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Research paper

Changes in symptoms of anhedonia in adults with major depressive or bipolar disorder receiving IV ketamine: Results from the Canadian Rapid Treatment Center of Excellence

Nelson B. Rodrigues[a,b], Roger S. McIntyre[a,b,c,*], Orly Lipsitz[a,b], Danielle S. Cha[a], Yena Lee[a,b], Hartej Gill[a,b], Amna Majeed[a], Lee Phan[a], Flora Nasri[a], Roger Ho[d], Kangguang Lin[e,f,g], Mehala Subramaniapillai[a,b], Kevin Kratiuk[b], Rodrigo B. Mansur[a], Joshua D. Rosenblat[a,b,c]

[a] Mood Disorders Psychopharmacology Unit, University Health Network, University of Toronto, Toronto, ON, Canada
[b] Canadian Rapid Treatment Center of Excellence, Mississauga, ON, Canada
[c] Brain and Cognition Discovery Foundation, University of Toronto, Toronto, ON, Canada
[d] Department of Psychological Medicine, National University of Singapore, Singapore
[e] Department of Affective Disorder, The Affiliated Brain Hospital of Guangzhou Medical University, (Guangzhou Huiai Hospital), Guangzhou Medical University, Guangzhou, China
[f] Laboratory of Emotion and Cognition, The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou Medical University, Guangzhou, China
[g] Laboratory of Neuropsychology, University of Hong Kong, Hong Kong, Hong Kong

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ABSTRACT

Background: Anhedonia is a trans-diagnostic, multidimensional phenotype that mediates patient outcomes and suicidality. Convergent evidence suggests that ketamine may be effective in targeting measures of anhedonia in adults with treatment resistant depression (TRD).

Methods: This retrospective, post-hoc analysis included 203 ($\bar{x}$ = 45 ± 14.6 years of age) patients receiving four infusions of intravenous (IV) ketamine at a community-based clinic. The primary outcome measure was change in anhedonia severity, as measured by the Snaith–Hamilton Pleasure Scale (SHAPS). Secondary measures sought to determine if improvement on the SHAPS mediated the effect of repeated IV ketamine infusions on symptoms of depression and suicidal ideations, as measured by the Quick Inventory for Depression Symptomatology-Self Report 16-Item (QIDS-SR_{16}) and anxiety, as measured using the Generalized Anxiety Disorder-7 (GAD-7).

Results: After adjusting for age, sex, primary diagnosis, concomitant medication, body mass index, and baseline depression severity, there was a statistically significant reduction in symptoms of anhedonia with IV ketamine treatment (F (2, 235.6) = 31.6, $p < 0.001$). Improvements in depressive symptoms, suicidal ideation, and anxiety symptoms with repeated-dose IV ketamine were significantly partially mediated by reduction in anhedonic severity. Moreover, the combination of number of infusions received and change in anhedonic severity accounted for 26% of the variance in depressive score improvements.

Limitations: This is a post-hoc analysis of retrospective data and lacks a control group.

Conclusion: Ketamine was effective in improving measures of anhedonia in this large, well-characterized community-based sample of adults with TRD. Improvements in anhedonia also partially mediated the significant improvement in depressive symptoms, suicidality, and anxiety.

1. Introduction

Anhedonia is a trans-diagnostic, multidimensional phenotype, defined as the decreased subjective experience of pleasure or decreased anticipation of pleasure. Anhedonia is a cardinal symptom of major depressive episodes (MDE) in the context of major depressive disorder (MDD) and bipolar disorder (BD). Anhedonia has been shown to be a principal mediator of patient-reported outcomes on dimensions such as

* Corresponding author at: Mood Disorders Psychopharmacology Unit, University Health Network, University of Toronto, 399 Bathurst Street, MP 9-325, Toronto, ON M5T 2S8, Canada.
E-mail address: roger.mcintyre@uhn.ca (R.S. McIntyre).

