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Safety, Tolerability, and Real-World Effectiveness of Intravenous Ketamine in Older Adults With Treatment-Resistant Depression: A Case Series

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ABSTRACT

Objective: *To evaluate the safety, tolerability, and effectiveness of repeated doses of intravenous (IV) ketamine in older adults (i.e., ≥60 years of age) with treatment-resistant depression.* ***Method:*** *In this case series, fifty-three older adults (M_{age} = 67, SD = 6; 57% female [n = 30]) received 4 IV ketamine infusions, administered over 1–2 weeks. Effectiveness of IV ketamine was measured using the Quick Inventory for Depressive Symptomatology–Self Report 16 (QIDS-SR16) approximately 2 days after infusions 1–3, and 1–2 weeks after infusion 4. Safety was measured as hemodynamic changes before, during, immediately after, and 20 minutes after each infusion. Tolerability was assessed via systematic reporting of treatment-emergent adverse events during and after each infusion, in addition to symptoms of dissociation measured using the Clinician Administered Dissociative States Scale. Partial response*

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(25%−50% symptomatic improvement from baseline), response (≥50% symptomatic improvement from baseline), clinically significant improvements (≥25% symptomatic improvement from baseline), and remission rates (QIDS-SR16 ≤5) were also calculated. ***Results:*** *Participants reported significant decreases in depressive symptoms (i.e., as measured by the QIDS-SR16) with repeated ketamine infusions (*F*(4, 92) = 7.412, p <0.001). The mean QIDS-SR16 score was 17.12 (SD = 5.33) at baseline and decreased to 12.52 (SD = 5.79) following 4 infusions. After 4 infusions, 31%* (n = 8) *of participants partially responded to IV ketamine, 27%* (n = 7) *responded, 58%* (n = 15) *experienced clinically significant improvements, and 10%* (n = 3) *met remission criteria. Thirty-six participants (69%) experienced treatment-emergent hypertension during at least 1 infusion, and 10 (19%) required intervention with an antihypertensive. Drowsiness was the most commonly reported adverse event (50% of infusions;* n = 73). ***Conclusion:*** *Ketamine was associated with transient treatment-emergent hypertension. Response and remission rates were comparable to those reported in general adult samples. Findings are limited by the open-label, chart review nature of this study.* (Am J Geriatr Psychiatry 2021; ■■:■■−■■)

INTRODUCTION

Major depressive disorder (MDD) is a prevalent psychiatric condition that affects 1%−3% of community dwelling older adults (i.e., ≥60), [1−5] and over 10% of long term care residents and medical outpatients.[6,7] MDD in older adults is associated with negative health outcomes including cognitive decline, frailty, obesity, and mortality; moreover, MDD incurs significant financial and social burdens.[8−10] Conversely, social isolation, poor physical health and financial hardship are risk factors for late-life MDD.[8,11−14] Furthermore, late-life depression is associated with higher relapse and recurrence rates as well as increased suicide risk compared to MDD in mid-life adults.[15,16]

Modern antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have shown benefits for many patients of all ages, but are inadequate for approximately 50% of older adults [17−25] and may increase the risks of bleeding and hyponatremia.[26,27] Many other drugs have been investigated as augmentation therapies for the general adult population (ages 18−65), however randomized controlled trials (RCTs) in older adults are scarce and most knowledge on the topic is derived from open label studies and case reports/series. For example, augmenting SSRI/SNRI therapy with aripiprazole (an atypical antipsychotic) or methylphenidate (a stimulant) has been shown to evoke a response in initial nonresponders and shorten the time to response in older adults,[28,29] but are associated with more severe and/or frequent adverse events than monotherapies, including increased Parkinsonism in the case of aripiprazole.

There is a critical need to identify effective antidepressants for older adults who do not respond to first- and second-line antidepressant pharmacotherapy. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that even after 4 successive treatment escalations with a variety of antidepressants and augmentations including cognitive behavioral therapy, 33% of participants did not experience remission, irrespective of age.[30] Furthermore, the onset of action of current antidepressants, including SSRIs, SNRIs, and tricyclic antidepressants, varies from within 1 week to several months.[31] For those who have failed to respond to conventional antidepressant treatments, or for whom a more rapid response is desirable, there is a need for safe and rapid-acting antidepressants.

Ketamine, a racemate consisting of esketamine and arketamine, is an N-methyl D-aspartate receptor antagonist that is safe and rapidly efficacious in treating depressive symptomatology, including treatment-resistant depression (TRD), in adults.[32−35] However, the safety and efficacy of ketamine has not been rigorously ascertained in elderly individuals; in addition to a few case reports, only 2 RCT in this population

have been published. The first, a small pilot RCT ($n = 16$), found subcutaneous ketamine to be safe and efficacious for treating geriatric (i.e., ≥60 years) TRD.[36] The second, larger study ("TRANSFORM-3") administered flexibly dosed intranasal esketamine twice weekly for 4 weeks ($N = 138$) and found the intervention to be well tolerated, but was not significantly more effective than placebo after 28 days when measuring depressive symptoms as a continuous variable.[37] Secondary analyses show response and remission rates of 27.0% and 17.5%, respectively, in the esketamine group, compared to 13.5% and 6.7% in the placebo group, however no statistically significant differences were reported.[37]

The potential of ketamine as a safe, rapid, and robust antidepressant highlights a need to ascertain the safety, tolerability, and effectiveness of the treatment for TRD in a real-world, treatment-seeking cohort of older adults, a population which suffers disproportionately compared to younger counterparts, and for whom rapidly efficacious antidepressant therapies are lacking. The objective of the current post-hoc chart review study was to evaluate the effectiveness as well as safety and tolerability of repeat-dose intravenous (IV) ketamine in a sample of older adults receiving treatment in an outpatient clinical facility.

METHOD

Participants and Study Design

This study represents data from an ongoing case series at the Canadian Rapid Treatment Center of Excellence (CRTCE) and is a post-hoc analysis to evaluate the safety, tolerability, and effectiveness of IV ketamine in older adults receiving treatment in a real-world clinical setting. Analysis of the CRTCE data has been approved by a community research ethics board (IRB#00000971). Findings of the primary outcome have been published elsewhere, and the study protocol has been previously described in detail.[38] This study is registered on clinicaltrials.gov under the identifier NCT04209296.

