Symptom Response to Repeat Dose Intravenous Ketamine in Adults with Major Depressive and Bipolar Disorder: Results from The Canadian Rapid Treatment Center of Excellence

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Abstract

Background: Multiple studies have demonstrated antidepressant effects of intravenous (IV) ketamine for unipolar and bipolar treatment-resistant depression (TRD). However, these studies have not delineated which specific symptoms of depression are more commonly improved by IV ketamine. Understanding which specific symptoms are more likely to improve with IV ketamine may be helpful for setting patient expectations and gauging treatment response.

Methods: Two hundred and twenty-six adults with treatment resistant major depressive disorder (MDD) and bipolar depression (BD) received repeated doses of IV ketamine at a community-based clinic. Depressive symptoms (sleep, mood, appetite/weight, concentration, self-criticism, suicidal ideation, general interest, energy, psychomotor restlessness/agitation) were measured by the Quick Inventory for Depression-Self-Report 16-Item ($QIDS\text{-}SR_{16}$) at five timepoints: (1) baseline, (2) post-infusion 1, (3) post-infusion 2, (4) post-infusion 3, and (5) post-acute assessment. The data were analyzed using mixed models to determine the effect of repeated IV ketamine treatment on each of the nine symptoms. Symptom improvements were categorized as clinically important if patients exhibited a 30% decrease in symptoms from baseline to the post-acute assessment.

Results: There was a significant effect of treatment on all symptoms of depression, as measured by the $QIDS\text{-}SR_{16}$. General interest (41%), mood (38%), energy (37%), SI (36%), self-criticism (34%), and concentration (30%) symptoms improved at a clinically important level from baseline to the post-acute assessment (i.e., point-reduction from baseline to the post-acute assessment). Psychomotor agitation/restlessness (25%), sleep (25%), and appetite (11%) symptoms did not meet the criteria for a clinically important symptom reduction at the threshold of a 30% symptom improvement.

Conclusion: Only general interest, mood, energy, SI, self-criticism, and concentration symptoms improved at both a statistically significant and clinically important level.

Introduction

Current monoamine-based antidepressants fail to provide sufficient symptom relief and remission for individuals with major depressive disorder (MDD) and bipolar disorder (BD) [1, 2].

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study found that only 36% of individuals with depression experience a full remission of depressive symptoms and after multiple medication trials, approximately 30% of individuals remain symptomatic and do not experience complete remission [3]. In fact, 25% of patients continue to use antidepressants for more than a decade [4,5]. Individuals who require more antidepressant trials are more likely to relapse within one year [3]. Furthermore, persistent depressive symptoms are the strongest predictor for relapse of a depressive episode [6]. Individuals with treatment-resistant depression (TRD) experience a significantly longer duration of depressive episodes and greater work impairment compared to individuals with non-TRD [7]. As such, there is a critical need for fast-acting and effective antidepressant treatments for individuals with TRD.

Randomized, double-blind, placebo-controlled trials have established the rapid efficacy of intravenous (IV) ketamine, an N-methyl-D-aspartate receptor antagonist, for patients with TRD [8–13]; [14]; [15]; [16]. The effectiveness of repeat-dose IV ketamine for unipolar and bipolar TRD has also been established in a real-world setting through large case series from clinics providing off-label IV ketamine treatment, typically for ultra-refractory cases with significant comorbidities [17].

However, despite top-line efficacy of IV ketamine, the effect of ketamine on specific depressive symptoms remains ambiguous [18]. The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5; [19] outlines nine core symptoms of MDD: (1) depressed mood, (2) anhedonia, (3) increase or decrease in weight/appetite, (4) insomnia or hypersomnia, (5) psychomotor agitation or restlessness, (6) fatigue/loss of energy, (7) feelings of worthlessness or guilt, (8) impairments in thinking, concentration, or decision-making and (9) recurrent thoughts of death or suicidal ideation (SI). These individual depressive symptoms are distinct from each other and differ in underlying pathophysiological mechanisms and degree of functional impairment, and therefore may not uniformly respond to antidepressant treatments [20]. Overall antidepressant response does not indicate which individual symptoms are alleviated by the antidepressant [20]. Indeed, as shown by the STAR*D data [6], and replicated in other clinical samples, symptoms of poor sleep, amotivation, low energy and cognitive dysfunction often persist with conventional antidepressants, despite achieving remission from other depressive symptoms (e.g., mood, negative cognitions, suicidal ideations, etc.).

