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Research Paper

Do baseline anxiety symptoms impact response to IV Ketamine in treatment resistant depression?

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ABSTRACT

Objective: In a retrospective study, we analyzed if anxious depression impacts outcomes in patients with treatment resistant depression (TRD) receiving IV Ketamine infusions at an academic center Ketamine clinic.
Methods: Forty-three patients with TRD received six IV Ketamine infusions over a three-week period. Anxious depression (ANX-TRD) was defined as a Hamilton Depression Rating Scale Anxiety/Somatization factor score of ≥ 7 at the baseline evaluation. Beck Depression Inventory (BDI-II) and Generalized Anxiety Disorder-7 (GAD-7) scales were used through the infusion course to assess symptom change.
Results: Twenty-three patients were categorized as ANX-TRD and 20 as non-anxious TRD. Generalized estimating equation (GEE) models revealed BDI-II and GAD-7 scores for ANX-TRD and NANX-TRD groups did not differ significantly during any time point. Symptoms of anxiety and depression improved after treatment in both groups, though the degree of change was significant and greater for depression.
Limitations: This was a naturalistic, retrospective study, without a control group.
Conclusions: Symptoms of depression show greater improvement than symptoms of anxiety. IV Ketamine is effective in the treatment of depression, regardless of the baseline anxiety level.

1. Do baseline anxiety symptoms impact response to IV Ketamine in treatment resistant depression?

40–60% of patients with MDD also have symptoms of anxiety (Gaspersz et al., 2017). In research trials, anxious depression is most commonly classified as a diagnosis of MDD along with a score of seven or greater on the anxiety/somatization factor of the 17 or 21-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1960). This score includes hypochondriasis, insight, general and gastrointestinal somatic symptoms, and psychic and somatic anxiety. This definition has been used to distinguish anxious depression as a clinically distinct subtype of depression (Hamilton, 1960).

Patients with anxious depression endorse higher scores on mood rating scales, more pain, more severe functional impairment, a more chronic course, poorer quality of life, worse psychosocial functioning, and have a greater risk of suicide and greater odds of completed suicide than non-anxious depression patients (Pfeiffer et al., 2009; Liu et al., 2019; Ionescu et al., 2013). Additionally, anxious depression is associated with poorer treatment response to monoaminergic antidepressants, greater side effect burden, and shorter time to relapse (Ionescu et al., 2015). Because anxious depression is a distinct subtype associated with worse outcomes, research has increasingly focused on how best to treat it, particularly among patients with TRD (Ionescu et al., 2013a; 2013b).

Ketamine, in subanesthetic infusions, has demonstrated positive results in patients with anxious TRD. Across three of four main secondary analyses of randomized clinical trials (Ionescu et al., 2014; Ionescu et al., 2015; Salloum et al., 2019), TRD patients with anxious depression have been shown to respond to Ketamine as well as – if not better than – patients without anxious depression, particularly with regard to its antidepressant effects. For example, Ionescu et al. (2014) found that unipolar TRD patients with anxious depression, who received a single intravenous Ketamine infusion of 0.5 mg/kg, did comparably well or better than patients with non-anxious depression, including lower depression scores and slower time to depression relapse compared to

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non-anxious TRD patients (Ionescu et al., 2014). Salloum et al. (2019) similarly found that 0.2, 0.5, and 1.0 mg/kg doses of IV Ketamine were efficacious for patients with and without anxious depression. In contrast, recent work by Chen et al. (2020) demonstrated that patients with non-anxious depression had greater depressive symptom reduction than patients with anxious depression when treated with IV Ketamine at 0.5 mg/kg.

Beyond the antidepressant effects of Ketamine, it is critical to understand to what extent symptoms of anxiety are also likely to change. Previous trials have been powered to analyze depression outcomes, though there is initial evidence that symptoms of anxiety can improve with IV Ketamine, including patients with anxious depression (Ionescu et al., 2014; Ionescu et al., 2015).

Taken together, research suggests that IV Ketamine may offer antidepressant benefits for TRD patients presenting with anxious depression – and that IV Ketamine may exert anxiolytic effects more broadly (Fortress et al., 2018; Parise et al., 2013). That said, much of this research has been conducted in proof-of-concept studies, following patients over a single infusion. Moreover, head-to-head comparisons of changes in anxiety relative to changes in depression are rare. It remains understudied how symptoms of anxiety change after a series of Ketamine infusions in real-world clinical TRD patients, relatively to changes in depression. Secondarily, it is unclear if the antidepressant response to a course of IV Ketamine is impacted by anxious symptoms. To this end, one recent study showed modest but significant anxiety improvements among a sample of TRD patients receiving a course of four infusions (McIntyre et al., 2020b), and two studies following anxious TRD patients over a course of four (McIntyre et al., 2020a) and six (Wang et al., 2019) infusions demonstrated significant improvement in symptoms of anxiety among anxious depressed patients. This growing body of work suggests that continuing to study patients in ecologically valid treatment contexts is essential to improving our capacity to match patients to the most effective of treatments, particularly patients with unremitting depressive disorders who have already demonstrated lack of response to previous antidepressant treatments.