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quality of life, wellbeing, and psychosocial function (Fried and Nesse, 2014; Yang et al., 2019). Anhedonia is also a commonly reported residual inter-episodic symptom in individuals with mood disorders treated with conventional pharmacotherapy (Cao et al., 2019a; Pan et al., 2017). Furthermore, amongst adults with remitted MDD, disturbances in positive valence systems have been shown to predispose and portend relapse and recurrence (IsHak et al., 2017). Moreover, adults with treatment-resistant depression (TRD) frequently endorse disturbance in reward capacity and are often difficult to treat (Pizzagalli, 2014; Uher et al., 2012).

Anhedonia can be disaggregated into anticipatory and consummatory dimensions (Keren et al., 2018). Anticipatory pleasure can be viewed as a wanting drive toward rewarding stimuli, whereas the consummatory aspect is the pleasure derived from a stimulus (Der-Avakian and Markou, 2012). The neurobiology subserving both of the foregoing subcomponents overlaps but is discrete, with dopamine neurotransmission implicated in the former and opioid and cannabinergic mechanisms in the latter (Pan et al., 2017). Moreover, murine data suggests consummatory pleasure to be associated with projections to the nucleus accumbens, ventral pallidum, and orbitofrontal cortex, whereas anticipatory pleasure is largely associated with the anterior cingulate cortex, basal ganglia, thalamus, and hypothalamus (Der-Avakian and Markou, 2012). In addition to the suboptimal outcomes of patients with TRD receiving monoamine-based psychotropic agents, nearly half the patients treated with selective serotonin reuptake inhibitors (SSRIs) report a worsening of reward capacity (e.g., emotional blunting) (Goodwin et al., 2017). Although emotional blunting and anhedonia may not be interchangeable phenotypes, there does appear to be neurobiological overlap, as SSRIs may blunt dopaminergic and noradrenergic activity associated with reward processing (Blier and Briley, 2011).

The frequent occurrence of reward-based disturbances in patients with mood disorders, notably in treatment-resistant populations, provides the impetus for exploring novel pharmacological avenues. The dissociative anesthetic, ketamine, demonstrates rapid antidepressive effects in individuals with treatment resistant mood disorders (aan het Rot et al., 2010; Coyle and Laws, 2015; Phillips et al., 2019; Wilkinson et al., 2018). In addition, available evidence suggests anti-suicide effects as an additional feature of ketamine-based treatments (Lee et al., 2016). Although the mechanism of action of ketamine remains unknown, antagonism of the N-methyl D-aspartate receptor has been implicated (Zanos and Gould, 2018). In addition to the foregoing glutamatergic targets, ketamine also affects dopaminergic and opioidergic neurotransmission (Kokane et al., 2020). Ketamine's effect on glutamatergic, dopaminergic, and opioidergic systems provides the neurochemical bases for hypothesizing that ketamine ameliorates measures of reward in adults with TRD.

In keeping with this view, preliminary evidence suggests that a single treatment of intravenous (IV) ketamine improves measures of anhedonia, as measured by the Snaith–Hamilton Pleasure Scale, in patients with BD (SHAPS; Lally et al., 2014). Thirty-six patients with BD were randomized to receive a single dose of IV ketamine or placebo. There was an overall rapid anti-anhedonic effect in the ketamine group within 40 min, that remained 14 days following the infusion (Lally et al., 2014). In a subsequent 52 participant open-label clinical trial by the same group, participants receiving a single dose of IV ketamine demonstrated a substantial improvement in anhedonic symptoms within an hour of the infusion, which remained until three days post-infusion (Lally et al., 2015).

Herein, we sought to replicate and extend these results in a community-based treatment facility that provided repeated IV ketamine treatment to adults with TRD. Based on extant literature, it was hypothesized that repeated IV ketamine will reduce symptoms of anhedonia (Lally et al., 2015). Moreover, the secondary outcome was evaluated to determine whether changes in anhedonia mediated the effect of repeated IV ketamine infusions on symptoms of depression, suicide, and anxiety. It was hypothesized that changes in anhedonia would significantly mediate anti-depressive, anti-suicidal, and anxiolytic effects from IV ketamine.

