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ORIGINAL RESEARCH

Safety and tolerability of IV ketamine in adults with major depressive or bipolar disorder: results from the Canadian rapid treatment center of excellence

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ABSTRACT

Objectives: Rigorous clinical trials suggest ketamine is safe and well-tolerated in patients with treatment-resistant depression (TRD). There is a paucity of data on the safety and tolerability of ketamine in community-based clinics treating patients with TRD.

Methods: Retrospective data was analyzed from 203 patients with TRD who received repeat-dose IV ketamine. Safety was operationalized as hemodynamic changes. Tolerability was evaluated through the reporting of adverse events and dissociation symptom severity, as measured by the Clinician-Administered Dissociative States Scale.

Results: Ketamine was well-tolerated, with less than 5% of patients withdrawing due to tolerability concerns. Blood pressure significantly increased during infusion, with 44.3% meeting criteria for treatment-emergent hypertension (i.e., blood pressure ≥ 165/100 mmHg). 12% of patients exhibiting hypertension required pharmacological intervention. The most frequently reported adverse events included drowsiness (56.4%), dizziness (45.2%), dissociation (35.6%), and nausea (13.3%). Dissociation severity significantly attenuated after the first infusion, but plateaued for subsequent infusions.

Conclusion: Intravenous ketamine was safe and well-tolerated. Hypertension was commonly observed and was often transient. Dissociation was most frequently reported after the first infusion but remained a consistent but not treatment-limiting adverse event thereafter. No patients exhibited psychosis, mania, or new onset suicidality with IV ketamine.

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Ketamine; treatment-resistant depression; major depressive disorder; bipolar disorder; tolerability; safety

1. Introduction

Major depressive disorder (MDD) is a leading cause of disability in both high- and low-income countries [1]. The majority of individuals with MDD receiving conventional antidepressants do not achieve full syndromal recovery, contributing to the illness burden [2,3]. The dissociative anesthetic and N-Methyl-D-Aspartate (NMDA) receptor antagonist, ketamine, has demonstrated rapid and robust efficacy in adults who have not experienced sufficient syndromal relief following multiple antidepressant treatment trials (i.e., treatment-resistant depression [TRD]) [4–7].

Notwithstanding the relatively well-established antidepressant efficacy of ketamine in TRD, as well as preliminary evidence supporting its anti-suicidality effects, the safety and tolerability of long-term ketamine treatment is insufficiently characterized. Results from short-term (i.e., < 2 weeks) randomized controlled trials indicate that ketamine is generally well tolerated and is safe [8,9]. The most frequently reported treatment-emergent adverse events and safety concerns include dissociation, nausea, blood pressure elevation, tachycardia, and headache [9].

Patients receiving sub-anesthetic doses of ketamine describe sensations of depersonalization, derealization, distortions of time or space, and transient amnesia [10]. The medication also has sympathomimetic effects on the cardiovascular system, thereby increasing heart rate and blood pressure [11,12]. As a result, blood pressure and heart rate must be carefully monitored during ketamine administration to avoid cardiovascular complications. Notably, the risk of respiratory depression is lower with ketamine than with other anesthetics and sedatives [13]. Other frequently reported adverse events included drowsiness, dizziness, nausea and vomiting [12].

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Trial registration: NCT04209296

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Supplemental data for this article can be accessed here.

Herein, we sought to determine the safety and tolerability of intravenous (IV) ketamine after repeat dose administration in an outpatient clinic providing care to adults with TRD. Given that extant data were derived from small clinical trial samples, the impetus for this analysis is provided by the need for real-world safety and tolerability data on a large sample of patients representative of TRD.

2. Patients and methods

2.1. Participants and study design

Patients included in this *post-hoc* analysis received repeat-dose IV ketamine infusions at the Canadian Rapid Treatment Center of Excellence (CRTCE) in Mississauga, Ontario, Canada, between July 2018 and December 2019. The CRTCE is the premier clinic in Canada to provide IV ketamine, outside of clinical trials, as a treatment for adults (aged ≥ 18 years) with TRD. Ketamine has not received approval for its use outside of anesthesia. As such, the cost of infusion is the responsibility of the patient or paid via private insurance plans for treatment.

Individuals were referred to the CRTCE by primary care physicians, psychiatrists, or nurse practitioners. The primary focus of the clinic was to treat intractable depressive symptoms, within the context of MDD and BD. Patients presenting with post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) were also eligible for treatment, as long as a depressive episode was the chief complaint. In order to be eligible, patients must meet Stage 2 treatment resistance or higher (i.e., failure of at least two adequate antidepressant trials of different medication classes) [14]. Exclusion criteria included inability to provide informed consent or a diagnosis of dementia, psychosis, and/or active substance or alcohol use disorder.

If a patient was deemed eligible based on the aforementioned criteria, the clinic provided a multidisciplinary approach to treatment. The staff psychiatrist was responsible for confirming patient diagnosis and assessing the appropriateness of IV ketamine treatment. If approved, the anesthesiologists reviewed patient medical history for unstable medical conditions (e.g., uncontrolled hypertension, supraventricular tachycardia, history of untreated seizure). The CRTCE staff also included registered nurses, clinical and research coordinators, and pharmacists responsible for providing care consistent with the American Psychiatric Association Consensus statement regarding safe administration of ketamine [15].

Ketamine was delivered adjunctively to current concomitant medications in order to attempt to increase patients' acceptability and feasibility of treatment. However, individuals currently prescribed monoamine oxidase inhibitors (MAOIs) were asked to taper two weeks prior to receiving ketamine in order to avoid the risk of serotonin syndrome. Patients undergoing any MAOI taper were closely monitored by their referring physician and the CRTCE. Moreover, patients on benzodiazepines or naltrexone were not permitted to take the medication 12 hours before and after the infusion, due to existing evidence that these medications may attenuate the antidepressive effect [16,17]. In order to minimize the potential of hazardous drug-drug interactions, patients were asked not to take any medications six hours prior to the infusion and four hours after infusion.