In summary, 311 participants with TRD (characterized as an insufficient response to 2 or more adequate antidepressant trials[39]) between the ages of 18 and 82 received 4 repeated doses of IV ketamine over a period of 1−2 weeks. Eligibility was assessed before the first infusion by a staff psychiatrist at the clinic. A mood disorder diagnosis was established clinically according to the *Diagnostic and Statistical Manual Fifth Edition* (DSM-5) criteria.[40] Participants were then assessed for medical eligibility and safety by a staff anesthesiologist at the clinic. Concomitant antidepressants were allowed during the treatment period, except for those outlined in Figure S1. Participants were ineligible for ketamine treatment if they were unable to provide informed consent, exhibited signs of dementia, had unstable or untreated medical conditions (i.e., hypertension, seizures, etc.), had an active substance-use disorder, had a history of psychosis, or if their primary diagnosis was not a mood disorder. Participants who presented with uncontrolled hypertension but were otherwise eligible for IV ketamine were first seen by their primary care provider to manage hypertension before their first infusion. If a participant presented with hypertension on the day of the infusion, before the infusion began ("pretreatment"), their eligibility and safety profile was evaluated by a clinic anesthesiologist on a case-by-case basis. Overall safety and tolerability of IV ketamine in the full sample has been previously reported by our group.[41]

Only participants who were 60 or older at baseline were included in the current analysis. Treatment was administered at a community-based clinic and research facility that specializes in IV ketamine for TRD. In the initial 2 ketamine infusions, all participants received a dose of 0.5 mg/kg, infused over 40−45 minutes. For the third and fourth infusions, participants who did not report sufficient symptomatic improvements (i.e., ≤20% improvement in depressive symptoms, as measured by the Quick Inventory in Depressive Symptomatology − Self Report 16 [QIDS-SR16][42]) were eligible to receive a dose increase to 0.75 mg/kg.[43] Participants were monitored by nursing staff for up to 2 hours after the treatment, until the acute effects of ketamine subsided.

Measures and Procedures

Depressive symptoms

Depression severity was measured using the QIDS-SR16. Symptoms were assessed at baseline, post-infusion 1, post-infusion 2, post-infusion 3, and post-infusion 4. Post-infusion 1, 2, and 3 QIDS-SR16 assessments

were completed on average 2 days after each infusion, and the post-infusion 4 assessment was completed approximately 7−14 days following the fourth infusion. The post-infusions 1−3 assessments were completed in the clinic, prior to the subsequent infusion. Post-infusion 4 assessments were also completed in the clinic when the participant returned for a follow-up appointment with the clinic psychiatrist.

Blood pressure and heart rate

Blood pressure, heart rate, respiratory rate, and oxygen saturation were measured by the anesthesiologist before each infusion began and were continuously reported every 5 minutes throughout the infusion.

Maximum systolic and diastolic blood pressure and heart rate during the infusion were recorded for analysis. Highest systolic blood pressure during the infusion was categorically coded as between 111 and 120 mmHg, 121−130 mmHg, or 131−140 mmHg. If the participant's systolic blood pressure was ≤110 mmHg or >140 mmHg, the exact value was recorded.

Highest diastolic blood pressure was coded as between 71 and 80 mmHg, 81−90 mmHg, or 91−100 mmHg. If the participant's diastolic blood pressure was ≤70 mmHg or >100 mmHg, the exact value was recorded. Maximum heart rate during the infusion was coded as between 61 and 70 bpm, 71−80 bpm, or 81−90 bpm. If heart rate was ≤60 bpm or >90 bpm, the exact value was recorded. For the purpose of analysis, when the participant's exact blood pressure or heart rate was not recorded, the higher value in the categorical range was used for analysis.

Hypertension was defined as a systolic blood pressure ≥165 mmHg or a diastolic blood pressure ≥100 mmHg. In addition to recording blood pressure and heart rate before and during the infusion, they were also recorded immediately after the infusion and 20 minutes post-infusion.

Treatment-emergent adverse events

Adverse events during and after the infusion were systematically reported using the checklist in Figure S2. During the infusion, participants were asked about 12 gastrointestinal, neurological, and dissociative treatment-emergent symptoms, and rated the severity of each symptom as "none" (i.e., not present), "mild," "moderate," or "severe." Treatment-emergent symptoms were assessed again 20 minutes post-infusion.

Five to 10 minutes postinfusion, the nurse administered the 23-item Clinician-Administered Dissociative States Scale[44] (CADSS) to assess the presence of dissociative symptoms and severity. A score greater than 4 is considered to indicate dissociation.[45] The CADSS is commonly analyzed as 3 subscales measuring amnesia (items 14, 15, and 22), depersonalization (items 3−7, 20, and 23), and derealization (items 1−2, 8−13, 16−19, and 21), however these subscales have not been validated. Each item on the CADSS is scored on a scale of 0−4, with a higher score indicating greater symptom severity. The maximum possible total score on the CADSS is 92, and the maximum possible scores on the amnesia, depersonalization, and derealization subscales are 12, 28, and 52, respectively.

Covariates

Characteristics including sex, body mass index,[46] pretreatment depression severity, pretreatment anxiety severity (measured using the Generalized Anxiety Disorder−7 Scale [47]), and level of treatment resistance (i.e., number of self-reported past antidepressant trials) were collected at baseline.

Statistical Analysis

Effectiveness of IV ketamine in older adults was evaluated using a mixed model with an autoregressive (AR1) matrix. Data were fit using a Restricted Maximum Likelihood (REML) in SPSS Version 26.0. The independent variable was *infusion number*, the dependent variable was *QIDS-SR16 score*, and the covariates included in the model were *sex, body mass index, pretreatment depression severity*, *pretreatment anxiety severity*, and *level of treatment resistance*.[48] Clinically significant improvements and response rates were also calculated using difference scores from baseline to postinfusion 4. Partial response was defined as a 25%−50% reduction in depressive symptoms (i.e., QIDS-SR16 scores). Clinically significant improvement was defined as a ≥25% reduction in depressive symptoms (i.e., QIDS-SR16 scores). Response was defined as a ≥50% reduction in depressive symptoms (i.e., QIDS-SR16 scores) from

baseline to postinfusion 4. Remission was defined as a QIDS-SR16 score ≤5 at the postinfusion 4 visit. Partial response, clinically significant improvements, response, and remission rates following three infusions were also evaluated.

An exploratory analysis of a subsample of participants who previously received electroconvulsive therapy (ECT) was also conducted with a mixed model using the same parameters ($N = 15$).