In the present study, we provide data from an effectiveness context, assessing unipolar TRD patients over an acute course of IV Ketamine in an academic center Ketamine clinic. This retrospective study intended to analyze how anxiety symptoms change in patients receiving a course of Ketamine, and their relationship to the change in depressive symptoms. Additionally, it sought to clarify if patients with anxious depression respond differently to the infusions, compared to non-anxious patients.

2. Methods

2.1. Participants

Data from participants aged 18 years and older from the Treatment Resistant Depression Clinic at [institution blinded for review] were used in the analysis. The TRD clinic serves a consultative role to referring community psychiatrists with regard to diagnosis and treatment planning, and offers interventional psychiatric treatment options for their TRD, including Ketamine, esketamine, non-invasive and invasive neuromodulation treatments. 87% of patients evaluated in the clinic have failed three or more antidepressant trials in the current episode. Analyses included participants who, having been evaluated in the TRD clinic, received a diagnosis of unipolar depression and initiated a single, acute course of intravenous subanesthetic Ketamine between June 2017 and February 2020, in order to (a) assess changes in anxiety relative to the changes in depression during an acute IV Ketamine course; and (b) evaluate whether the categorization of patients in "anxious" or "non-anxious" depression had a difference in clinical outcomes.

The protocol was approved by the Institutional Review Board (IRB00093806); the IRB approved data inclusion and analysis for all clinic patients, including those previously collected under a quality assurance project. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Procedures and measures

Consultation visits included psychiatric and psychosocial evaluations with multi-disciplinary team members, and all patients met with a psychiatrist. The primary psychiatric diagnosis was determined after a consensus conference using DSM5 criteria (American Psychiatric Association, 2013).

2.2.1. Determination of anxious depression

A reliably trained interviewer assessed prior-week symptoms with the 17-item Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1960), which consists of nine items rated 0 to 4 and eight items rated 0 to 2, for a score range of 0–52. A subset of the interviews was watched and coded by a second team member, achieving a very good intraclass correlation coefficient (0.95, 95% CI: 0.87–0.98). In line with previous research (Ionescu et al., 2014; Ionescu et al., 2015; Salloum et al., 2019; Chen et al., 2020), to categorize patients as anxious (ANX-TRD) and non-anxious (NANX-TRD), a summary score of six items from the HDRS-AS was comprised: psychic anxiety, somatic anxiety, somatic symptoms (gastrointestinal), somatic symptoms (general), hypochondriasis, and insight. ANX-TRD was defined as a score of 7 or greater.

2.2.2. Intravenous Ketamine infusions

The clinical protocol for administration of IV Ketamine for the treatment of depression was approved by the Medical Practice Committee of [institution blinded for review] University Hospital. The data collection and retrospective analysis presented in this report was authorized by the university's Institutional Review Board. All infusions were administered in the ECT/Neuromodulation Suite at [institution blinded for review] University Hospital and conducted as part of regular clinical care. The neuromodulation suite is dedicated solely to the delivery of ECT and Ketamine infusions and is staffed by nurses who are trained in the management of interventional procedures in patients with psychiatric illnesses. All nurses were ACLS certified and proficient in the management of patients with mild sedation (i.e., ECT recovery) and the physicians were certified in moderate sedation practices.

Racemic Ketamine was administered by continuous IV infusion using an electronic infusion pump (Sigma Spectrum, Baxter, IL). Dosing was determined based on body weight. All participants received 0.5 mg/kg of Ketamine in a 100-cc saline solution infused at a rate of 150 cc/h over 40 min. An acute course of Ketamine consisted of six infusions delivered over a period of three weeks, on a Tuesday/Thursday schedule. Ketamine was prepared by the hospital pharmacy the morning of the infusion. Patients were permitted to take all prescribed medications the morning of the infusion, especially antihypertensive medications.

2.2.3. Mood and anxiety assessments

During the acute course of treatment, patients completed the Beck Depression Inventory-II questionnaire (Beck et al., 1996), which was completed prior to the first infusion ("baseline"), prior to the 2nd infusion ("post-infusion 1″), prior to the 6th infusion ("post-infusion 5″), and prior to infusion 7 ("post-acute course"). The BDI-II is a 21-item measure

of depression severity with responses ranging from 0 to 3 and a total score ranging from 0 to 63. The clinic began collecting routine anxiety data subsequent to initiation of the BDI-II data collection.[2] As such, a subset of patients completed the Generalized Anxiety Disorder-7 Scale (GAD-7; Spitzer et al., 2006), following the same assessment schedule. GAD-7 measures anxiety symptoms with responses ranging from 0 to 3 and a total score ranging from 0 to 21. At the time of the first infusion, patients were asked to evaluate their mood over the preceding two weeks, and each rating scale onward evaluated the time since their last infusion.

2.2.4. Statistical analysis

Demographic and clinical history was completed for all participants, as well as separated by the anxious depression category. BDI-II and GAD-7 values were calculated as means and standard deviation at all assessment points, and also stratified in the anxious depression categories. Independent samples *t*-tests were used to compare the two groups at each time point.