2.2. Ketamine administration protocol

Patients received a total of four infusions over one-to-two weeks. The first two infusions were dosed at 0.5 mg/kg. If patients experienced a suboptimal response to ketamine (as determined by the Quick Inventory for Depressive Symptomatology-Self Report 16-item), they were given the option to increase their dose to 0.75 mg/kg for the remaining two infusions. Patients remained at the index dose if they experienced a clinically significant antidepressant effect (i.e., ≥20% improvement in depression scores), had difficulty tolerating the index dose, or if they preferred to remain at the lower dose. All infusions were administered by an anesthesiologist, who diluted the medication into 0.9% saline solution and administered the treatment over 40–45 minutes. Patients were then monitored by nursing staff until the acute effects of ketamine subsided (up to two hours) and they were safe to be discharged.

2.3. Systematic adverse event monitoring

Prior to the start of infusion, patient baseline blood pressure, heart rate and standard telemetry (i.e., respiratory rate and oximetry) were collected by anesthesiologists. Patient safety was continually monitored and recorded at 5-minute intervals throughout the infusion. The highest heart rate, systolic, and diastolic blood pressure during infusion were recorded into the dataset for analysis. Patient cardiovascular and respiratory monitoring continued until 20 minutes post-infusion, wherein most patients' blood pressure returned to baseline levels.

Adverse events were assessed by the anesthesiologist and nurse staff both during infusion and directly after treatment. While patients are receiving the infusion, they are systematically asked about symptoms (Figure S1). The terms 'depersonalization' and 'derealization' are also described on Figure S1 for patients not familiar with them. The adverse events were then reassessed 20 minutes after the infusion. In addition to the treatment-emergent adverse events, the Clinician-Administered Dissociative States Scale (CADSS) was used to further characterize current symptoms of dissociation severity. A score greater than 4 is typically indicative of dissociation [18]. A nurse administered the CADSS assessment within 5 to 10 minutes after the infusion.

2.4. Data collection, reporting and statistical analysis

All adverse events and safety data were collected at point-of-care by clinic nurses and anesthesiologists on a paper form developed by the CRTCE and entered into the REDCap platform by research staff [19,20]. All data were de-identified prior to entry and stored separately from the patients' electronic medical record. Retrospective data analysis was approved by a community institutional research ethics board and is registered on clinicaltrial.gov (NCT04209296).

The co-primary outcomes of this retrospective analysis were to evaluate the safety and tolerability of IV ketamine in

patients with TRD. Safety was operationalized using transient changes in blood pressure and heart rate. The preinfusion, during infusion, post infusion blood, and 20-minute post-infusion pressure and heart rate were each averaged across the four infusions and these average values were used for analysis. The number of patients who met treatment-emergent hypertension are reported. As part of the CRTCE clinical protocol, hypertension was defined as a systolic blood pressure greater than or equal to 165 mmHg or diastolic blood pressure greater than or equal to 100 mmHg. If patients presented with hypertension during infusion, the decision was made by the anesthesiologist whether pharmacological intervention was necessary.

Tolerability was operationalized as dissociative symptom severity, as measured by the CADSS. These were assessed at all four timepoints: (1) infusion 1, (2) infusion 2, (3) infusion 3, and (4) infusion 4. The 23-item CADSS was used to evaluate three domains: amnesia (sum of items 14, 15, and 22), depersonalization (sum of items 3–7, 20, and 23), and derealization (sum of items 1, 2, 8–13, 16–19, and 21) [21]. Tolerability also evaluated treatment-emergent adverse events during infusion and 20 minutes post-infusion. In addition, ketamine adherence was evaluated by the number of patients who withdrew from treatment due to medication intolerability. Patient safety, tolerability, and adherence are reported following each infusion. Dissociation severity was captured through the use of a patient-reported treatment-emergent adverse event form and through the patient-reported CADSS.

Treatment-emergent adverse events were collected during and after infusion. These adverse events were separated into three categories: gastrointestinal symptoms, neurological symptoms and dissociative symptoms. Total number of reported symptoms at each infusion was reported.

Changes in blood pressure from pre-infusion to during infusion was evaluated using a paired-samples t test. A mixed model was used to evaluate whether the CADSS total, depersonalization, derealization, and amnesia scores changed across infusions controlling for age, sex, and infusion dose. Another mixed model was done in order to evaluate whether there was a difference in CADSS total and component scores between the two dosage groups (i.e., 0.5 mg vs 0.75 mg). The model terms for this analysis were *group, infusion*, and *group by infusion* interaction. For all mixed models, we used a compound symmetry covariance matrix and the data was fit using Restricted Maximum Likelihood. Sphericity was not assumed, so a Greenhouse-Geisser correction was applied. Individual item scores at each infusion were also reported. A linear regression was used to evaluate change in the total number of treatment emergent adverse events with each infusion. Data were analyzed using Graphpad prism 8.4.0. All data was evaluated with the alpha set to 0.05.

Regression analyzes were conducted to investigate the relationship between clinical outcome variables and the dissociation variables. The Quick Inventory for Depressive Symptomatology-Self Report (QIDS-SR_{16}) and the Generalized Anxiety Disorder 7-item (GAD-7) was completed by patients prior to beginning infusions (i.e., baseline) and one-week after completing a series of four infusions (i.e. post-ketamine treatment). Change in QIDS-SR_{16} total score and GAD-7 total score was calculated and used as the dependent variables in the linear regression. Four models were run for each dependent variable with the predictors as the average depersonalization, derealization, amnesia, or total scores. All regression models statistically adjusted for age, sex, and infusion dosage. Furthermore, spearman correlation analyzes were completed in order to evaluate whether there was an association between patient blood pressure and dissociation symptoms severity.