The mechanism of action of ketamine is distinct from conventional antidepressants, as ketamine primarily targets the glutamate system, rather than monoamines (e.g., serotonin, norepinephrine, dopamine). Therefore, depressive symptoms that preferentially improve with ketamine may differ from conventional antidepressant response symptom trajectories. Moreover, understanding which specific symptoms are more likely to improve with IV ketamine may allow for improved counseling and informed consent for patients considering this novel treatment option, along with improving the ability to gauge treatment response.

Extant literature has established that IV ketamine is associated with reduced SI, with one study reporting sustained reductions in SI for up to 12 days following infusions [21–23]. Anhedonia (lack of interest or pleasure) has also been found to decrease following IV ketamine, however the effect was only maintained for three days post-infusion [24]. Additional research reported significant treatment effects of IV ketamine on reducing all core symptoms of depression except for appetite [25].

The current study aims to characterize the specific effects of IV ketamine in a community clinic setting by identifying which DSM-5 core symptoms of depression improve with repeat-dose IV ketamine treatment, as measured by the Quick Inventory for Depressive Symptomatology Self-Report 16-Item ($QIDS\text{-}SR_{16}$) [26].

Method

Participants

All participants included in this study were patients who were receiving care at the Canadian Rapid Treatment Center of Excellence (CRTCE) in Mississauga, Ontario, Canada. The CRTCE is an outpatient clinical and research center that specializes in the administration of off-label IV ketamine for adults with unipolar or bipolar TRD, obsessive compulsive disorder (OCD), and post-traumatic stress disorder (PTSD).

Patients with comorbid psychiatric conditions are eligible for IV ketamine treatment as long as they have a primary diagnosis of a mood disorder. All patients must meet Stage 2 Resistance

criteria or higher (insufficient symptom relief from at least two separate antidepressant trials), as defined by [27], in order to be eligible for IV ketamine treatment. Available evidence indicates that ketamine may benefit patients with TRD [28,29]; however, ketamine is an off-label treatment that is not approved for any psychiatric indications. The CRTCE follows the best practices for safe and appropriate ketamine delivery according to the Consensus Statement for the American Psychiatric Association Council of Research Task Force [30]. Patients must be able to provide written and verbal informed consent to be eligible for IV ketamine treatment. Patients also consented to their data being used for research purposes and publication.

Patients are ineligible to receive IV ketamine at the CRTCE if they have dementing disorders, psychotic disorders, or a current substance use/alcohol use disorder (less than three months of abstinence), or if they do not have a primary diagnosis of a mood disorder. For patients with previous psychotic episodes or mood episodes with psychotic features, a minimum of 3 months since psychotic symptoms were experienced is required to move forward with ketamine infusions.

A total of 226 adult outpatients with a primary diagnosis of either MDD, BD, post-traumatic stress disorder (PTSD), or obsessive compulsive disorder (OCD) received IV ketamine treatment at the CRTCE between the time of the clinic inception in July 2018 to December 2019. Demographic information of included participants is presented in Table 1.

Analysis of this data was approved by a community Institutional Review Board and is registered under NCT04209296 on the clinicaltrials.gov website.

Procedure

A staff psychiatrist at the CRTCE confirmed the primary diagnosis of a mood disorder according to the DSM-5 [19] before patients began IV ketamine treatment, and staff anesthesiologists medically approved each patient for ketamine infusions. Most patients were taking adjunctive medications in addition to IV ketamine; however, patients were required to discontinue irreversible monoamine oxidase inhibitors (MAOIs) at least two weeks prior to their first infusion and were prohibited from taking naltrexone during the period of IV ketamine treatment

[31]. Additionally, patients were instructed not to take benzodiazepines for at least 12 hours before each IV ketamine infusion [32].

Patients received four acute ketamine infusions over a period of 7 to 14 days. At infusions 1 and 2, all patients received 0.5mg/kg of ketamine hydrochloride diluted in 0.9% saline solution, infused over 40-45 minutes. The patient's body weight was used to determine the total ketamine dose at each infusion (ideal body weight was used to calculate dose for patients with a body mass index greater than 35kg/m^2). If patients had a suboptimal response to the treatment after infusion 2 (i.e., $\leq$ 20% reduction in QIDS-SR_{16} score) without tolerability difficulties, they were eligible to receive a dose optimization to 0.75mg/kg for infusions 3 and 4. Patients met with the staff psychiatrist for the post-acute assessment one week after the fourth infusion.

