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The Impact of Childhood Maltreatment on Intravenous Ketamine Outcomes in Adult Patients with Treatment-Resistant Depression

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Abstract: Childhood maltreatment is associated with a poor treatment response to conventional antidepressants and increased risk for treatment resistant depression (TRD). The N-methyl-D-aspartate receptor (NDMAR) antagonist ketamine has been shown to rapidly improve symptoms of depression in patients with TRD. It is unknown if childhood maltreatment could influence ketamine's treatment response. We examined the relationship between childhood maltreatment using the Childhood Trauma Questionnaire (CTQ) and treatment response using the Quick Inventory of Depressive Symptoms–Self Report (QIDS-SR) in TRD patients receiving intravenous ketamine at a community outpatient clinic. We evaluated treatment response after a single infusion (n=115) and a course of repeated infusions (n=63). Repeated measures general linear models and Bayes Factor (BF) showed significant decreases in QIDS-SR after the first and second infusions, which plateaued after the third infusion. Clinically significant childhood sexual abuse, physical abuse, and cumulative clinically significant maltreatment on multiple domains (maltreatment load) were associated with better treatment response to a single and repeated infusions. After repeated infusions, higher load was also associated with a higher remission rate. In contrast to conventional antidepressants, ketamine could be more effective in TRD patients with more childhood trauma burden, perhaps due to ketamine's proposed ability to block trauma-associated behavioral sensitization.

Keywords: ketamine, depression, childhood trauma, childhood maltreatment, treatment schedule, behavioral sensitization

1. Introduction

Approximately 12.2% of US residents 13 years and older have a lifetime history of recurring major depressive episodes associated with major depressive disorder (MDD) or bipolar disorder (BD) [1]. An estimated 35% of depressed patients have treatment resistant depression (TRD), defined as an inadequate treatment response (< 50% improvement in depression severity) to at least two different types of antidepressant medications, the majority of which target monoaminergic neurotransmitter systems [2]. Compared to treatment responders, TRD is associated with lower quality of life and increased mortality [3,4]. It is important to identify factors that may predict response to specific interventions in order to provide timely, effective treatment.

The N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine is a promising treatment option for TRD [5]. Randomized controlled trials in patients with TRD have consistently shown favorable antidepressant responses to single and repeated subanesthetic doses of ketamine compared to saline or active

placebo [6–9]. Ketamine's antidepressant effect has been related to pre- and post-synaptic NMDAR blockade, enhancing prefrontal [10] and hippocampal [11] glutamate concentrations which activate the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), enhancing synaptic plasticity via AMPAR-induced elevation of brain derived neurotrophic factor (BDNF) [12] and activation of the mammalian target of rapamycin (mTOR) signaling pathway [13]. The antidepressant response is often rapid and dramatic, with patients maintaining substantial gains for up to two weeks [14–16].

A risk factor for TRD in adulthood is maltreatment in early life [17,18]. Approximately 12.5% of US children and adolescents have been exposed to sexual abuse, physical abuse or neglect, or emotional abuse or neglect [19]. A history of childhood maltreatment has been associated with a diminished treatment response to conventional antidepressant treatments [17]. No information to our knowledge is available regarding the relationship between childhood maltreatment and ketamine treatment response, although there is emerging support for the efficacy of IV ketamine in reducing symptoms of PTSD in adults [20,21].

In this study, we examine the influence of childhood maltreatment on ketamine treatment response after a single and repeated infusions in moderate to severely depressed adults receiving treatment at an outpatient ketamine clinic. We hypothesized that a history of childhood maltreatment would predict an unfavorable treatment response to acute (single infusion) and chronic (repeated infusions) ketamine. Our secondary hypothesis was that ineffectiveness would be related to severity of burden from childhood trauma.

2. Results

Table A1 (Appendix A) summarizes key demographic, treatment and clinical features of (i) patients who received a single infusion followed by a clinic visit 3-4 or 7 days later at time of post-infusion assessment (TPIA) (n=115) and (ii) patients who received at least 5 infusions on a twice weekly (every 3-4 days) or weekly schedule (every 7 days) with a baseline or post-infusion assessment prior to each infusion (n=63). Patients had moderate to severe levels of depression at pre-treatment baseline (operationalized as scores >10 on the Quick Inventory of Depressive Symptoms –Self Report, QIDS-SR [22,23]). The majority of patients had MDD as their primary diagnosis. Concurrent psychiatric medications spanned 12 different drug classes (mean 2.2 per patient). Patients received on average 0.62 (single infusion) or 0.70 (repeated infusions) mg/kg of IV ketamine per infusion.