3. Results

3.1. Patient characteristics

A total of 203 participants received 723 IV ketamine infusions at the CRTCE between August 2018 and December 2019 and were included in these analyzes. Approximately 40% of patients (n = 81) did not have a dose optimization, receiving all four infusions at the index dose (i.e., 0.5 mg/kg), whereas 60% (n = 123) of patients received two doses at the index dose and subsequently received two optimized doses (i.e., 0.75 mg/kg). A total of 213 infusions were delivered at the optimized dose. Baseline characteristics for the patients included herein are reported in Table 1.

The overall attrition rate was 4.93% (n = 10) due to tolerability concerns. Five patients withdrew after a single infusion, 4 patients withdrew after two infusions, and one individual withdrew after the third infusion. Three patients stopped treatment due to intolerable nausea and 7 patients withdrew due to heightened anxiety due to dissociation symptoms. All patients withdrew due to intolerability of IV ketamine. Three infusions were postponed, two of which were due to a vasovagal response to the insertion of the IV line and one was due to a supraventricular tachycardia on the day of infusion. These patients were referred to a cardiologist in order to ensure it was safe to proceed with infusion.

3.2. Blood pressure and heart rate

There was a significant transient increase in mean blood pressure and heart rate during infusion. Specifically, systolic blood pressure rose by 17.9 ± 13.4 mmHg ($t[649] = -34.1$, $p < 0.0001$), diastolic pressure rose by 12.9 ± 10.3 mmHg ($t[647] = -32.1$, $p < 0.0001$; Figure 1(a)), and patients' heart rate increased by 8.4 ± 10.1 beats per minute ($t[628] = -20.8$, $p < 0.0001$; Figure 1B). Blood pressure and heart rate began

Table 1. Baseline characteristics of patients receiving IV ketamine infusion.

Patient Characteristics (n = 203)	
Sex n (%)	
Male	92 (45.3)
Female	111 (54.7)
Mean Age in Years (SD)	45.4 (14.9)
BMI (Kg/m^2) (SD)	28.29 (6.89)
Primary Diagnosis n (%)	
MDD	171 (84.2)
BD	24 (11.8)
PTSD	5 (2.5)
OCD	3 (1.5)
Mean Number of Prior Lifetime Antidepressant Trials (SD)	5.96 (4.19)
Mean Number of Antidepressants at time of Infusion (SD)	1.37 (1.60)

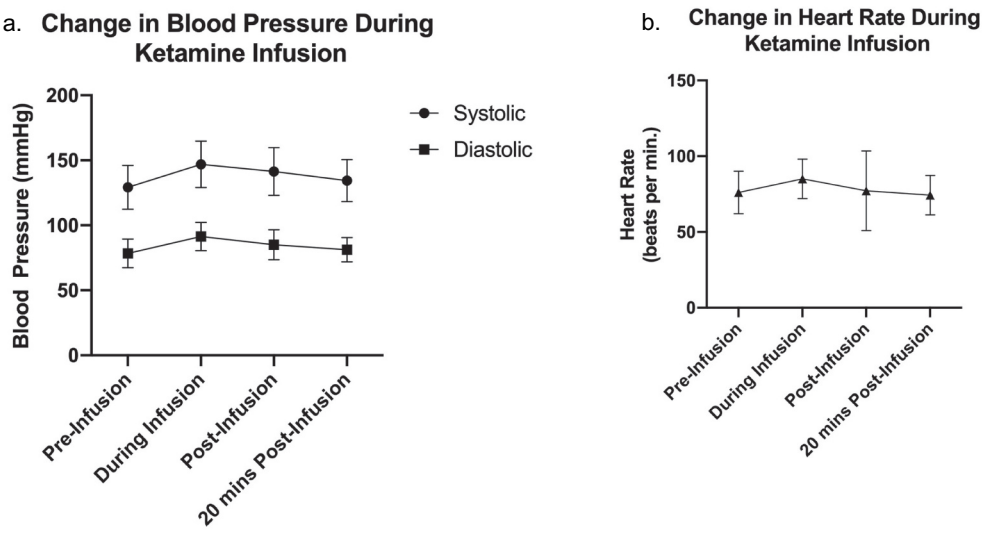

Figure 1. (a). Mean (SEM) systolic and diastolic blood pressure change over the course of infusion, with each timepoint representing the average across four infusions. (b). Mean (SEM) change in heart rate over the course of infusion, with each timepoint representing the average across four infusions.

to decline once one the infusion was completed, and by 20-minutes post-infusion most patients' cardiovascular measures had returned to within 10% of the baseline value.

Treatment-emergent hypertension was defined as a systolic blood pressure ≥ 165 mmHg or diastolic blood pressure ≥ 100 mmHg. A total of 153 infusions (21.2% of all infusions) across 90 patients met criteria for treatment emergent hypertension, however only 17 infusions (2.4% of all infusions) across 11 patients required the administration of antihypertensives. The anesthesiologists used labetalol (range 5–30 mg) to manage hypertension except for one infusion in which amlodipine 10 mg was administered.

3.3. Ketamine effect on dissociation, as measured by the CADSS

Dissociation symptom severity was assessed within 5 to 10 minutes following the completion of an infusion. After adjusting for age, sex, and infusion dosage, there was a significant main effect of infusion (F [3,480] = 13.3, $p < 0.0001$, Cohen's $f = 0.28$) (Figure 2(a)). Pairwise comparison indicated that there was a significant reduction in total dissociative severity from infusion 1 to infusion 2, infusion 3, and infusion 4 (ps < 0.0001). Pairwise comparisons between infusions 2, 3, and 4 did not suggest a significant difference in total score. Mean scores from individual CADSS items across infusions are shown in Table 2.

