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ORIGINAL ARTICLE

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The effectiveness of ketamine on anxiety, irritability, and agitation: Implications for treating mixed features in adults with major depressive or bipolar disorder

Roger S. McIntyre[1,2,3,4] | Orly Lipsitz[1,2] | Nelson B. Rodrigues[1,2] | Yena Lee[1,2] | Danielle S. Cha[1] | Maj Vinberg[5] | Kangguang Lin[6,7] | Gin S. Malhi[8,9,10] | Mehala Subramaniapillai[1,2] | Kevin Kratiuk[2] | Andrea Fagiolini[11] | Hartej Gill[1,2] | Flora Nasri[1] | Rodrigo B. Mansur[1,4] | Trisha Suppes[12,13] | Roger Ho[14] | Joshua D. Rosenblat[1,2,3,4]

[1]Mood Disorders Psychopharmacology Unit, Poul Hansen Family Centre for Depression, University Health Network, Toronto, ON, Canada

[2]Canadian Rapid Treatment Center of Excellence, Mississauga, ON, Canada

[3]Brain and Cognition Discovery Foundation, Toronto, ON, Canada

[4]Department of Psychiatry, University of Toronto, Toronto, ON, Canada

[5]Psychiatric Research Unit, Psychiatric Centre North Zealand, Hillerød and Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[6]Department of Affective Disorder, the Affiliated Brain Hospital of Guangzhou Medical University, (Guangzhou Huiai Hospital), Guangzhou Medical University, Guangzhou, China

[7]Laboratory of Emotion and Cognition, the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou Medical University, Guangzhou, China

[8]Department of Psychiatry, Faculty of Medicine and Health, Northern Clinical School, The University of Sydney, Sydney, New South Wales, Australia

[9]Academic Department of Psychiatry, Royal North Shore Hospital, Northern Sydney Local Health District, St Leonards, NSW, Australia

[10]CADE Clinic, Royal North Shore Hospital, Northern Sydney Local Health District, St Leonards, NSW, Australia

[11]Department of Molecular Medicine, School of Medicine, University of Siena, Siena, Italy

[12]VA Health Care System, Palo Alto, CA, USA

[13]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA

[14]Department of Psychological Medicine, National University of Singapore, Singapore

Correspondence
Roger S. McIntyre, University Health Network, 399 Bathurst Street, MP 9-325, Toronto, ON, Canada M5T 2S8.
Email: roger.mcintyre@uhn.ca

Abstract

Objective: To determine the effectiveness of intravenous (IV) ketamine on anxiety, irritability, agitation, and suicidality, in adults with treatment-resistant major depressive disorder (MDD) or bipolar disorder (BD).

Method: Adults (N = 201) with treatment-resistant MDD or BD received repeat-dose IV ketamine treatment at a community-based clinic. Mixed features were measured using symptoms of anxiety, irritability, and agitation (AIA), as measured by the Generalized Anxiety Disorder-7 (GAD-7) scale. The Quick Inventory for Depressive Symptomatology Self-Report-16 (QIDS-SR_{16}) was used to measure overall treatment response, and the QIDS-SR_{16} suicidal ideation (SI) item was used to measure change in SI symptoms with ketamine treatment. The anxiety, irritability, and agitation items

on the GAD-7 were used to assess effectiveness of IV ketamine in treating symptoms of mixed features.

Results: In this retrospective analysis, 113 participants met AIA criteria. Participants with AIA experienced a significantly greater reduction in overall depressive symptoms ($F(1, 558) = 9.49$, $P = .002$), SI ($F(1, 558) = 3.103$, $P = .079$), anxiety ($F(1, 198) = 5.52$, $P = .007$), irritability ($F(1, 198) = 28.35$, $P < .001$), and agitation as measured by "trouble relaxing" ($F(1, 198) = 6.70$, $P = .010$) from baseline compared to the non-AIA group, regardless of number of treatments received.

Conclusions: Our preliminary results suggest that IV ketamine is effective in rapidly treating AIA and SI in adults with treatment-resistant mood disorders. This observation suggests that IV ketamine could be considered a treatment alternative for adults with MDD or BD presenting with mixed features.

KEYWORDS

bipolar depression, intravenous ketamine, NMDA, suicidal ideation, treatment-resistant depression

1 | BACKGROUND

Mixed features during a depressive episode as part of major depressive disorder (MDD) or bipolar disorder (BD) have been variably defined.[1] Consequently, the estimated percentage of individuals presenting with mixed features is approximately 20%-60%.[2,3] Individuals with mixed features often have a more complex illness presentation, higher rates of non-recovery and chronicity, as well as less favourable response to conventional antidepressants.[4-6] Moreover mixed features during a depressive episode are associated with higher rates of comorbidity, suicidality, and overall healthcare costs when compared to depression without mixed features.[7]

The DSM-5 operationalizes the definition of a major depressive episode with mixed features as having three or more hypomanic symptoms (eg, mood elevation, grandiosity, excessive energy, reckless behaviour, etc) during a syndromal major depressive episode.[8] A criticism of the DSM-5 definition of mixed features is the exclusion of "overlapping" symptoms.[1] For example, anxiety, irritability, and agitation (AIA), which are some of the most common symptoms in patients presenting with both hypomanic and depressive symptoms, are excluded from the DSM-5 criteria of the mixed features specifier.[9-12] The exclusion of non-overlapping symptoms was intended to enhance the specificity of the mixed features specifier; however, a potential unintended consequence was decreased sensitivity, which could compromise its ecological validity.[13] Along this line, a review of more than 3000 patients with BD and MDD showed that those with agitated-irritable depression or dysphoric (hypo)mania differed from those without such mixed features, including having a less favorable clinical course and repeated mixed episodes.[14]