2. Methods

2.1. Participants and study design

All patients in this post-hoc analysis received care at the Canadian Rapid Treatment Center of Excellence (CRTCE), located in Mississauga, Canada. The CRTCE is a multidisciplinary clinical facility composed of psychiatrists, pharmacists, anaesthesiologists, registered nurses, and research staff focused on providing IV ketamine treatment for patients 18 years or older with TRD. Referrals to the CRTCE must be received from either community family physicians, psychiatrists, or nurse practitioners.

The CRTCE specializes in providing ketamine treatment to individuals with TRD in the community. Therefore, eligibility criteria for candidates were not as stringent as those typically reported within clinical trials. Patients receiving treatment must be experiencing a MDE and meet criteria for Stage 2 Resistance (i.e., failure of at least one adequate trial of antidepressant monotherapy plus failure of an adequate trial using a different antidepressant class (Thase and Rush, 1997). Psychiatric comorbidities were also accepted, including post-traumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), and personality disorders. Patients were excluded if they were unable to provide informed consent, or presented with dementing disorders, psychosis, or active substance/alcohol use disorder. A history of drug or alcohol use was accepted as long as the patient did not meet disorder criteria, or, if they did meet criteria, abstained from substance/alcohol use for at least three months.

Once a referral was received, a staff psychiatrist evaluated the patient to determine if ketamine was a suitable treatment option. If approved, an anesthesiologist reviewed their medical history to ensure IV ketamine was safe. If approved by both doctors, patients underwent a consenting process prior to receiving IV ketamine.

In general, IV ketamine was provided to patients adjunctively to their prescribed medication regimen. Over the course of the infusions, concomitant psychotropic medications were not modified, with the exception of three pharmaceutical agents. Patients were asked to completely taper off monoamine oxidase inhibitors up to two weeks prior to infusion. Moreover, participants were prohibited from using naltrexone and benzodiazepines for at least 12 h prior to each infusion as these medications have been shown to attenuate ketamine's antidepressive effect (Frye et al., 2015; Williams et al., 2018).

2.2. Ketamine infusions

All patients received IV ketamine in accordance with the available best practices recommended by the American Psychiatric Association (Sanacora et al., 2017). Once approved by medical staff, patients began acute treatment consisting of four infusions over one-to-two weeks. On the day of an infusion, patients were asked to complete a series of self-report measures to characterize their symptoms. The self-report scales reported herein included the Quick Inventory for Depressive Symptomatology Self-Report 16-Item (QIDS-SR_{16}), Generalized Anxiety Disorder 7-Item (GAD-7), and the Snaith–Hamilton Pleasure Scale (SHAPS). The QIDS-SR_{16} measured depression severity and is scored from 0, indicating no depressive symptoms, to 27, suggesting severe depression. The GAD-7 reports on symptoms of anxiety also ranging from 0 (i.e., no anxiety symptoms) to 21 (i.e., severe anxiety symptoms). The SHAPS scale is a measure of consummatory pleasure and anhedonic severity, ranging from 0 to 14, with a score higher than 2 indicating the presence of anhedonia (Franken et al., 2007; Snaith et al., 1995). Consistent with Vrieze et al. (2013), a SHAPS score of 7 or less denoted ‘low anhedonic symptoms’, whereas a score greater than 7

denoted 'high anhedonic symptoms' (Vrieze et al., 2013). The QIDS-SR_{16} scale was employed at all four infusions and follow-up appointments, whereas the GAD-7 and SHAPS were collected prior to the first infusion, prior to the last infusion, and at all subsequent follow-up visits. The first two IV ketamine infusions were dosed at 0.5 mg/kg, diluted in a 0.9% saline solution and delivered over 40–45 min. If patients exhibited a sub-clinical response (i.e., ≤ 20% reduction in QIDS-SR_{16} score from baseline) following two infusions, participants were offered a dose optimization of 0.75 mg/kg for the remaining two infusions (Cusin et al., 2017). Dose optimization was not provided to patients who: (1) experienced a >20% reduction in depression severity, (2) were unable to tolerate side effects at the index dose, or (3) decided to remain at the index dose. Following the initial four infusions, patients were followed up by the clinic psychiatrist approximately 7–14 days based on their availability.