Symptoms of depersonalization were calculated through the summation of CADSS items 3–7, 20, and 23. There was a significant main effect of infusion (F [3,478] = 7.36, $p < 0.0001$, Cohen's $f = 0.20$) (Figure 2(b)) on symptoms of depersonalization. Subsequent pairwise comparisons suggested a significant reduction in symptoms from infusion 1 to infusion 2 ($p < 0.0001$), infusion 3 ($p = 0.003$), and infusion 4 ($p = 0.002$). No subsequent comparisons were significant from infusion 2 and onward.

Derealization symptom severity was assessed using the sum of CADSS item 1, 2, 8–13, 16–19, and 21 scores. The mixed model indicated a significant main effect of infusion (F [3,470] = 11.0, $p < 0.0001$, Cohen's $f = 0.25$) (Figure 2(c)). Similar to the depersonalization results, symptoms of derealization were most severe at infusion 1. Compared to the first infusion, symptoms were significantly reduced at infusion 2, infusion 3, and infusion 4 (ps < 0.0001).

Amnesia severity was quantified by summing items 14, 15, and 22 of the CADSS. A main effect of infusion was observed (F [3,481] = 7.750, $p < 0.0001$, Cohen's $f = 0.20$) (Figure 2(d)). Pairwise comparison indicated that symptoms of amnesia decreased from infusion 1 to infusion 2 ($p < 0.0001$). However, there were no significant differences between infusion 1 and infusion 3 ($p = 0.176$) or between infusion 1 and infusion 4 ($p = 0.849$). Moreover, symptoms of amnesia significantly increased between infusion 2 and 4 ($p = 0.008$).

A subanalysis was done in order to assess if patients receiving dose optimization at infusion 3 had a differential outcome on the CADSS total and component score than those who did not receive dose optimization. For the CADSS total score there was a significant main effect of infusion (F [3,454] = 16.47, $p < 0.0001$). The main effect of group (F [1,201] = 3.65, $p = 0.057$) and the group by infusion interaction (F [3,514] = 1.98, $p = 0.11$) were not significant (Figure S2A). For CADSS depersonalization score, there was a significant main effect of infusion (F [3,418] = 10.14, $p < 0.0001$), but no significant main effect of group (F [1,201] = 1.78, $p = 0.18$) or a group by infusion interaction (F [3,509] = 1.95, $p = 0.12$) (Figure S2B). In addition, the analysis of the CADSS derealization score yielded similar results. There was a significant main effect of infusion (F [3,474] = 13.52, $p < 0.0001$), but no significant main effect of group (F [1,201] = 2.80, $p = 0.09$) or a group by infusion interaction (F [3,501] = 0.64, $p = 0.58$) (Figure S2C). Regarding the CADSS amnesia subtotal score, there was a significant group by infusion interaction (F [3,514] = 2.68, $p = 0.046$) as well as a main effect of infusion

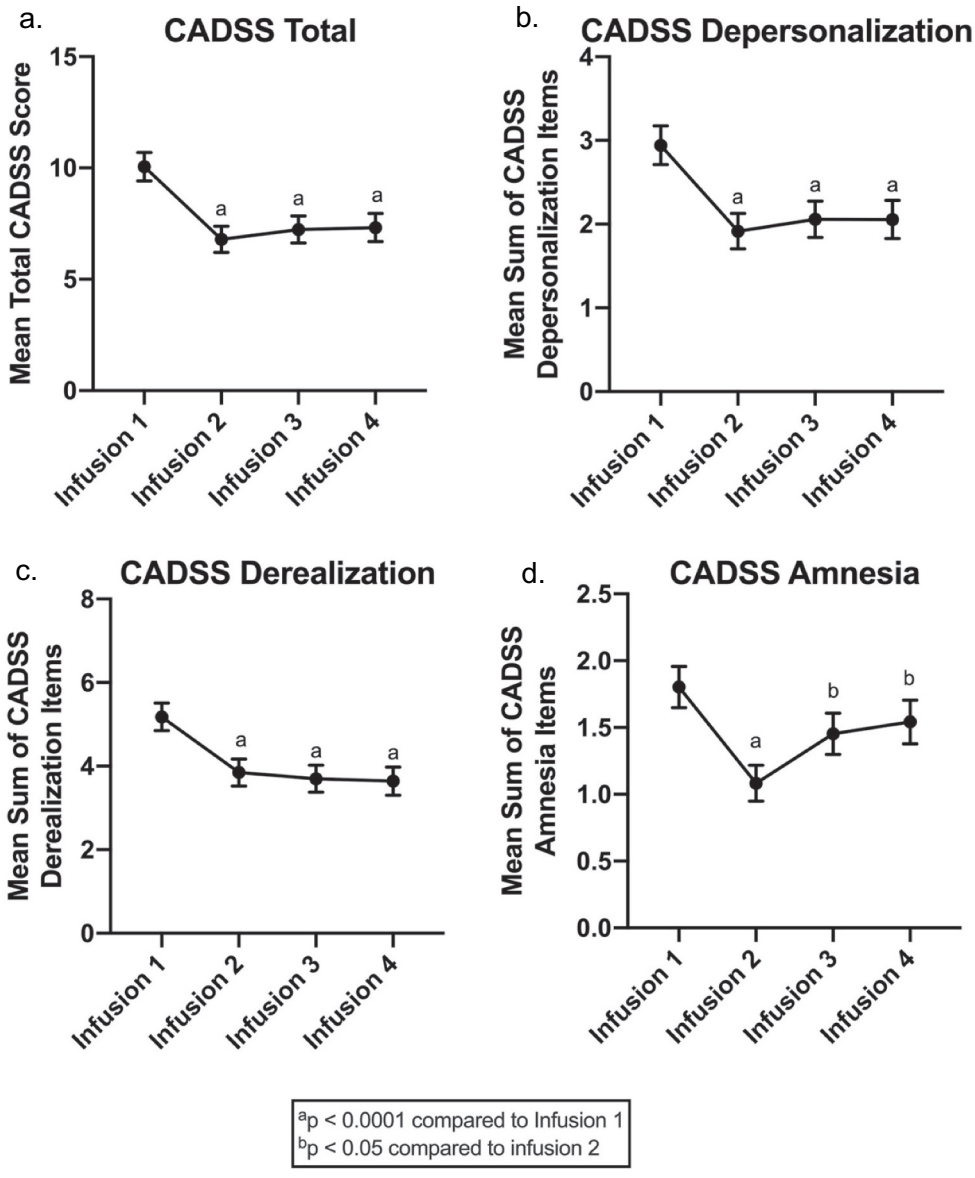

Figure 2. (a). Changes in mean (SEM) CADSS total score across four infusions. (b). Change in mean (SEM) CADSS depersonalization item score across four infusions. (c). Change in mean (SEM) CADSS derealization item score across four infusions. (d). Change in mean (SEM) CADSS amnesia item score across four infusions.