In response to the unknown potential hazards posed by the mixed features specifier, as well as inadequate evidence-based treatment, guidelines for adults with mood disorders provide explicit, largely opinion-based, guidance with respect to selecting and sequencing treatment for adults with mixed features.[5,15,16] Consensus exists that conventional antidepressants should be avoided in adults who present with depression with mixed features as part of bipolar disorder.[17] In their guidelines, the World Federation of Society of Biological Psychiatry (WFSBP) concluded that the current treatment recommendations (using atypical antipsychotics, valproate, or lithium) are based on limited evidence, and that there is a clear demand for confirmatory studies adopting the DSM-5 specifier with mixed features concept.[14] Genuine uncertainty remains regarding the safe treatment of mixed features in adults with MDD due to a paucity of data.[15] However, conventional antidepressant treatment alone may have limited efficacy as well as the potential to induce, maintain, or even worsen mixed features during depressive episodes in BD.[18] Available evidence suggests that for some individuals, second-generation antipsychotic agents (ie, lurasidone) may be effective at mitigating both hypomanic and depressive symptoms in adults with depressive episodes with mixed features.[19,20]

The functional impairment and suicidality associated with mixed features invites the need for effective treatments capable of offering rapid symptom relief. The dissociative anesthetic, and N-methyl-D-aspartate antagonist, ketamine, has demonstrated rapid and robust symptom relief in adults with treatment-resistant mood disorders.[21,22] In addition, ketamine exhibits short-term efficacy on measures of suicidality (eg, suicidal ideation).[23] However, the efficacy and/or effectiveness of ketamine in adults with mixed features have not been sufficiently characterized, and the over-representation of mixed features and suicidality in adults with treatment-resistant depression (TRD) provides an impetus to evaluate ketamine in this population.

Mixed features historically have been conceptualized as a multi-domain psychopathological disturbance, including

disturbance in general cognitive, as well as emotional valence, and circadian systems.[4] Clinically, patients present with symptomatic disturbance in psychomotor activity, cognitive function, and emotion.[6] The foregoing disturbance is usually accompanied by AIA, along with suicidality and intractable insomnia in BD.[24] In one secondary analysis of a controlled trial, it was reported that greater than 60% of adults with bipolar mania present with AIA during a mixed state.[24] In fact, in our sample, the more severe mixed symptoms were also associated with the most severe AIA, consistent with other studies.[22] In addition to the high prevalence of AIA symptoms, patients themselves report that treating their AIA symptoms is a priority and a key therapeutic objective in managing MDD and BD.[25]

Herein, we sought to determine the effectiveness of intravenous (IV) ketamine in adults with TRD in the context of MDD or BD, who were presenting with AIA and suicidal ideation (SI). We were also interested in documenting the prevalence of AIA in a well-characterized outpatient population with TRD, and chose to focus on AIA given the common occurrence of AIA and its correlation with mixed features.

2 | METHOD

2.1 | Participants

Data included in this analysis were derived from patients receiving care at the Canadian Rapid Treatment Center of Excellence (CRTCE) in Mississauga, Ontario, Canada. The CRTCE is an outpatient clinical and research centre that specializes in the administration of IV ketamine for adults with treatment-resistant MDD or BD. The clinic follows the best practices for safe and appropriate ketamine administration guidelines, as outlined by the Consensus Statement for the American Psychiatric Association Council of Research Task Force.[26] Participants were referred to the CRTCE by their primary care physician, nurse practitioner, or by psychiatrists from academic and community-based practices.

Participants with comorbid psychiatric conditions were eligible for IV ketamine treatment if their primary diagnosis was MDD or BD, meeting Stage 2, or higher (inadequate response to at least two antidepressant trials),[27] criteria for TRD (inadequate response to at least two antidepressant trials).[28,29] A small subpopulation of participants had a primary diagnosis of OCD or PTSD (Table 1). As opposed to the practice in clinical trials, participants with SI were eligible for IV ketamine. All participants who received care at the CRTCE provided informed consent, including understanding the potential risks and benefits of ketamine treatment.

Participants with psychosis, dementia, substance use disorder, and alcohol use disorder were excluded from receiving IV ketamine at the CRTCE. For those with substance use or alcohol use disorders, at least three months of abstinence from substance use was required to be eligible to receive ketamine infusions. Participants who were unable to provide informed consent, who were unable to adhere to the protocol, or who were unable to identify a responsible adult to safely transport them home following ketamine infusions were also not eligible for treatment. Additionally, participants who were over 275 lbs., pregnant, experiencing symptomatic traumatic brain injury, or who had uncontrolled medical conditions (eg, allergy to ketamine, uncontrolled hypertension), were ineligible for IV ketamine treatment at the CRTCE.

