials have characteristics that are often not generalizable to clinical practice (Lorenzo-Luaces et al., 2018). For example, individuals with suicidality, mental and medical disorder comorbidity, and receiving complex pharmacotherapeutic regimens (i.e., often encountered in real world practice) are excluded from clinical trials, reducing the external validity of clinical trial results. Integrating both efficacy and effectiveness data provides a composite of the overall benefits and safety of ketamine which provides more valid guidance as to the overall therapeutic profile of this novel treatment avenue (van der Lem et al., 2012).

Herein, we report on the effectiveness, tolerability, and safety of IV ketamine in adults with treatment-resistant mood disorders, including both bipolar and unipolar depression, receiving IV ketamine treatment at a community-based integrated center for adults with mood disorders.

2. Methods

2.1. Participants and study design

The data presented herein were obtained from patients who were referred to the Canadian Rapid Treatment Center of Excellence (CRTCE) in Mississauga, Ontario, Canada. The CRTCE is an outpatient clinical and research facility that provides IV ketamine treatment for adults (i.e., age ≥18 years) with TRD as part of MDD or BD. The CRTCE is the first Canadian clinic to offer IV ketamine for TRD outside of clinical trials. The CRTCE is a multi-disciplinary center that is comprised of psychiatrists, primary care providers, pharmacists, anesthesiologists, nursing staff, patient coordinators as well as research staff. Patients referred to the CRTCE are referred by primary care providers or psychiatrists either in the community or academic-based practices. Treatment-resistant depressive symptoms are the primary focus of clinical attention at the CRTCE; persons presenting with comorbidities (e.g., obsessive compulsive disorder, post-traumatic stress disorder) are also eligible for IV ketamine treatment, as long as the mood disorder is the primary diagnosis. All patient who received treatment at the CRTCE had two or more inadequate prior treatments. Patients with suicidal ideation are not excluded from receiving IV ketamine at the CRTCE.

Canadian Rapid Treatment Center of Excellence eligibility for ketamine treatment, as well as best practices with respect to the safe and appropriate delivery of ketamine, are in accordance with the Consensus Statement for the American Psychiatric Association (APA) Council of Research Task Force (Sanacora et al., 2017). All individuals must meet criteria for Stage 2 Resistance, or higher, as defined by Thase & Rush (Thase and Rush, 1997). That is, patients must have had an insufficient response from two major antidepressant drug classes. Additionally, investigation of ketamine across disparate formulations and routes of delivery have most commonly embraced the Thase and Rush level criteria. The justification for ketamine eligibility in patients who insufficiently respond to two or more prior treatments is based on replicated evidence (e.g. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study) indicating remission rates with monoamine-based psychotropics in a person with two prior failures is less than 20% (Rush et al., 2006). Currently, ketamine is recommended in select medication treatment guidelines for MDD as a treatment option when two prior antidepressants are insufficient (Kennedy et al., 2016; McIntyre et al., 2017).

Each patient is assessed prior to their first infusion by a staff psychiatrist affiliated with the CRTCE to confirm a primary diagnosis of a mood disorder and to provide psychoeducation regarding diagnosis and treatment. The diagnosis of MDD or BD was established clinically based on Diagnostic and Statistical Manual Fifth Edition (DSM-5) criteria. All patients must be medically cleared prior to their first infusion by CRTCE staff anesthesiologists who evaluated individuals for any unstable medical disorder contraindicated against IV ketamine (e.g., malignant hypertension, supraventricular tachycardia). In most cases, IV ketamine was delivered adjunctively to insufficient prescribed psychotropic medication regimens. The decision to deliver ketamine adjunctive to current treatments (in most cases) was made to enhance patient's acceptability, improve feasibility, and facilitate more efficient delivery of ketamine treatment (i.e., not having to wait for medication washout syndrome/mitigation). Patients who were currently taking an irreversible monoamine oxidase inhibitor (MAOI) were required to discontinue the MAOI for at least two weeks prior to administration. Naltrexone was not permitted during ketamine treatment; patients could not take benzodiazepines for at least 12 h prior to IV ketamine administration. The rationale for these restrictions is based on preliminary evidence that naltrexone and benzodiazepines may attenuate ketamine efficacy (Frye et al., 2015; Williams et al., 2018). Patients undergoing a medication taper or change for IV ketamine treatment were closely monitored by their referring physician and the CRTCE. No patients reported adverse events to the clinic during this period. In order to minimize the risk of drug-drug interactions from medications other than benzodiazepine, naltrexone, or MAOIs, patients were asked to temporarily stop all other medications six hours prior to infusion. These medications could then be restarted four hours following the infusion.