2.1. Single infusion

2.1.1. Treatment Effect

A repeated-measures general linear model (RM-GLM) analysis showed that a single ketamine infusion significantly decreased QIDS-SR scores (mean ± SD; baseline 18.63 ± 3.70; post-single infusion: 13.12 ± 5.13) ($F(1,114) = 175.70$, $p < .001$, effect size [ES] $\eta^2_p = 0.61$; $BF > 1.27x10^{+10}$). Of the 115 patients, 19% (n=22) were responders (≥50% reduction of QIDS-SR score from baseline) and 7% (n=8) achieved remission (QIDS-SR <6).

2.1.2. Effect of Childhood Maltreatment

Table 1 summarizes mean CTQ total and subscale scale scores, the number and percentage of patients with clinically significant maltreatment based on recommended cut-off scores [24], and the number and percentage of patients with maltreatment loads 0-5 defined as the sum of subscales that met criteria for clinical significance. Figure B1 (Appendix B) displays the density and frequency plots for CTQ scores. About two-thirds of the sample had a maltreatment load of 1 or higher.

Table 1.
CTQ Maltreatment Characteristics of Single Infusion Study Sample (N=115)

	CTQ Scores		**Clinically Significant**			**Maltreatment Load**	
	Mean	**SD**	**N**	**%**		**N**	**%**
Total	45.33	18.11	-	-	0	34	29.6
SA[1]	7.07	4.40	24	20.9	1	26	22.6
PA[1]	7.57	4.22	34	29.6	2	23	20.0

PN[1]	7.64	3.68	44	38.3	3	14	12.2
EA	11.10	5.66	56	48.7	4	8	7.0
EN	11.95	5.39	38	33.0	5	10	8.7

CTQ: Childhood Trauma Questionnaire; SA: sexual abuse; PA: physical abuse; PN: physical neglect; EA: emotional abuse; EN: emotional neglect. [1]distributions were inversely transformed before statistical analyses.

2.1.2.1. QIDS-SR

We first examined correlations between QIDS-SR change score (baseline minus post-infusion) and CTQ measures. Change score correlated significantly with maltreatment load ($r = .31$, $p < .001$; $BF_{10} = 29.07$), SA ($r = .29$, $p = .001$; $BF_{10} = 17.22$), PN ($r = .24$, $p = .01$; $BF_{10} = 3.11$), total CTQ ($r = .24$, $p = .01$; $BF_{10} = 2.75$) and PA ($r = .18$, $p = .05$; $BF_{10} = 0.80$), but not EA or EN ($r < .17$, $p > .07$; $BF_{10} < 0.57$). Based on r and BF values, we tested effects of maltreatment load, and of SA and PN on treatment response using two separate RM-GLM analyses.

RM-GLM with load as grouping variables showed the effect of time and a significant time by load interaction. Separate ANOVA's for baseline and follow-up QIDS-SR revealed no significant differences between loads ($F[5,109] < 1.71$, $p > .13$). However, an ANOVA with QIDS-SR change score revealed that patients with load 5 (clinically significant maltreatment on all 5 subscales) had a larger reduction in QIDS-SR scores from baseline than patients with loads 0, 1 or 3 ($t > 3.18$, $p < .03$; $BF_{10} > 5.56$); differences were not significant with loads 2 or 4 ($t \approx 2.4$, $p > .18$; $BF_{10} \approx 2.50$).

Subscale RM-GLM analysis included SA and PN as continuous independent variables, showing the effect of time and a time by SA interaction ($F(1,112) = 5.37$, $p = .022$, $\eta^2_p = 0.046$). Testing the interaction showed that those with SA ≥8 (n=24) had a mean decrease in QIDS-SR of 8.08 points (SD = 4.33) compared to 4.82 (4.25) points of those with SA <8 (n=91) ($F(1,113) = 11.07$, $p = .001$, $\eta^2_p = 0.089$; $BF_{10} = 25.81$). However, this translated to only a 2-point difference at post-infusion (low: 13.62 ± 5.22; high: 11.25 ± 4.37; $F(1,113) = 4.15$, $p = .04$; $BF_{10} = 1.41$), without a significant difference at baseline (low: 18.44 ± 3.80 high: 19.33 ± 3.28; $F(1,113) = 1.11$, $p = .38$; $BF_{10} = 25.81$).