To assess the degree of change in anxious symptoms during an acute course of treatment, and to understand this change relative to change in depressive symptoms, two generalized estimating equation (GEE) models were calculated. GEE is an extension of generalized linear models (GLMs), designed to accommodate the modeling of inter-correlated data, making it ideal to analyze longitudinal data. GEE achieves an extra level of robustness by inferring the correlations between observations and creates a system for performing inference using a mean model approach. In the first 2 GEE models, the degree of change in BDI-II and GAD-7, respectively, were examined, with time as the predictor, including the timepoints of baseline, post-infusion 1, post-infusion 5, and post-acute course. Two-tailed $p < .05$ was considered statistically significant.

To compare demographic and clinical data between ANX-TRD and NANX-TRD, continuous and nominal variables were analyzed with independent samples *t*-tests and Fisher's chi square tests, respectively. To examine the effect of ANX-TRD on change in depression during an acute course of Ketamine, three models were tested to evaluate model fit. The first model included ANX-TRD (dichotomous) and time as predictors; the second model included ANX-TRD, time, and the interaction between time and ANX-TRD as predictors; and the third model included ANX-TRD, the interaction between time and ANX-TRD, and baseline depression severity as predictors. Best model of fit was identified by comparing Quasilikelihood under the Independence model Criterion (QIC), which is a statistical parameter used to evaluate GEE model fit. An exploratory, parallel set of analyses modeled GAD-7, though with reduced power due to the fact that only 25 patients who completed the HDRS-AS had a GAD-7. Last, to examine if anxious depression impacts treatment completion, chi-square test of homogeneity to compare rates of dropout between the two groups were conducted.

3. Results

Anxiety symptom change relative to depression symptom change. Forty-three participants who completed both the BDI-II and the GAD-7 were included in the analysis. Demographic and clinical history is presented in Table 1, and symptom scores at each assessment are presented in Table 3. The GEE model for change in depression indicated that symptoms of depression significantly changed throughout a course of treatment. For every standardized unit increase in time, there was a corresponding standardized unit decrease of 2.88 ($\beta = -2.88$, SE = 0.93, $p = 0.002$) in depression (Table 4). The GEE model for change in anxiety did not reach statistical significance (Table 4); for every unit increase in time, there was a corresponding (standardized) unit decrease of 1.04 ($\beta = -1.04$, SE = 0.53, $p = .051$). Thus, depression scores as measured with the BDI-II changed significantly over an acute course of Ketamine, whereas change in anxiety as measured with the GAD-7 did not reach significance. The change in anxiety was roughly half the magnitude of depression symptom change.

Impact of anxious depression. 43 unipolar depressed participants who completed the HDRS-17 at baseline consultation and the BDI-II throughout their acute course of Ketamine were included[2]. Anxious depression scores (HDRS-AS) were calculated, and BDI-II was used as the primary outcome to calculate the trajectory of change over the acute course of infusions. Demographic and clinical history is presented in Table 2, and symptom scores at each assessment are presented in Table 3. Based on the GAD-7, the ANX-TRD group had scores that would be qualitatively classified as moderate-severe at baseline, and the NANX-TRD group had scores that would be classified as moderate at baseline.

There was no statistical difference in the symptom scores at any timepoint between groups (Table 3). Three sequential GEE models were compared to evaluate change in BDI-II scores. The most parsimonious model included time and ANX-TRD as predictors; the second model additionally included the interaction between time and ANX-TRD as predictors; and the third model additionally included baseline depression severity. The first model yielded a QIC value of 17,651.40; the second model yielded a QIC value of 17,479.35; and third model yielded a QIC value of 6,527.09, demonstrating improved fit with the four-level model, which was retained for the final analysis. As shown in Table 5, time ($p < .001$) and baseline depression severity ($p < .0001$) were significant predictors. Importantly, ANX-TRD was not significant when added to the BDI-II model (also see Fig. 1) .[3]

Table 1
Demographic and clinical variables.

	Full sample ($n = 43$)
Age	
Mean	53.63
SD	17.03
Min, Max	18, 84
	n (%)
Gender (female)	18 (41.86)
Education Level (Bachelor's degree or higher)	36 (83.70)
Employment status (disability/unemployed)	6 (13.95)
History of >/1 psychiatric hospitalization	23 (53.49)
History of >/1 suicide attempt	13 (30.23)
3 or greater antidepressant failures in current episode[a]	37 (94.9)
Previous history of ECT	16 (37.21)
Benzodiazepine >/1 mg/day during treatment[b]	14 (34.1)

Note.
[a] Total $n = 39$ (4 participants missing data).
[b] Total $n = 41$ (2 participants missing data).

[2] Due to the clinical infrastructure, routine collection of the GAD-7 began after routine collection of the BDI-II initiated, and collection of the HDRS-17 has varied by availability. 43 patients completed both the BDI-II and the GAD-7 concurrently and were represented in the first set of analyses. 43 patients completed the HDRS-17 at consultation and the BDI-II throughout an acute course of treatment and were represented in the second set of analyses; 25 of these patients were common across both sets of analyses because they had completed the HDRS-17 at consultation as well as the BDI-II and GAD-7 concurrently. At the consultation, ketamine patients who completed the HDRS-17 did not significantly differ on symptoms of depression ($p = .56$) or anxiety ($p = .96$) compared to ketamine patients without the HDRS-17. Ketamine patients who completed the GAD-7 did not significantly differ on symptoms of depression compared to patients without GAD-7 data ($p = .35$).