In addition, eligibility for ketamine requires that persons are able to consent to IV ketamine, which involves a full understanding of the risks and benefits of IV ketamine, as well as treatment alternatives. Persons with dementing disorders, psychotic disorders, active substance use, alcohol use disorders or persons whose primary diagnosis was not a mood disorder (e.g., personality disorder) as determined by the staff psychiatrist are ineligible for IV ketamine at the CRTCE. For persons with a history of substance and/or alcohol use disorder, abstinence for at least three months is required. It should be noted, however, that alcohol and recreational drug use was not contraindicated as long as patients did not meet criteria for substance use disorder. Unfortunately, data was not captured on the frequency of the drug or alcohol use, preventing further moderation analysis of drug and alcohol use on IV ketamine. All patients must agree to remain at the CRTCE premises for up to one-hour post-infusion for safety surveillance. In addition, following IV ketamine infusion, all eligible patients need to be escorted home by a responsible adult and are prohibited from driving until the following day.

The primary clinical measure obtained prior to the first infusion (i.e., baseline infusion), as well as each subsequent infusion during the initial protocol, and follow-up with the clinic psychiatrist (i.e., post-initiation treatment visit) was the Quick Inventory for Depressive Symptomatology Self-Report 16-Item (QIDS-SR_{16}). Additional measures that were included were the Generalized Anxiety Disorder 7-item (GAD-7), Sheehan Disability Scale (SDS), Snaith Hamilton Pleasure Scale (SHAPS), and the Endicott Work Productivity Scale (EWPS), each of which was completed prior to the first and fourth infusions, as well as the post-initiation treatment visit (Fig. 1). The results of the SHAPS and EWPS are not reported herein.

All patients at the CRTCE begin with two infusions of ketamine hydrochloride 0.5 mg/kg diluted in 0.9% saline solution infused over 40–45 min. The total dose of ketamine was determined using the patient's actual body weight (i.e., rather than ideal body weight). For patients whose body mass index (BMI, kg/m^2) was greater than 35 kg/m^2, the patient's ideal body weight was used to calculate the dose out of concern for tolerability. Any patient who exhibited a sub-optimal

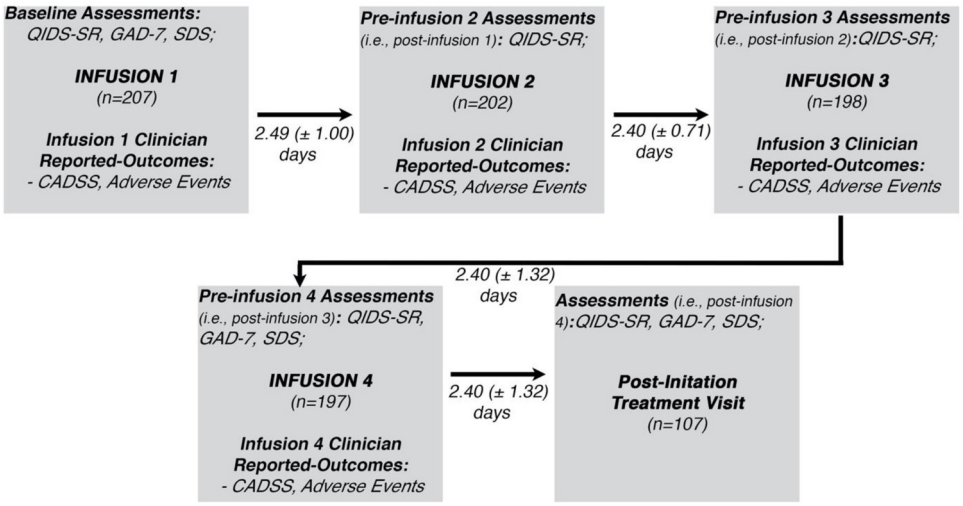

Fig. 1. Intravenous ketamine protocol followed by patients at the CRTCE. Sample sizes are the total number of patients who received IV ketamine treatment at each infusion and post-initiation treatment visit with the clinic psychiatrist.

response after the first two infusions (i.e. ≤ 20% reduction in total depression symptom severity as measured by the QIDS-SR_{16}) received a dose optimization to 0.75 mg/kg for the subsequent two infusions. Patients who were exempted from dose optimization were those exhibiting a > 20% reduction in total depression symptom severity as measured by the QIDS-SR_{16}, difficulties with tolerability at 0.5 mg/kg (e.g., dissociation), and/or patient preference. The frequency of ketamine administration during the initial protocol was four infusions delivered across 7 - 14 days based on patient availability/scheduling, with the post-initiation treatment visit scheduled one week after the fourth infusion. Current consensus guidelines suggest patients undergoing ketamine treatment should first begin on a series of 2–3 infusions per week over two weeks followed by maintenance infusions to extend the antidepressant effect (Sanacora et al., 2017). At the CRTCE, the initial four IV ketamine infusion treatments were termed the 'initiation treatment' and any IV ketamine treatments beyond the initial four infusion were termed 'maintenance treatments'. The analysis herein did not assess outcomes beyond the post-initiation treatment visit as there is significant variability in patient scheduling during the maintenance treatments.

Tolerability and safety were assessed during and immediately following each infusion. Tolerability was assessed by capturing spontaneously reported treatment-emergent adverse events (e.g., nausea, dizziness, depersonalization etc.). Safety assessments were conducted by the anesthesiologists and staff nurse, and included assessment of vital signs (e.g., blood pressure), as well as oxygen saturation and pulse oximetry. In addition, the Clinician-Administered Dissociative States Scale (CADSS) was used to evaluate dissociative symptoms and severity immediately upon completion of ketamine infusion (i.e. at 40–45 min post-infusion initiation).