(F [3,479] = 6.93, p = 0.0002) and a main effect of group (F [1,201] = 5.29, p = 0.022)(Figure S2D). Subsequent Bonferroni corrected pairwise analysis indicated significant between group differences at infusion 3 (p = 0.015) and infusion 4 (p = 0.012).

Correlation analyzes indicated that systolic and diastolic blood pressure during infusion were not significantly correlated with the CADSS depersonalization (systolic: $r_s(707) = -0.04$, $p = 0.25$; diastolic: $r_s(707) = 0.01$, $p = 0.85$), derealization (systolic: $r_s(698) = -0.03$, $p = 0.46$; diastolic: $r_s(698) = 0.02$, $p = 0.55$), amnesia (systolic: $r_s(711) = 0.03$, $p = 0.49$; diastolic: $r_s(711) = 0.05$, $p = 0.21$), or total scores (systolic: $r_s(711) = -0.02$, $p = 0.56$; diastolic: $r_s(711) = 0.04$, $p = 0.32$).

3.4 Treatment emergent adverse events: self-reported gastrointestinal, neurological, dissociation gastrointestinal

Side effects of IV ketamine were recorded during infusion and during the post-infusion recovery period. The most commonly reported gastrointestinal symptom was nausea (13.3%). Patients who reported moderate or severe symptoms of nausea were provided antiemetics to manage the symptoms. Antiemetics, most commonly ondansetron or dimenhydrinate, were administered in 145 infusions (20.5% of all infusions). Patients reporting severe cases of nausea at the first infusion were offered ondansetron as a prophylaxis on subsequent infusions. The most frequent neurological adverse events included drowsiness (56.4%) and dizziness (45.2%). Both depersonalization (35.6%) and derealization (35.3%) were common dissociative symptoms (Table 3).

After controlling for infusion dose (i.e., 0.5 mg/kg vs 0.75 mg/kg), there was a significant negative correlation between the number of infusions and the total number of adverse events during infusion (r[722] = −0.15, p < 0.0001) and after infusion (r[772] = −0.10, p = 0.004).

Table 2. Mean CADSS individual item descriptive statistics at each infusion.

CADSS Item per Infusion	Mean (SD)
1 – Things moving in slow motion	
Infusion 1	0.98 (0.96)
Infusion 2	0.83 (0.92)
Infusion 3	0.70 (0.96)
Infusion 4	0.58 (0.85)
2 – Things seem unreal	
Infusion 1	0.93 (0.97)
Infusion 2	0.62 (0.86)
Infusion 3	0.76 (0.98)
Infusion 4	0.67 (0.89)
3 – An experience separating you from what is happening	
Infusion 1	0.44 (0.75)
Infusion 2	0.29 (0.70)
Infusion 3	0.31 (0.66)
Infusion 4	0.29 (0.66)
4 – Looking at things outside your body	
Infusion 1	0.40 (0.73)
Infusion 2	0.28 (0.62)
Infusion 3	0.28 (0.64)
Infusion 4	0.25 (0.63)
5 – Watching the situation as an observer or spectator	
Infusion 1	0.42 (0.72)
Infusion 2	0.31 (0.68)
Infusion 3	0.36 (0.71)
Infusion 4	0.32 (0.73)
6 – Disconnected from your own body	
Infusion 1	0.75 (0.95)
Infusion 2	0.44 (0.74)
Infusion 3	0.52 (0.82)
Infusion 4	0.57 (0.91)
7 – Sense of your body feel changed	
Infusion 1	0.54 (0.78)
Infusion 2	0.44 (0.78)
Infusion 3	0.41 (0.78)
Infusion 4	0.43 (0.76)
8 – People seem motionless, dead, mechanical	
Infusion 1	0.19 (0.54)
Infusion 2	0.15 (0.47)
Infusion 3	0.18 (0.53)
Infusion 4	0.18 (0.58)
9 – Objects look different than expected	
Infusion 1	0.30 (0.63)
Infusion 2	0.21 (0.57)
Infusion 3	0.21 (0.57)
Infusion 4	0.21 (0.60)
10 – Colors diminished in intensity	
Infusion 1	0.13 (0.43)
Infusion 2	0.13 (0.40)
Infusion 3	0.12 (0.40)
Infusion 4	0.08 (0.30)
11 – See things through tunnel, wide-angle lens	
Infusion 1	0.37 (0.73)
Infusion 2	0.22 (0.54)
Infusion 3	0.22 (0.50)
Infusion 4	0.26 (0.66)
12 – Interview taking longer than expected	
Infusion 1	0.38 (0.76)
Infusion 2	0.24 (0.52)
Infusion 3	0.19 (0.52)
Infusion 4	0.23 (0.62)
13 – Things happening very quickly	
Infusion 1	0.29 (0.60)
Infusion 2	0.25 (0.60)
Infusion 3	0.26 (0.68)
Infusion 4	0.21 (0.51)
14 – Things which happened that you cannot account for	
Infusion 1	0.40 (0.65)
Infusion 2	0.20 (0.62)
Infusion 3	0.24 (0.53)
Infusion 4	0.26 (0.84)
15 – Spaced out or lost track of time	
Infusion 1	1.03 (1.16)
Infusion 2	0.65 (0.99)
Infusion 3	0.88 (1.12)
Infusion 4	0.89 (1.14)
16 – Sounds disappeared or become stronger	
Infusion 1	0.46 (0.80)
Infusion 2	0.30 (0.66)
Infusion 3	0.24 (0.57)
Infusion 4	0.37 (0.74)
17 – Things seem very real	
Infusion 1	0.38 (0.78)
Infusion 2	0.21 (0.58)
Infusion 3	0.24 (0.62)
Infusion 4	0.26 (0.68)
18 – Looking at the world through a fog	
Infusion 1	0.44 (0.70)
Infusion 2	0.35 (0.66)
Infusion 3	0.37 (0.71)
Infusion 4	0.44 (0.75)
19 – Colors brighter than expected	
Infusion 1	0.16 (0.45)
Infusion 2	0.14 (0.54)
Infusion 3	0.15 (0.40)
Infusion 4	0.11 (0.40)
20 – Feel confused about who you really are	
Infusion 1	0.27 (0.70)
Infusion 2	0.10 (0.41)
Infusion 3	0.12 (0.40)
Infusion 4	0.15 (0.51)
21 – Different parts of yourself don't fit together	
Infusion 1	0.31 (0.64)
Infusion 2	0.17 (0.51)
Infusion 3	0.11 (0.36)
Infusion 4	0.15 (0.50)
22 – Gaps in your memory	
Infusion 1	0.37 (0.77)
Infusion 2	0.24 (0.64)
Infusion 3	0.34 (0.75)
Infusion 4	0.39 (0.82)
23 – More than one identity	
Infusion 1	0.12 (0.50)
Infusion 2	0.04 (0.23)
Infusion 3	0.05 (0.35)
Infusion 4	0.04 (0.22)