[3] In a supplementary analysis we re-calculated the trajectory of change in BDI-II over the acute ketamine course, this time defining ANX-TRD based on a GAD-7 cut-point of greater than or equal to 11. Doing so allowed us to utilize the same 43 participants as the first set of analyses. Notably, results were comparable.

Table 2
Demographic and clinical variables of ANX-TRD and NANX-TRD.

	ANX-TRD	NANX-TRD	Between Group Comparison	
			t/ χ^2	*p*-value
n	23	20		
Age				0.34
Mean	58.00	53.65		
SD	14.51	14.82		
Min, Max	25, 79	31, 84		
Gender (female)			0.18	0.67
n	13	10		
%	56.5	50.00		
Education Level (Bachelor's degree or higher)			1.83	0.18
n	17	18		
%	73.90	90.00		
Employment status (disability/unemployed)			0.61	0.43
n	7	4		
%	30.40	20.00		
History of >/1 psychiatric hospitalization			0.51	0.47
n	14	10		
%	60.90	50.00		
History of >/1 suicide attempt			.11	0.74
n	8	6		
%	34.80	30.00		
3 or greater antidepressant failures in current episode			2.94	0.09
n	19[a]	20		
%	86.40	100		
Previous history of ECT			0.08	0.78
n	9	7		
%	39.10	35.00		
Benzodiazepine >/1 mg/day during treatment			0.00	.99
n	8	7		
%	34.80	35.00		

Note. Each percentage is calculated by the total participants in each group, ANX-TRD ($n = 23$) and NANX-TRD ($n = 20$), except where noted.
[a] Total $n = 22$ (1 participant missing data).

Table 3
Means and standard deviations for all participants across assessments.

	Full Sample *M* (*SD*)	ANX-TRD *M* (*SD*)	NANX-TRD *M* (*SD*)
BDI-II Baseline	30.79 (9.72)	31.00 (11.07)	29.35 (10.80)
BDI-II Post Infusion 1	26.80 (10.29)	26.22 (12.72)	25.10 (10.73)
BDI-II Post Infusion 5	22.88 (10.80)	22.06 (13.33)	20.81 (9.96)
BDI-II Post-acute course	24.67 (10.79)	16.78 (13.68)	24.00 (9.14)
GAD-7 Baseline	11.72 (5.90)	13.38 (5.78)	11.25 (5.86)
GAD-7 Post Infusion 1	10.15 (6.10)	10.92 (5.94)	10.69 (6.89)
GAD-7 Post Infusion 5	8.84 (6.13)	11.33 (5.59)	7.78 (6.18)
GAD-7 Post-acute course	9.50 (5.99)	9.00 (5.66)	8.83 (5.95)

Note. BDI-II = Beck Depression Inventory-II. GAD-7 = Generalized Anxiety Disorder-7 Scale. No symptom score comparisons between ANX-TRD and NANX-TRD were significant at any time point.

The impact of ANX-TRD on symptoms of anxiety was exploratory, as only 25 patients had both the HDRS-17 at baseline and GAD-7 scores throughout the infusion acute course. In this parallel analysis examining change in GAD-7 scores, comparing the QIC suggested a better fit with a four-level predictor model, consistent with the model retained in the BDI-II analysis. As shown in Table 5, and also consistent with the BDI-II analysis, time ($p = .01$) and baseline depression ($p < .0001$) were significant predictors, but ANX-TRD was not (also see Fig. 2).

Finally, we explored if ANX-TRD impacted treatment completion. Dropout rates were low and did not differ significantly between ANX-TRD (3/23) and NANX-TRD (3/20), $X^2 = 0.034$, $p = .853$. Taken together, the ANX-TRD group did not have an impaired degree of improvement compared to patients with NANX-TRD: both groups had similar improvement in symptoms of depression and anxiety and similar rates of treatment completion.

Table 4
Change in symptoms of depression and anxiety during an acute course of treatment.

Parameter	β_1	SE	95% CI		Wald	Pr > |Z|
BDI-II						
Intercept	33.01	2.09	28.9	37.1	250.26	<0.0001***
Time	−2.88	0.93	−4.00	−1.05	9.51	0.002**
GAD-7						
Intercept	12.48	1.23	10.1	14.9	102.5	<0.0001***
Time	−1.04	0.53	−2.09	0.00553	3.8	0.051

Note. BDI-II = Beck Depression Inventory-II. GAD-7 = Generalized Anxiety Disorder-7 Scale. *$p < .05$.
** $p < .01$.
*** $p < .001$

Time significantly predicted change in depression symptoms but not anxiety symptoms during treatment. A one unit increase in time was associated with a 2.88 unit decrease in BDI-II scores.

Table 5
Effect of anxious depression and treatment session on symptoms of depression and anxiety.