Changes in blood pressure and heart rate from baseline (i.e., immediately before each infusion) to the maximum recorded blood pressure and heart rate during the infusion were described, and vital signs 20 minutes postinfusion were reported in comparison to baseline measurements. Treatment-emergent adverse events were described as percentages of the total number of treatments at which adverse events were recorded. Total dissociative symptoms (i.e., total CADSS score), depersonalization, derealization, and amnesia were also described. Mixed models were used to evaluate whether symptoms of dissociation, amnesia, depersonalization, and derealization attenuated with repeated ketamine infusions. Mixed models were implemented in SPSS Version 26.0 with an autoregressive (AR1) matrix, and fit using REML.

Follow-up Bonferroni pairwise comparisons were conducted if models were significant, with infusion 1 as the comparator.

RESULTS

Participant Characteristics

A total of 53 older adults (i.e., ≥60 years of age at baseline) received treatment at the CRTCE from July 2018 to September 2020. Participants ranged in age from 60 to 82. Amongst the 53 participants, 235 IV ketamine infusions were administered. Baseline characteristics of the included sample are described in Table 1. At the third infusion, 27 (58.70%) participants received a dose increase to 0.75 mg/kg, while 19 participants remained on the index dose of 0.5 mg/kg. Post-infusion 4 assessments were completed on average 7.81 days after the fourth infusion (SD = 12.55).

Effectiveness of IV Ketamine

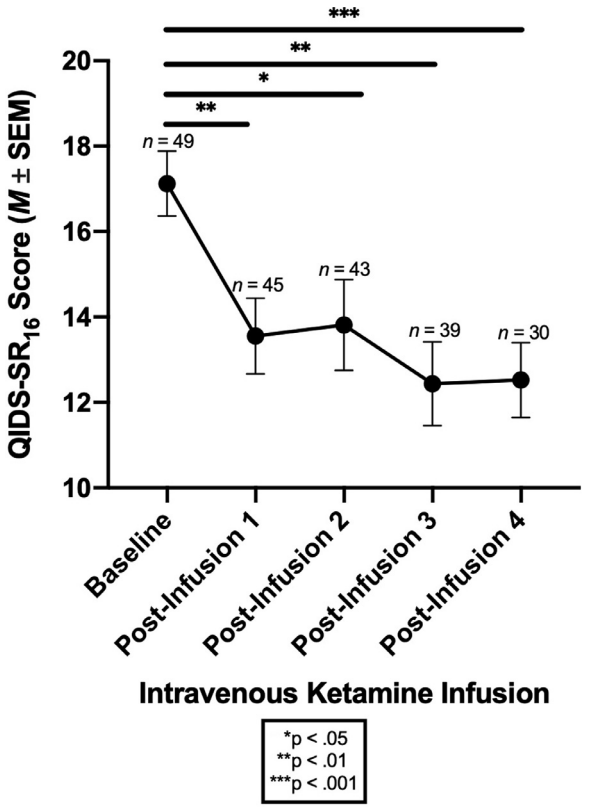
There was a significant main effect of infusion on QIDS-SR16 scores, $F(4, 60) = 6.89$, $p < 0.001$, Cohen's $f = 0.60$ (Fig. 1). Depressive symptoms significantly decreased from baseline to postinfusion 1 ($t[77] = -3.96$, $p = 0.001$, Cohen's $d = 0.83$, $\beta = -3.29$, SE = 0.83, 95% CI [−4.94, −1.64]), postinfusion 2 ($t[72] = -2.90$, $p = 0.020$, Cohen's $d = 0.61$, $\beta = -2.69$, SE = 0.93, 95% CI [−4.54, −0.84]), postinfusion 3 ($t[53] = -3.87$, $p = 0.001$, Cohen's $d = 0.84$, $\beta = -3.79$, SE = 0.98 95% CI [−5.75, −1.83]), and postinfusion 4 ($t[56] = -4.41$, $p < 0.001$, $\beta = -4.93$, Cohen's $d = 1.04$,

TABLE 1. Baseline Characteristics of Participants

Characteristic	Participants ($n = 53$)
Age in years, *M* (SD)	66.77 (5.91)
Age 60−75, *n* (%)	47 (88.68)
Age 76−82, *n* (%)	6 (11.32)
Sex, *n* (%)	
Male	23 (43.40)
Female	30 (56.60)
Baseline BMI (kg/m^2), *M* (SD)	27.89 (5.22)
Primary diagnosis, *n* (%)	
MDD	44 (83.02)
BD	9 (16.98)
Baseline depressive symptom severity (QIDS-SR$_{16}$), *M* (SD)	17.12 (5.33)
Post-Infusion 4 depressive symptom severity (QIDS-SR$_{16}$), *M* (SD)	12.52 (5.79)
Number of previous antidepressant trials, *M* (SD)	7.03 (5.23)
Number of concomitant antidepressants during ketamine treatment, *M* (SD)	1.73 (1.46)
History of ECT, *n* (%)	15 (28.30)
History of rTMS, *n* (%)	5 (9.43)
Baseline anxiety symptom severity GAD-7, *M* (SD)	13.21 (6.06)

Abbreviations: SD: standard deviation; BMI: body mass index; MDD: major depressive disorder; BD: bipolar disorder; QIDS-SR$_{16}$: Quick Inventory for Depressive Symptomatology−Self Report-16; ECT: electroconvulsive therapy; TMS: transcranial magnetic stimulation; GAD-7: Generalized Anxiety Disorder−7.

FIGURE 1. Average changes in depressive symptoms, as measured by the Quick Inventory for Depressive Symptomatology −Self Report-16 (QIDS-SR16), with repeated intravenous (IV) ketamine infusions in older adults. Figure represents actual sample data and not model estimates. The figure shows significant pairwise comparisons with Bonferroni corrections from baseline to post-infusion 1 (*df* = 77), 2 (*df* = 72), 3 (*df* = 53), and 4 (*df* = 56).



SE = 1.12, 95% CI [−7.17, −2.69]). Of the 26 participants with available baseline and end-point data, 10% ($n = 3$) reported remission of depressive symptoms. Thirty participants had both baseline and end-point data. Of the 30 participants, 58% ($n = 15$) reported clinically significant improvements in depressive symptoms with repeat ketamine infusions (i.e., 25% or greater decrease in depressive symptoms compared to baseline, measured by the QIDS-SR16). Response and remission are further described in Table 2. The ECT subanalysis is presented in Table S1.