Depressive symptoms were measured at five timepoints throughout the acute treatment period: (1) before the first infusion (i.e., baseline) , (2) before the second infusion (i.e., post-infusion 1), (3) prior to the third infusion (i.e.,post-infusion 2), (4) before the fourth infusion (i.e., post-infusion 3), and (5) one week post-infusion follow-up (i.e., post-acute assessment). Post-infusion assessments were completed approximately two days after each infusion. The QIDS-$SR_{16}$was the primary measure used to monitor depressive symptoms. The QIDS-SR_{16} was administered at the CRTCE on a tablet device. Data were de-identified and stored on Research Electronic Data Capture (REDCap; [33,34].

After each infusion, patient safety was monitored at the CRTCE clinic for one to two hours. All patients were escorted home by a responsible adult and were prohibited from driving until the following day.

Measures

The QIDS-SR_{16} (Rush et al., 2003) is a patient-administered self-report measure that maps onto the nine core symptoms of a major depressive episode as defined by the DSM-5 [19]. The scale consists of 16 items that assess the following symptoms: (1) sleep disturbance (including insomnia and hypersomnia), (2) low mood, (3) appetite/weight, (4) concentration, (5) self-criticism, (6) suicidal ideation, (7) interest, (8) energy/fatigue, and (9) psychomotor restlessness/agitation. The scores for the sleep disturbance, appetite/weight, and psychomotor

restlessness/agitation symptoms were based on the highest score from two or more items which measured those symptoms, respectively. The other six symptoms were measured by one item each. Each item was rated on a scale of 0 to 3, with 0 representing an absence of the symptom and 3 representing a severe symptom.

Other clinical and self-report measures were collected at each point of care but were not analyzed in the present study.

Data Analysis

Data were retrospectively analyzed in IBM Statistical Package for the Social Sciences Version 23 (SPSS Inc., Chicago, IL, United States). Mixed models were conducted for each symptom measured by the QIDS-SR_{16} in order to examine the effect of repeat dose IV ketamine across the five time points of interest (i.e., baseline, post-infusion 1, post-infusion 2, post-infusion 3, and the post-acute assessment) on each of the nine core depressive symptoms. Mixed models were implemented to accommodate for missing data and uneven timing between visits. First-order autoregressive matrices were used to account for repeated measures, and the data were fit using Restricted Maximum Likelihood (REML) with an alpha set to 0.05. Follow-up pairwise comparisons were conducted when there was a significant effect of treatment on the QIDS-SR_{16} symptom, and Bonferroni corrections were applied to account for multiple comparisons.

Mean percent change from baseline to the post-acute assessment was also calculated for each symptom in order to determine which symptoms improved at a clinically important level. While there is no established minimum clinically important difference for individual QIDS-SR_{16} symptoms, we defined a clinically important improvement as a 30% or greater symptom reduction at the population level.

Results

The sample consisted of 226 participants and a total of 994 data points. Post-infusion assessments that were completed more than four days after the previous infusion were excluded from the analyses. Post-acute assessments that were completed more than 14 days after infusion 4 were excluded from the analyses. Twenty-two assessments were excluded from the analyses

because they were not completed within this specified time period. Some patients also chose not to complete the assessments at some time points and others were lost to follow-up ($n_{\text{baseline}} = 226$; $n_{\text{post-infusion 1}} = 207$; $n_{\text{post-infusion 2}} = 195$; $n_{\text{post-infusion 3}} = 200$; $n_{\text{post-acute assessment}} = 116$). Fifty-nine percent of patients received a dose optimization to 0.75mg/kg for infusions 3 and 4.

Statistically Significant Symptom Improvement

Sleep

Overall, there was a significant effect of treatment on QIDS-SR_{16} sleep scores, $F(4, 581) = 4.497$, $p = .001$, $\eta_p^2 = .030$. There was a significant reduction in QIDS-SR_{16} sleep scores from baseline to post-infusion 3 ($p = .008$) and the post-acute assessment ($p = .001$), and from post-infusion 1 to the post-acute assessment ($p = .018$). No other treatment points differed significantly.

