Original Article

The effectiveness of intravenous ketamine in adults with treatment-resistant major depressive disorder and bipolar disorder presenting with prominent anxiety: Results from the Canadian Rapid Treatment Center of Excellence

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Abstract

Background: Individuals meeting criteria for treatment-resistant depression (TRD) are differentially affected by high levels of anxiety symptoms.
Aims: There is a need to identify the efficacy of novel rapid-onset treatments in adults with mood disorders and comorbid anxious-distress.
Methods: This study included patients with treatment-resistant major depressive disorder (MDD) or bipolar disorder (BD) who were receiving intravenous (IV) ketamine treatment at a community-based clinic. Anxious-distress was proxied using items from the Quick Inventory of Depressive Symptomatology–Self Report 16-item (QIDS-SR_{16}) and Generalized Anxiety Disorder 7-item (GAD7) scales. The difference in QIDS-SR_{16} total score, QIDS-SR_{16} suicidal ideation (SI) item and GAD7 score were analyzed between groups.
Results: A total of 209 adults with MDD ($n = 177$) and BD ($n = 26$) were included in this analysis. From this sample, 94 patients (mean = 45 ± 13.9 years) met the criteria for anxious-distress. Individuals meeting the criteria for anxious-distress exhibited a significantly greater reduction in QIDS-SR_{16} total score following four infusions ($p = 0.02$) when compared with patients not meeting the anxious-distress criteria. Both anxious-distressed and low-anxiety patients exhibited a significant reduction in SI ($p < 0.0001$) following four infusions. Finally, there was a significantly greater reduction in anxiety symptoms in the anxious-distress group compared with the non–anxious distress group following three ($p = 0.02$) and four infusions ($p < 0.001$).
Conclusion: Patients with TRD and prominent anxiety receiving IV ketamine exhibited a significant reduction in depressive, SI and anxiety symptoms.

Keywords
Ketamine, treatment-resistant depression, major depressive disorder, bipolar disorder, anxiety, distress

Introduction

Individuals with mood disorders frequently manifest clinically important anxiety-related symptoms. For example, available studies indicate that approximately 60–80% of patients suffering from major depressive disorder (MDD) or bipolar disorder (BD) manifest prominent anxiety during affective episodes (Gorman, 1996; Lyche et al., 2010). The relevance of anxiety in the mood disorder population is underscored by its association with greater illness complexity, chronicity, suicidality and less favorable psychosocial outcomes (Lyche et al., 2010; Rush et al., 2008; Weiss et al., 2016).

The prevalence of, and hazards posed by, anxiety symptoms in mood disorders provided the impetus for the Diagnostic and Statistical Manual-5 (DSM-5) to introduce the anxious-distress specifier for individuals experiencing a major depressive episode (American Psychiatric Association, 2013). To meet the criteria for the "with anxious distress" specifier, patients must present with two of the following symptoms: (a) feeling keyed up or tense; (b) feeling unusually restless; (c) difficulty concentrating because of worry; (d) fear that something awful may happen; and (e) feeling of potential loss of control (American Psychiatric Association, 2013).

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Existing treatments have yielded less favorable outcomes for the treatment of anxious-distress patients compared with patients with melancholic depression. For example, a *post hoc* analysis of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial suggested that patients with anxious depression have worse outcomes when compared with those with melancholic depression (Fava et al., 2008). While adjunctive antipsychotics have been demonstrated to provide symptomatic relief in some individuals with treatment-resistant depression (TRD), poor tolerability and safety concerns with atypical antipsychotics limit their overall acceptability (Bandelow et al., 2014). Taken together, there is an urgent need to identify novel, effective, acceptable, well-tolerated and safe treatments for adults with mood disorders and prominent anxiety symptoms.

Ketamine is an N-methyl-D-aspartate receptor antagonist shown to provide rapid antidepressant effects in patients with TRD (aan het Rot et al., 2010; Coyle and Laws, 2015; Feifel et al., 2017; Murrough et al., 2013; Phillips et al., 2019). Moreover, available evidence from controlled clinical trials suggests that ketamine is effective in treating symptoms of anxiety as well as anxious depression (Ionescu et al., 2015; Salloum et al., 2019). However, it has been reported that patients who enroll in clinical trials may not be representative of persons receiving care in clinical practice (Lorenzo-Luaces et al., 2018). For example, patients enrolled in clinical research who have multiple comorbidities and suicidal ideation (SI) are often excluded, limiting the generalizability of clinical research results. Against this background, data obtained from naturalistic settings would have external validity relevant to practicing clinicians. Herein, we report on the effectiveness of intravenous (IV) ketamine in adults meeting the DSM-5 criteria for MDD or BD presenting with anxious-distress receiving repeat-dose IV ketamine at a community-based mood disorders center.