Overall, the results reported herein were assessed at three timepoints: (1) baseline, (2) post-infusion 3, and (3) post-initiation treatment follow-up. All data was collected at point of care on a tablet device and stored directly into the REDCap platform by the patient. Data analysis was approved by a community institutional research ethic board (IRB#00000971) and registered under the identifier NCT04209296 at clinicaltrials.gov.

2.3. Statistical analysis

Retrospective data were analyzed using the Statistical Product and Service Solutions (SPSS version 23, SPSS Inc. Chicago, IL, United States) and Graphpad Prism 8.4.0. A mixed model was used in order to examine the effect of repeated IV ketamine infusions across the five time points on anhedonic severity, as measured by the SHAPS. A mixed model was used in order to account for missing data and unbalanced timepoints between visits. The model adjusted for baseline depression severity, age, sex, psychiatric diagnosis, concomitant psychotropic medication, and body mass index. A compound symmetry covariance matrix was used to fit the data, and all hypotheses were evaluated at an alpha set to 0.05. A Bonferroni correction was used to compare changes in SHAPS score between timepoints.

To investigate whether changes in anhedonia mediated the antidepressant, anti-suicidal and anxiolytic effects of ketamine, the Process macro version 3.4 for SPSS (Hayes, 2017) was used. The predictor (X) was the total number of infusions, the mediator (M) was SHAPS total score and the outcome variables (Y) were QIDS-SR_{16} total score, QIDS-SR_{16} suicidal ideation, and GAD-7 total score. Indirect effects were calculated using a bootstrapping technique to generate 95% confidence intervals (CIs). Unstandardized beta coefficients and kappa squared (κ^2) are reported herein. In accordance with Preacher and Kelley (2011), a κ^2 of 0.01 denotes a small effect size, 0.09 denotes a medium effect size, and 0.26 denotes a large effect size (Preacher and Kelley, 2011). Mediation models included age, sex, psychiatric diagnosis, concomitant psychotropic medication, and body mass index as covariates.

3. Results

3.1. Baseline characteristics

A total of 228 patients with TRD underwent IV ketamine treatment at the CRTCE between July 2018 and December 2019. For this analysis, 25 patients were excluded due to missing SHAPS data at all three timepoints. The analysis herein reports on 203 participants. Baseline demographics are reported in Table 1. Descriptive statistics of QIDS-SR_{16}, GAD-7 and SHAPS are reported in Table 2. Analysis results of the QIDS-SR_{16} and GAD-7 are reported in McIntyre et al. (2020).

3.2. Anhedonic severity

At baseline, 92% of patients (n = 186) met criteria for clinically significant anhedonia (i.e., SHAPS ≥ 2). After adjusting for sex, age, psychiatric diagnosis, concomitant medications, body mass index, and baseline depression severity, there was a significant reduction (i.e., symptom improvement) in SHAPS total score across infusions (F (2, 235.6) = 31.6, p < 0.001, Cohen's f = 0.50; Fig. 1). Pairwise comparisons indicated that there was a significant decrease in SHAPS total score from baseline to post-infusion 3 (p < 0.001) and the post-initiation treatment visit (p < 0.001). No significant difference emerged between post-infusion 3 and post-initiation treatment visit (p > 0.9).

Table 1
Demographic information of patients at baseline.

Patient characteristics (n = 203)	
Sex n (%)	
Male	89 (43.8)
Female	114(56.2)
Mean age in years (SD)	45 (14.6)
BMI (Kg/m^2) (SD)	28.1 (6.83)
Primary diagnosis n (%)	
MDD	169 (83.3)
BD	25 (12.3)
PTSD	5 (2.5)
OCD	4 (1.9)
Mean number of prior lifetime antidepressant trials (SD)	5.84 (4.27)
SSRIs	2.66 (1.78)
Tricyclic antidepressants	0.71 (1.04)
SNRIs	1.42 (1.17)
MAOIs	0.28 (0.65)
Other	1.34 (1.09)
Mean number of antidepressants at time of infusion (SD)	1.36 (1.47)
SSRIs	0.40 (0.66)
Tricyclic antidepressants	0.09 (0.35)
SNRIs	0.25 (0.47)
MAOIs	0.02 (0.15)
Other	0.67 (0.85)

3.3. Mediational role of anhedonic severity

Mediation analyses were completed in order to determine if there was an indirect effect of anhedonia on the relationship between number of infusions and depression severity, suicidal severity and symptoms of anxiety.