Safety of IV Ketamine

Blood pressure data were available for 194 (83%) infusions, and for 52 participants at infusion 1, 48 at infusion 2, 46 at infusion 3, and 48 participants at infusion 4. On average, during the infusion, systolic blood pressure increased by 21.47 mmHg (SD = 13.55) and diastolic blood pressure increased by 11.18 mmHg (SD = 10.07) from baseline. Twenty minutes after the infusion, median systolic blood pressure was 3.25% higher than baseline and median diastolic blood pressure was 2.56% higher than baseline. Changes in systolic and diastolic blood pressure before, during, immediately after the infusion, and 20 minutes postinfusion are illustrated in Figure 2. Eight participants (15%) presented with hypertension prior to one infusion. Two participants (4%) presented with hypertension prior to 2 infusions. Blood pressure continued to be elevated at some point during all 12 of these infusions. Seven participants (70%) with pretreatment hypertension had hypertension during all 4 infusions, even if they did not have hypertension before the infusion began. Two (20%) participants with pretreatment hypertension had hypertension during three infusions. One (10%) participant with pretreatment hypertension only had hypertension during that infusion, and did not have hypertension before or

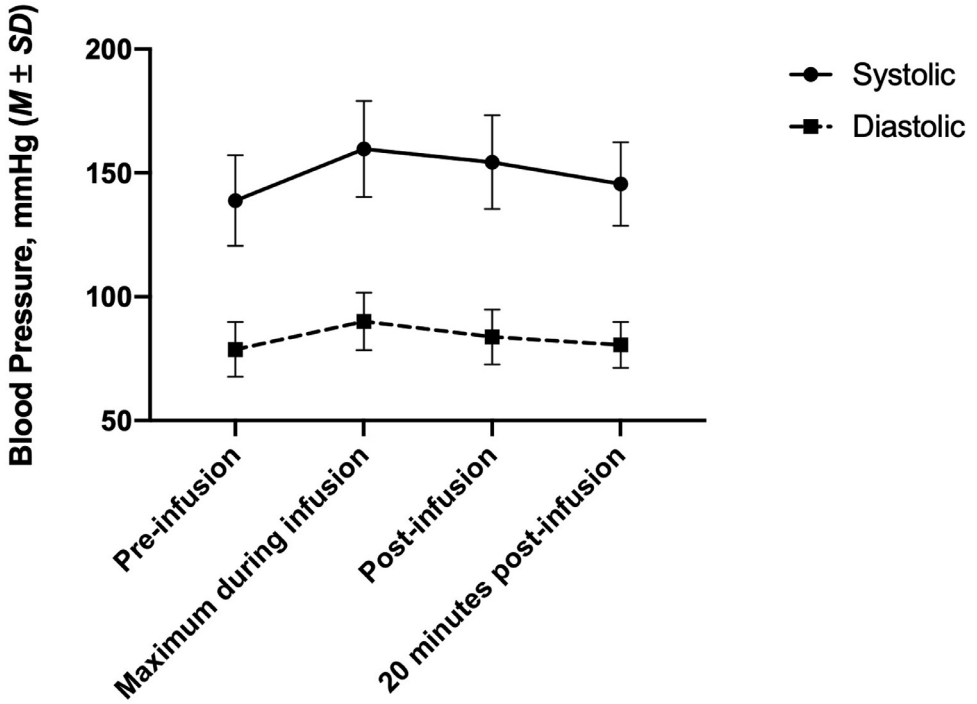
TABLE 2. Categorical Outcomes Following Four Intravenous Ketamine Infusions

Categorical Outcome	Following Three Infusions	Following Four Infusions
Partial Response Rate (QIDS-SR_{16} decrease between 25% to 50%)	11 (29.73)	8 (30.77)
Response Rate (≥50% QIDS-SR_{16} decrease)	9 (24.32)	7 (26.92)
Clinically Significant Improvements (≥25% decrease in QIDS-SR_{16})	20 (54.05)	15 (57.69)
Remission Rate (QIDS-SR_{16} ≤ 5)	5 (12.82)	3 (10.00)

Abbreviations: QIDS-SR_{16}: Quick Inventory for Depressive Symptomatology−Self Report-16.

Note: Post-infusion 3 data were available for 39 participants. Of those 39 participants, 2 were missing baseline data. Therefore, percent change scores from baseline to postinfusion 3 were calculated for 37 participants. Remission data were available for 39 participants, since baseline data were not needed. Postinfusion 4 data were available for 30 participants. Of those 30 participants, 4 were missing baseline data. Therefore, percent change scores from baseline to postinfusion 4 were calculated for 26 participants. Remission data were available for 30 participants, since baseline data were not needed.

FIGURE 2. Average change in blood pressure from pre-intravenous (IV) ketamine infusion to 20 minutes post-IV ketamine infusion.



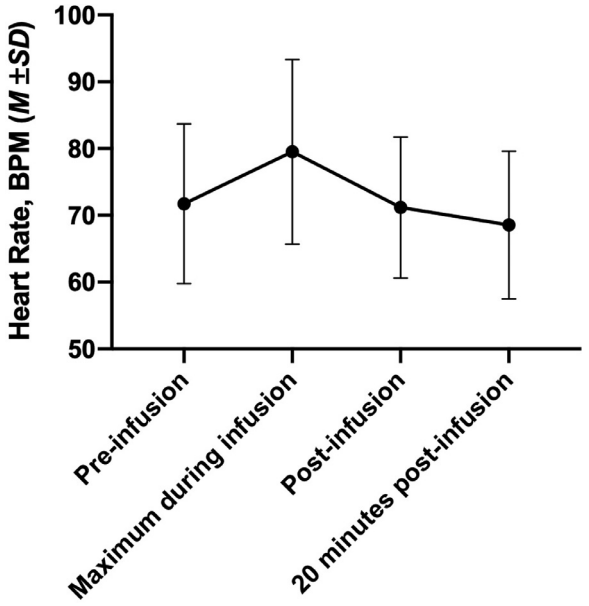
during any other infusions. An additional 35 (66%) participants experienced treatment-emergent hypertension (i.e., did not have hypertension before the infusion, but experienced hypertension during the infusion) across 87 infusions (45% of infusions). Including participants with pretreatment hypertension, 36 (68%) participants experienced hypertension across 99 infusions (42%).

All participants who received an antihypertensive were treated with labetalol intravenously (5−15 mg), except for 1 participant in which labetalol was administered orally and one participant who was administered amlodipine orally. Antihypertensives were administered based on clinical judgment of the anesthesiologist who monitored the patient throughout the entire infusion, and considered multiple factors in assessing the safety profile and the necessity for administrating an antihypertensive. Overall, 11 (21%) patients required an antihypertensive across 18 infusions (8%). Five of these participants were those who presented with pretreatment hypertension. Seven only required an antihypertensive at a single infusion.