Herein, we report on 213 male and female outpatients' (M_{age} = 45, age range: 18–82) with either MDD or BD, who received care at the CRTCE from July 2018 to November 28, 2019. This analysis was approved by a community Institutional Review Board and registered under NCT04209296 on the clinicaltrials.gov website.

2.2. Data collection, reporting and analysis

All collected data were de-identified, stored on REDCap, and kept separate to the electronic medical records of the patient (Obeid et al., 2013). All clinical measures were recorded in digital form and administered at point of care using an iPad, with direct data entry into the REDCap platform. The tolerability and safety measures were captured at point-of-care with a paper form and were then entered digitally by the CRTCE staff.

The primary outcome was the change in the total QIDS-SR_{16} score from baseline (i.e., infusion 1) to the post-initiation treatment visit. Secondary outcomes were quartile response rates (i.e., ≥75%, ≥50% and ≥25% change in QIDS-SR_{16} baseline score compared to each subsequent infusion) and remission rates (i.e. QIDS-SR_{16} total score ≤ 5 at any post-baseline infusion visit). Additional secondary outcomes were changes from baseline to the post-initiation treatment visit in the QIDS-SR_{16} suicidality item, total GAD-7, and SDS scores. We also report spontaneously reported treatment-emergent adverse events, as well as change from baseline to endpoint in CADSS total score. An exploratory analysis was conducted to determine whether changes in depression severity were independent of dissociative symptoms severity, as measured by CADSS. Moreover, depersonalization and derealization subdomain items, as originally reported in Bemner and colleagues (1998) of the CADSS were compared to the spontaneously reported treatment-emergent adverse events to evaluate concordance (Bremner et al., 1998).

Accommodation for missing data and unequal timing between study visits was handled using a mixed model, implemented within GraphPad Prism 8.0. A compound symmetry covariance matrix was used, and the data is fit using Restricted Maximum Likelihood (REML) with an alpha set to 0.05. The mixed model analyses controlled for sex and age. Pairwise comparisons were evaluated using a Bonferroni multiple comparisons test. A linear regression was used to determine whether change in QIDS-SR_{16} score was independent of dissociation severity, where the dependent variable was change in QIDS-SR_{16} from baseline to post-initiation treatment visit, and the predictor was the average CADSS score over four infusions. Spearman correlation test was used to evaluate the association between CADSS depersonalization and derealization subdomain scores and reported adverse events. Statistical analyses were conducted using R version 3.4.0, using the dplyr and tidyr packages, and GraphPad Prism 8.0.

3. Results

A total of 213 patients received IV ketamine at the CRTCE when this analysis was conducted. Six patients were excluded from the analyses due to the absence of baseline and post-infusion QIDS-SR_{16} scores. The final sample consisted of 207 participants, for a total of 764 observation points. For the safety analysis, complete CADSS data were available for 163 patients, representing a total of 553 observation points. 41% of patients received 0.5 mg/kg for all four infusions as part of the initial protocol, while 59% of patients received a dose optimization to

Table 1
Demographic data of the included sample of patients.

Characteristic	(*n* = 213)
Sex, *n* (%)	
Male	95 (44.6)
Female	118 (55.4)
Mean Age in years (*SD*)	45 (15)
Mean BMI (Kg/m2) (*SD*)	28.04 (6.55)
Primary Diagnosis, *n* (%)	
Major Depressive Disorder	183 (85.9)
Bipolar Disorder	30 (14.1)
Medical Comorbidities, *n* (%)	
Obsessive Compulsive Disorder	9 (4.2)
Post-Traumatic Stress Disorder	16 (7.5)
Generalized Anxiety Disorder	33 (15.5)
Social Anxiety Disorder	9 (4.2)
Personality Disorder	11 (5.2)
Mean Number of Prior Lifetime Antidepressants Trials (*SD*)	6.02 (4.11)
Mean Number of Antidepressants at Time of Infusion (*SD*)	1.41 (1.71)

0.75 mg/kg for infusions 3 and 4. Patient sex, age, BMI, primary diagnosis, medical comorbidities, mean number of prior and current antidepressants are reported in Table 1.

3.1. Depressive symptom severity

Overall, there was a significant effect of treatment on QIDS-SR_{16} total score: $F(4.0, 465.1) = 53.0$, $p < 0.0001$, Cohen's $f = 0.67$ (Table 2). There was a significant reduction in QIDS-SR_{16} score from baseline to all subsequent timepoints ($ps < 0.0001$; Fig. 2A). Moreover, there was a significant reduction in QIDS-SR_{16} score from the post-infusion 1 to post infusion 3 ($p < 0.0001$) and post-initiation treatment visit ($p < 0.0001$). There was also a significant improvement in depression score (i.e., reduction) in the post-infusion 2 score compared to the post-infusion 3 ($p = 0.02$) and post-initiation treatment visit ($p = 0.03$). There were no significant differences between the post-infusion 3 and post-initiation treatment visit scores ($p > 0.9$.).