Parameter	β_1	SE	95% CI		Wald	Pr > |Z|
BDI-II						
Intercept	4.27	2.23	−0.09	8.63	3.68	0.06
Time	−3.36	0.95	−5.22	−1.51	12.63	<0.001**
ANX-TRD	0.62	1.06	−1.46	2.69	0.34	0.56
Baseline BDI-II	0.84	0.07	0.69	0.98	127.41	<0.0001***
Time* ANX-TRD	−0.8	1.25	−3.25	1.64	0.41	0.52
GAD-7						
Intercept	0.80	1.70	−2.53	4.13	0.22	0.64
Time	−1.43	0.58	−2.58	−0.29	6.02	0.01*
ANX-TRD	−0.22	1.33	−2.83	2.39	0.03	0.87
Baseline BDI-II	0.37	0.04	0.288	0.45	83.05	<0.0001***
Time* ANX-TRD	0.39	0.88	−1.34	2.12	0.2	0.66

Note. BDI-II = Beck Depression Inventory-II. GAD-7 = Generalized Anxiety Disorder-7 Scale.
* $p < .05$.
** $p < .01$.
*** $p < .001$

For both models, time and baseline depression severity were significant predictors of the change in depression and anxiety symptoms over the course of treatment. A one unit increase in time was associated with a 3.36 unit decrease in BDI-II scores and 1.43 unit decrease in GAD7 scores. On the other hand, baseline depression severity played a negative role in the improvement of depression and anxiety symptom: a one unit increase in baseline BDI-II scores was associated with a 0.84 unit increase in BDI-II scores and 0.37 increase in GAD7 scores.

4. Discussion

This retrospective study examined how patients with anxious TRD fared over an acute course of Ketamine compared to patients without prominent anxious symptomatology and more broadly the extent to which Ketamine provided anxiolytic effects in unipolar depression.

Notably, and consistent with emerging research across studies high in internal (e.g., Salloum et al. 2019) and external (e.g. McIntyre et al. 2020a) validity, individuals in our study who met criteria for anxious depression at the time of treatment selection were just as likely to experience the antidepressant, and, to a lesser extent, anxiolytic benefits of an acute course of IV Ketamine. Moreover, individuals with anxious depression were just as likely to tolerate the treatment, as inferred by high rates of treatment completion. There was no statistical difference between patients with anxious or non-anxious depression. This finding is in line with previous reports, and important given that anxious depressed patients show decreased tolerance and response to traditional monoaminergic antidepressants (Ionescu et al., 2013a; 2013b). This work aids our understanding of broader determinants of who will respond to IV Ketamine for treatment resistant depression and suggests that anxious TRD is not a contraindication for this treatment modality.

Secondly, the change in anxiety symptoms was approximately half as large as the change in depressive symptoms across analyses, though analyses of the full sample did not reach statistical significance. This finding is in accordance with other published studies which demonstrated that the degree of change in depressive symptoms is greater than anxiety symptoms (McIntyre et al., 2020b), though interpretation of these results are limited by a modestly sized sample among patients who were not selected for high levels of anxiety.