2.1.2.2. Response and remission rates

Relationships between maltreatment and response and remission rates were examined with X^2 tests or t-tests corrected for 6 comparisons ($p < 0.0083$ for load and five subscales). Neither load nor CTQ subscales were related to response or remission rates after a single infusion.

2.1.3. Influence of Demographic and Treatment Variables on Maltreatment Effects

A RM-GLM was performed to determine if effects of maltreatment on treatment response remained after controlling for effects of demographic (age, gender) and treatment (ketamine dose, time of post-infusion assessment [TPIA]) variables. Maltreatment load was included as a continuous variable to avoid empty cells when load was included as grouping factor. Table C1 (Appendix C) provides outcomes of that analysis. Outcomes of the tests examining possible modulating effects of self-reported diagnosis and of prescribed psychopharmacological treatment are provided in Table D1 (left-hand column; Appendix D). Demographic, clinical and treatment variables did not affect the time by CTQ maltreatment load interaction.

2.2. Repeated Infusions

Table A1 (Appendix A) summarizes demographics, treatment variables and diagnostic characteristics of 63 clinic patients who received at least 5 repeated ketamine infusions on a twice weekly (every 3-4 days) or weekly (every 7 days) treatment schedule. Table 2 summarizes CTQ characteristics.

Table 2.
CTQ Characteristics of Repeat Infusion Sample (N=63)

CTQ Scores		**Clinically Significant**		**Maltreatment Load**	
Mean	**SD**	**N**	**%**	**N**	**%**

Total	45.92	18.63	-	-	0	17	27.0
SA[1]	7.27	4.69	15	23.8	1	16	25.4
PA[1]	7.33	4.51	14	22.2	2	11	17.5
PN[1]	8.03	3.63	29	46.0	3	8	12.7
EA	11.27	5.74	32	50.8	4	6	9.5
EN	12.02	5.87	21	33.3	5	5	7.9

CTQ: Childhood Trauma Questionnaire; SA: sexual abuse; PA: physical abuse; PN: physical neglect; EA: emotional abuse; EN: emotional neglect. [1]distributions were inversely transformed before statistical analyses.

2.2.1. Treatment Effect

A RM-GLM analysis for QIDS-SR across 5 visits and 4 infusions showed a significant effect of time ($F[4,248] = 97.60$, $p < .001$, $\eta^2_p = 0.61$, $BF_{10} = 1.77x10^{+46}$). Table 3 displays outcomes of post-hoc tests correcting p for multiple comparisons, showing significant reductions in QIDS-SR after the first and second infusions. These outcomes were found irrespective of treatment schedule. The Bayes Factor (BF) indicates that the evidence for these improvements is strong. Although the improvement in depression after the third infusion was not statistically significant and effect size (d) is low, BF suggests moderate evidence in favor of an improvement. Additional decreases in QIDS-SR scores after the fourth infusion were not significant and BF evidence for improvement was low.

Of the 63 patients, 46.03% (n=29) were responders and 23.81% (n=15) achieved remission after 4 infusions.

Table 3.
Post-hoc Comparisons Corrected for Multiple Comparisons Testing Changes in QIDS-SR Scores between Clinic Visits.

			QIDS-SR							
Infusion		**Visit**	**Mean**	**SD**	**Comparison**	**Change**	**t**	**p**	**d**	**BF_{10}**
Baseline (BL)		1	19.19	3.71	-	-	-	-	-	-
Infusion (I-1)	1	2	13.92	4.94	**BL vs I-1**	**5.27**	**9.12**	**<.001**	**1.15**	**$1.73x10^{+10}$**
Infusion (I-2)	2	3	11.16	5.32	**I-1 vs I-2**	**2.76**	**6.50**	**<.001**	**0.82**	**$7.9x10^{+5}$**
Infusion (I-3)	3	4	10.16	5.81	I-2 vs I-3	1.00	2.67	.097	0.34	3.537
Infusion (I-4)	4	5	9.91	5.52	I-3 vs I-4	0.25	0.53	.999	0.07	0.158