TABLE 1 Demographic information of included participants with and without anxiety, irritability and agitation (AIA)

Characteristic	AIA (n = 113)	Non-AIA (n = 88)
Sex, n (%)		
Male	47 (42)	42 (48)
Female	66 (58)	46 (52)
Age, Mean Years (SD)	43 (13)	48 (16)
Primary Diagnosis, n (%)		
MDD	96 (85)	72 (82)
BD	12 (11)	12 (14)
PTSD	4 (4)	2 (2)
OCD	1 (1)	2 (2)
Number of Previous Antidepressant Trials, Mean (SD)	5 (4)	5 (4)
Number of Current Antidepressant Trials, Mean (SD)	3 (2)	3 (2)

2.2 | Measures

As the DSM-5-defined mixed features specifier was not assessed at baseline, we decided to evaluate AIA as a proxy for mixed features given their high level of correlation.[24,30,31] We defined AIA using items 1, 4, 5, and 6 of the General Anxiety Disorder-7 (GAD-7) scale. The AIA subgroup was defined by a score of ≥2 on the following GAD-7 items: (a) Anxiety: item 1 ("feeling nervous, anxious, or on edge") AND (b) Irritability: item 6 ("becoming easily annoyed or irritable") AND (c) Agitation: item 4 ("trouble relaxing") OR (d) Agitation: item 5 ("being so restless that it's hard to sit still"). Scores on the two agitation items were not summed. The GAD-7 is scored on a Likert-scale, which ranges from 0 ("not at all sure") to 3 ("nearly every day"), when responding to how often participants were bothered by each symptom over the last two weeks. Based on these items, participants were grouped as either "AIA" or "non-AIA." A score of ≥2 was used as the cutoff in an attempt to identify a minimum threshold of clinically relevant symptom severity. These items were also used individually as continuous measures of effectiveness of IV ketamine for treating mixed features of MDD and BD.

The Quick Inventory for Depressive Symptomatology-Self Report-16 ($QIDS\text{-}SR_{16}$) was the primary depression measure used to assess response to IV ketamine treatment in participants with and without AIA through reduction in overall depressive symptoms. The $QIDS\text{-}SR_{16}$ SI item was used to measure reduction in SI.

2.3 | Procedure

A primary diagnosis of a DSM-5—defined mood disorder (or, for a small subsample, obsessive compulsive disorder or post-traumatic stress disorder) was confirmed by a staff psychiatrist at the CRTCE, and general medical contraindications for ketamine were ruled out by staff anesthesiologists. Adjunctive medications were permitted over the course of ketamine treatment, but participants were required to abide by the following guidelines: (a) no naltrexone during the course of ketamine infusions (b) discontinuation of monoamine oxidase inhibitors a minimum of two weeks prior to initial ketamine infusion (c) no benzodiazepines for a minimum of 12 hours prior to each treatment.[32,33]

Following approval by a staff psychiatrist and anesthesiologist, participants began ketamine treatment initiation infusions. The initiation treatment consisted of four ketamine infusions over 1-2 weeks. In the first two infusions, all participants received a dose of 0.5 mg/kg of ketamine hydrochloride diluted in 0.9% saline solution, which was infused over 40-45 minutes. The total dose of ketamine was determined at each infusion based on the participant's actual body weight. If a participant had a BMI greater than 35kg/m^2, ideal body weight was used to calculate their dose. Following the second ketamine infusion, participants who experienced insufficient response (ie, ≤20% reduction QIDS-SR$_{16}$ total score[34]) were eligible for a dose optimization to 0.75kg/mg for subsequent infusions. Participants were monitored at the clinic for 1-2 hours following each infusion and were required to be escorted home by a responsible adult.

Participants completed assessments of treatment response (ie, post-infusion assessments) approximately two days after each infusion, and met with the staff psychiatrist for the post-initiation treatment visit one week after the fourth infusion. At each of the five assessment points (ie, baseline, post-infusion 1, post-infusion 2, post-infusion 3, post-initiation treatment visit), participants completed the QIDS-SR$_{16}$. At baseline, post-infusion 3, and the post-initiation treatment visit, participants completed the GAD-7. Scales were administered on a tablet device at the CRTCE and de-identified data were stored on Research Electronic Data Capture (REDCap).[35,36] Other self-report and clinical measures were obtained at each treatment point but were not analyzed for this report. Analysis of this data was approved by a community institutional review board and is registered at clinicaltrials.gov under the identifier NCT04209296.

2.4 | Data analysis

Retrospective analyses were conducted using IBM SPSS Version 23 for Mac (SPSS Inc) and GraphPad Prism 8.0. Data were analyzed using a repeated measures hierarchical model to evaluate changes in QIDS-SR$_{16}$ total score, QIDS-SR$_{16}$ SI score, GAD-7 anxiety score, GAD-7 irritability score, and GAD-7 agitation scores across infusions.

We fit the data to a mixed model using a compound symmetry covariance matrix and Restricted Maximum Likelihood (REML) to accommodate for missing data, and used an alpha level set to 0.05. Follow-up pairwise comparisons were conducted for significant interactions and main effects, and Bonferroni corrections were applied to adjust for multiple comparisons.