Ketamine significantly reduced overall depressive symptom severity directly and indirectly via reductions in anhedonic severity (Fig. 2A). Ketamine reduced anhedonic severity (a = −0.68, SE = 0.12) and reductions in anhedonic severity were significantly associated with reductions in overall depressive symptom severity (b = 0.73, SE = 0.05). The indirect effect of anhedonic severity on QID-SR_{16} total score was significant (b = −0.49, SE = 0.09, 95% CI [−0.68, −0.32]). There was a significant total effect (c = −1.46, t(379) = −9.58, p < 0.001, 95% CI [−1.8, −1.2]) and direct effect (c' = 0.96, t(379) = −7.5, p < 0.001, 95% CI [−1.2, −0.71]) of IV ketamine infusions on QID-SR_{16} total score, indicating that anhedonic improvement partially mediated the regression between predictor and outcome. When assessing the number of IV ketamine infusions combined with change in anhedonic severity, these variables accounted for a total of 26% of the variance in QIDS-SR_{16} total score. Overall there was a medium effect size (κ^2 = 0.12).

Similarly, ketamine significantly reduced measures of suicide severity directly and indirectly through effects on anhedonia (Fig. 2B). Ketamine reduced anhedonic severity (a = −0.68, SE = 0.12)), which reduced suicidal severity (b = 0.09, SE = 0.01). Both total (c = −0.16, t(379) = −5.7, p < 0.001, 95% CI: [−0.21, −0.10]) and direct effects (c' = −0.10, t(379) = −3.6, p < 0.001, 95% CI: [−0.15, −0.05]) were significant, as was the indirect effect of anhedonic severity (b = −0.06, SE = 0.01, 95% CI [−0.08, −0.04]). Overall, the predictor (i.e., number of infusions) and mediator (i.e., SHAPS) accounted for 17% of the variance in the suicide item score. Overall the effect size

Table 2
Descriptive statistics of QIDS-SR_{16} total score, GAD-7 total score and SHAPS total score and baseline, following three infusions and following four infusions of IV ketamine.

	Baseline	Post-infusion 3[a]	Post-initiation follow-up visit[b]
QIDS-SR_{16} total score			
Total number	203	138	103
Number of missing values	0	65	100
Mean QIDS-SR_{16} score (SE)	18.55 (0.33)	13.43 (0.50)	12.75 (0.55)
GAD-7 total score			
Total number	201	105	100
Number of missing values	2	98	103
Mean GAD-7 score (SE)	14.18(0.38)	10.33 (0.63)	10.21 (0.57)
SHAPS total score			
Total number	203	139	105
Number of missing values	0	64	98
Mean SHAPS score (SE)	8.82(0.27)	6.26 (0.39)	6.19 (0.45)

[a] Data collected an average of 7.62 (± 3.54) days following baseline infusion.
[b] Data collected an average of 7.83 (± 9.27) days following 4th infusion.