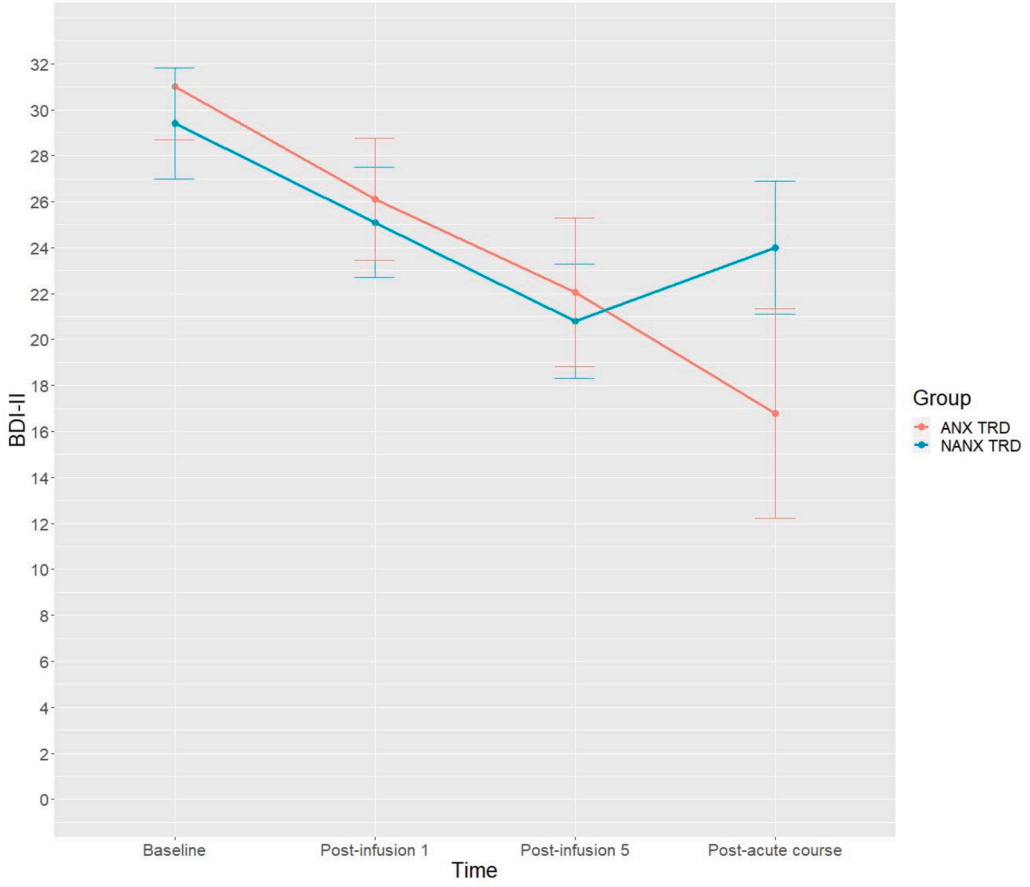

Fig. 1. Change in BDI-II scores for ANX-TRD and NANX-TRD patients.
Note. No statistically significant differences were observed between the 2 groups across 4 timepoints. Both groups demonstrated a significant decrease in BDI-II scores over the course of treatment.

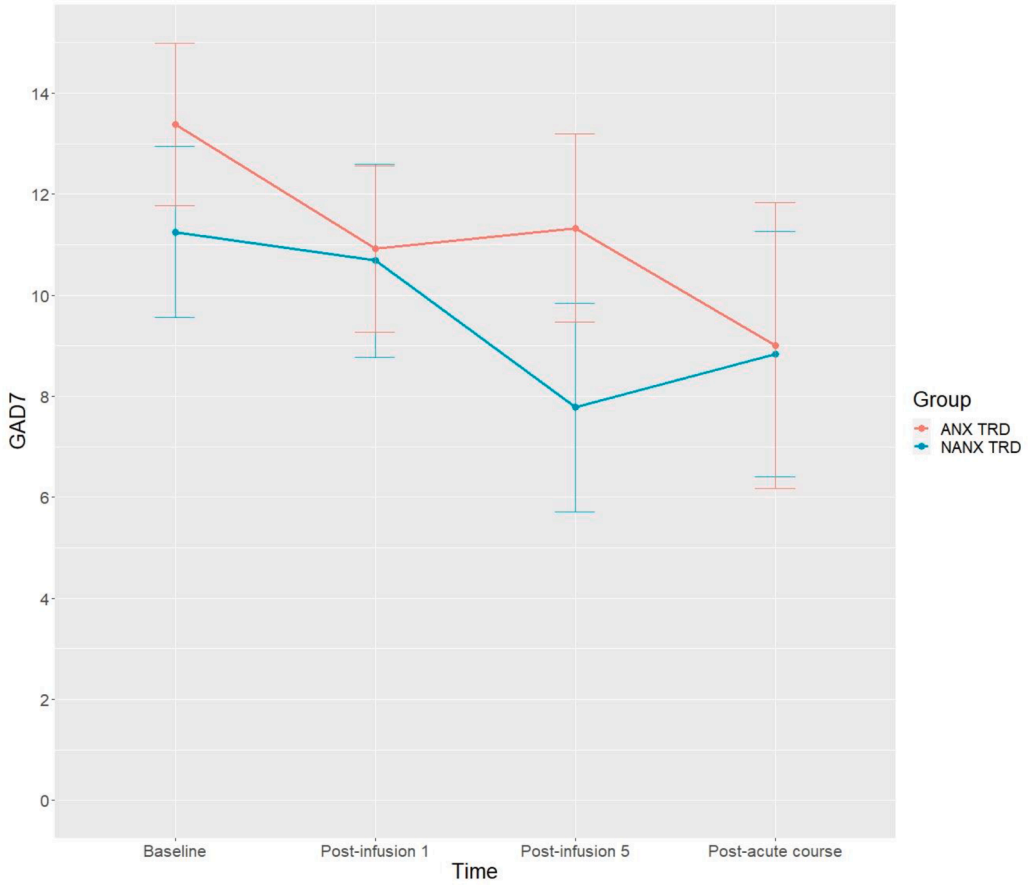

Fig. 2. Change in GAD-7 scores for ANX-TRD and NANX-TRD patients.
Note. No statistically significant differences were observed between the 2 groups across 4 timepoints. Both groups demonstrated a significant decrease in GAD-7 scores over the course of treatment.

Overall, our study aimed to assess changes in mood and anxiety symptoms in a real-world clinical setting, valuing generalizability. At the same time, this study is limited by methodological constraints, notably that internal validity was poorly controlled. Thus, findings must be interpreted in light of study limitations, including a modest sample size, lack of a control group, self-report scales assessing symptom change over treatment, and the classification of anxious depression at the time of the consultation rather than the day of the first infusion. Additionally, it is important to emphasize that patients with prominent anxiety tend not to be referred to IV Ketamine, including in our clinic, leaving the most anxious of patients excluded from post-hoc analyses.