Five repeated measures hierarchical linear models were conducted to evaluate changes in each of the outcomes of interest across infusions. The model terms were *group* (AIA vs non-AIA), *infusion*, and a *group by infusion* interaction. Baseline overall depressive severity, anxiety, irritability, and agitation were controlled for in each of those models, respectively, as the AIA and non-AIA groups significantly differed with respect to these symptoms at baseline. Baseline QIDS-SR$_{16}$ SI scores were not controlled for in the model of suicidality as baseline QIDS-SR$_{16}$ SI scores did not significantly differ between the AIA and non-AIA groups ($P = .054$).

Furthermore, analysis of the least square mean (LSM) difference was conducted to evaluate whether the magnitude of symptom reduction was greater within the AIA group relative to the non-AIA group. LSM difference scores were created from baseline to each infusion on all of the outcome measures and were analyzed using a two-way analysis of variance (ANOVA).

3 | RESULTS

In total, 228 participants received initiation IV ketamine treatment at the CRTCE between July 2018 and December 2019. Post-infusion assessments completed more than two days after the infusion of interest, and post-initiation treatment visit assessments that were completed more than 14 days after the fourth infusion, were excluded from analyses (n = 22). Ultimately, 201 participants were included in this retrospective chart review analysis; however, the sample size differed across analyses as some patients chose not to complete all assessments. Demographic information of the included participants is described in Table 1. Overall, 56% of participants reported experiencing all three AIA symptoms, which further underscores the prevalence of these symptoms in TRD.

3.1 | Depressive symptoms

There was a significant main effect of infusion on QIDS-SR$_{16}$ total scores, $F(4, 598) = 68.35$, $P < .001$, $\eta_p^2 = 0.314$ (Figure 1A). There was not a significant main effect of AIA group on QIDS-SR$_{16}$ scores, $F(1, 215) = 1.05$, $P = .308$, $\eta_p^2 = 0.005$. However, there was a significant interaction between infusion number and AIA group on total QIDS-SR$_{16}$ scores, $F(4, 599) = 4.20$, $P = .002$, $\eta_p^2 = 0.027$. Follow-up pairwise comparisons showed that, regardless of whether or not participants presented with AIA, QIDS-SR$_{16}$ total scores significantly decreased from baseline to all subsequent treatment points (Ps < .001). Participants with AIA experienced a significant reduction in overall depressive symptoms from baseline to all subsequent treatment points (Ps < .001). Similarly, participants without AIA also showed a significant reduction in QIDS-SR$_{16}$ scores from baseline to all subsequent treatment points ($P < .001$).

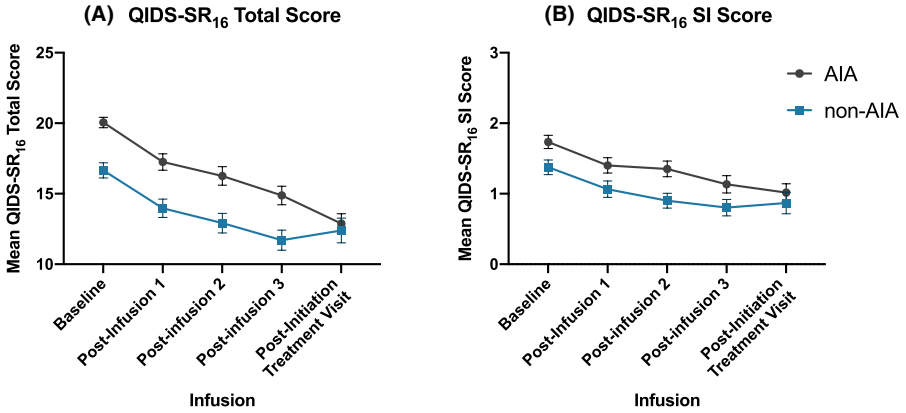
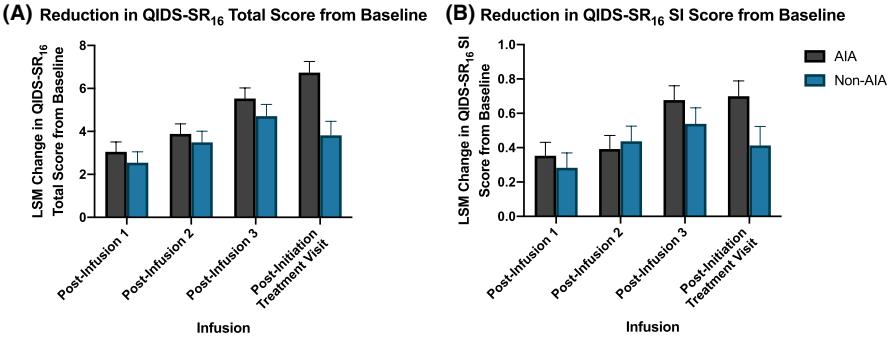


FIGURE 1 Mean and standard error of Quick Inventory for Depressive Symptomatology-16-Self Report (QIDS-SR_{16}) total scores (1A) and QIDS-SR_{16} suicidal ideation (SI) scores (1B) in participants with vs without anxiety, irritability and agitation (AIA) across four infusions

FIGURE 2 Least square mean difference and standard error from baseline to each infusion on QIDS-SR_{16} total (2A) and SI (2B) scores for patients with and without anxiety, irritability and agitation (AIA), as measured by the Generalized Anxiety Disorder-7 (GAD-7) scale



Analysis of the LSM difference showed significant main effects of infusion, $F(3, 558) = 10.38$, $P < .001$, $\eta_p^2 = 0.053$, and AIA group, $F(1, 558) = 9.49$, $P = .002$, $\eta_p^2 = 0.017$, such that individuals with AIA experienced significantly greater reductions in depressive symptoms from baseline than individuals without AIA; however, the interaction effect between infusion number and AIA group was not significant, $F(3, 558) = 2.03$, $P = .109$, $\eta_p^2 = 0.011$ (Figure 2A).