Bold: p <.0125 across 4 comparisons

2.2.2. Effect of Childhood Maltreatment

2.2.2.1. QIDS-SR

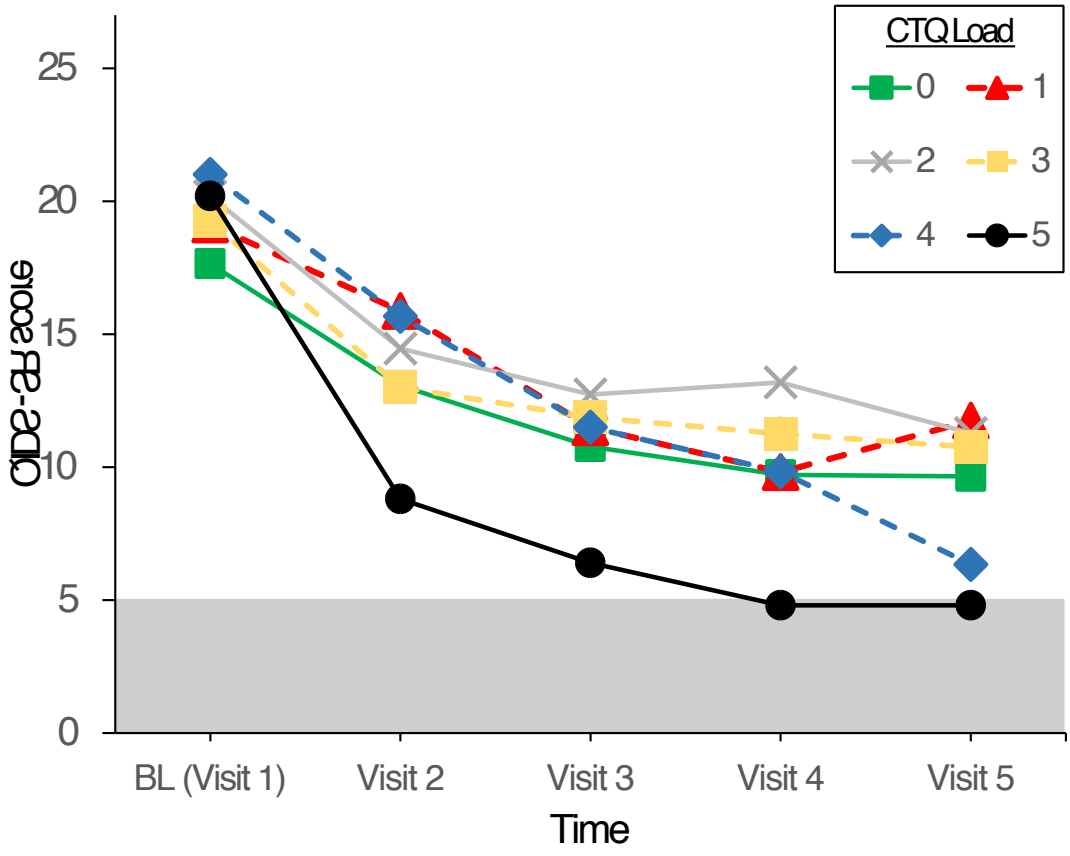
We first examined correlations between QIDS-SR change score (QIDS-SR baseline minus visit 5) and CTQ variables. Possible effects of childhood maltreatment were examined further with RM-GLM analyses that included CTQ variables that the initial correlation analysis showed to have a significant relationship with QIDS-SR change. QIDS-SR change correlated significantly with maltreatment load ($r = .427$, $p < .001$; $BF_{10} = 59.89$), PN ($r = 0.390$, $p = .002$; $BF_{10} = 20.61$), total CTQ ($r = 0.360$, $p = .004$; $BF_{10} = 9.52$), PA ($r = 0.359$, $p = .004$; $BF_{10} = 9.25$), and SA ($r = 0.335$, $p = .007$; $BF_{10} = 5.29$). Correlations were not

significant for EA (r = 0.137, p = .284; BF_{10} = 0.275) and EN (r = 0.164, p = .200; BF_{10} = 0.351). Separate RM-GLM analyses tested for effects of maltreatment load, and of PN, PA and SA.