Two participants who presented with pretreatment hypertension were administered an antihypertensive before the infusion began. These 2 participants did not require an additional antihypertensive during or after that infusion, but did require an antihypertensive during other infusions (but not before other infusions). One of these 2 participants required an antihypertensive during all three other infusions (1 antihypertensive was administered during 2 infusions, and 3 antihypertensives were required during 1 infusion), and the other participant required 1 antihypertensive during 1 other infusion.

Ten participants were administered an antihypertensive during/after an infusion, across 15 infusions. Six participants (5 at 1 infusion only, and 1 participant at 2 infusions) required a second antihypertensive either during or after the infusion. Three participants required a third antihypertensive during the infusion, across 4 infusions. One participant required a fourth antihypertensive at 1 infusion. One additional participant required 2 antihypertensives (metoprolol), but the

FIGURE 3. Average change in heart rate from pre-intravenous (IV) ketamine infusion to 20 minutes post-IV ketamine infusion. Abbreviations: BPM: Beats per minute.



timing or route of administration was not specified (i.e., before, during, or after the infusion).

From preinfusion to the maximum heart rate recorded during the infusion, heart rate increased by a mean of 7.57 BPM (SD = 10.57). By 20 minutes after the infusion, the median heart rate was 3.50% lower than the participant's baseline heart rate. Changes in heart rate are shown in Figure 3.

Tolerability of IV Ketamine

Drowsiness was the most commonly reported adverse event, with participants reporting drowsiness at 73 (50%) infusions (data available for 147 infusions), followed by confusion ($n = 55$; 40%; data available for 149 infusions) and derealization ($n = 55$; 41%; data available for 136 infusions). Figure 4 depicts the percentage of infusions at which mild, moderate, or severe adverse events were reported during (Fig. 4A) or after (Fig. 4B) the infusion and the sample size of available data for each adverse event.

Changes in total CADSS scores, amnesia, depersonalization, and derealization across infusions are illustrated in Figure 5. Total CADSS scores significantly attenuated across infusions, $F(3, 71) = 9.08$, $p < 0.001$, Cohen's $f = 0.57$. Total dissociative symptoms (i.e., CADSS score) significantly decreased from infusion 1 to all subsequent infusions (infusion 1 to 2: $t[112] = -4.95$, $p < 0.001$, Cohen's $d = -1.00$, $\beta = -4.84$, SE = 0.91, 95% CI [−6.28, −2.69]; infusion 1 to infusion 3: $t[99] = -2.60$, $p = 0.033$, Cohen's $d = -0.53$, $\beta = -2.78$, $SE = 1.07$, 95% CI [−4.91, −0.66]; infusion 1 to infusion 4: $t[49] = -3.38$, $p = 0.004$, Cohen's $d = -0.68$, $\beta = -3.74$, SE = 1.11, 95% CI [−5.97, −1.52]). The mean total CADSS score after the first infusion was 10.79 (SD = 9.83) out of a maximum possible score of 92, after the second infusion was 6.67 (SD = 9.83), after the third infusion was 8.42 (SD = 9.43), and after the fourth infusion the average total CADSS score was 7.04 (SD = 9.88).

Symptoms of amnesia ($F[3, 86[= 5.12$, $p = 0.003$, Cohen's $f = 0.37$), depersonalization ($F[3, 79] = 6.15$, $p = 0.001$, Cohen's $f = 0.43$), and derealization ($F[3, 71] = 6.48$, $p = 0.001$, Cohen's $f = 0.47$) significantly differed with repeated infusions. Follow-up pairwise comparisons showed that amnesia symptoms significantly attenuated between infusion 1 and 2 ($t[109] = -3.72$, $p = 0.001$, Cohen's $d = -0.75$, $\beta = -0.90$, SE = 0.24, 95% CI [−1.37, −0.42]), between infusion 1 and 3 ($t[112] = -2.85$, $p = 0.016$, Cohen's $d = -0.59$, $\beta = -0.76$, $SE = 0.27$, 95% CI [−1.30, −0.23]), and between 1 infusion and 4 ($t[76] = -2.56$, $p = 0.037$, Cohen's $d = -0.52$, $\beta = -0.69$, SE = 0.27, 95% CI [−1.22, −0.15]). At infusion 1, the mean amnesia score was 1.88 (SE = 0.29) out of a maximum possible score of 12, at infusion 2 the mean score was 1.06 (SE = 0.26), at infusion 3 the mean score was 1.20 (SE = 0.26), and at infusion 4 the mean amnesia score was 1.23 (SE = 0.28).

Depersonalization symptoms also significantly attenuated between infusions 1 and 2 ($t[110] = -4.11$, $p < 0.001$, Cohen's $d = -0.83$, $\beta = -1.66$, SE = 0.40, 95% CI [−2.46, −0.86]), between infusion 1 and 3 $t(102) = -2.51$, $p = 0.040$, Cohen's $d = -0.52$, $\beta = -1.14$, SE = 0.45, 95% CI [−2.05, −0.24]), and between 1 infusion and 4 $t(63) = -2.94$, $p = 0.014$, Cohen's $d = -0.59$, $\beta = -1.35$, SE = 0.46, 95% CI (−2.26, −0.43). Out of a maximum possible score of 28, the mean depersonalization score at infusion 1 was 3.50 (SE = 0.52), at infusion 2 the mean score was 1.94 (SE = 0.54), at infusion 3 the mean score was 2.49 (SE = 0.53), and at infusion 4 the mean depersonalization score was 2.17 (SE = 0.53).

Derealization symptoms significantly attenuated between infusions 1 and 2 ($t[98] = -3.78$, $p = 0.001$,

FIGURE 4. Percent of intravenous (IV) ketamine infusions at which mild, moderate, or severe treatment-emergent adverse events were reported during the infusion (A) or after the infusion (B). Sample sizes of severity are reported in each bar, and total sample size of available data for each adverse event is reported above each bar. Where the sample sizes was below 3, the number was not indicated.