Methods

Participants and study design

This report is a post hoc analysis of data previously described elsewhere (McIntyre et al., 2020). All individuals reported in this retrospective analysis herein were patients receiving care at the Canadian Rapid Treatment Center of Excellence (CRTCE) in Mississauga, Ontario, Canada. The CRTCE is an outpatient clinical facility specialized in providing IV ketamine treatment for adults with TRD. Patients were referred to the clinic by primary care physicians or psychiatrists from academic and community-based practices. This facility is the first Canadian clinic that can offer this treatment outside of clinical trials. At this time, IV ketamine is prescribed off-label and therefore is not covered under provincial health insurance plans. Additionally, the enantiomer esketamine, while available in the United States, remains commercially unavailable in Canada.

The CRTCE is a multidisciplinary center focused on treating adult patients (age $\geqslant$ 18 years) with TRD, defined as having at least two inadequate prior antidepressant treatments (i.e. stage 2 resistance defined by Thase and Rush (1997)). Patients presenting with psychiatric comorbidities, such as obsessive–compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) are eligible for treatment at the CRTCE, as long as the mood disorder is the primary diagnosis. SI is not an exclusion criterion for receiving IV ketamine treatment. All patients receiving IV ketamine at the CRTCE must be able to provide full informed consent to treatment, which involves full understanding of potential risks and benefits of the treatment.

The exclusion criteria for IV ketamine include patients presenting with psychosis, dementia, substance use disorder or alcohol use disorder as determined by the staff psychiatrist. Importantly, patients can use recreational drugs or alcohol, as long as they do not meet the criteria for the disorder. Patients must agree to remain on the premises for up to an hour following infusion for safety surveillance and must be escorted home by a responsible adult. All patients must be medically cleared by the staff anesthesiologist who screens for medical disorders contraindicated against ketamine (e.g. malignant hypertension, uncontrolled seizures, etc.). Concomitant psychotropic medications are permitted with the exception of benzodiazepines and naltrexone which may attenuate IV ketamine's efficacy (Frye et al., 2015; Williams et al., 2018). Patients are also required to discontinue monoamine oxidase inhibitors in order to minimize the risk of developing serotonin syndrome.

In the study described here, once approval for treatment was provided by the clinic psychiatrist and anesthesiologist, patients received a series of four infusions of ketamine hydrochloride, diluted in a 0.9% saline solution The first two infusions were dosed at 0.5 mg/kg, calculated using the patient's actual body weight. Any patients who had a suboptimal clinical response, as measured by a $\leqslant$20% reduction in the total Quick Inventory for Depressive Symptomatology–Self Report 16-item ($QIDS\text{-}SR_{16}$) score, were eligible to receive a dose optimization to 0.75 mg/kg for the third and fourth infusion. Exempted from dose optimization were individuals who had a $>$20% improvement in $QIDS\text{-}SR_{16}$ score, poor tolerability to the index dose and/or patient preference. Treatments were infused over a period of 40–45 min. Immediately following the completion of each infusion, the Clinician-Administered Dissociative States Scale (CADSS) was used to assess dissociative symptom severity.

Depending on scheduling, the four treatments were booked over a period of 7–14 days. Following these initial four treatments, patients were scheduled for a follow-up assessment by the staff psychiatrist one week after their fourth infusion (i.e. the post-ketamine treatment visit). Figure 1 describes the clinic protocol.

Assessments

The primary outcome was to determine whether there was a difference in improvement in depressive symptoms, as measured by the $QIDS\text{-}SR_{16}$, between the two cohorts. Secondary outcomes evaluated if there was a difference in improvement in SI, measured by the $QIDS\text{-}SR_{16}$ item 12 score, and anxiety symptoms, measured with the General Anxiety Disorder 7-item (GAD7) scale. In addition, the tolerability of IV ketamine was evaluated between the two cohorts, measured by the CADSS.

The $QIDS\text{-}SR_{16}$ was administered at five time points (i.e. baseline, post-infusion 1, post-infusion 2, post-infusion 3 and the post-ketamine treatment visit). The GAD7 scale was administered at baseline, post-infusion 3 and the post-ketamine treatment visit. The CADSS was administered at each of the four infusions (i.e. infusion 1, infusion 2, infusion 3 and infusion 4).