The RM-GLM analysis with load as grouping variable revealed a significant effect of time (F[4,248] = 106.93, p < .001, η^2_p = 0.65, BF_{10} = 1.77x10^{+46}) and time by load interaction (F[4,248] = 2.40, p = .003, η^2_p = 0.17; BF = 6.57) (for extracting BF for interaction terms, see Appendix E and [25]). Load by itself was not significant (F[5,57] = 1.32, p = .27, η^2_p = 0.10, BF_{10} = 0.213).

The time by load interaction is displayed in Figure 1. ANOVA's showed that the load groups did not differ in QIDS-SR score at any of the time points (F[5,57] < 2.08, p > 0.81, η^2_p < 0.16; BF_{10} = 0.185 – 0.680). By contrast, examination of load effects on QIDS-SR change score revealed Bonferroni-corrected higher change scores for load 4 (QIDS-SR change score = 14.67 ± 4.41) and 5 (15.40 ± 2.30) compared to load 1 (7.38 ± 4.87) (respectively, t = 3.19, p = .035, d = 1.53; BF_{10} = 2.35, and t = 3.28, p = .027, d = 1.80; BF_{10} = 3.78), and a trend for a difference between load 0 (8.0 ± 4.85) and load 5 (t = 3.04, p = .053, d = 1.66; BF_{10} = 2.56). No significant differences were found between the other groups, indicating ketamine could benefit patients with a very high maltreatment load more than patients with a low load.

Figure 1.
Time by Maltreatment Load Interaction for QIDS-SR. QIDS-SR < 6 indicates remission.



RM-GLM for CTQ subscales included SA, PA and PN as continuous independent variables. Outcomes showed the significant effect of time, and a significant time by PA interaction (F[4, 236] = 5.83, p < .001, η^2_p = 0.090) with the time by PN interaction approaching significance (F[4, 236] = 2.38, p = .052, η^2_p = 0.039). Main effects of the CTQ subscales (F[1, 59] < 2.49, p > .11) and the time by SA interaction (F[4, 236] = 1.57, p = .18, η^2_p = 0.026) were not significant. As noted by the correlation analysis, those with higher scores on PA had a greater decline in QIDS-SR from baseline to visit 5. A final RM-GLM with CTQ total score revealed also the interaction with time (F[4,244] = 3.08, p = .017, η^2_p = 0.048) with the same effect as that found for PA.

2.2.2.2. Response and remission rates

Relationships between maltreatment and response and remission rates at Visit 5 were examined with X^2 statistics. Outcomes were corrected for multiple comparisons ($p_{cor} < 0.0083$ for CTQ load and the five subscales). Table 4 displays the outcomes of the statistical analyses, revealing significant effects of maltreatment load and PN. BF showed very strong evidence for remission with higher than lower maltreatment load, strong evidence for remission with PN, and moderate evidence for remission with both SA and PA. There were no variable-specific effects on response rate.

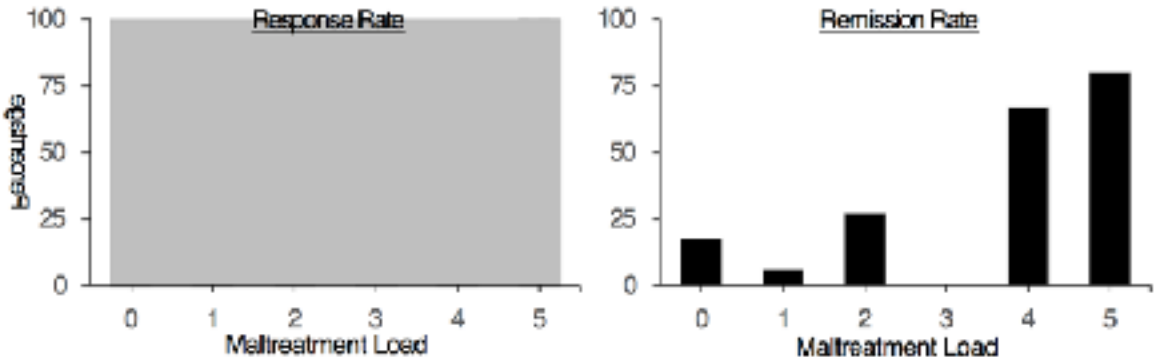
Table 4.
Maltreatment Effects on Response and Remission Rates after Infusion 4 at Visit 5