Mood

There was a significant overall effect of treatment on mood, $F(4, 588) = 27.155$, $p < .001$, $\eta_p^2 = .156$. There was a significant reduction in QIDS-SR_{16} mood symptoms from baseline to each subsequent assessment ($ps < .001$), from post-infusion 1 to post-infusion 3 ($p < .001$) and the post-acute assessment ($p < .001$), from post-infusion 2 to post-infusion 3 ($p = .005$) and from post-infusion 2 to the post-acute assessment ($p = .027$). There were no significant differences in mood symptoms between any other treatment points.

Appetite

There was a significant overall effect of treatment on appetite, $F(4, 586) = 9.999$, $p < .001$, $\eta_p^2 = .639$. There was a significant reduction in appetite symptoms from baseline to each subsequent treatment point ($p < .001$; $p < .001$; $p < .001$; $p = .019$). There were no significant differences in appetite symptoms between any other treatment points.

Concentration

There was a significant overall effect of treatment on concentration, $F(4, 583) = 13.537$, $p < .001$, $\eta_p^2 = .085$. There was a significant reduction in concentration symptoms from baseline to each subsequent treatment point ($ps < .001$), from post-infusion 1 to post-infusion 3 ($p = .028$)

and the post-acute assessment (p = .001) and from post-infusion 2 to the post-acute assessment (p = .007). There were no significant differences between any other treatment points.

Self-Criticism

There was a significant overall effect of treatment on self-criticism, $F(4, 586) = 13.922$, $p < .001$, $\eta_p^2 = .087$. There was a significant reduction in self-criticism symptoms from baseline to each subsequent treatment point (ps < .001), from post-infusion 1 to post-infusion 3 and the post-acute assessment ($p < .001$; $p = .007$), and from post-infusion 2 to post-infusion 3 (p = .021). There were no significant differences between any other treatment points.

SI

There was a significant overall effect of treatment on SI, $F(4, 590) = 18.130$, $p < .001$, $\eta_p^2 = .109$. SI symptoms significantly decreased from baseline to each subsequent treatment point (ps < .001), from post-infusion 1 to post-infusion 3 and the post-acute assessment ($p < .001$; $p = .049$), and from post-infusion 2 to post-infusion 3 (p = .005). There were no significant differences between any other treatment points.

General Interest

There was a significant overall effect of treatment on general interest, $F(4, 594) = 17.554$, $p < .001$, $\eta_p^2 = .106$. General interest symptoms significantly decreased from baseline to each subsequent treatment point (ps < .001), from post-infusion 1 to post-infusion 3 and the post-acute assessment (p = .003; $p < .001$), and from post-infusion 2 to the post-acute assessment (p = .008). There were no significant differences between any other treatment points.

Energy

There was a significant overall effect of treatment on general interest, $F(4, 591) = 20.015$, $p < .001$, $\eta_p^2 = .119$. General interest symptoms significantly decreased from baseline to each subsequent assessment point (ps < .001), from post-infusion 1 to post-infusion 3 and the post-acute assessment (p = .004; $p < .001$), and from post-infusion 2 to the post-acute assessment (p = .007). There were no significant differences between any other treatment points.

Psychomotor Agitation/Restlessness

There was a significant overall effect of treatment on general interest, $F(4, 588) = 10.011$, $p < .001$, $\eta_p^2 = .064$. Psychomotor symptoms significantly decreased from baseline to each subsequent assessment point (*p*s < .001), but there were no significant differences in symptoms between any other treatment points.

Clinically Important Symptom Improvement

General interest (41%), mood (38%), energy (37%), SI (36%), self-criticism (34%), and concentration (30%) symptoms improved at a clinically important level from baseline to the post-acute assessment (i.e., point-reduction from baseline to the post-acute assessment). Psychomotor agitation/restlessness (25%), sleep (25%), and appetite (11%) symptoms did not meet the criteria for a clinically important symptom reduction at the threshold of a 30% symptom improvement. The frequency of patients who reported no change or a 1-, 2-, or 3-point change in each symptom from baseline to the post-acute assessment is reported in Table 2.

Discussion

The primary objective of this study was to examine which specific symptoms of depression improved with repeat-dose IV ketamine treatment. While the results showed significant improvement in all symptoms, not all of these improvements were clinically significant. We found that general interest, mood, energy, SI, self-criticism, and concentration symptoms improved at both a statistically significant and clinically important level with IV ketamine treatment. Psychomotor agitation/restlessness, sleep, and appetite symptoms did not improve at a clinically important level from baseline to the post-acute assessment (i.e., on average, patients did not show a 30% or greater decrease in symptoms). Patients receiving IV ketamine reported improvements in symptoms of depression that are typically less responsive to monoamine-based antidepressants (i.e., general interest, reduced activity, and concentration/decision-making), which presents IV ketamine as a novel and beneficial treatment option for patients with these symptoms [35].