3.2 | Suicidality

Significant main effects of group, $F(1, 199) = 4.54$, $P = .034$, $\eta_p^2 = 0.022$, and infusion, $F(3, 439) = 30.02$, $P < .001$, $\eta_p^2 = 0.170$, on QIDS-SR_{16} SI scores were detected (Figure 1B). There was not a significant interaction between infusion number and AIA group on QIDS-SR_{16} SI scores, $F(4, 588) = 1.59$, $P = .174$, $\eta_p^2 = 0.011$. Regardless of AIA group, participants experienced a significant reduction in QIDS-SR_{16} SI scores from baseline to each subsequent treatment point ($Ps < .001$). Additionally, overall participants with AIA had significantly higher QIDS-SR_{16} SI scores than participants without AIA.

Analysis of the LSM difference from baseline found significant main effects of infusion, $F(3, 558) = 4.648$, $P = .003$, $\eta_p^2 = 0.024$, and AIA group, $F(1, 558) = 3.103$, $P = .079$, $\eta_p^2 = 0.006$ (Figure 2B), such that individuals with AIA had a significantly greater reduction in SI than the non-AIA group. There was not a significant interaction between AIA group and infusion, $F(3, 558) = 1.07$, $P = .360$, $\eta_p^2 = 0.006$.

3.3 | Anxiety, irritability, and agitation (AIA) symptoms

3.3.1 | Anxiety

There was a significant main effect of infusion on anxiety symptoms, $F(2, 335) = 53.73$, $P < .001$, $\eta_p^2 = 0.243$, but not a significant main effect of AIA group on anxiety symptoms, $F(1, 222) = 1.62$, $P = .204$, $\eta_p^2 = 0.007$ (Figure 3A). There was also a significant interaction between AIA group and infusion number on anxiety symptoms, $F(2, 335) = 10.70$, $P < .001$, $\eta_p^2 = 0.600$. Follow-up pairwise comparisons showed that overall, regardless of AIA group, anxiety symptoms decreased from baseline to post-infusion 3 and from baseline to the post-initiation treatment visit ($Ps < 0.001$). Anxiety symptoms decreased from baseline to post-infusion 3 and from baseline to the post-initiation treatment visit within both the AIA and non-AIA groups, respectively ($Ps < .001$).

Analysis of the LSM difference was conducted to evaluate whether the magnitude of anxiety symptom reduction was greater within the AIA group relative to the non-AIA group. The main effect of AIA group was significant, $F(1, 198) = 5.52$, $P = .007$, $\eta_p^2 = 0.027$, such that, regardless of the number of infusions, the AIA group experienced a significantly greater reduction in anxiety symptoms from baseline than the non-AIA group. A main effect of infusion number was not found, $F(1, 198) = 0.14$, $P = .708$, $\eta_p^2 = 0.001$. The interaction effect between treatment and AIA group was significant, $F(1, 198) = 6.02$, $P = .015$, $\eta_p^2 = 0.030$ (Figure 4A). Follow-up pairwise comparisons of LSM