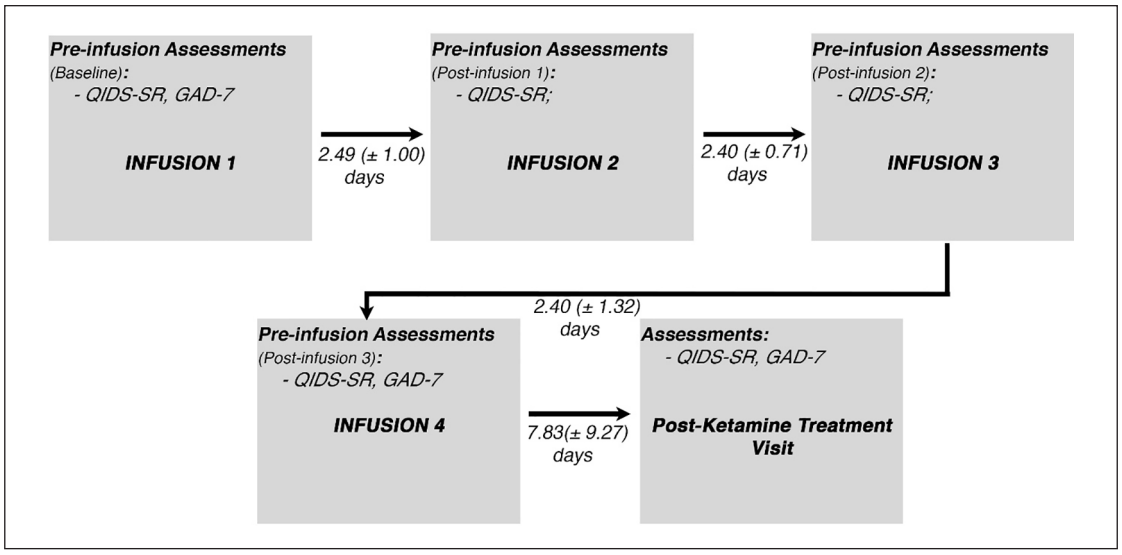

Figure 1. Clinical protocol for patients receiving intravenous ketamine at the Canadian Rapid Treatment Center of Excellence.

Given that specific diagnosis for the DSM-5-defined "with anxious distress" specifier was not established at entry, proxies were developed *post hoc* to determine the presence of prominent anxiety amongst the patients. Each symptom was defined a priori with scale items within the QIDS-SR_{16} and GAD7. Proxies were defined as follows: feeling keyed up or tense: GAD7 question 1 = 3; feeling unusually restless: GAD7 question 5 = 3; difficulty concentrating because of worry: QIDS-SR_{16} question 10 = 3 AND GAD7 question 3 = 3; fear that something awful may happen: GAD7 question 7 = 3. No proxy question could be established for "feeling of potential loss of control." As a result, patients were stratified into the anxious-distress group if they met 2 of 4 symptoms (rather than 2 of 5). Question proxies are further described in Table 1.

Analysis was approved by a community institutional review board and registered at clinicaltrials.gov under NCT04209296.

Statistical analysis

Deidentified data were collected at point-of-care using a tablet device and stored directly into the REDCap platform (Harris et al., 2009, 2019). Data were analyzed using the Statistical Product and Service Solutions (SPSS version 22 for Mac; SPSS Inc., Chicago, IL, United States) and GraphPad Prism 8.0.

A repeated measures hierarchical model was conducted to evaluate the change in QIDS-SR_{16} total score, QIDS-SR_{16} SI score, GAD7 total score and the CADSS total score across infusions. Baseline depressive severity, SI severity and anxiety severity were controlled for in their respective models. The model terms were *group, infusion* and *group by infusion interaction*. In order to assess whether cohorts responded differently to ketamine, the least square mean difference from baseline to subsequent time points in QIDS-SR_{16} total score, QIDS-SR_{16} SI score and GAD7 total score were also analyzed using a repeated measures hierarchical model. A compound symmetry covariance matrix was used and the data were fit using restricted maximum likelihood with the alpha set at 0.05. A Bonferroni correction was applied to adjust for multiple comparisons. In order to assess collinearity between the QIDS-SR_{16} total score, SI score and the GAD7 total score, the change in each variable from baseline to the post-ketamine treatment visit was calculated. A Spearman correlation test was used to evaluate the association between the depressive severity, SI severity and anxiety severity variables.

Results

In total, 230 patients were evaluated at the CRTCE from July 2018 to December 2019. Twenty-one patients were excluded from this analysis as they could not be grouped due to unavailable GAD7 or QIDS-SR_{16} data at baseline. The analysis herein reports on 94 patients (mean = 45 ± 13.9 years) with anxious-distress and 115 patients (mean = 46 ± 15.1 years) who did not meet the specifier's criteria. Forty-five percent of participants met our proxy criteria for the "with anxious distress" specifier. Baseline demographics are described in Table 2. There were no significant between-group differences in age, body mass index, or sex. Notwithstanding, the individuals meeting the criteria for anxious-distress presented with a worse symptom profile compared with those who did not meet the criteria, as measured by the baseline QIDS-SR_{16} and GAD7 scores.

Depressive symptom severity

After adjusting for baseline depressive severity, there was an overall significant main effect of infusion ($F(4, 635.9) = 81.4$, $p < 0.001$) as well as a significant group by infusion interaction ($F(4, 635.9) = 3.2$, $p = 0.013$; Figure 2(a)) on QIDS-SR_{16} total score. The low–anxious distress group depression scores significantly improved from baseline to post-infusion 1 ($p < 0.001$), post-infusion 2 ($p < 0.001$), post-infusion 3 ($p < 0.001$) and post-ketamine treatment ($p < 0.001$). Moreover, there was

Table 1. Question proxies for determining if patient meets the criteria for the specifier "with anxious distress".