	Response rate				**Remission rate**			
	X^2	**df**	**p**	**BF_{10}**	**X^2**	**df**	**p**	**BF_{10}**
Load	8.95	5	.111	1.19	***20.43***	***5***	***.001***	***41.83***
Any	0.01	1	.921	0.34	0.49	1	.485	0.35
SA	3.37	1	.066	1.18	0.98	1	.321	0.51
PA	2.41	1	.120	1.15	*6.81*	*1*	*.009*	*6.73*
PN	3.43	1	.064	1.63	***9.14***	***1***	***.002***	***23.97***
EA	0.41	1	.521	0.37	1.99	1	.159	0.68
EN	0.51	1	.475	0.41	*6.30*	*1*	*.012*	*5.36*

Bold: $p < .0083$ (Bonferroni-corrected). *Italic*: $BF > 3$ indicating at least moderate evidence of alternative hypothesis over null hypothesis.

Exploring the effect of maltreatment load on response and remission rates, figure 2 displays percentages of patients who met criteria for response and remission at Visit 5. The figure suggests that patients with clinically significant maltreatment on at least 4 CTQ subscales have a higher rate of response and remission than those with a load of 3 and lower, although the effect of load was significant for remission and not response rate. This indicates that meeting clinical significance of childhood maltreatment on at least 4 CTQ subscales could predict a higher likelihood of remission after 4 once- or twice-weekly infusions.

Figure 2.
Response and Remission Rates as a Function of CTQ Childhood or Adolescent Maltreatment Load.



2.2.3. Influence of Demographic and Treatment Variables on Maltreatment Effects

Examining possible moderating effects of demographic variables (age, gender), treatment variables (ketamine dose, treatment schedule), self-reported diagnosis, and prescribed psychopharmacological treatment on the relationship between childhood maltreatment and ketamine treatment response revealed a minimal influence of those variables on the time by load interaction and the effect of load on remission rate.

Effects of diagnosis and of medication on the time by load interaction is provided in Table D1 (right-hand column; Appendix D).

3. Discussion

Contrary to our hypotheses, this naturalistic study in TRD patients showed that those with childhood maltreatment not only benefit as much as those without clinically significant maltreatment history, but may benefit more from a single and repeated ketamine infusions. Childhood sexual abuse (single dose) and physical abuse (repeated doses) are also associated with a better treatment response. The effects of maltreatment load on treatment response and on remission rates suggests that the summation of clinically significant childhood maltreatment domains is a better predictor than clinical significance on a specific category of maltreatment.

Outcomes were minimally affected by age, gender, ketamine dose, psychiatric diagnoses and concurrent medication, suggesting that ketamine could benefit TRD patients with high maltreatment load across a variety of diagnoses and concurrent treatment. Although women had higher QIDS-SR scores than men irrespective of treatment, we found no evidence of different treatment responses between men and women, extending the lack of gender effects reported in controlled clinical trials using a single dose infusion [26] to a clinical setting. Further, the difference in depression scores between men and women in our study is only 1.61 points on the QIDS-SR, suggesting that this effect is clinically not meaningful.

The relationship between more severe childhood maltreatment and a better treatment response to ketamine could be associated with processes of trauma-induced behavioral sensitization. Thirty years of evidence across species show that trauma (but also uncontrollable stress in general, repeated use of substances of abuse, mood or anxiety episodes, and suicide attempts) could induce sensitization of behavioral, motivational and stress systems, thereby increasing behavioral and physiological reactivity (expression) to subsequent stressors [27–30]. Induction and expression of behavioral sensitization require activation of NMDARs [31,32] albeit via different neural pathways [33–37]. In preclinical models, NMDAR antagonists blocked induction [38] and expression [31] of behavioral sensitization by stress, and in humans with PTSD, a subanesthetic dose of ketamine [20,21] or NMDR antagonist memantine [39] could improve symptoms of hyperarousal and depressive symptoms which are considered expressions of behavioral sensitization. It is, therefore, possible that resistance to conventional antidepressants may be related to expression of sensitization by early stressful events that could be blocked in this population by ketamine. There are currently no validated markers of sensitization, but development of such markers might make it possible to identify and treat "treatment-resistant" depression in a physiologically-based manner.