The results of the responder and remitter analysis are presented in Table 2. At follow-up, approximately one week after the fourth infusion, 4 (3.6%) patients had a 75% reduction in depressive symptoms; 26 (27%) patients achieved a response of ≥50%; and 55 (50%) individuals improved by at least 25%. 14 (13%) patients met remission criteria.

A sub-analysis was completed in order to determine if the dose optimization benefited patients who had a poor clinical response following two infusions at the index dose. In total, 88 patients remained on the index dose while 125 individuals received 0.75 mg/kg at infusion 3 and 4. There was a significant group by timepoint interaction $F(4, 549) = 26.6$, $p < 0.0001$, $\eta_p^2 = 0.16$; a significant main effect of group $F(1, 205) = 20.4$, $p < 0.0001$, $\eta_p^2 = 0.09$; and a significant main effect of time $F(3.1, 428.2) = 88.20$, $p < 0.0001$, $\eta_p^2 = 0.38$. Between-group comparison indicated that the patient who remained at the index dose had a significantly lower QIDS-SR_{16} total score at the post-infusion 1 ($p < 0.0001$), post-infusion 2 ($p < 0.0001$), and post-infusion 3 ($p < 0.05$). There was no statistical difference in depression score at the post-initiation treatment visit between the two groups (Fig. S1).

3.2. Suicidality (Fig. 2B)

The QIDS-SR_{16} suicidality item score significantly decreased over time with treatment, $F(4.0, 461.7) = 25.4$, $p < 0.0001$, Cohen's $f = 0.46$ (Table 2). There was a significant reduction in suicidality score from baseline to post-infusion 1, post-infusion 2, post-infusion 3, and post-initiation treatment visit score ($ps < 0.0001$). Additionally, there was a significant improvement from the post-infusion 1 score to post-infusion 3 ($p = 0.001$) and post-initiation treatment visit scores ($p = 0.03$).

Overall, 28 (13%) patients presented at baseline without exhibiting any symptoms of suicidality (i.e., QIDS-SR_{16} suicidality item = 0). Suicidality scores were re-analyzed with only patients who had a score ≥ 1, and there remained a significant decrease over time with treatment $F(4.0, 394.9) = 27.6$, $p < 0.0001$, Cohen's $f = 0.52$ (Fig. 2B). There was a significant reduction in this score from baseline ($M = 1.9$, SE = 0.08) to post-infusion 1 ($M = 1.5$, SE = 0.08; $p < 0.0001$), post-infusion 2 ($M = 1.3$, SE = 0.08; $p < 0.0001$), post-infusion 3 ($M = 1.1$, SE = 0.09; $p < 0.0001$), and post-initiation treatment ($M = 1.2$, SE = 0.09; $p < 0.0001$). Moreover, suicidality symptoms significantly decreased from post-infusion 1 to post-infusion 3 ($p = 0.001$) and post-initiation treatment ($p = 0.02$).

3.3. Anxiety symptoms (Table S2)

A total of 188 patients had available scores in the GAD-7. There was a significant effect of treatment on anxiety score, measured by the GAD-7, $F(2, 192.8) = 40.6$, $p < 0.0001$, Cohen's $f = 0.64$. After adjusting using Bonferroni correction, the results indicate that there was a significant decrease from baseline anxiety score to post-infusion 3 and post-initiation (ps < 0.0001) scores (Figure 2C), as measured by the GAD-7. There was no significant difference between the post-infusion 3 and post-initiation treatment visit GAD-7 scores ($p > 0.9$).

Table 2
Mean QIDS-SR_{16} total score and suicidality item score and number of responders and remitters following infusions.

	Baseline	Post-infusion 1[a]	Post-infusion 2[b]	Post-infusion 3[c]	Post-initiation treatment visit[d]
QIDS-SR_{16} total score					
Total number	190	168	162	137	107
Number of missing values	17	29	45	70	100
Mean QIDS-SR_{16} Score (SE)	18.54 (0.34)	15.86 (0.45)	14.96 (0.48)	13.31 (0.50)	12.68 (0.54)
Mean QIDS-SR_{16} Change from Baseline (SE)	N/A	2.69 (0.32)	3.59 (0.36)	5.23 (0.39)	5.86 (0.48)
QIDS-SR_{16} suicidality score					
Mean QIDS-SR_{16} Suicide (SE)	1.58 (0.07)	1.27(0.08)	1.13 (0.08)	1.02 (0.09)	1.00 (0.10)
Mean QIDS-SR_{16} Suicide Item Change from Baseline (SE)	N/A	0.31 (0.05)	0.44 (0.06)	0.56 (0.07)	0.59 (0.07)
Responder and remitter analysis					
Total number	N/A	166	157	134	111
Responder ≥ 25%	N/A	49 (30%)	55 (35%)	69 (52%)	55(50%)
Responder ≥ 50%	N/A	18 (11%)	24 (16%)	28 (21%)	26 (27%)
Responder ≥ 75%	N/A	1 (0.6%)	5 (3.2%)	9 (6.7%)	4 (3.6%)
Remitter ≤ 5	N/A	6 (3.6%)	11 (7%)	16 (12%)	14 (13%)

a Data collected an average of 2.49 (± 1.00) days following baseline infusion.
b Data collected an average of 2.40 (± 0.71) days following 2nd infusion.
c Data collected an average of 2.49 (± 1.32) days following 3rd infusion.
d Data collected an average of 7.83 (± 9.27) days following 4th infusion.