Symptom	Proxy	Item Description
Tension	GAD7 Item item 1	Feeling nervous, anxious, or on edge
		0 Not Not at all sure
		1 Several Several Daysdays
		2 Over Over half the days
		3 Nearly Nearly every day
Restlessness	GAD7 Item item 5	Being so restless that it's hard to sit still
		0 Not Not at all sure
		1 Several days
		2 Over Over half the days
		3 Nearly Nearly every day
Concentration	QIDS-SR_{16} Item item 10	Concentration/Decision decision Makingmaking
		0 There is no change in my usual capacity to concentrate or make decisions.
		1 I occasionally feel indecisive or find that my attention wanders.
		2 Most of the time, I struggle to focus my attention or to make decisions.
		3 I cannot concentrate well enough to read or cannot make even minor decisions
	GAD7 Item item 3	Worrying too much about different things
		0 Not at all sure
		1 Several Daysdays
		2 Over half the days
		3 Nearly every day
Apprehension	GAD7 Item item 7	Feeling afraid as if something awful might happen
		0 Not at all sure
		1 Several Daysdays
		2 Over half the days
		3 Nearly every day

GAD7: Generalized Anxiety Disorder 7-item; QIDS-SR_{16}: Quick Inventory of Depressive Symptomatology–Self Report 16-item.

Table 2. Baseline Characteristics.

Characteristic at Baseline	Anxious Distress (n = 94)	Low–Anxious distress (n = 115)
Sex, *n* (% within cohort)		
Male	37 (39.4)	55 (47.8)
Female	57 (60.6)	60 (52.2)
Age in years, mean (SD)	45 (13.9)	46 (15.1)
BMI (Kg/m^2), mean (SD)	27.5 (6.7)	28.8 (6.7)
Primary diagnosis, *n* (% within cohort)		
MDD	80 (85.1)	95 (82.6)
BD	11 (11.7)	14 (12.1)
PTSD	2 (2.1)	3 (2.6)
OCD	1 (1.1)	3 (2.6)
Number of prior lifetime antidepressant trials, mean (SD)	6.27 (4.7)	5.37 (3.6)
Number of antidepressants at time of infusion, mean (SD)	1.23 (1.00)	1.45 (1.81)
Baseline QIDS-SR_{16} total score, mean (SD)*[a]	20.84 (3.4)	16.55 (4.8)
Baseline QIDS-SR_{16} total score, mean (SD)*[a]	1.71 (0.99)	1.43 (0.97)
Baseline GAD7 total score, mean (SD)*[a]	17.96 (2.4)	10.93 (5.0)

(*[a]) Indicates a significant difference between the two cohorts.
BD: bipolar disorder; BMI: body mass index; GAD7: Generalized Anxiety Disorder 7-item; MDD: major depressive disorder; OCD: obsessive–compulsive disorder; PTSD: post-traumatic stress disorder; QIDS-SR_{16}: Quick Inventory of Depressive Symptomatology–Self Report 16-item; SD: standard deviation.