3.4. Relationship between clinical and dissociative outcomes

The change in depressive severity, as measured by the QIDS-SR_{16} total score, were independent of the average depersonalization ($F(1, 71) = 0.69$, $p = 0.60$), derealization ($F(1, 71) = 0.80$, $p = 0.53$), amnesia ($F(1, 71) = 0.63$, $p = 0.64$), and total CADSS score ($F(1, 71) = 0.74$, $p = 0.57$). Similarly, GAD-7 total score was independent of average depersonalization ($F(1, 67) = 1.15$, $p = 0.34$), derealization ($F(1, 67) = 1.18$, $p = 0.33$), amnesia ($F(1, 67) = 1.14$, $p = 0.34$), and total scores ($F(1, 67) = 1.16$, $p = 0.34$).

4. Discussion

The results of this post-hoc, retrospective study indicate that IV ketamine is a safe and well-tolerated treatment in a large, real-world sample of adults with TRD receiving care at a community-based clinic. Moreover, only 5% of patients (10/203) discontinued the treatment due to intolerability and/or safety concerns. Patients experienced a mild transient increase in blood pressure and heart rate during IV ketamine infusions.

It was noted that 44.3% of all patients exhibited transient treatment-emergent hypertension (i.e., systolic blood pressure ≥ 165 mmHg or diastolic blood pressure ≥ 100 mmHg) at any

Table 3. Total number and percentages of reported treatment-emergent adverse events at during and after each infusion.