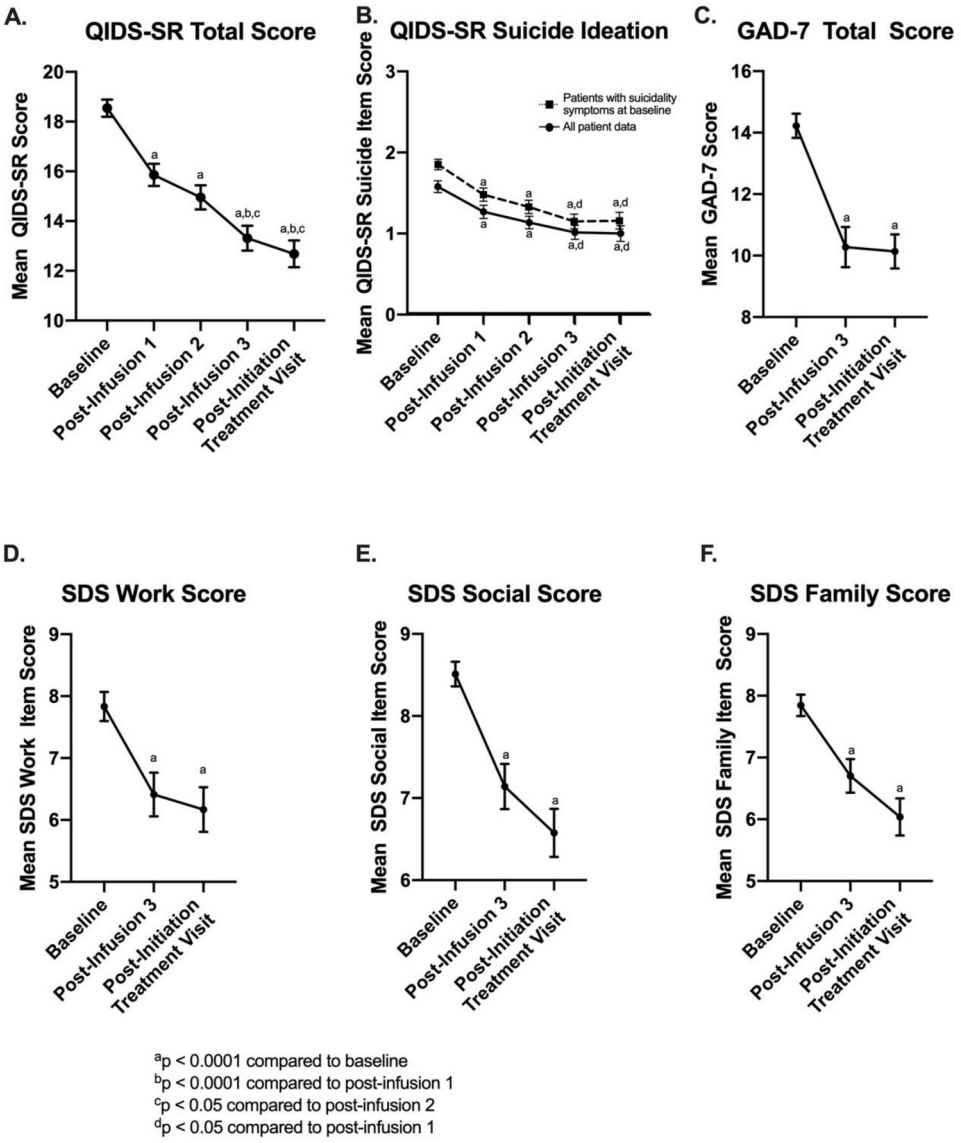

Fig. 2. (A) Mean (±SE) QIDS-SR$_{16}$ Score over the acute protocol. (B) Mean (±SE) QIDS-SR$_{16}$ Suicidality Item Score in all patients and those who reported suicidality at baseline. (C). Acute changes to mean anxiety score following ketamine infusion. (D). Acute change to the SDS Work Score. (E). Acute change to the SDS Social Score. (F). Acute change to the SDS Family Score.