The finding that repeat-dose IV ketamine was related to significant improvements in mood supports multiple extant studies which have established the antidepressant effects of ketamine [9,13,17]. Improved general interest with repeated ketamine infusions is in keeping with previous placebo-controlled research, which has found that a single dose of IV ketamine correlates with sustained improvement in anhedonic symptoms in patients with bipolar TRD [24]. Furthermore, medications with procognitive effects may also facilitate reward processing via the glutamate system (i.e., hedonic effects), which supports the present finding that patients experienced both clinically important improvements in concentration and general interest symptoms [36,37].

The orbitofrontal cortex (OFC) may also be a critical region of interest that is targeted by IV ketamine, specifically improving anhedonia and self-criticism symptoms. This is further supported by imaging studies that have reported decreased regional metabolism in prefrontal networks associated with depressive symptoms [40–42]. Notably, one study reported significant normalization of subgenual cingulate (CG25) activity in 14 MDD patients following IV ketamine infusions [41]. This region has been strongly associated with core symptoms of depression (i.e., emotional regulation and reward anticipation) and stereotactic targeting of CG25 with neurostimulation has produced a similar rapid resolution of depressive symptoms [43,44]. The OFC also plays a role in social cognition, negative thought patterns, and self-criticism [45–47]. IV ketamine may thereby improve self-criticism symptoms by acting on the OFC, however the exact mechanism of action is unknown.

Furthermore, the findings indicated that mood, concentration, self-criticism, suicidal ideation, general interest, and energy symptoms significantly improve with repeated infusions, which suggests that repeated infusions are beneficial for specific symptom reduction. However, patient-reported symptoms did not significantly improve on any of these six core symptoms between post-infusion 3 and the post-acute assessment. It can be conjectured that either patient response to treatment reaches a plateau following infusion 3, or that symptoms do in fact continue to significantly improve within 1-2 days following infusion 4, but the effects are not sustained until the post-acute assessment which occurs one week after the fourth infusion. Extant literature has reported that repeated doses of IV ketamine produce sustained effects lasting from a few days

post-infusion to up to one-week post-infusion, with a high degree of variability amongst patients [48].

Psychomotor agitation/restlessness symptoms significantly improved from baseline to all treatment points, but there were no significant changes between any other treatment points, although symptoms did continue to decrease. This suggests that psychomotor agitation/restlessness symptoms only improve after the first infusion, and the function of the remaining 3 acute infusions is to maintain that effect, as opposed to further reducing symptoms. In clinical practice, this would suggest that depressed patients who present with psychomotor agitation/restlessness as a principle concern may only require one ketamine infusion in order to see a significant symptom reduction in the acute treatment period, and that subsequent infusions are for the purpose of maintaining the effect. While previous literature has found that IV ketamine is associated with a rapid improvement in psychomotor agitation symptoms, which has been found to be sustained for two days post-infusion [49], randomized controlled trials are needed to further explore whether repeated-dose ketamine infusions significantly improve symptoms, or whether a single ketamine infusion is sufficient.

The limitations of this study must be considered when interpreting the findings. Since the present study collected data from a real-world sample of patients receiving treatment at a community clinic, there was no control group to act as a comparison. Therefore, we cannot conclude that repeat-dose IV ketamine treatment caused the symptom improvements, only that they were associated with one another. Additionally, while all four acute infusions occurred within 14 days, the variance in time between each infusion differed depending on clinic and patient scheduling availability, thereby leading to differences in timing between each measure of depressive symptoms. Similarly, there was no assessment completed immediately after the fourth infusion, only one-week later; thus, it is unclear whether the post-acute assessment measures response to the fourth infusion or if it is a measure of sustained symptom relief one week after the fourth infusion. This poses a challenge in discerning whether four ketamine infusions provide significantly greater benefit than three ketamine infusions during the acute treatment period. Finally, the use of the QIDS-SR_{16} as the primary outcome measure limits the generalizability of these findings. For feasibility purposes and in order to limit the burden on patients, only quick

self-report scales were administered. Therefore, the findings presented in this study were not confirmed by structured clinical interviews. Additionally, the QIDS-SR_{16} is a condensed scale, and many of the symptoms analysed in the present study are measured by only a single item. Further research is needed using more rigorous and multi-faceted measures of each depression symptom in order to further support the findings presented herein.