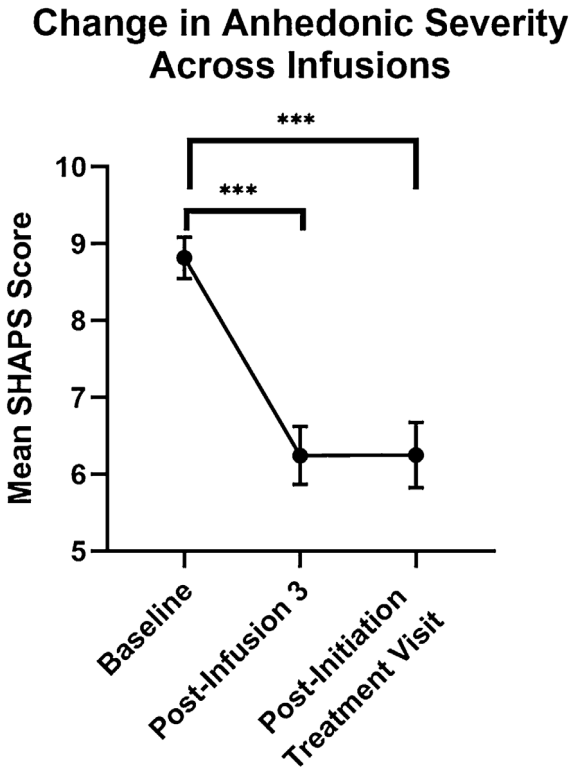

Fig. 1. Overall reduction in symptoms of anhedonia following three and four infusions of IV ketamine (Cohen's $f = 0.50$). *** indicates significant associations at $p < 0.001$.

was small ($\kappa^2 = 0.08$).

Finally, ketamine significantly improved symptoms of anxiety, partially mediated through the improvement of anhedonia (Fig. 2C). Ketamine reduced anhedonic severity ($a = -0.68$, $SE = 0.13$)), which reduced anxiety severity ($b = 0.46$, SE = 0.07). There was a significant total effect ($c = -1.01$, $t(354) = -5.77$, $p < 0.001$, 95% CI [−1.3, −0.66]) and direct effect ($c' = -0.69$, $t(354) = -4.04$, $p < 0.001$, 95% CI [−1.0, −0.35]) of infusion on GAD-7 total score. There was also a significant indirect effect of SHAPS ($b = -0.31$, $SE = 0.07$, 95% CI [−0.47, −0.18]) on the GAD-7 total score. Number of IV ketamine infusions and changes in anhedonic severity accounted for 12% of the variance. The effect size was small ($\kappa^2 = 0.08$).

4. Discussion

Herein, patients receiving IV ketamine at the CRTCE exhibited a significant improvement in measures of anhedonia following an acute series of four infusions, confirming the primary hypothesis. At baseline, 92% of patients presented with clinically significant anhedonia (i.e., SHAPS > 2), with approximately 67% of patients meeting criteria for high anhedonic symptoms. A week following the fourth infusion (i.e., the post-initiation treatment visit), 29% of patients reported no clinically significant anhedonia. Approximately 40% of patients still met criteria for high anhedonic symptoms. In addition, we report that the improvement in anhedonic symptoms partially mediated the improvement in depression severity, suicidality, and symptoms of anxiety. Moreover, once age, sex, psychiatric diagnosis, concomitant psychotropic medication, and body mass index were adjusted for in the model, the number of infusions and the overall improvement in anhedonia accounted for 26% of the variance observed in depression severity scores. If replicated, these results suggest that IV ketamine may partly mediate its antidepressive effects through the reward system.

Significant reductions in anhedonia were observed by the fourth infusion (i.e. post-infusion 3) and lasted for at least one week after treatment (i.e., post-initiation treatment visit). One open-label study of 52 participants using IV ketamine demonstrated that symptoms of anhedonia were significantly attenuated within 40 min of a single infusion and lasted for up to 3 days (Lally et al., 2015). Moreover, leveraging positron emission tomography scans, the authors demonstrated that the reduction in anhedonia was associated with increased glucose metabolism in the hippocampus and dorsal anterior cingulate cortex as well as decreased metabolism at the orbitofrontal cortex (Lally et al., 2015). Additional research by the same group, investigating the effect of a single dose of IV ketamine in bipolar patients ($n = 36$), reported a significant reduction in anhedonia that continued for 14 days following infusion (Lally et al., 2014). There was an overall increase in glucose metabolism at the dorsal anterior cingulate cortex and putamen (Lally et al., 2014). Indeed, these regions have been associated with anticipatory reward processing and suggest overlapping anhedonia targets between MDD and BD patients (i.e., the dorsal anterior cingulate cortex) (Schott et al., 2008). Available pharmacology research in ketamine indicates that, in addition to modulating the glutamatergic system, there may be indirect effects by increasing cerebral dopamine (Cao et al., 2019b; Zanos and Gould, 2018). Taken together, these findings suggest that unlike most monoaminergic medications, ketamine may provide clinicians with the capacity to rapidly ameliorate symptoms of anhedonia through glutamatergic modulation of reward regions.