3.4. General functioning (Table S2)

General functioning was measured using the SDS (n_{SDS} = 168). There were significant treatment effects in the SDS Work score, F(2.0, 183.1) = 14.5, $p < 0.0001$, Cohen's $f = 0.38$, SDS Social score, F(2.0, 221.7) = 22.7, $p < 0.0001$, Cohen's $f = 0.44$, and SDS Family score, F (2.0, 211.7) = 19.5, $p < 0.0001$, Cohen's $f = 0.42$. The SDS Work scores decreased (i.e. improved) from baseline to the post-infusion 3 score and post-initiation treatment visit score ($ps < 0.0001$; Fig. 2D). Similarly, the SDS Social score improved from baseline to both post-infusion 3 and post-initiation treatment visit ($ps < 0.0001$) scores (Fig. 2E). Finally, pairwise comparison of the SDS Family score suggested a decrease in score from baseline to both the post-infusion 3 and post-initiation treatment visit ($p < 0.0001$) scores (Fig. 2F). There were no significant differences between post-infusion 3 and post-initiation treatment visit for Work ($p > 0.9$.), Social ($p = 0.2$), or Family scores ($p = 0.7$).

3.5. Safety and tolerability

No adverse events were reported for patients withdrawing from restricted medications (i.e., MAOIs). Overall, IV ketamine was well tolerated, as captured by spontaneously reported treatment-emergent adverse events (Table 3). Drowsiness (57.1%) and dizziness (48.2%) were the two most commonly reported adverse events experienced during and immediately after infusion. Treatment-emergent adverse events were transient and significantly attenuated post-infusion at time of discharge from the CRTCE. No relationships emerged between demographic factors (i.e., age and gender) and reported treatment adverse events. Average systolic blood pressure increased by 18 mmHg while the average diastolic blood pressure increased by 14 mmHg (Fig. 3A and 3B). A total of 151 patients experienced at least one infusion with a rise in systolic blood pressure >20 mmHg or a rise in diastolic blood >10mmgHg rise in diastolic blood pressure. On average, the hemodynamic effect of ketamine subsided within 20 min following the completion of an infusion. Eleven infusions (1.6% of all treatments) required the administration of antihypertensive medication to manage blood pressure. Overall, nine patients (4.2%) dropped out following one

Table 3
Treatment-emergent adverse events reported across all infusions.

Side effect	During infusion, *n* (%)	After infusion, *n* (%)
Nausea	47 (13.9)	38 (11.1)
Vomiting	1 (0.29)	8 (2.50)
Dizziness	153 (48.2)	152 (49.2)
Headache	42 (13.2)	59 (19.3)
Double vision	69 (20.8)	58 (18.8)
Blurred vision	105 (31.9)	92 (29.8)
Drowsiness	184 (57.1)	164 (53.1)
Confusion	141 (43.5)	78 (25.1)
Jerky muscle movements	18 (5.42)	7 (2.3)
Depersonalization	113 (38.2)	54 (17.6)
Derealization	119 (40.8)	51 (16.7)

infusion or two infusions at the index dose due to intolerability of IV ketamine.

Dissociation severity, as measured by the CADSS, was highest immediately following the baseline infusion ($M = 10.52$, SE = 0.78; Fig. 3C). All subsequent infusions demonstrated a significant attenuation of dissociation severity compared to baseline, despite dose optimization to 0.75 mg/kg at infusions 3 and 4. There were no significant differences in CADSS score between infusion 2 ($M = 6.68$, SE = 0.67), infusion 3 ($M = 7.05$, SE = 0.65), or infusion 4 ($M = 7.49$, SE = 0.69). A linear regression indicated that the change in QIDS-SR_{16} total score could not be predicted by mean CADSS dissociation severity, $F(1, 70) = 1.762$, $p = 0.189$, Cohen's $f = 0.10$, suggesting the two variables are independent. There was a significant correlation between the CADSS depersonalization items score and spontaneous reported treatment-emergent adverse events during infusion ($r_s(295) = 0.477$, $p < 0.0001$) and after infusion ($r_s(305) = 0.460$, $p < 0.0001$). Moreover, there was a significant association between the CADSS derealization items and the adverse events reported during ($r_s(291) = 0.357$, $p < 0.0001$) and after infusion ($r_s(303) = 0.382$, $p < 0.0001$).

4. Discussion

Adults with TRD receiving IV ketamine at the CRTCE experienced a rapid reduction in depressive symptom severity. In addition to a significant improvement observed on the QIDS-SR_{16} total symptom severity, a significant improvement was also noted when defining improvement according to the response and/or remission criteria. It is noteworthy that the response and remission rates that we have observed are lower than what has been reported by randomized, double-blind, placebo-controlled IV ketamine studies. For example, a Canadian trial of 41 individuals reported that following six repeated ketamine infusions, 59% of participants met criteria for response (i.e., decrease by ≥50% in the Montgomery-Asberg Depression Rating Scale (MADRS) total score) and 23% achieved remission (i.e., MADRS ≤ 10; (Phillips et al., 2019). Similarly, a separate study reported an overall response rate of 71% following six infusions (Murrough et al., 2013). Notwithstanding, the overall remission rate (i.e., 13%) observed within our sample at the post-initiation treatment visit was equal to the rates reported in the STAR*D study of patients receiving monoamine-based antidepressants in TRD patients (Rush et al., 2006). It should be further noted, that the majority of patients in our sample had a level of treatment resistance far exceeding what was operationalized in STAR*D trial, insofar as the average number of failed antidepressants over a patient's lifetime was 6.02. On average, patients reported a 5.9 point reduction in QIDS-SR_{16} score following four infusions, suggesting a reclassification of depressive severity from severe to moderate (Rush et al., 2003).