	During Infusion n(%)				After Infusion n(%)			
Side Effect	Infusion 1	Infusion 2	Infusion 3	Infusion 4	Infusion 1	Infusion 2	Infusion 3	Infusion 4
Gastrointestinal Symptoms								
Nausea or Vomiting								
Mild	21 (16.1)	10 (8.5)	11 (10.1)	7 (6.0)	18 (14.0)	3 (2.6)	10 (9.7)	9 (7.7)
Moderate	7 (5.4)	0 (0)	2 (1.8)	4 (3.4)	8 (6.2)	5 (4.3)	4 (3.9)	2 (1.7)
Severe	1 (0.8)	0 (0)	1 (0.9)	0 (0)	3 (2.3)	0 (0)	1 (0.9)	0 (0)
Neurological Symptoms								
Dizziness								
Mild	34 (28.1)	24 (20.5)	22 (21.2)	23 (21.5)	45 (38.1)	40 (35.7)	30 (28.8)	25 (23.4)
Moderate	14 (11.6)	12 (10.3)	14 (13.5)	10 (9.3)	14 (11.9)	7 (6.3)	19 (18.3)	17 (15.9)
Severe	21 (17.4)	7 (6.0)	9 (8.7)	13 (12.1)	2 (1.7)	1 (0.9)	1 (1.0)	4 (3.7)
Headache								
Mild	14 (11.7)	7 (5.9)	11 (10.6)	9 (8.3)	16 (13.7)	21 (18.8)	12 (11.8)	12 (11.4)
Moderate	2 (1.7)	1 (0.8)	1 (1.0)	4 (3.7)	2 (1.7)	3 (2.7)	2 (2.0)	6 (5.7)
Severe	0 (0)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)	2 (2.0)	1 (1.0)
Double Vision								
Mild	11 (8.8)	6 (5.0)	9 (8.5)	11 (9.8)	13(10.9)	20 (17.9)	16 (15.2)	12 (11.4)
Moderate	9 (8.0)	10 (8.4)	11 (10.4)	5 (4.5)	1(0.8)	1 (0.9)	6 (5.7)	7 (6.7)
Severe	6 (4.8)	3 (2.5)	4 (3.8)	7(6.3)	2(1.7)	0 (0)	0 (0)	2 (1.9)
Blurred Vision								
Mild	24 (19.0)	16 (13.6)	13 (12.1)	19 (17.3)	24 (20.2)	24 (21.4)	24 (22.9)	24 (22.9)
Moderate	19 (15.1)	14 (11.9)	11 (10.3)	10 (9.1)	2 (1.7)	4 (3.6)	9 (10.5)	11 (10.5)
Severe	8 (6.3)	3 (2.5)	4 (3.7)	5 (4.5)	3 (2.5)	0 (0)	1 (1.0)	1 (1.0)
Drowsiness								
Mild	36 (29.0)	32 (27.6)	25 (23.6)	25 (23.6)	48 (40.7)	45 (40.5)	31 (29.5)	33 (31.4)
Moderate	29 (23.4)	18 (15.5)	23 (21.7)	19 (21.7)	13 (11.0)	11 (9.9)	17 (16.2)	15 (14.3)
Severe	16 (12.9)	9 (7.8)	11 (10.4)	12 (10.4)	4 (3.4)	4 (3.6)	3 (2.9)	6 (5.7)
Confusion								
Mild	22 (17.7)	15 (12.7)	20 (18.9)	19 (17.6)	16 (13.3)	14 (12.3)	25 (24.0)	18 (17.1)
Moderate	18 (14.5)	12 (10.2)	13 (12.3)	10 (9.3)	10 (8.3)	4 (3.5)	6 (5.8)	7 (7.6)
Severe	14 (11.3)	6 (5.4)	12 (11.3)	14 (13.0)	3 (205)	0 (0)	1 (1.0)	1 (1.0)
Jerky muscle movements								
Mild	14 (11.1)	2 (1.7)	5 (4.6)	3 (2.7)	1 (0.8)	1 (0.9)	4 (3.8)	1 (1.0)
Moderate	1 (0.8)	0 (0)	1 (0.9)	0 (0)	0 (0)	1 (0.9)	0 (0)	0 (0)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dissociation Symptoms								
Depersonalizat- ion								
Mild	16 (14.2)	8 (7.1)	14 (14.0)	10 (10.3)	18 (15.3)	9 (8.0)	10 (9.6)	9 (8.7)
Moderate	20 (17.7)	14 (12.5)	12 (12.0)	11 (11.3)	6 (5.1)	5 (4.5)	5 (4.8)	4 (3.9)
Severe	19 (16.8)	5 (4.5)	10 (10.0)	7 (7.2)	1 (0.8)	0 (0)	0 (0)	0 (0)
Derealization								
Mild	19 (17.0)	8 (7.2)	9 (9.0)	14 (14.9)	16 (13.6)	6 (5.4)	9 (8.7)	5 (4.9)
Moderate	15 (13.4)	12 (10.8)	14 (14.0)	11 (11.7)	7 (5.9)	5 (4.5)	2 (1.9)	5 (4.9)
Severe	17 (16.1)	7 (6.3)	10 (10.0)	9 (10.6)	1 (0.8)	0 (0)	1 (1.0)	3 (2.9)

point during the infusion protocol. Moreover, 12% of these hypertensive patients required a pharmacological intervention to treat hypertension (i.e., labetalol 5–30 mg or amlodipine 10 mg). This relatively low percentage of individuals experiencing hypertension in our sample concords with a review by Wan et al. (2013) of 84 patients receiving 0.5 mg/kg IV ketamine across three clinical trials that reported 30% of participants experienced hypertension and only 14% required pharmaceutical intervention [22]. However, Wan and colleagues operationalized hypertension as a blood pressure exceeding 180/110 mmHg. A total of 33 patients (16%) in our sample would have met this higher criterion. The difference in findings between our data and the forgoing review may be due to difference in protocol, wherein patients at CRTCE received IV ketamine over a period of 45 minutes, whereas the constituent trials in the review administered ketamine over 40 minutes. It remains a testable hypothesis whether hemodynamic changes are influenced by infusion duration. Additionally, patients at the CRTCE were not required to stop most concomitant medications, including antihypertensives. As a result, these medications may have contributed to the lower blood pressure measured in our sample compared to reports from clinical trials. Consonant with clinical trial data, with 20 minutes following infusion completion, 89% of patients had their blood pressure normalize [4,9,23].

In addition, we report that symptoms of dissociation and derealization, as assessed using the CADSS, were highest at the first infusion, followed by a significant attenuation but plateau in subsequent infusions. Extant literature does indicate that symptoms of dissociation do attenuate with repeat doses of IV ketamine [4,9,24]. Contrary to the symptoms of depersonalization and derealization, symptoms of amnesia increased in the third and fourth infusion compared to infusion 2. Subsequent analysis indicated that the increase in amnesia symptoms was a function of the dose increase offered at the third infusion. A review of 11 trials of healthy adults (N = 295) receiving IV ketamine reported that males experienced a greater degree of memory impairment, as assessed by the CADSS [25]. It was speculated that estrogen

mediated NMDA receptor function can stimulate synaptogenesis and thus be protective against the amnesic effect of ketamine [25]. Moreover, studies investigating the enantiomer S-ketamine suggested that healthy women exhibited 20% greater elimination of the drug compared to men [26]. There is an inverse relationship between ketamine metabolites and CADSS scores, which may also contribute to sex differences in disassociation symptoms severity [27]. Importantly, the validity of the CADSS for IV ketamine has been criticized as there is no robust association between dissociation symptoms and antidepressive response [28,29].

A systematic review of 60 studies reported that headaches, dizziness, dissociation, and elevated blood pressure were the most frequently reported adverse events of IV ketamine [9]. The findings herein comport with existing literature, suggesting that drowsiness, dizziness, dissociation, and confusion were the most frequently reported symptoms during infusion. Similar to symptoms of dissociation, the total number of treatment emergent adverse events reduced with subsequent infusions, once dosage was controlled. Notably, patients reported herein more frequently requested antiemetic administration (i.e., 20.5%). In part, this may be attributed to the prophylactic use of ondansetron, if patients reported moderate or severe symptoms of nausea during the first infusion. Although patients reported adverse events following infusion completion, all patients recovered sufficiently during the one-hour post-infusion monitoring and were alert to time, place, and person at discharge and presented with no residual medical sequelae.