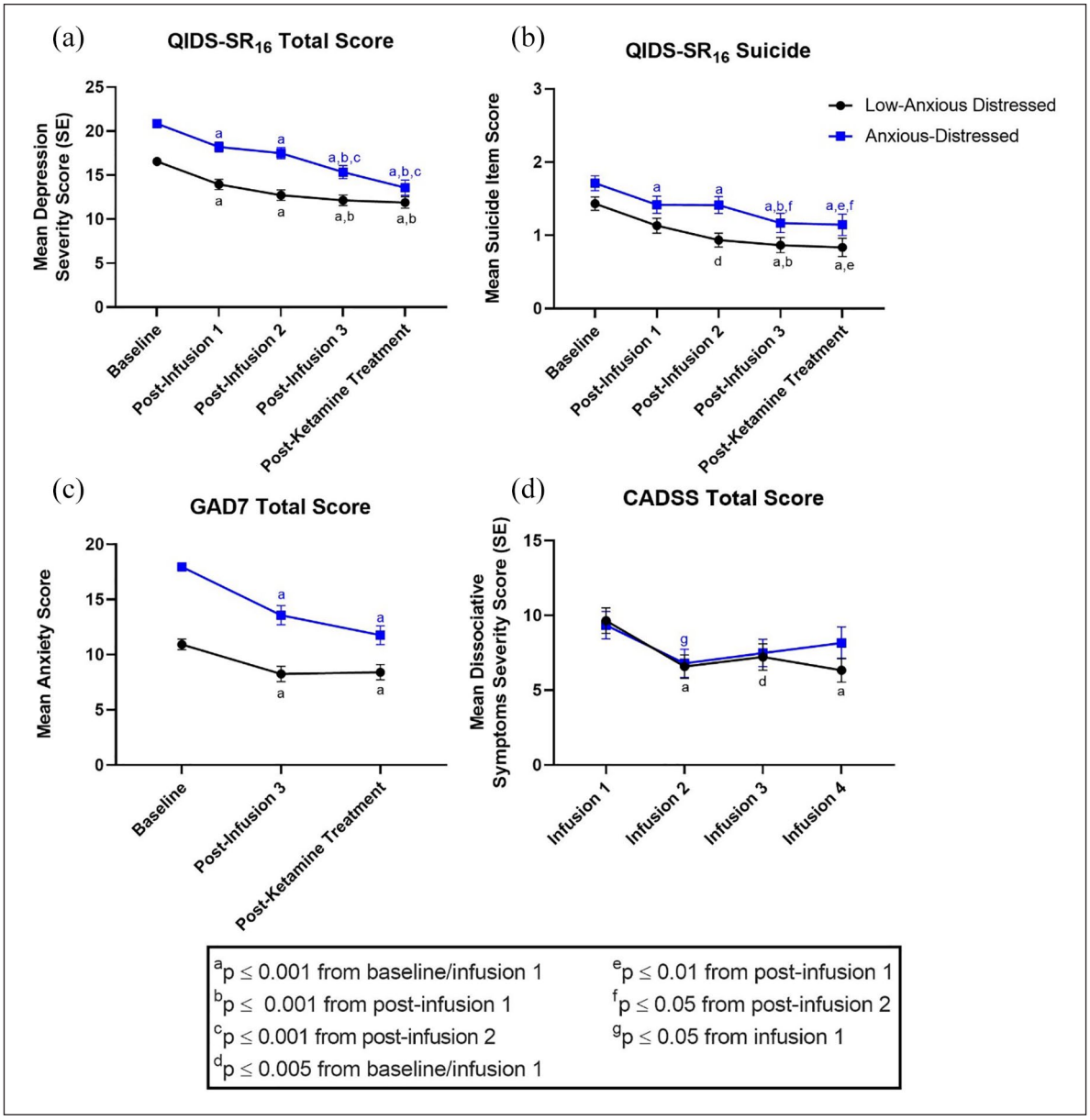

Figure 2. (a) Mean (±SE) total QIDS-SR_{16} score in both cohorts across four infusions. (b) Mean (±SE) score of the QIDS-SR_{16} suicidal ideation item in both groups across four infusions. (c) Mean (±SE) GAD7 total score in both cohorts across four infusions. (d) Mean (±SE) CADSS total score in both groups across four infusions.

CADSS: Clinician-Administered Dissociative States Scale; GAD7: Generalized Anxiety Disorder 7-item; QIDS-SR_{16}: Quick Inventory of Depressive Symptomatology–Self Report 16-item; SE: standard error.

a significant reduction from post-infusion 1 to post-infusion 3 ($p = 0.001$) and the post-ketamine visit ($p < 0.001$). Similarly, the anxious-distress group had a significant reduction in depressive symptoms from baseline to all subsequent time points (all $p < 0.001$). Moreover, the depression scores significantly decreased from post-infusion 1 to post-infusion 3 and post-ketamine treatment (all $p < 0.001$). Finally, the anxious-distress patients' depression scores significantly decreased from post-infusion 2 to post-infusion 3 and post-ketamine treatment (all $p < 0.001$).

Although both cohorts significantly improved, analysis of the least square mean difference from baseline of QIDS-SR_{16} total score indicated a significant effect of group ($F(1, 596) = 10.3$, $p = 0.001$) and infusion ($F(3, 596) = 18.7$, $p < 0.001$; Figure 3(a)). Pairwise comparison indicated that the patients with anxious-distress experienced significantly greater improvement than the low–anxious distress patients at the post-ketamine treatment ($p = 0.02$).

In order to evaluate the change in QIDS-SR_{16} total score, without accounting for the change in questions used as proxies, a separate mixed model was run, removing QIDS-SR_{16} item 10. There was a significant main effect of infusion ($F(4, 636.8) = 80.3$, $p < 0.001$) and a significant group by infusion interaction ($F(4, 636.9) = 2.7$, $p = 0.03$). The low–anxious distress group