In addition to effects of childhood maltreatment on treatment response, we also showed that ketamine's antidepressant effects were similar across infusion treatment schedules (twice or once weekly infusions), with improvements in depression after the first infusion, a further improvement after the second infusion, and perhaps a further improvement after the third infusion before plateauing. A twice weekly infusion schedule for the first 3 infusions followed by weekly infusions for maintenance may therefore maximize benefit and minimize patient burden.

Limitations of the current study include the relatively small sample size for a naturalistic study, complicating interpretations of outcomes for analyses of possible effects of diagnosis or medication on treatment outcomes in the context of childhood maltreatment. Further, the CTQ measures maltreatment, but not other sources of trauma such as parental divorce, death of a parent or loved one, war/combat exposure, or natural disasters. Finally, although we accounted for PTSD diagnosis, we did not address possible further moderating effects of adulthood trauma on ketamine treatment response.

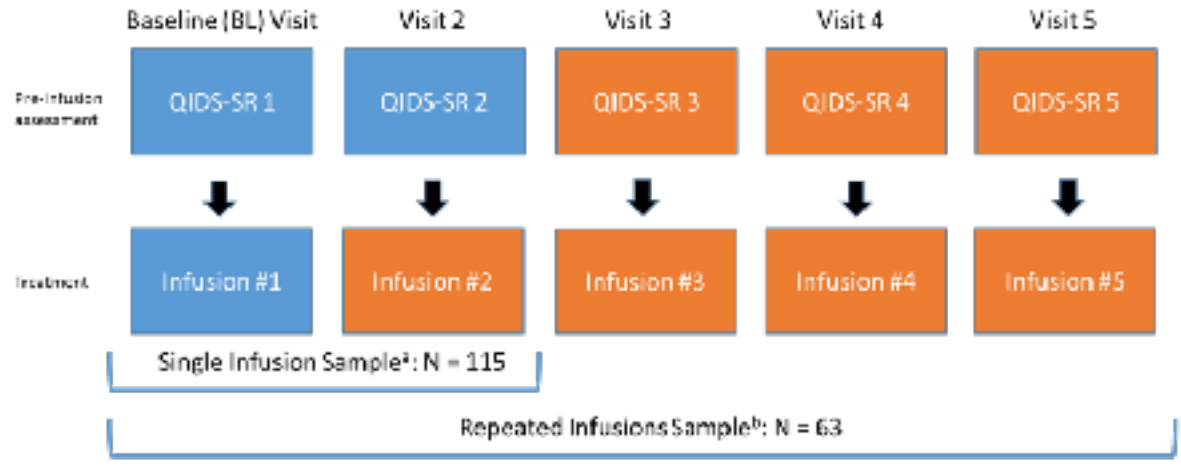
4. Materials and Methods

4.1 Study Samples

This study included adult patients with moderate to very severe depressive symptoms (baseline QIDS-SR >10) presenting for treatment at a ketamine treatment clinic. Patients had failed at least one trial of antidepressant medication. The study examined the effects of childhood maltreatment, operationalized as sexual abuse, physical abuse or neglect and emotional abuse and neglect before the age of 18 measured with

the Childhood Trauma Questionnaire (CTQ) [40,41], on ketamine's antidepressant response after a single infusion or at 4 repeated infusions of ketamine. The first sample of patients (n=115) received at least 1 infusion of IV ketamine with a post-infusion assessment 3 or 7 days after the infusion. The second sample comprised a subset of patients (n=63) who continued treatment to receive at least 5 infusions on a twice weekly or weekly basis on Wednesdays and/or Saturdays. The Quick Inventory of Depressive Symptomatology- Self Report (QIDS-SR) [Rush, Trivedi et al Bio Psych 2003] was administered at baseline prior to the first infusion, and prior to each subsequent infusion to assess treatment effects. Figure 3 displays the study samples and order of study procedures at each visit.

Figure 3.
Study samples and schedule of procedures



[a] Patients in the Single Infusion sample (denoted in blue) received an infusion at Baseline Visit and were assessed with QIDS-SR prior to next infusion at Visit 2. QIDS-SR 2 scores reflect treatment effects from a single infusion of ketamine.
[b] Patients in the Repeated Infusions sample (denoted in orange) were a subset of patients from the single infusion sample that continued ketamine treatment beyond 2 infusions and received at least 5 infusions on a weekly or twice weekly infusion schedule.