In summary, this study found that repeat-dose IV ketamine in a real-world community clinic was associated with both statistically significant and clinically important reductions in general interest, mood, energy, SI, self-criticism, and concentration symptoms. Psychomotor agitation/restlessness, appetite, and sleep symptoms did not improve at a clinically important level with repeated ketamine infusions. This study contributes to the current literature which proposes that IV ketamine is an effective treatment option for patients with TRD who have not experienced symptom relief from typical monoamine-based antidepressants. Given the expenditure of resources and financial cost associated with repeat-dose IV ketamine, the above findings should be considered when counseling patients who are contemplating IV ketamine treatment.

Table 1. Demographic information of patients included in the analyses.

Demographic	*N* = 226
Sex	
Male, *n* (%)	100 (44)
Female, *n* (%)	126 (56)
Age, *M* (*SD*)	46 (14.38)
Age range (min, max)	(18, 82)
Primary Diagnosis	
MDD, *n* (%)	171 (76)
BD, *n* (%)	31 (14)
PTSD, *n* (%)	6 (3)
OCD, *n* (%)	4 (2)
Other, *n* (%)	14 (6)

Table 2. Frequency of patients who experienced an increase (i.e., worsening), decrease (i.e., improvement), or no change in symptoms from baseline to the post-acute assessment (*n* = 91).

	Symptom Worsening (i.e., increase in symptoms)				Symptom Improvement (i.e., decrease in symptoms)		
	3-point increase *n* (%)	2-point increase *n* (%)	1-point increase *n* (%)	No change *n* (%)	1-point decrease *n* (%)	2-point decrease *n* (%)	3-point decrease *n* (%)
Sleep	0 (0)	0 (0)	9 (10)	53 (58)	26 (29)	3 (3)	0 (0)
Mood	0 (0)	1 (1)	5 (5)	27 (30)	28 (31)	26 (29)	4 (4)
Appetite ($n = 90$)	0 (0)	7 (8)	12 (13)	37 (41)	17 (19)	14 (16)	3 (3)
Concentration	0 (0)	1 (1)	8 (9)	33 (36)	40 (44)	7 (8)	2 (2)
Self-Criticism	0 (0)	1 (1)	5 (5)	36 (40)	29 (32)	12 (13)	8 (9)
SI	0 (0)	0 (0)	3 (3)	47 (52)	31 (34)	8 (9)	2 (2)
General Interest	1 (1)	1 (1)	4 (4)	31 (34)	24 (26)	18 (20)	12 (13)
Energy	0 (0)	0 (0)	2 (2)	37 (41)	35 (38)	10 (11)	7 (8)
Psychomotor Symptoms/Agitation	0 (0)	1 (1)	6 (7)	47 (52)	26 (29)	9 (10)	2 (2)

Table 3. Means and Standard Errors of each QIDS-SR_{16} symptom at each assessment point*.

Domain	Mean	SE
Sleep		
Baseline	2.57	0.046
Post-infusion 1	2.48	0.054
Post-infusion 2	2.43	0.057
Post-infusion 3	2.27	0.067
Post-acute assessment	2.28	0.085
Mood		
Baseline	2.42	0.060
Post-infusion 1	1.96	0.072
Post-infusion 2	1.81	0.077
Post-infusion 3	1.60	0.083
Post-acute assessment	1.51	0.100
Appetite/Weight		
Baseline	1.52	0.073
Post-infusion 1	1.15	0.078
Post-infusion 2	1.13	0.078
Post-infusion 3	1.03	0.077
Post-acute assessment	1.15	0.100
Concentration		
Baseline	2.03	0.054
Post-infusion 1	1.75	0.061
Post-infusion 2	1.70	0.064
Post-infusion 3	1.56	0.065
Post-acute assessment	1.43	0.082
Self-Criticism		
Baseline	2.18	0.074
Post-infusion 1	1.83	0.086
Post-infusion 2	1.69	0.086
Post-infusion 3	1.46	0.096
Post-acute assessment	1.44	0.114
Suicidal Ideation		
Baseline	1.59	0.070
Post-infusion 1	1.24	0.075
Post-infusion 2	1.14	0.075
Post-infusion 3	0.97	0.081
Post-acute assessment	1.02	0.100
General Interest		
Baseline	2.35	0.065
Post-infusion 1	1.97	0.085
Post-infusion 2	1.78	0.087
Post-infusion 3	1.65	0.092
Post-acute assessment	1.39	0.118
Energy		
Baseline	2.20	0.058
Post-infusion 1	1.82	0.075