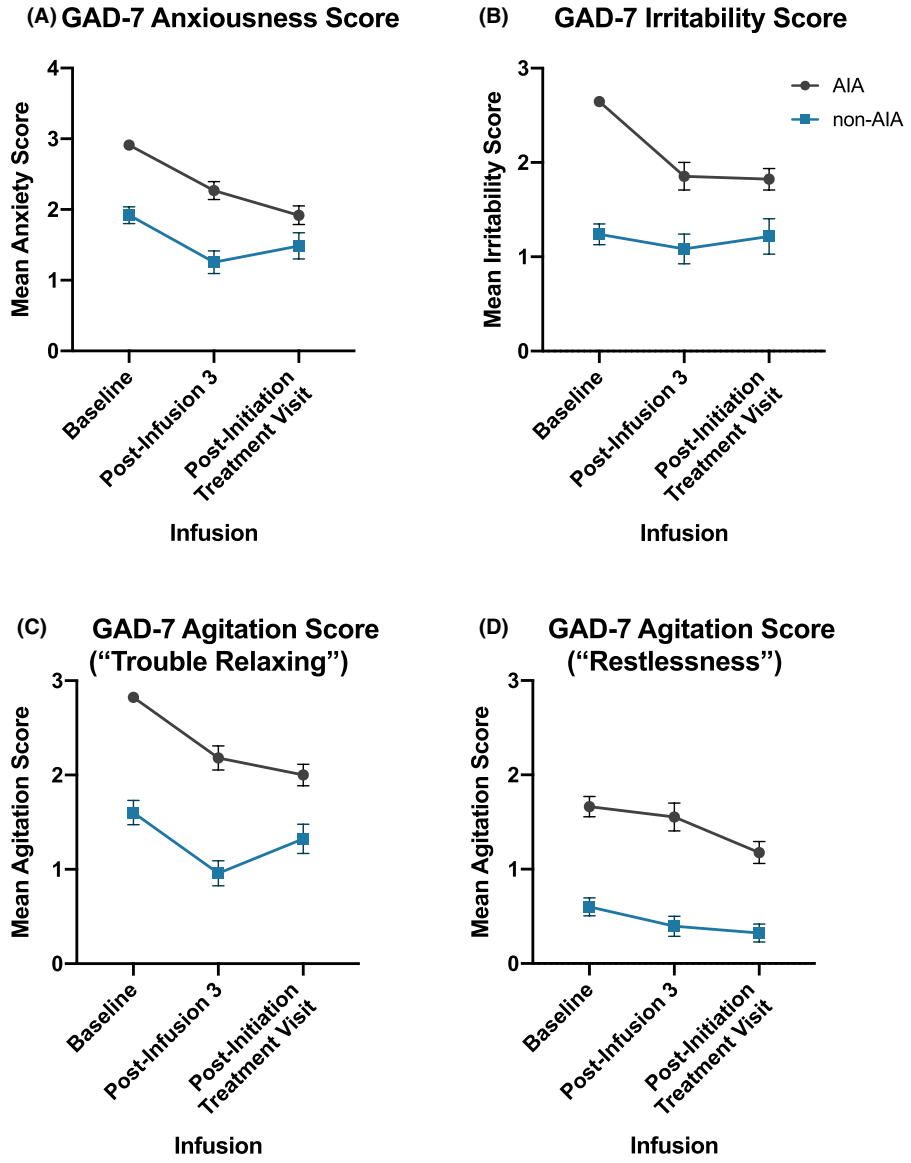


FIGURE 3 Mean and standard error of anxiety (3A), irritability (3B) and agitation ("trouble relaxing" and "restlessness"; 3C, 3D) scores at baseline, post-infusion 3 and at the post-initiation treatment visit for participants with and without anxiety, irritability and agitation (AIA), as measured by the Generalized Anxiety Disorder-7 (GAD-7) scale

differences showed that the AIA group experienced a significantly greater reduction in symptoms than the non-AIA group from baseline to the post-initiation treatment visit ($P < .001$); however, there were no significant between-group differences in anxiety symptom relief from baseline to post-infusion 3 ($P > .999$).

3.3.2 | Irritability

There was a significant main effect of infusion on irritability symptoms, $F(2, 357) = 25.26$, $P < .001$, $\eta_p^2 = 0.124$, but not a significant main effect of AIA group on irritability symptoms $F(1, 202) = 3.68$, $P = .057$, $\eta_p^2 = 0.018$ (Figure 3B). There was a significant interaction between infusion and AIA group, $F(2, 357) = 15.63$, $P < .001$, $\eta_p^2 = 0.081$. Follow-up pairwise comparisons between infusions showed a significant decrease in irritability symptoms from baseline to post-infusion 3 and from baseline to the post-initiation treatment visit (*P*s < .001). Within the AIA group, irritability symptoms improved from baseline to post-infusion 3 and from baseline to the post-initiation treatment visit (*P*s < .001); however, within the non-AIA group, irritability scores did not significantly differ from baseline to post-infusion 3 ($P = .563$) or from baseline to the post-initiation treatment visit ($P > .999$).

Analysis of the LSM difference in irritability revealed that the overall magnitude of irritability symptom reduction was not significantly different from baseline to post-infusion 3 compared to the reduction from baseline to the post-initiation treatment visit, $F(1, 198) = 0.12$, $P = .733$, $\eta_p^2 = 0.001$ (Figure 4B). However, the magnitude of irritability symptom reduction was greater within the AIA group relative to the non-AIA group, $F(1, 198) = 28.35$, $P < .001$, $\eta_p^2 = 0.125$, regardless of number of infusions received. The interaction effect between treatment and AIA group was not significant, $F(1, 198) = 0.33$, $P = .565$, $\eta_p^2 = 0.002$.