Sub-analysis results comparing patients who remained on the index dose versus those who were optimized to 0.75 mg/kg had a similar QIDS-SR_{16} scores at endpoint. Indeed, extant literature suggests early intervention, given an insufficient response, provides patients with a

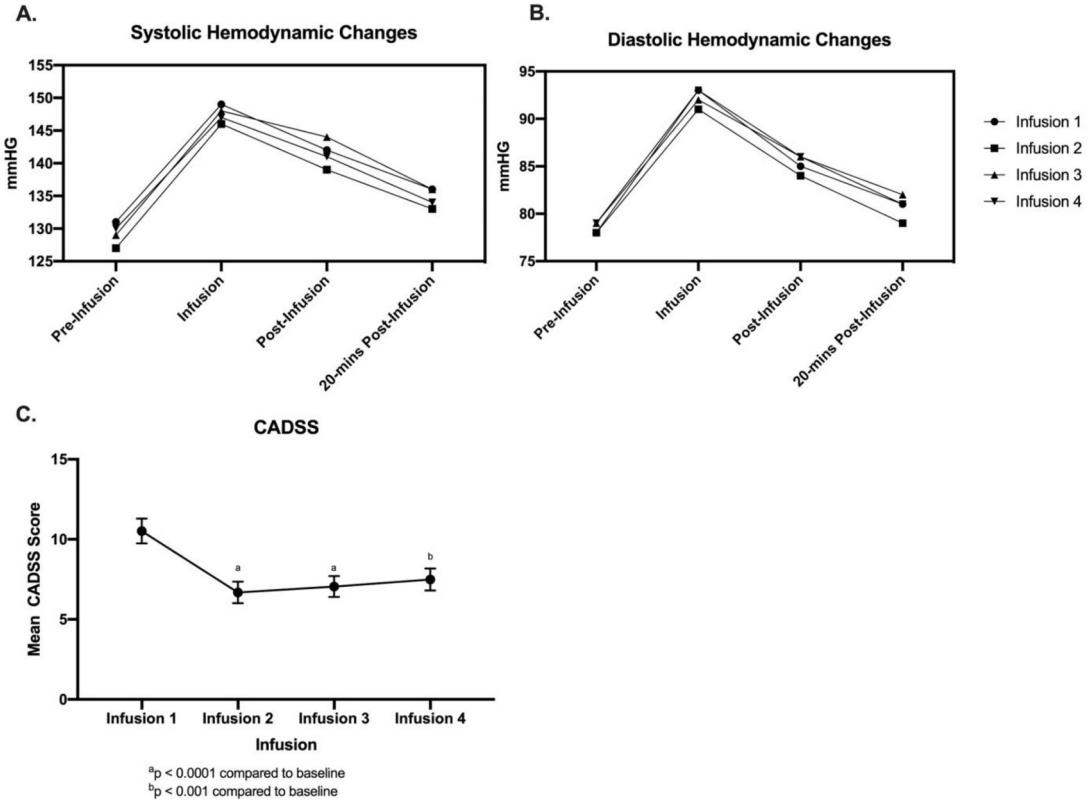

Fig. 3. (A) Systolic hemodynamic change over the course of each infusion. (B) Diastolic hemodynamic change over the course of each infusion. (C). Mean change in dissociation severity, as measured by the CADSS, over four infusions.

better opportunity for symptom amelioration (Kudlow et al., 2014).

Major Depressive Disorder and BD are psychiatric disorders most often associated with suicide completion. Available evidence suggests that ketamine reduces suicidality (Grunebaum et al., 2018; Ionescu et al., 2016). In addition, it has been suggested that the anti-suicide effect of ketamine in MDD is independent of the effect of total depression symptom severity (Lee et al., 2016). Herein, we observed that ketamine infusion treatment was significantly associated with reduced suicidal ideation as measured by the suicidal ideation item of the QIDS-SR_{16}. We did not, however, have data regarding the relationship between IV ketamine treatment and non-suicidal self-injury. Importantly, no patients reported amplification of pre-existing suicidal ideation with ketamine treatment.

In addition to a mitigation of depressive symptoms, a significant reduction was also observed in concurrent anxiety symptomatology. The 4.1 point reduction in GAD-7 suggests a similar reduction from severe anxiety to moderate (Spitzer et al., 2006). This observation is in accordance with other published studies on ketamine in adults with MDD, wherein a significant reduction in anxiety symptoms was noted (Ionescu et al., 2015; Salloum et al., 2019). The relevance of reducing anxiety symptoms in adults with MDD is substantiated by their co-morbid prevalence, association with illness complexity (e.g., treatment-resistant depression), and suicidality (Fava et al., 2004; Wiethoff et al., 2010). Although ketamine has been less studied in adults with primary anxiety disorders, available randomized-control trial evidence is suggesting that ketamine may be efficacious in adults with select anxiety disorders (e.g., Social Anxiety Disorder, Generalized Anxiety Disorder; Glue et al., 2019). Moreover, repeated ketamine infusions have been associated with improvements in neurocognition in anxious TRD patient (Liu et al., 2019).