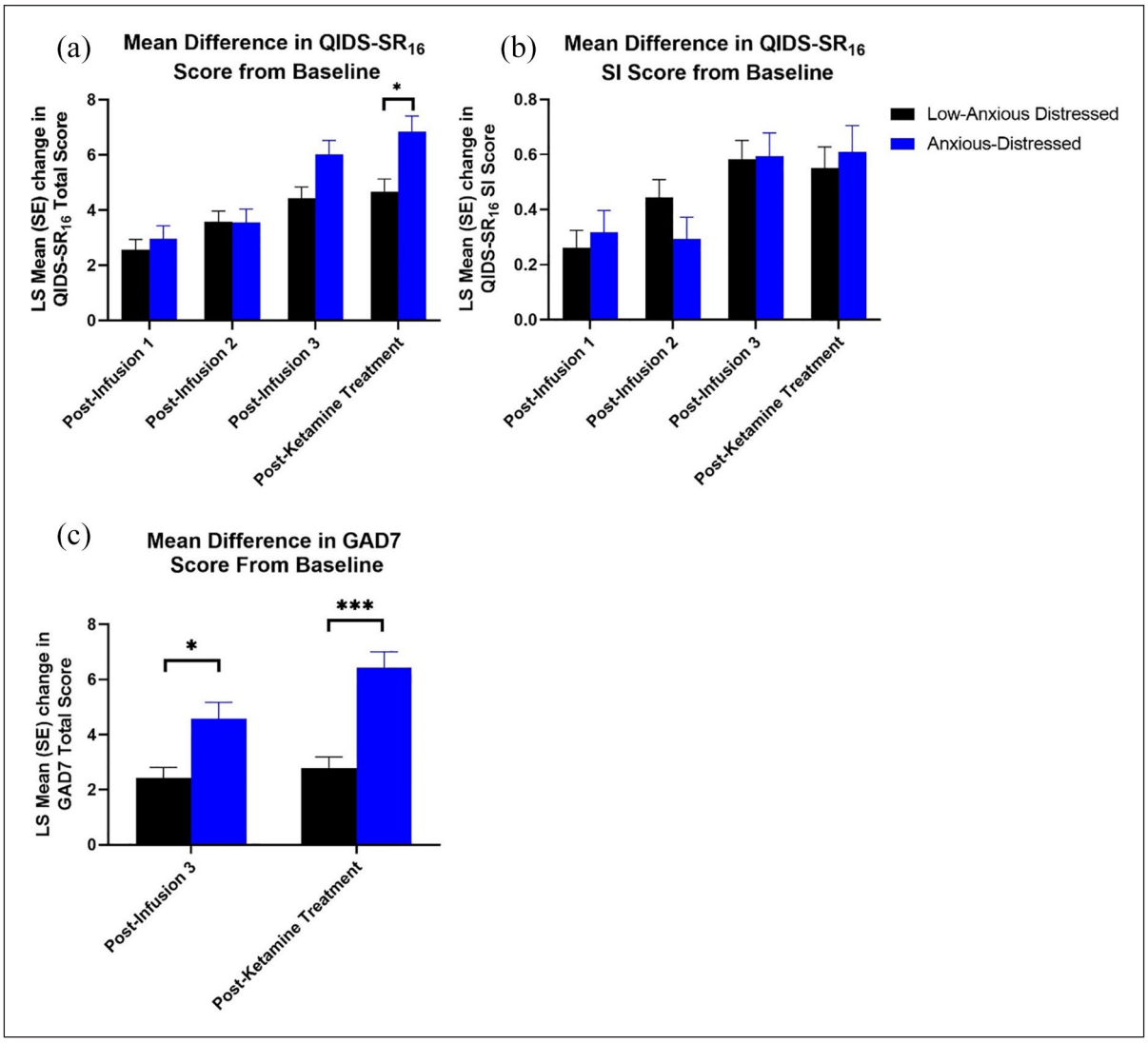

Figure 3. (a) Least square mean difference in the QIDS-SR_{16} total score (i.e., depressive symptom reduction) from baseline to each subsequent time point between the two cohorts. (b) Least square mean difference in the QIDS-SR_{16} suicidal ideation (i.e., suicidal ideation symptom reduction) from baseline to each subsequent time point between the two cohorts. (c) Least square mean difference in the GAD7 (i.e., anxiety symptom reduction) from baseline to each subsequent time point between the two cohorts.

GAD7: Generalized Anxiety Disorder 7-item; LS: least square; QIDS-SR_{16}: Quick Inventory of Depressive Symptomatology–Self Report 16-item; SE: standard error; SI: suicidal ideation.

had a significant reduction in depressive score from baseline to all subsequent time points (all $p < 0.001$). There was also a significant reduction from post-infusion 1 to post-infusion 3 and the post-ketamine treatment visit (all $p < 0.001$). Similarly, the anxious-distress patients had a significant reduction in depressive symptoms from baseline to all subsequent time points (all $p < 0.001$). In addition, scores from post-infusion 1 and post-infusion 2 were significantly higher than scores from post-infusion 3 and the post-ketamine infusion visit (all $p < 0.001$).