The benefits observed in our sample on measures of anhedonia and suicidality are consistent with previously reported findings. In a study by Ballard et al. (2017), 100 participants with TRD ($n_{MDD} = 65$, $n_{BD} = 35$) received a single infusion of IV ketamine which resulted in improvement on SHAPS total score one day post-infusion (Ballard et al., 2017). Moreover, they reported that approximately 13% of the variance

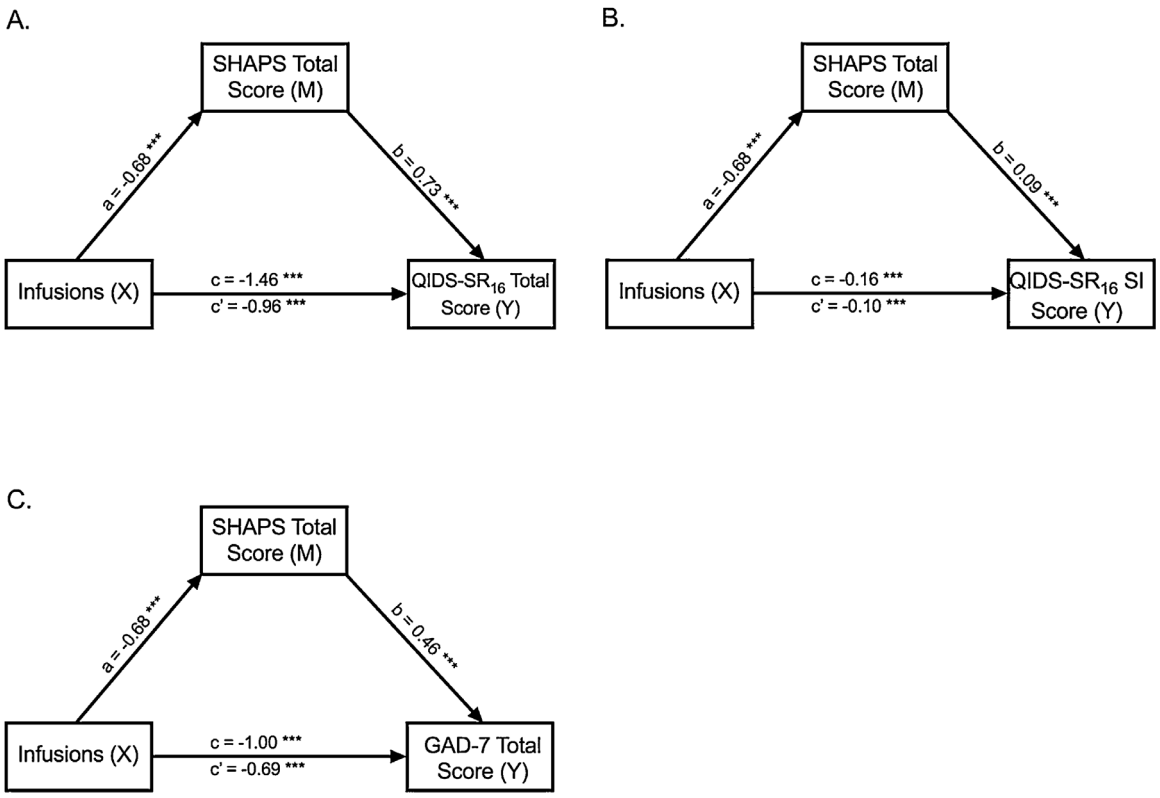

Fig. 2. Unstandardized regression coefficients for the relationship between number of infusions and (A) QIDS-SR_{16} Total Score, (B) QIDS-SR_{16} SI Score, and (C) GAD-7 Total Score, as mediated by SHAPS Total Score. *** indicates significant associations at $p < 0.001$.

in the reduction in suicidality, as measured by the Scale for Suicide Ideation 5-item, was attributable to improvement in anhedonia. Our study both replicate and extend these results further by observing improvement in both measures of anhedonia and suicidal ideation in repeated doses of IV ketamine. Similarly, we report that 17% of the variance in suicidality can be accounted for by improvement in anhedonia as a result of repeated IV ketamine infusions.