Despite these limitations, this study meaningfully adds to converging areas of research, which demonstrate that IV Ketamine can be efficacious for patients with primary anxiety disorders such as generalized anxiety disorder and social anxiety disorder (Taylor et al., 2018) as well as disorders with a significant anxiety component including post-traumatic stress disorder (Feder et al., 2014; Feder et al., 2021) and obsessive-compulsive disorder (Rodriguez et al., 2013). Considered in this way, converging findings suggest that co-occurring symptoms of anxiety are not a contraindication for intravenous subanesthetic Ketamine infusions, even if core symptoms of depression are likely to demonstrate more appreciable improvement.

Moving forward, it will be helpful to prospectively recruit TRD patients with high levels of anxiety and to model out changes in depression and anxiety relative to one another in the same analytic plan. Consistent with this, future research would benefit from examining if anxiolytic usage changes throughout a course of IV Ketamine and if patients currently engaged in evidence-based psychotherapy for anxiety, such as cognitive behavioral therapy, would demonstrate greater treatment benefit. Doing so may help to clarify if residual anxiety symptoms become more responsive to first line strategies, including medication and psychotherapy, subsequent to completion of an acute course of Ketamine, and how best to space out longer term maintenance infusions for patients with anxious depression.

A key strength of the present study is the assessment and treatment of severe TRD patients in a real-world treatment context over an acute treatment course, which serves to strengthen the conclusions drawn from randomized clinical trials and bridge the efficacy-effectiveness gap. Continuing to examine how symptoms of anxiety impact response to IV Ketamine among patients with treatment resistant depression is an important area for continued clinical research.

CRediT authorship contribution statement

Zoe Schreiber: Writing – original draft, Writing – review & editing. **Chenyang Wang:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Amanda Tan:** Data curation, Formal analysis, Writing – review & editing. **Patricio Riva-Posse:** Visualization, Writing – review & editing. **William M. McDonald:** Visualization, Writing – review & editing. **Andrea Crowell:** Visualization, Writing – review & editing. **Adriana P. Hermida:** Visualization, Writing – review & editing. **Rachel Hershenberg:** Visualization, Data curation, Formal analysis, Writing – original draft.

Declaration of Competing Interest

Declaration of Competing Interests Dr. Riva-Posse has served on the consulting board for Janssen Pharmaceuticals. Dr. McDonald is a paid

consultant for Signant Health; grant support from NeoSync and the Stanley Foundation. Dr. Hermida is currently funded by the National Institute of Aging/National Institute of Health.

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References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Association, Arlington, VA.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual For the Beck Depression Inventory-II. Psychological Corporation, San Antonio, TX.

Chen, M.H., Lin, W.C., Wu, H.J., Bai, Y.M., Li, C.T., Tsai, S.J., Hong, C.J., Tu, P.C., Cheng, C.M., Su, T.P., 2020. Efficacy of low-dose Ketamine infusion in anxious vs nonanxious depression: revisiting the adjunctive Ketamine study of Taiwanese patients with treatment-resistant depression. CNS Spectr. 1–6. https://doi.org/10.1017/S1092852920001194.

Feder, A., Parides, M.K., Murrough, J.W., Perez, A.M., Morgan, J.E., Saxena, S., Kirkwood, K., aan het Rot, M., Lapidus, K.A.B., Wan, L.B., Iosifescu, D., Charney, D. S., 2014. Efficacy of intravenous Ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. JAMA Psychiatry 71 (6), 681. https://doi.org/10.1001/jamapsychiatry.2014.62.

Feder, A., Costi, S., Rutter, S.B., Collins, A.B., Govindarajulu, U., Jha, M.K., Horn, S.R., Kautz, M., Corniquel, M.A., Collins, K.A., Bevilacqua, L., Glasgow, A.M., Brallier, J., Pietrzak, R.H., Murrough, J.W., Charney, D.S., 2021. A randomized controlled trial of repeated Ketamine administration for chronic posttraumatic stress disorder. Am. J. Psychiatry 178 (2), 193–202.

Fortress, A.M., Smith, I.M., Pang, K.C.H., 2018. Ketamine facilitates extinction of avoidance behavior and enhances synaptic plasticity in a rat model of anxiety vulnerability: implications for the pathophysiology and treatment of anxiety disorders. Neuropharmacology 137, 372–381. https://doi.org/10.1016/j.neuropharm.2018.05.009.

Gaspersz, R., Lamers, F., Wittenberg, G., Beekman, A.T.F., van Hemert, A.M., Schoevers, R.A., Penninx, B.W.J.H., 2017. The role of anxious distress in immune dysregulation in patients with major depressive disorder. Transl. Psychiatry 7 (12). https://doi.org/10.1038/s41398-017-0016-3.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatr. 23 (1), 56–62.

Ionescu, D.F., Niciu, M.J., Mathews, D.C., Richards, E.M., Zarate, C.A., 2013a. Neurobiology of anxious depression: a review. Depress. Anxiety 30 (4), 374–385. https://doi.org/10.1002/da.22095.

Ionescu, D.F., Luckenbaugh, D.A., Niciu, M.J., Richards, E.M., Slonena, E.E., Vande Voort, J.L., Brutsche, N.E., Zarate, C.A., 2014. Effect of baseline anxious depression on initial and sustained antidepressant response to Ketamine. J. Clin. Psychiatry 75 (9), e932–e938. https://doi.org/10.4088/JCP.14m09049.