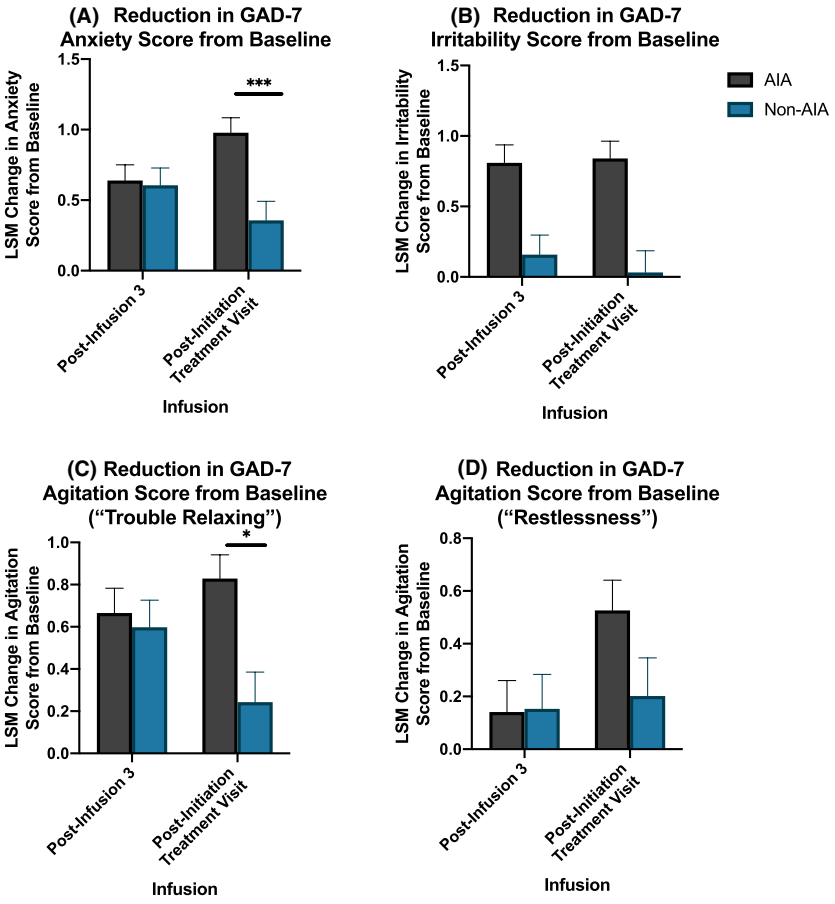


FIGURE 4 Least square mean difference from baseline to post-infusion 3 and from baseline to the post-initiation treatment visit on anxiety (4A), irritability (4B), and agitation (AIA) ("trouble relaxing" [4C]and "restlessness"[4D]) for participants with and without AIA

3.3.3 | Agitation—"trouble relaxing"

There was a significant main effect of infusion on agitation symptoms as measured by "trouble relaxing" (GAD-7 item 4), $F(2, 358) = 44.31$, $P < .001$, $\eta_p^2 = 0.198$ (Figure 3C). There was not a significant main effect of AIA on agitation symptoms, $F(1, 194) = 1.07$, $P = .301$, $\eta_p^2 = 0.005$. However, there was a significant interaction between infusion and AIA, $F(2, 358) = 8.52$, $P< .001$, $\eta_p^2 = 0.045$. Regardless of AIA group, agitation symptoms improved from baseline to post-infusion 3 and from baseline to the post-initiation treatment visit (Ps < .001). Within both groups, symptoms significantly improved from baseline to post-infusion 3 (Ps < .001). However, from baseline to the post-initiation treatment visit, symptoms only significantly improved within the AIA group ($P < .001$) and not within the non-AIA group ($P = .083$).

Analysis of the LSM difference in "trouble relaxing" showed that the overall magnitude of the "trouble relaxing" symptom reduction was not significantly different from baseline to post-infusion 3 compared to the reduction from baseline to the post-initiation treatment visit $F(1, 198) = 0.58$, $P = .447$, $\eta_p^2 = 0.003$ (Figure 4C). The overall magnitude of "trouble relaxing" symptom reduction was greater in the AIA group than in the non-AIA group, $F(1, 198) = 6.70$, $P = .010$, $\eta_p^2 = 0.033$. There was also a significant interaction effect between AIA group and number of treatments, $F(1, 198) = 4.23$, $P = .041$, $\eta_p^2 = 0.021$. Follow-up pairwise comparisons showed that there was not a significant difference in agitation symptom reduction between the two groups from baseline to post-infusion 3 ($P > .999$); however, from baseline to the post-initiation treatment visit, the AIA group had a significantly greater reduction in agitation symptoms than the non-AIA group ($P = .003$).

3.3.4 | Agitation—"restlessness"

There was a significant main effect of infusion on agitation symptoms as measured by "restlessness" (GAD-7 item 5), $F(2, 400) = 10.92$, $P < .001$, $\eta_p^2 = 0.052$. There was not a significant main effect of AIA group on agitation symptoms, $F(1, 182) = 3.43$, $P = .066$, $\eta_p^2 = 0.018$ (Figure 3D). There was a significant interaction effect between infusion and AIA group, $F(2, 401) = 4.69$, $P = .010$, $\eta_p^2 = 0.023$. Agitation symptoms did not significantly improve from baseline to post-infusion 3 ($P = .055$), but did significantly improve from baseline to the post-initiation treatment visit ($P < .001$). In both the AIA ($P = .729$) and non-AIA groups ($P = .102$), agitation symptoms did not significantly improve from baseline to post-infusion 3. However, in both the AIA ($P < .001$) and non-AIA groups ($P = .015$), symptoms significantly improved from baseline to the post-initiation treatment visit.

Analysis of the LSM difference showed that the magnitude of "restlessness" symptom reduction from baseline did not significantly differ between post-infusion 3 and the post-initiation

treatment visit, $F(1, 199) = 2.873$, $P = .092$, $\eta_p^2 = 0.014$ (Figure 4D). Additionally, the magnitude of "restlessness" symptom reduction overall did not significantly differ depending on AIA group $F(1, 199) = 1.48$, $P = .225$, $\eta_p^2 = 0.007$. There also was not a significant interaction effect between AIA group and number of infusions on the magnitude of "restlessness" symptom reduction, $F(1, 199) = 1.73$, $P = .189$, $\eta_p^2 = 0.009$.