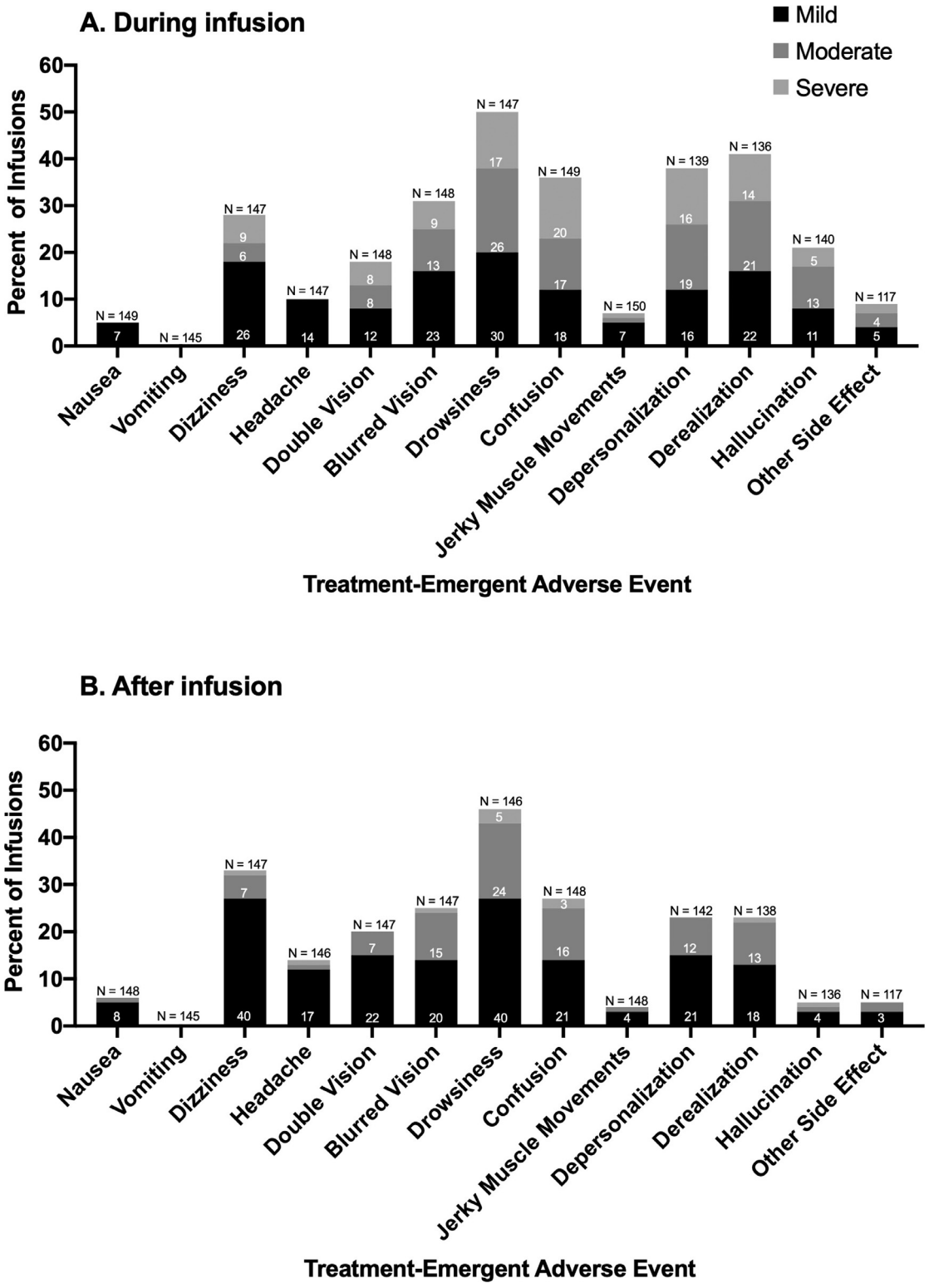
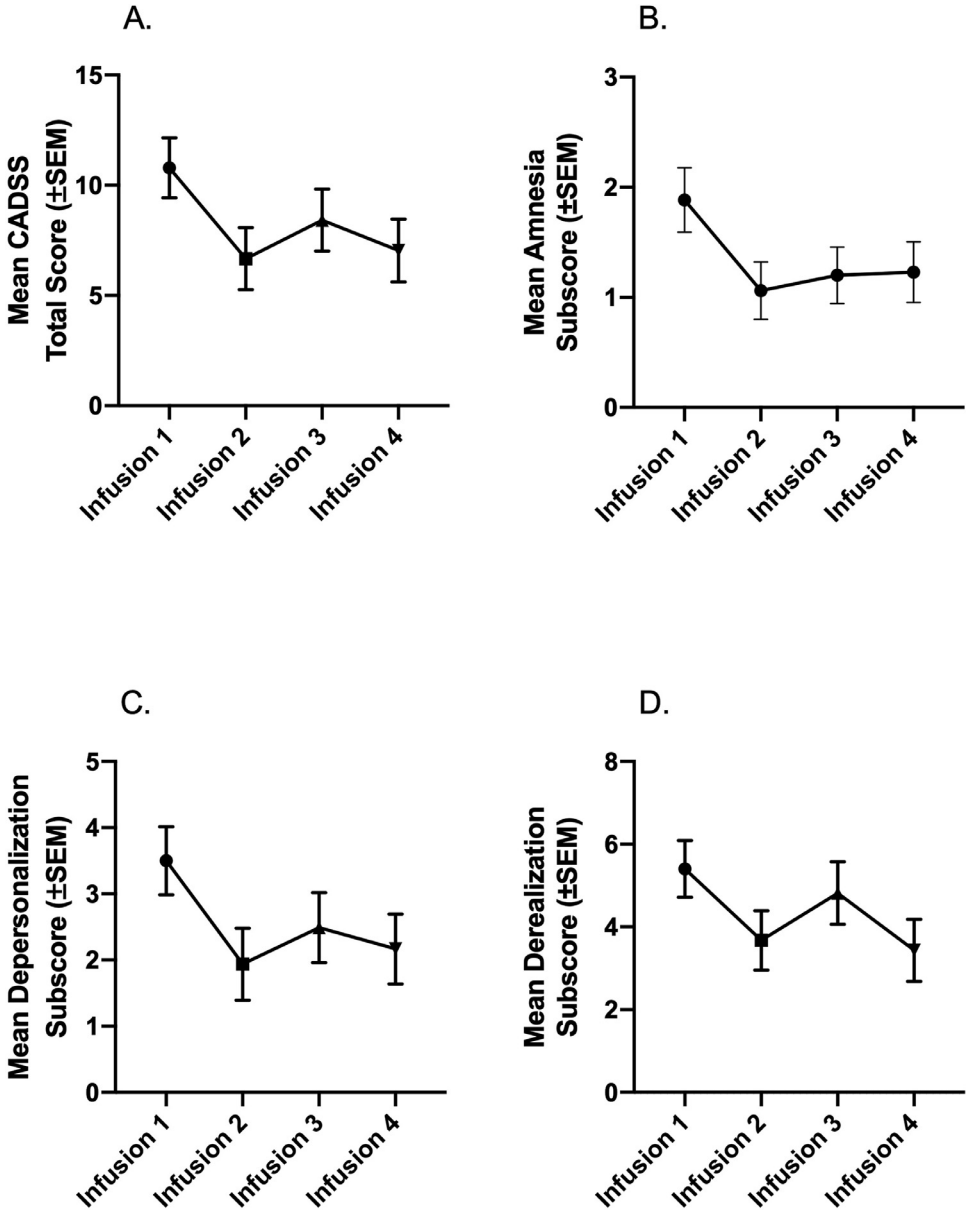


FIGURE 5. Changes in total treatment-emergent dissociative symptoms (A), as well as amnesia (B), depersonalization (C), and derealization (D) with repeat intravenous (IV) ketamine infusions.