Ionescu, D.F., Luckenbaugh, D.A., Niciu, M.J., Richards, E.M., Zarate, C.A., 2015a. A single infusion of Ketamine improves depression scores in patients with anxious bipolar depression. Bipolar Disord. 17 (4), 438–443. https://doi.org/10.1111/bdi.12277.

Ionescu, D.F., Rosenbaum, J.F., Alpert, J.E., 2015b. Pharmacological approaches to the challenge of treatment-resistant depression. Dialogues Clin. Neurosci. 17 (2), 111–126.

Ionescu, D.F., Niciu, M.J., Henter, I.D., Zarate, C.A., 2013b. Defining anxious depression: a review of the literature. CNS Spectr. 18 (5), 252–260. https://doi.org/10.1017/S1092852913000114.

Liu, W., Zhou, Y., Zheng, W., Wang, C., Zhan, Y., Lan, X., Zhang, B., Li, H., Chen, L., Ning, Y., 2019. Repeated intravenous infusions of Ketamine: neurocognition in patients with anxious and nonanxious treatment-resistant depression. J. Affect. Disord. 259, 1–6. https://doi.org/10.1016/j.jad.2019.08.012.

McIntyre, R.S., Rodrigues, N.B., Lipsitz, O., Nasri, F., Gill, H., Lui, L.M.W., Subramaniapillai, M., Kratiuk, K., Teopiz, K., Ho, R., Lee, Y., Mansur, R.B., Rosenblat, J.D., 2020a. 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. J. Psychopharmacol., 269881120954048 https://doi.org/10.1177/0269881120954048 (Oxford).

McIntyre, R.S., Rodrigues, N.B., Lee, Y., Lipsitz, O., Subramaniapillai, M., Gill, H., Nasri, F., Majeed, A., Lui, L.M.W., Senyk, O., Phan, L., Carvalho, I.P., Siegel, A., Mansur, R.B., Brietzke, E., Kratiuk, K., Arekapudi, A.K., Abrishami, A., Chau, E.H., Rosenblat, J.D., 2020b. The effectiveness of repeated intravenous Ketamine on depressive symptoms, suicidal ideation and functional disability in adults with major depressive disorder and bipolar disorder: results from the Canadian rapid treatment center of excellence. J. Affect. Disord. 274, 903–910. https://doi.org/10.1016/j.jad.2020.05.088.

Parise, E.M., Alcantara, L.F., Warren, B.L., Wright, K.N., Hadad, R., Sial, O.K., Kroeck, K. G., Iñiguez, S.D., Bolaños-Guzmán, C.A., 2013. Repeated Ketamine exposure induces an enduring resilient phenotype in adolescent and adult rats. Biol. Psychiatry 74 (10), 750–759. https://doi.org/10.1016/j.biopsych.2013.04.027.

Pfeiffer, P.N., Ganoczy, D., Ilgen, M., Zivin, K., Valenstein, M., 2009. Comorbid anxiety as a suicide risk factor among depressed veterans. Depress. Anxiety 26 (8), 752–757. https://doi.org/10.1002/da.20583.

Rodriguez, C.I., Kegeles, L.S., Levinson, A., Feng, T., Marcus, S.M., Vermes, D., Flood, P., Simpson, H.B., 2013. Randomized controlled crossover trial of Ketamine in obsessive-compulsive disorder: proof-of-concept. Neuropsychopharmacology 38 (12), 2475–2483. https://doi.org/10.1038/npp.2013.150. Official Publication of the American College of Neuropsychopharmacology.

Salloum, N.C., Fava, M., Freeman, M.P., Flynn, M., Hoeppner, B., Hock, R.S., Cusin, C., Iosifescu, D.V., Trivedi, M.H., Sanacora, G., Mathew, S.J., Debattista, C., Ionescu, D. F., Papakostas, G.I., 2019. Efficacy of intravenous Ketamine treatment in anxious versus nonanxious unipolar treatment-resistant depression. Depress. Anxiety 36 (3), 235–243. https://doi.org/10.1002/da.22875.

Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch. Intern. Med. 166 (10), 1092–1097. https://doi.org/10.1001/archinte.166.10.1092.

Taylor, J.H., Landeros-Weisenberger, A., Coughlin, C., Mulqueen, J., Johnson, J.A., Gabriel, D., Reed, M.O., Jakubovski, E., Bloch, M.H., 2018. Ketamine for social anxiety disorder: a randomized, placebo-controlled crossover trial. Neuropsychopharmacology 43 (2), 325–333. https://doi.org/10.1038/npp.2017.194. Official Publication of the American College of Neuropsychopharmacology.

Wang, C., Zhou, Y., Zheng, W., Liu, W., Zhan, Y., Li, H., Chen, L., Zhang, B., Walter, M., Li, M., Li, M.D., Ning, Y., 2019. Association between depression subtypes and response to repeated-dose intravenous Ketamine. Acta Psychiatr. Scand. 140 (5), 446–457. https://doi.org/10.1111/acps.13096.