There was a significant difference in baseline QIDS-SR_{16} SI score and this was therefore adjusted for in subsequent analysis. Analysis of QIDS-SR_{16} SI yielded a significant main effect of infusion ($F(4, 639.4) = 32.1$, $p < 0.001$) but no significant main effect of group ($F(1, 219.3) = 1.2$, $p = 0.277$) or group by infusion interaction ($F(4, 639.5) = 0.97$, $p = 0.42$; Figure 2(b)). Low–anxious distress patients' SI significantly decreased from baseline to post-infusion 2 ($p = 0.003$), post-infusion 3 ($p < 0.001$) and post-ketamine visit ($p < 0.001$). There was also a significant reduction from post-infusion 1 to post-infusion 3 ($p < 0.001$) and the post-ketamine infusion visit ($p = 0.009$). The anxious-distress patients had a significant reduction in SI from baseline to all subsequent time points (all $p < 0.0001$); from post-infusion 1 to post-infusion 3 ($p < 0.0001$) and the post-ketamine visit ($p < 0.002$); and from post-infusion 2 to all subsequent time points ($p = 0.01$; $p = 0.03$). Analysis of least square mean difference of the suicide item scores indicated a significant main effect of infusion ($F(3, 596) = 7.9$, $p < 0.001$; Figure 3(b)). After correction, no significant differences emerged between the groups. There was a significant correlation between the change in

QIDS-SR$_{16}$ total score and change in QIDS-SR$_{16}$ SI score ($r_s(109) = 0.60$, $p < 0.001$).

Anxiety symptom severity

After controlling for the effects of baseline anxiety symptoms, there was a significant main effect of infusion ($F(2, 326.9) = 81.4$, $p < 0.001$) and a significant group by infusion interaction ($F(2, 326.9) = 11.2$, $p < 0.001$) but no significant main effect of group ($F(1, 241.7) = 2.7$, $p = 0.99$) in anxiety scores (Figure 2(c)). Pairwise comparison revealed that low–anxious distress patients had a significant reduction in GAD7 score from baseline to post-infusion 3 ($p < 0.001$) and the post-ketamine treatment visit ($p < 0.001$). Patients who met the anxious-distress criteria had a significant reduction in GAD7 score from baseline to post-infusion 3 and post-ketamine treatment (all $p < 0.001$). Moreover, analysis of the least square mean difference from baseline indicated that anxious-distress patients experienced significantly more relief of symptoms compared with low–anxious distress patients at post-infusion 3 ($p = 0.04$) and post-ketamine treatment ($p = 0.0002$; Figure 3(c)). There were significant correlations between the change in GAD7 total score and the change in QIDS-SR$_{16}$ total score ($r_s(105) = 0.65$, $p < 0.001$) and the change in QIDS-SR$_{16}$ SI score ($r_s(109) = 0.42$, $p < 0.001$).

Tolerability

There was a significant main effect of infusion ($F(3, 508.6) = 10.3$, $p < 0.001$) but no main effect of group ($F(1, 189.6) = 0.298$, $p = 0.59$) or group by infusion interaction ($F(3, 508.6) = 1.4$, $p = 0.23$; Figure 2(d)). Pairwise comparisons for low-anxiety patients indicated there was a significant reduction in CADSS total score from infusion 1 to infusion 2 ($p < 0.001$), infusion 3 ($p < 0.004$) and infusion 4 ($p < 0.001$). Patients who met the criteria for anxious-distress exhibited a significant decrease from infusion 1 to infusion 2 ($p = 0.02$).

Discussion

Individuals with TRD and a proxy definition of anxious-distress manifest significant reduction in depressive and anxiety symptom severity as well as SI after repeat-dose IV ketamine. Significant reductions in overall depressive symptom severity, as measured by QIDS-SR$_{16}$ scores, were seen in both the anxious-distress and low–anxious distress groups with greater reductions observed in the anxious-distress group. We also observed a significant and sustained reduction in SI with IV ketamine treatment in both the anxious-distress and low–anxious distress groups. Anxiety symptoms also significantly reduced in patients with anxious depression, a finding that aligns with extant studies (Ionescu et al., 2015; Salloum et al., 2019; Wang et al., 2019).

Overall, IV ketamine was well tolerated by both groups, who experienced mild to moderate dissociation during infusion. Dissociation symptom severity resolved during the recovery period, and all discharged patients were oriented in time, person and place. Dissociation symptoms were highest immediately following infusion 1 for patients in the low–anxious distress group. There was a significant attenuation in dissociation severity in subsequent infusions, compared with the baseline infusion, despite 60% ($n = 66$) of patients receiving a dose increase to 0.75 mg/kg. For patients in the anxious-distress cohort, dissociation severity reduced from the baseline infusion to the second infusion. Dissociation severity at the third and fourth infusions, comparatively, were not significantly different than dissociation severity at baseline, indicating a resurgence in dissociation symptoms. Similarly, 60% ($n = 56$) of patients in this cohort also received the dose increase, suggesting that patients with high baseline anxiety may be more sensitive to the dissociative effects of IV ketamine.