Post-infusion 2	1.69	0.080
Post-infusion 3	1.52	0.081
Post-acute assessment	1.39	0.095
Psychomotor Restlessness/Agitation		
Baseline	1.71	0.066
Post-infusion 1	1.46	0.072
Post-infusion 2	1.31	0.072
Post-infusion 3	1.28	0.078
Post-acute assessment	1.29	0.088

Figure 1. Mean (±SE) changes in QIDS-SR_{16} symptoms across treatment points.

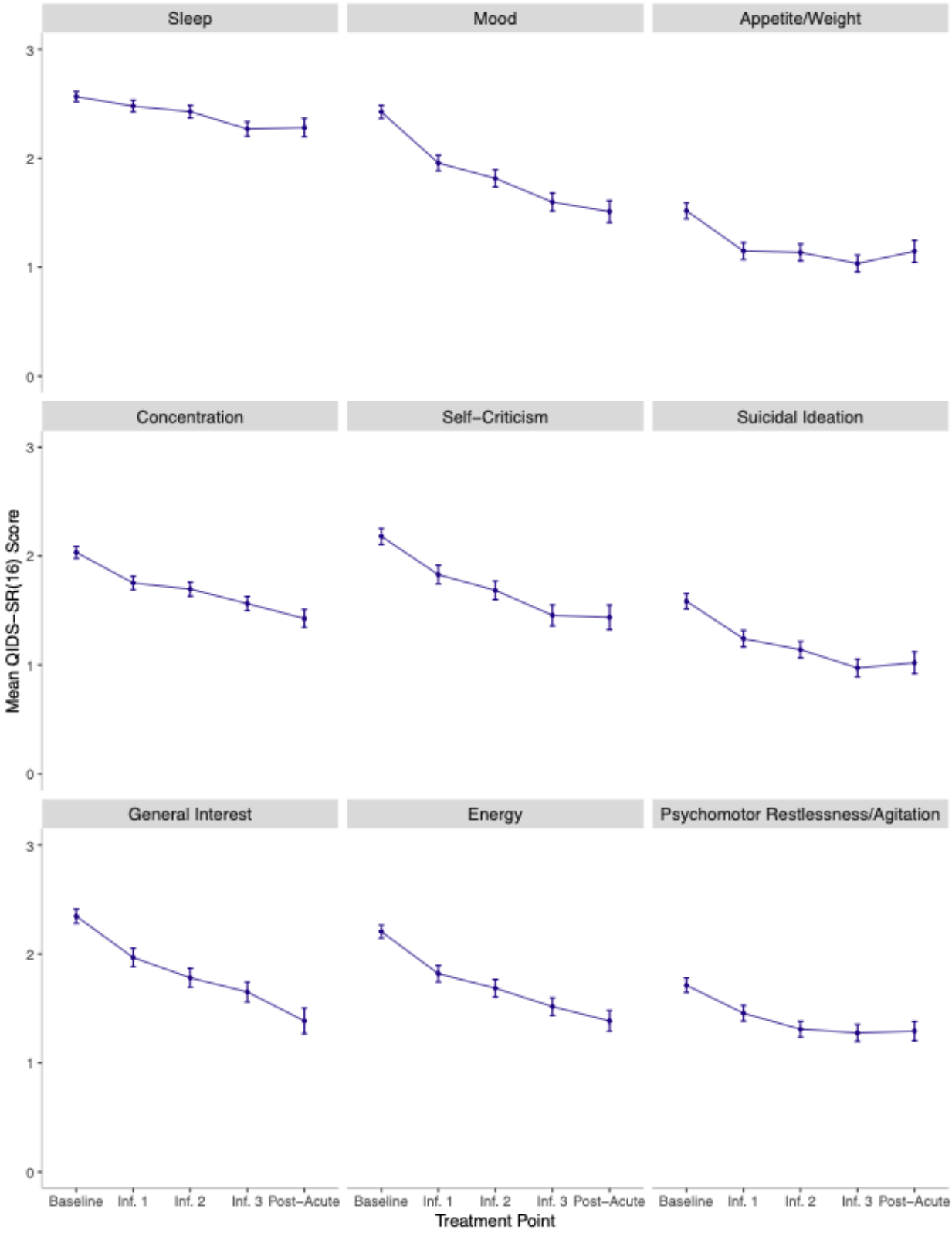
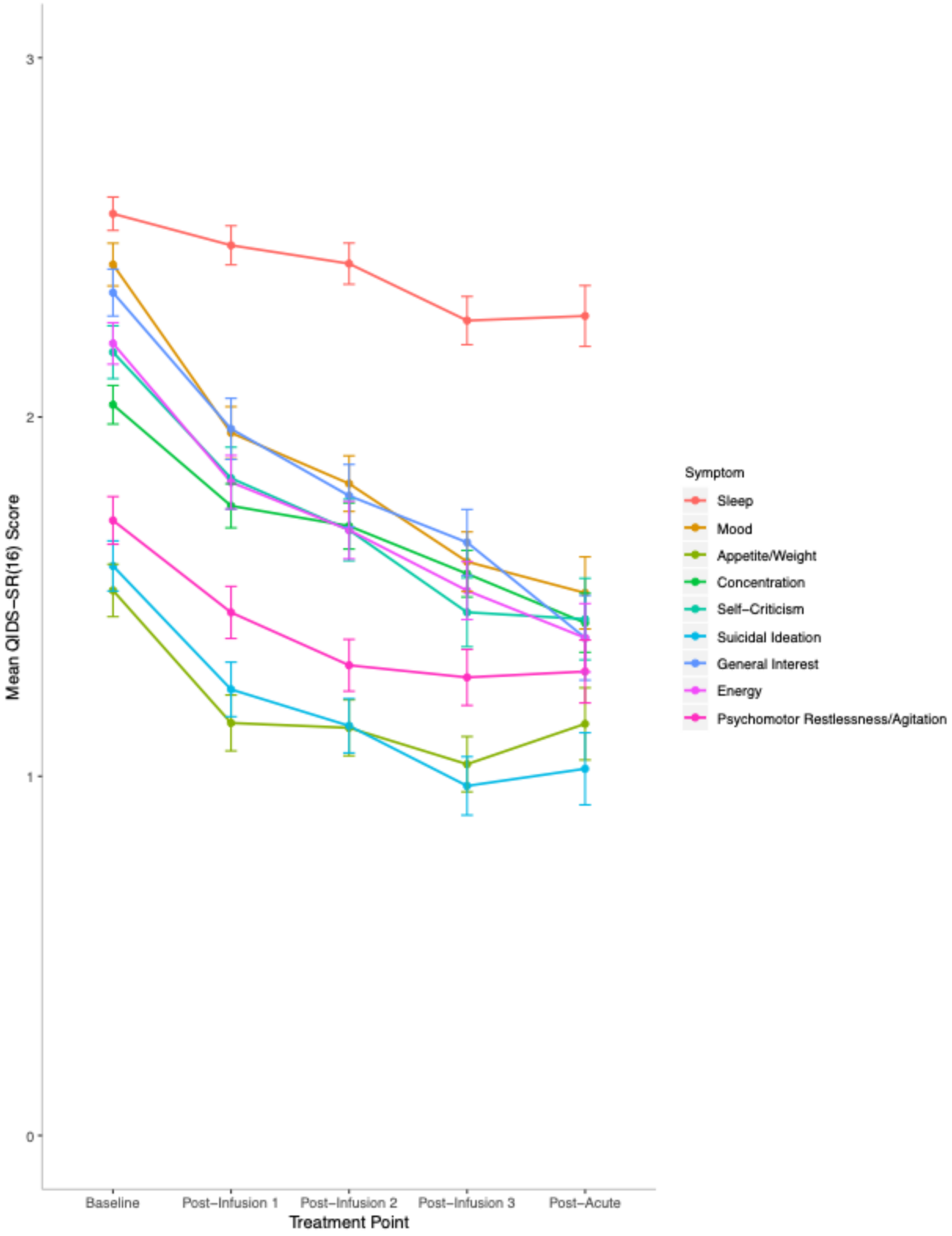


Figure 2. Graphical abstract



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