Cohen's $d = -0.77$, $\beta = -1.89$, SE = 0.50, 95% CI [−2.89, −0.89]) as well as between 1 and 4 (t [57] = −3.27, p = 0.005, Cohen's $d = -0.67$, $\beta = -1.86$, SE = 0.57, 95% CI [−3.00, −0.72]), but did not significantly differ between infusions 1 and 3 (t[94] = -1.45, p = 0.454, Cohen's $d = -0.30$, $\beta = -0.82$, SE = 0.56, 95% CI [−1.94, 0.30]). Out of a maximum possible score of 52, the mean derealization score at infusion 1 was 5.40 (SE = 0.68), at infusion 2 was 3.67 (SE = 0.72), at infusion 3 was 4.82 (SE = 0.76), and at infusion 4 was 3.43 (SE = 0.75).

The type of depersonalization during the infusion (i.e., pleasant, neutral, distressing) was only recorded at 45 infusions (19% of infusions). During 11 (24%)

infusions, depersonalization was reported as a pleasant experience, at 18 (40%) infusions it was neutral, and at 16 (36%) infusions, it was reported as distressing. The type of depersonalization after the infusion was recorded at 29 (12%) infusions. At five (17%) infusions, it was reported as positive, at 13 (45%) it was reported as neutral, and at 11 (38%) it was reported as distressing. The type of derealization experience during the infusion was recorded at 54 (23%) infusions. At 12 (22%) infusions it was positive, at 24 (44%) it was neutral, and at 18 (33%) it was a distressing experience. The experience of derealization after the infusion was recorded for 33 (14%) infusions. At 6 (18%) it was positive, at 16 (48%) it was neutral, and at 11 (33%) it was distressing.

Three participants (5.6%) discontinued treatment during the acute 4-infusion protocol. One patient dropped out following a single infusion due to worsening anxiety symptoms. The 2 other patients dropped out following 2 infusions due to an inability to tolerate the dissociative symptoms and worsening anxiety.

DISCUSSION

The findings presented herein indicate that repeat IV ketamine infusions are associated with a significant decrease in depressive symptoms in older adults with TRD, with large effect sizes. Rates of partial response, response, and remission in this sample of older adults were similar to response and remission rates in the full sample of adults previously reported on by our group,[38] suggesting that ketamine has comparable effectiveness in older adults with TRD. While we did find a significant reduction in depressive symptoms in older adults with a history of ECT, the sample size was very small and underpowered. However, these findings are promising for older adults who have not experienced sufficient symptom relief with ECT and suggest that this sample may still benefit from IV ketamine. Further data with adequately powered samples must be collected before the effectiveness of IV ketamine can be ascertained in older adults who have not responded to ECT. Similar to the results presented herein, extant literature suggests that augmenting SSRI/SNRI therapy with aripiprazole, can significantly improve remission rates and outcomes in older adults who have not sufficiently responded to previous antidepressants[49] TRD.

Similar to observations in the general adult population,[30] in this sample of older adults, blood pressure and heart rate increased during infusions and normalized to within 5% of the baseline measurement within 20 minutes postinfusion for most participants. In this sample of older adults with TRD, a large number of individuals experienced treatment-emergent hypertension during at least one infusion. Treatment-emergent hypertension occurred at 45% of infusions, similar in frequency to previously reported treatment-emergent hypertension in the full sample of adults receiving treatment at the CRTCE.[41] Antihypertensives were required for a number of participants (21%), however hypertension was transient and resolved with pharmacological intervention before participants left the clinic. Almost half (45%) of participants who required an antihypertensive before, during, or after an infusion had presented with pretreatment hypertension at 1 of the 4 infusions. Of note, although uncontrolled hypertension was an exclusion criteria for IV ketamine, 15% of participants presented with pretreatment hypertension. Elevated blood pressure before any of the 4 infusions may help identify individuals who may be more at risk for treatment-emergent hypertension or intervention with antihypertensives at other infusions.

The majority of treatment-emergent adverse events were mild in severity, and total dissociative symptoms as well as symptoms of amnesia, derealization, and depersonalization attenuated with repeated infusions. Importantly, during 52 infusions participants reported depersonalization, during 57 infusions participants reported derealization, and during 29 infusions participants experienced hallucinations. Of note, although many participants experienced dissociative symptoms, more participants reported pleasant or neutral dissociative experiences as opposed to negative experiences. The presence of dissociative symptoms also greatly decreased after the infusion, and all participants recovered by one-hour post-infusion, before being discharged from the clinic. Furthermore, the intensity of dissociation within this sample of older adults was relatively low compared to other samples of individuals receiving IV ketamine treatment,[50] which reported a total CADSS score of 25.1 (SD = 18.6, n = 126) following 0.5 mg/kg IV ketamine infused over 40 minutes. Important consideration must be given to the fact that the CADSS is designed to measure dissociative symptoms associated with

post-traumatic stress disorder and is not a validated measure of IV ketamine-associated dissociation.[51] Furthermore, severity and type of depersonalization, derealization, and hallucination as reported using the side effects form were subjective self-report measures of a participant's experiences and the side effects form is not a validated measure.

Moreover, there was a commensurate degree of treatment discontinuation (i.e., ~5%) between this older sample and the general adult sample previously reported on by our group,[41] and no participants discontinued treatment due to safety concerns. In comparison with our previously reported findings on the safety and tolerability of IV ketamine in the full sample of adults (Age: M = 45, SD = 14.9), IV ketamine appears to be similarly safe and well-tolerated in older adults.