Preclinical models indicate that ketamine also exerts anti-anhedonic effects in animals exposed to chronic, mild stress (Papp et al., 2017). Pharmacologic studies have also established that ketamine exerts relative effects on catecholamine signaling and opioidergic systems (Cao et al., 2019b; Pan et al., 2017). Indirect evidence suggesting the engagement of opioidergic systems in adults receiving IV ketamine for TRD is provided by the observation that pre-treatment with naltrexone attenuates ketamine's antidepressive efficacy (Williams et al., 2018). Additional evidence also suggests that anti-suicidality effects of ketamine may be in part mediated by opioidergic systems (Williams et al., 2019). Indeed, several lines of evidence indicate that anhedonia is associated with suicidality (Yang et al., 2019). Taken together, it may be hypothesized that treatments capable of clinically significantly improving measures of anhedonia may be relevant to the additional objective of reducing suicidality.

Limitations of our study are that we did not primarily enroll patients with the overarching aim of exploring the association of the variables explored herein. It should be further noted that our variables of interest were examined independently within each mediation model, thus we did not account for the issue of collinear improvement between the improvement anhedonia, suicidality and other depressive symptoms. As IV ketamine was delivered as an open label, we cannot be certain as to the extent to which benefits on measures of anhedonia can be explained by expectancy. Moreover, the primary measure was SHAPS, which disproportionately measures consummatory hedonism. We did not include other measures of reward-based decision making (e.g., effort expenditure for reward). It would have been preferred to have additional measures, as we have previously reported that performance on the SHAPS reflects activity in a different subdomain in reward when compared to anticipatory subdomains (Subramaniapillai et al., 2019). In this study, suicide severity was assessed by one question on the QIDS-SR_{16}, making it difficult to determine the degree of suicidal ideation present in this cohort. Further research is required to study the effect of ketamine on different aspects of suicide by using detailed suicide assessment inventories (e.g., Columbia Suicide Severity Rating Scale) that measures suicidal ideation, intensity, and behaviors. Finally, as this was a retrospective analysis of clinical data, there is data missing from each clinical measure. Missing data was largely due to patients opting to skip assessments at point of care. Long-term data beyond the post-initiation treatment visit is not available due to variability in the scheduling for when patients return for maintenance infusions.

The strengths of this study are, to our knowledge, that our sample represents the largest group of well-characterized adults with MDD or BD who have received IV ketamine in a community-based treatment center. We are of the view that the patient's enrolled herein are highly representative of adults with TRD that are commonly encountered in clinical practice. Patient diagnoses were established by experts in mood disorders and we employed validated measures of anhedonia, anxiety, and depression severity.

Future research should attempt to parse the central nervous system substrates that subserve improvements in anhedonia in adults with TRD. It would be additionally interesting to determine whether other formulations (e.g., esketamine) are also capable of improving validated measures of anhedonia. It is also important to determine whether ketamine's beneficial effects on alcohol use and cocaine use disorder is at all influenced by resetting reward based decision making (Dakwar et al., 2020, 2017).

Taken together, patients receiving repeat-dose IV ketamine were significantly associated with reductions to symptoms of anhedonia. Moreover, the reduction in anhedonia partially mediated the anti-depressive, anti-suicidal, and anxiolytic responses also observed with IV

ketamine. Given these findings, it is important for further clinical trials to measure aspects of anhedonia when administering IV ketamine.

Declaration of Competing Interest

Roger S. McIntyre is a consultant to speak on behalf of, and/or has received research support from Lundbeck, Janssen, Shire, Purdue, Pfizer, Otsuka, Allergan, Takeda, Neurocrine, Sunovion, Stanley Medical Research Institute, and CIHR/GACD/Chinese National Natural Research Foundation.

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All other authors have no conflicts of interest to disclose.

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Authors RSM, NBR, and JDR developed research hypothesis, study design, conducted data analysis and wrote the final draft of the manuscript. Authors RSM, YL, MS, KK, and JDR were involved with data collection. All authors contributed to the final manuscript proofreading, edits and approval for submission. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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