4 | DISCUSSION

To date, ketamine's efficacy in treating agitation and irritability in adults with TRD has not been comprehensively evaluated. It is also the first time that ketamine's effects on suicidality in a TRD population with AIA have been characterized. Herein, we report that a large percentage of individuals with MDD or BD presenting with TRD manifest AIA. Our results support the efficacy of IV ketamine in reducing total depressive symptoms, as well as measures of AIA in this well-characterized, large, outpatient population presenting with TRD. Furthermore, we found a significant attenuation of suicidality regardless of AIA status. It is notable that participants with AIA, a group known to be at especially high risk of suicide, experienced similar anti-SI effects as participants without AIA.[9,37,38] We did not observe any evidence of treatment-emergent mania or psychosis, nor were there any other notable tolerability or safety concerns in this population.

Also, to the best of our knowledge, this is the first report to specifically evaluate the effectiveness of IV ketamine in a population characterized by AIA. Available evidence indicates that IV ketamine is highly efficacious in treating anxiety-related symptoms in adults with TRD (Ionescu et al, 2015; Salloum et al, 2019). One hypothesis is that ketamine's anti-suicide effects may in part reflect its ability to reduce impulsivity by enhancing cognitive control.[39] If this is evinced, then it can be further imputed that any improvement in cognitive control achieved with ketamine treatment also likely reduces irritability and agitation.

Lithium is one of only a few pharmacological agents that has been reported to exert anti-suicide effects, though high quality prospective clinical trials are still needed.[40,41] Ketamine's pro-cognitive effects when administered in sub-anesthetic doses in TRD may also contribute to its anti-suicide effects, as well as its effects on other manifestations of impulsivity (eg, irritability, agitation). An interesting proposal would be to consider combining ketamine with lithium or other agents in this population to determine whether synergistic effects on psychopathology and/or suicidality can be enacted.

There are a number of methodological limitations that affect inferences and interpretations of our findings. First, we did not a priori enroll individuals on the basis of having AIA (ie, enriched sample). Moreover we permitted disparate combinations of pharmacologic treatments with IV ketamine, as IV ketamine at CRTCE is often administered adjunctively. This allows for the possibility that symptom improvement may be attributed to concomitant medications, and not IV ketamine. Additionally, as all participants were experiencing TRD, we are not able to extrapolate our findings to less treatment-resistant populations. It is also notable that the majority of the participants in our sample (n = 168, 84%) were experiencing MDD, and the extent to which our findings can fully extrapolate to BD is uncertain. Furthermore, we did not have a control group, and the extent to which expectancy has contributed to our observed effects cannot be quantified. In addition, we developed a proxy for mixed features using the definition of AIA, rather than adhering to any validated construct of AIA. For example, we did not include a validated measure of irritability (eg, Sheehan Disability Scale, Brief Irritability Test).[42,43] Our effort was to be pragmatic and to identify phenomena that are highly correlated with mixed features in MDD and BD. In addition, we did not include a structured assessment tool for suicidality (eg, Columbia Suicide Severity Rating Scale). Notwithstanding, we are of the view that changes on an SI item remain conceptually interesting and our findings are in accordance with what has been previously reported with respect to effects of ketamine on SI.[44] Importantly, however, a fundamental limit is that changes on SI do not have robust predictive power with respect to predicting anti-suicide effects.[45,46] Furthermore, only outpatients were included so it would be of interest to investigate whether the present result translates into more severe inpatients with AIA.

It is important to note that we recognize that AIA cannot be considered synonymous with agitated depression, mixed-features specifier, or depressive-mixed states in either MDD or BD.[4] Furthermore, we also appreciate that there is a rich literature in psychiatry describing and operationalizing agitated depression in both MDD and BD.[47,48] Consequently, we can only conclude that ketamine is associated with attenuation of measures of AIA. It is quite possible that IV ketamine may be especially effective in adults with agitated depression and recognize this remains a testable hypothesis. In accordance with this hypothesis, ketamine has demonstrated anti-agitation effects without sedation in medically ill populations, especially in acute and emergency settings.[49]

A strength of our population is its representativeness, insofar as this large sample was enrolled at a community-based treatment centre for adults with TRD. A further strength of our study sample is that patients were permitted to have comorbidity as well as concomitantly administered medication, reflecting the reality of treating TRD patients. The inclusion of participants with suicidality, we also see as an advantage because patients with suicidality are often systematically excluded from such clinical studies.[50] Adding further robustness, participants in our study were evaluated by expert clinicians in the clinical care and research of mood disorders and validated measures of depression, anxiety, and suicidality were included.

Taken together, IV ketamine seems highly effective for AIA in adults with MDD or BD. Although AIA are not included as criteria for mixed features, these are some of the most commonly encountered symptoms in adults presenting with DSM-5-defined mixed features.[22] Furthermore, our results point toward an anti-suicide effect of ketamine in this vulnerable population experiencing AIA, which, to the best of our knowledge, is the first time this has been reported.

It is axiomatic that a controlled study needs to be conducted, testing the effects of ketamine in adults with narrowly defined and specified mixed features.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Roger S. McIntyre https://orcid.org/0000-0003-4733-2523
Orly Lipsitz https://orcid.org/0000-0001-9110-7951
Maj Vinberg https://orcid.org/0000-0002-5982-1335
Andrea Fagiolini https://orcid.org/0000-0001-5827-0853

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