The results of this study are also in accord with the extant literature on the safety, tolerability, and effectiveness of ketamine in older adult samples. Randomized controlled trials and open-label studies have assessed subcutaneous, oral, and intranasal formulations; however, only case series/reports have reported on IV ketamine for MDD in older adults, which lacks generalizability and reliability. One study examining the effects of repeat doses of subcutaneous ketamine (ranging from 0.1 to 0.5 mg/kg; ≥1 week between doses) in older adults ($n = 16$) with TRD reported that 68.8% of participants responded/remitted to ketamine, although symptoms began to increase 1 day postinjection and returned to near-baseline levels at day 7.[36] In contradistinction to the report using the subcutaneous route,[36] we observed a more sustained antidepressant effect following repeated IV ketamine infusions, likely due to the shorter dosing intervals and consistent use of therapeutic doses in the current study. However, route of administration is also an important consideration, with distinct pharmacokinetic profiles (maximum concentration [Cmax] and area under the curve [AUC]) and engage distinct metabolic pathways, which could, in turn influence responses.[52]

The largest RCT to date in older adults ($n = 138$) administered intranasal esketamine (28 mg, 56 mg, or 84 mg) twice weekly, co-initiated with an oral antidepressant, for 4 weeks and did not find a significant reduction in depressive symptoms in the esketamine group compared to placebo after 28 days.[53] Importantly, the intranasal route of administration and co-initiation with an oral antidepressant precludes the extrapolation of their results to those observed in our study using IV ketamine without a co-initiated oral antidepressant. This was indeed confirmed in a random-effects meta-analysis comparing disparate routes and formulations of ketamine, in which no conclusions could be made regarding their comparative efficacies.[54] Nevertheless, the reported response rate of 27% is comparable to the response rate of 28% reported in our study. In an open-label phase following the TRANSFORM RCT, participants reported response and remission rates of 69.5% and 46.3%, respectively, similar to those of younger adults. These results indicate that, even though the participants included in our study improved with four doses of ketamine treatment, outcomes may be enhanced with maintenance therapy. A study conducted in hospice patients with a mean age of 63 (SD = 18) also reported a similar response rate (57%) with daily, open-label oral ketamine therapy.[55] In both RCTs, participants who continued onto an open-label phase after the initial study had the best treatment outcomes (i.e., greatest remission and response rates), suggesting that administering ketamine in an experienced and well-equipped open-label setting may lead to better outcomes.

The findings of our study should be interpreted in consideration of the limitations associated with post-hoc chart reviews. For example, participants were not enrolled into the study on the basis of age, and there was no control group to account for placebo/expectancy effects or regression to the mean with repeated sampling. Furthermore, IV ketamine was administered in conjunction with concomitant medications, although participants were advised not to alter antidepressants during treatment. Notably, data on long-term safety and tolerability were not available as participants are not followed once they have discontinued treatment. Information on past medical history (e.g., history of hypertension prior to the first IV ketamine infusion), medical comorbidities, and frailty was not available for analysis. It is important to further explore the safety and tolerability of IV ketamine in these subpopulations. Additionally, our findings are not necessarily generalizable to the safety and efficacy of more than four IV ketamine infusions for older adults. It is also important to consider that "remission" has been operationalized as a score ≤5 on the QIDSR-16

at any one timepoint and does not indicate a stable recovery or "cure" of depressive symptoms. This operationalization of remission that is commonly used in longer clinical trials may not be as generalizable to a rapid-acting treatment and requires further analysis.

The findings presented herein represent a sample of older adults with an average of 7 previous monoamine-based antidepressant trials that did not result in sufficient symptomatic relief. Furthermore, 15% of participants in the included sample had a history of electroconvulsive therapy (ECT), and 5% had a history of repetitive transcranial magnetic stimulation (rTMS). This sample is a strong representation of older adults with TRD that may be encountered in real-world clinical practice, and as such, the findings of this study are generalizable to this patient population. The demographic characteristics of the included sample highlight the need for effective antidepressant treatments that are safe and well-tolerated by older adults. Further research should determine whether ketamine has antisuicidal properties in geriatric populations with consideration of its effect on cognitive function among individuals with MDD and major neurocognitive disorders (e.g., Alzheimer's disease). Hitherto, relatively few treatments that are proven effective for MDD across any age group have demonstrated independent and direct effects on objective cognitive measures.[56] The foregoing deficiency in treatments that are proven efficacious in cognitive function in adults with mood disorders is a significant unmet need.[57] Furthermore, understanding the safety and tolerability of IV ketamine for TRD in adults over the age of 70 and 75 is an important area of future research. Taken together, the current findings suggest that IV ketamine offers a favorable risk-benefit profile with rapid-onset antidepressant effects in older adults with TRD.

AUTHOR CONTRIBUTIONS

Orly Lipsitz: Conceptualization, Methodology, Formal analysis, Writing − original draft, Writing − reviewing & editing. Joshua D. Di Vincenzo: Writing − original draft, Writing − reviewing & editing. Nelson B. Rodrigues: Conceptualization, Methodology, Writing − reviewing & editing. Yena Lee: Writing − reviewing & editing. Danielle S. Cha: Writing − reviewing & editing. David Greenberg: Writing − reviewing & editing. Kayla M. Teopiz: Writing − reviewing & editing. Roger Ho: Writing − reviewing & editing. Bing Cao: Writing − reviewing & editing. Kangguang Lin: Writing − re- viewing & editing. Mehala Subramaniapillai: Data curation. Alastair J. Flint: Writing − reviewing & editing. Kevin Kratiuk: Project administration. Roger S. McIntyre: Conceptualization, Methodology, Supervision, Writing − reviewing & editing. Joshua D. Rosenblat: Conceptualization, Methodology, Supervision, Writing − reviewing & editing.

DISCLOSURE

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JDR has received research grant support from the Canadian Cancer Society, Canadian Psychiatric Association, American Psychiatric Association, American Society of Psychopharmacology, University of Toronto, University Health Network Centre for Mental Health, Joseph M. West Family Memorial Fund and Timeposters Fellowship and industry funding for speaker/consultation/research fees from Janssen, Allergan, Lundbeck, Sunovion and COMPASS. JDR is the medical director of a private clinic providing intravenous ketamine infusions and intranasal esketamine for depression.

KK is the Vice President of Operations at the Canadian Rapid Treatment Center of Excellence (CRTCE) and is a shareholder of Champignon Brands.

YL received salary support from the Global Alliance for Chronic Diseases/Canadian Institutes of Health Research (CIHR)/National Natural Science Foundation of China's Mental Health Team Grant and the CIHR Frederick Banting and Charles Best Canada Graduate Scholarship; personal fees from Champignon Brands.

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SUPPLEMENTARY MATERIALS

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