Available studies indicate that IV ketamine may preferentially reduce depression symptoms in patients presenting with anxious depression compared with non–anxious depression. For example, it has been reported that individuals meeting the criteria for anxious depression ($n = 84$) exhibited significantly higher response and remission rates with six repeated doses of IV ketamine (Wang et al., 2019). It has also been reported that IV ketamine and its enantiomer esketamine are able to significantly reduce severe anxiety symptoms after a single infusion (Falk et al., 2020; Ionescu et al., 2015; Salloum et al., 2019).

Replicated evidence suggests that IV ketamine may be a viable treatment option for patients presenting with anxiety spectrum disorders. For example, an open-label study of IV ketamine infusions ($n = 6$) reported that 80% of patients experienced remission of PTSD symptoms (Albott et al., 2018). In addition, a recent report from the Canadian Agency for Drugs and Technologies in Health updated guidelines to include IV ketamine as a potential therapeutic agent for patients suffering from refractory PTSD (CADTH, 2014). A separate study investigating generalized anxiety disorder and social anxiety disorder indicated a 50% reduction in anxiety, as measured by the Hamilton Anxiety Rating Scale, within an hour of completing infusion (Glue et al., 2018). The reduction in anxiety reported was sustained in 25% of patients at the 3-month follow-up (Glue et al., 2018). Conversely, research has yielded mixed results for patients suffering from OCD. An initial open-label study suggested that ketamine improved OCD symptoms by less than 12%; however, a subsequent randomized, cross-over, placebo-controlled study reported that 50% met the response criteria (defined as a >35% reduction in the Yale-Brown Obsessive–Compulsive Scale) following a single 0.5 mg/kg dose of IV ketamine (Bloch et al., 2012; Rodriguez et al., 2013). Overall, the efficacy of IV ketamine in treating anxiety symptoms remains preliminary but promising in this population that is not only often resistant to conventional approaches including psychotherapy but is also highly comorbid in adults with TRD. It should be noted, however, that although patients meeting the anxious-distress specifier had a greater reduction in anxiety symptoms following IV ketamine, the low–anxious distress group presented with low-anxiety symptom severity at baseline, and therefore further decline would not have been expected. Therefore, further randomized control trials would be needed to determine if IV ketamine has a preferential effect in treating TRD patients with anxious-distress, compared with those who do not meet the specifier's criteria.

We also observed a significant reduction in SI in the anxious-distress and low–anxious distress groups. A recent meta-analysis

further extended the observation that anxiety is highly associated with SI and suicidal risk in adults with mood disorders (Stanley et al., 2018). The notion that reducing anxiety in adults with mood disorders may contribute to the reduction in SI was substantiated by recent study results indicating that a single IV ketamine infusion in adults with mood disorders reduces anxiety and SI. It was further reported that the reduction in anxiety accounted for nearly 16% of the variance in the change of SI score (Ballard et al., 2014).

There are several methodological limitations that affect inferences and interpretations of our data. Primarily, herein, results are from a retrospective, naturalistic, open-label dataset of patients receiving IV ketamine at a treatment facility. As a result, no control group is included that would serve as a comparator. Moreover, given that the data were not collected as a part of a clinical trial, a large amount of data is missing due to patients refusing to complete questionnaires or being lost to follow-up. There is also a significant degree of variability in the timing of the post-ketamine treatment visit as patients were scheduled based on their availability. In addition, long-term data beyond the post-ketamine treatment visit are not available, as many patients returned to the clinic for maintenance infusions once symptoms relapsed, thus introducing significant variability to the data. Moreover, the anxious-distress specifier group was not determined by a clinician, but rather proxied through the QIDS-SR_{16} and the GAD7. Therefore, the questionnaire items may not accurately reflect symptoms observed in the anxious-distress modifier. As an example, the symptom of "difficulty concentrating due to worry" was proxied through the QIDS-SR_{16} item 10 and GAD7 item 3. However, neither item directly determines if the difficulty concentrating was due to worrying. While combining the two items aimed to increase the construct validity, there remains uncertainty. Finally, it should also be noted that the models assessing anxiety severity were assessed independently of depressive severity. We therefore did not account for the issue of colinear improvement between depression and anxiety. Notwithstanding these limitations, the analysis herein included a large sample that is representative of patients with TRD. Additional strengths of this study are its real-world representativeness of the patients, the use of standardized rating measures and the use of IV ketamine in a community-based clinic.

Taken together, repeat-dose IV ketamine significantly reduced depressive and anxiety symptoms, as well as SI, in adults with TRD. It is a testable hypothesis that the reduction in SI observed in adults with mood disorders may in part be mediated by reduction in anxiety-related symptoms. The observation from our study, which comports with available literature, that IV ketamine is capable of significantly reducing anxious symptoms has tremendous clinic relevance insofar as anxiety symptoms pose significant hazards and are associated with significant psychosocial impairment and suicidality.

Declaration of conflicting interests

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