It is notable, that despite the treatment-resistance of the patients included in this analysis, significant improvement was seen on the total SDS as well as all subdomain scores. Hitherto, insufficient reporting of functional outcomes in adults with MDD receiving ketamine has been a limitation with respect to interpreting the clinical relevance of controlled trial results. The notion that an antidepressant intervention could rapidly improve interpersonal, psychosocial, and workplace functioning has enormous cost-effectiveness implications, as well as appeal to patients.

With respect to the tolerability and safety of ketamine, the type and percentage of patients experiencing side effects (e.g., gastrointestinal, sedation) were similar to what has been reported in the controlled-trial literature (Feifel et al., 2017; Short et al., 2018). With respect to safety herein, the percentage of individuals requiring antihypertensive treatment for blood pressure elevation and/or dissociation as a treatment-emergent adverse event was relatively small, often transient and consonant with available literature (Acevedo-Diaz et al., 2019). Moreover, scores on the CADSS scale indicate that the severity of dissociation in most cases was mild. In keeping with published literature, we also observed an attenuation of CADSS-measured dissociation severity as a function of infusion frequency. We did, however, notice a plateau in dissociation severity attenuation after the second infusion, which may be a function of the dose optimization that took place at that time (Coyle and Laws, 2015; Phillips et al., 2019; Singh et al., 2016). Moreover, despite the fact that the sub-population of adults in our sample with BD was relatively small ($n = 30$), we did not observe clinical evidence of emergence of mania or psychosis.

It has been suggested that the CADSS is an insufficient safety measure with respect to ketamine-associated dissociation as it does not fully capture the multidimensionality and phenomenology of dissociation related to ketamine (van Schalkwyk et al., 2018). We observed that individuals who spontaneously reported depersonalization during and after infusion were more likely to score higher on the CADSS depersonalization measures. Similarly, there was a significant correlation between patients who spontaneously reported derealization during and after infusion and a higher score on the CADSS derealization items. Finally, consistent with other studies, the improvement in depressive symptoms, measured by the QIDS-SR_{16}, was independent of dissociation severity (Williams et al., 2018).

The strengths of this study are primarily a function of representativeness of the patients who were included. As this is a naturalistic dataset with minimal exclusion criteria, allowing for patients to be enrolled with comorbidity, suicidality, and disparate concomitant medications reflects the type of patient who would be most likely to utilize ketamine treatment. To our knowledge, our study represents one of the larger samples of well-characterized adults with MDD or BD experiencing TRD receiving treatment at a community-based center. An additional strength is the reliance on the QIDS-SR_{16} as the primary outcome measure. The QIDS-SR_{16} has excellent conceptual coverage of depression and psychometric properties (Rush et al., 2003). Moreover, it is a testable hypothesis that the QIDS-SR_{16} may also be more suitable as an outcome measure for rapid-onset treatments, wherein observable improvement may have a different temporal course when compared to subjective improvement.

A major limitation of our study is that it is a retrospective analysis without rigorous control of many potential confounding variables. For example, the possibility of expectancy would likely be significant with such a novel intervention for depression. Also, the data presented solely consisted of patients who received open-label IV ketamine infusion and, therefore, there was no control group used to compare the data. As this study was not a part of a clinical trial, there was a large amount of missing data due to participants skipping assessments or being lost to follow-up. Moreover, individuals receiving care at the CRTCE need to cover the full cost of the treatment prior to receiving the first infusion, resulting in a selection bias. An additional limitation is that although we had clinical metrics as well as safety and tolerability outcomes, there was insufficient capture of other outcomes relevant to patients (e.g. quality of life, cognition). Moreover, there was a high degree of variability in the number of days between the fourth infusion and the post-initiation treatment visit, largely due to patient scheduling reasons. This is a limitation, insofar, as the analysis does not have a consistent time-based endpoint and limits the interpretability of the outcomes at the timepoint. It should be also noted that we were unable to ascertain the immediacy of the antidepressant effect, as the QIDS-SR_{16} was administered at point of care, when patients were available for infusions. Moreover, dissociation severity, as measured by the CADSS, was only assessed after the infusion was completed due to patient intolerability during infusion.

Taken together, adult patients with TRD receiving IV ketamine experienced a rapid antidepressant effect. Patients receiving IV ketamine also reported antidepressant and anxiolytic effects, as well as improvements in functional outcomes. The safety and tolerability of IV ketamine was also observed, underscoring the importance of a multidisciplinary best-practices approach to providing ketamine in TRD.

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Authors RSM, NBR, and JDR developed research hypothesis, study design, conducted data analysis and wrote the final draft of the manuscript. Authors RSM, YL, MS, KK, AKA, AA, EHC, WS, and JDR were involved with data collection. All authors contributed to the final manuscript proofreading, edits and approval for submission. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.05.088.

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