There are several methodological aspects that may affect inferences and interpretations of our data. The report herein is a naturalistic, retrospective analysis of outpatients without a control group, and consequently we are unable to ascertain the extent to which some of the safety and tolerability events observed are attributable to expectancy. Moreover, patients receiving IV ketamine at our center received relatively short-term treatment and we do not have data on long-term exposure (6–12 months or greater). We used the CADSS as the primary safety instrument to quantify the severity of dissociation. The CADSS was not developed primarily as a safety measure for ketamine treatment and likely underestimates the extent of dissociation experience with ketamine [29]. It should also be recognized that the CADSS was initially developed for dissociative symptoms of PTSD and may not adequately capture the phenomenology of IV ketamine treatment for TRD. Moreover, patients were permitted to receive concomitant medications, which may have, in some cases, decreased the intensity of some side effects (e.g., anti-nausea effects of antipsychotics). Data regarding history of hypertension or use of antihypertensives at baseline was unavailable.

Notwithstanding these foregoing methodological aspects, the safety and tolerability of IV ketamine in our sample likely have robust generalizability. It's difficult to generalize the safety and tolerability of esketamine to real world settings as its safety and tolerability profile has been entirely characterized within randomized controlled clinical trials. The inclusion of patients with severe, persistent TRD, who have comorbid conditions and are receiving ketamine concomitant with multiple other pharmacological agents represents how most patients in a community setting will receive ketamine. Moreover, safety and tolerability data were captured with valid measures and gold-standard clinical practice. While existing ketamine trials often require concomitant medication tapers, the findings herein suggest that IV ketamine is safe to administer as an adjunctive.

Taken together, the results from our analysis indicate that ketamine is safe and well tolerated when administered to adults with TRD in a community-based setting. Critical to the interpretation of our results is that the CRTCE is a multidisciplinary center with expertise in psychiatry, anesthesia, primary care, pharmacy, nursing as well as psychosocial services. In keeping with recommendations from the American Psychiatric Association task force, it is essential that all persons receiving ketamine for TRD receive the treatment as part of a multidisciplinary approach. In contradistinction of Spravato (esketamine) a risk evaluation and mitigation strategy (REMS) is not required for safe administration of IV ketamine. Notwithstanding the absence of a REMS, the safe administration of ketamine in adults with TRD can be realized in a multidisciplinary setting. Implementing adverse event scales at the point of care for individuals receiving ketamine provides the basis for improving quality and the safety of this treatment modality [9,30]. Furthermore, longer term studies are required to determine whether for some patients the use of ketamine may increase their risk for later substance use disorders [31].

4.1. Expert opinion

Ketamine and esketamine are both proven effective and safe in relatively short-term clinical trials in adults with treatment-resistant mood disorders. Notwithstanding the relatively low dose of ketamine used in the treatment of mood disorders, valid concerns with respect to the safety and tolerability of this intervention remains. The relative lack of long-term studies with any ketamine formulation in adults with mood disorders invites the need for cautious surveillance of treatment-emergent, especially delayed, onset adverse events and safety concerns.

The hypothesis that ketamine's mechanism of action may involve opioid-ergic and related rewards systems raises the very real possibility that some individuals may be susceptible to addictive behaviours after being exposed to ketamine treatment. A non-mutually exclusive hypothesis, supported by several lines of research, is that ketamine treatment may be an 'exit drug' insofar as it may, when combined with psychosocial interventions, facilitate sobriety from alcohol and illicit drugs (e.g., cocaine).

The observation that ketamine may mitigate dimensions of suicidality is an exciting possibility and unmet need in psychiatry. It is not known whether ketamine may, in select vulnerable individuals, may engender and/or amplify measures of suicidality. The foregoing possibility may also coexist with its anti-suicidality effects. Certainly, longer and larger studies will be required to have an evidence base to inform the field.

Recent findings reported on the effects of the R-enantiomer (arketmaine) of IV ketamine in patients with TRD (n = 7). In addition to a significant reduction in depressive symptoms, patients exhibited significantly lower dissociative and sympathomimetic symptoms over the course of the infusion compared to esketamine trials [32]. Although the sample was small, this study confirmed preclinical murine model data and healthy volunteer studies suggesting differential psychotomimetic profiles between the two enantiomers [33,34]. Neuroimaging data suggested while S-ketamine increased cerebral glucose metabolism, equimolar doses of R-ketamine reduce this metabolism, promoting a state of relaxation [35]. While this early data is positive, further randomized control trials are required to disambiguate usage of different enantiomers.

The relevance of our analysis is that the patients included are patients typically encountered in a community-based center offering treatments to individuals with mood disorders. We observe that ketamine was generally well-tolerated with discontinuation due to an adverse event, an unlikely outcome. Most adverse events were transient and attenuated with subsequent infusions. Treatment -induced hypertension is commonly encountered, as is dissociation, and does not interfere with treatment acceptability in most cases. Furthermore, we did not observe treatment emergent psychiatric disorders (e.g., psychosis and mania). Taken together, our clinical experience indicates that ketamine is generally well-tolerated and safe when given largely as an acute treatment. Nonetheless, we strongly advocate for multi-disciplinary treatments at the point of care to assure the safe and deft administration of this treatment.

Author contributions

RSM, NBR, OL and JDR developed research hypothesis, study design, conducted data analysis and wrote the final draft of the manuscript. RSM, YL, LMWL, MS, KK, RBM and JDR were involved with data acquisition. YL, DSC, FN, HG, KL and RH assisted in data interpretation. All authors contributed to the final manuscript proofreading, edits and approval for submission and are accountable for all aspects of the work.

Reviewer disclosures

A reviewer on this manuscript has disclosed that they have a contract with Douglas Pharma to develop ketamine tablets for TRD. Another reviewer on this manuscript has disclosed that they are an inventor of the patent of R-ketamine through Chiba University. All other peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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