4.2 Administration of IV ketamine

Treatment infusions took place in a private room equipped with vital sign monitoring and were administered by a board-certified anesthesiologist or anesthetist. Weight based dosing of IV ketamine was delivered over 40 min-2 hours as per standard procedures described in numerous publications [6,42]. For nausea, patients were given ondansetron.

4.3. Data Set

A waiver of consent was obtained from the Baylor College of Medicine Investigational Review Board (IRB) to analyze de-identified demographic and clinical data from patients who received treatment a ketamine treatment center. Data was collected by clinic staff as part of routine clinical care from April 2016 to April 2019. Researchers received de-identified information in a database.

4.2. Materials

The QIDS-SR [22] is a 16-item self-report scale assessing the severity of depressive symptoms. The QIDS-SR assesses all the criterion symptom domains designated by the American Psychiatry Association Diagnostic and Statistical Manual of Mental Disorders - 5th edition (APA, 2013) to diagnose a major depressive episode. The QIDS-SR is easy to administer and is sensitive to change. Its psychometric properties have been established in various study samples [22,23].

The CTQ [40,41] is a 28-item self-report scale measuring childhood maltreatment prior to the age of 18. It has been validated in clinical and non-clinical samples and evidences sound psychometric properties (internal consistency α>0.78; test-retest reliability r=0.88). Twenty-five items assess the presence of abuse or neglect across 5 domains of childhood maltreatment: sexual, physical and emotional abuse, and physical and emotional neglect. Each item is scored on a 5-point Likert scale from "Never True" to "Very Often True" and

is in reference to "When I was growing up." Scores range from 5 to 25 on each of the 5 subscales with higher scores indicating more severe maltreatment. Following previously established guidelines, clinically significant maltreatment in each domain is defined as a score of at least 8 (sexual abuse, physical abuse, physical neglect), 10 (emotional abuse), and 15 (emotional neglect) [24]. We were interested also in the influence of trauma load across maltreatment domains. The CTQ total score does not take into account clinically relevant scores on each subscale. For that reason, we calculated a "maltreatment load" score to denote the total number of domains a patient scored above threshold for clinically significant maltreatment (score 0 – 5). A higher load indicates more extensive clinically significant childhood maltreatment.

4.3 Data Analysis

Ketamine treatment effects on QIDS-SR and the possible influence of childhood maltreatment were tested with repeated measures general linear models (RM-GLM). Time was included as dependent variable for analyses for a single infusion (baseline, time of post-infusion assessment [TPIA]) and for repeated infusions (baseline [visit 1], visit 2, visit 3, visit 4, visit 5). First, effects of treatment were examined. Second, CTQ variables were included as dichotomous or continuous variables where appropriate. CTQ variables were included only when an initial correlation analysis showed a significant correlation between the CTQ variable and QIDS-SR change score (baseline minus TPIA or visit 5). Finally, demographic characteristics (age, gender), treatment characteristics (ketamine dose, TPIA or treatment schedule), diagnosis and/or concurrent psychoactive medication were included as independent variables to examine possible moderating effects on relationships between maltreatment and treatment response. For all RM-GLM, significant interactions were tested with appropriate follow-up analyses. Relationships between response rate (≥ 50% reduction from QIDS-SR baseline) and remission rate (QIDS-SR < 6) with demographic, clinical and CTQ variables were tested with X^2 or t-tests where appropriate.

Besides providing p-values to express the rejection of a null hypothesis, extra information is provided by the Bayes Factor (BF) about the strength of the evidence in favor of the alternative hypothesis over the null hypothesis (BF_{10}) or vice versa [43–45].

Data distributions of ketamine absolute dose and dose in mg/kg, SA, PA and PN were normalized with inverse transformations. Statistical outcomes of inversely transformed data are in opposite directions compared to analyses with the original data; we report outcomes in the non-normalized direction (e.g., negative r-values with transformed variables will be presented as positive r-values as if non-normalized). All other variables were normally distributed. All statistical analyses were performed in JASP 0.9.0.1 [44].

5. Conclusions

The outcomes from this naturalistic study suggests that in TRD populations with high childhood maltreatment, ketamine treatment could be considered before other add-on antidepressant medications. Outcomes also suggest that the optimal treatment response can be obtained with two or three infusions on a twice-weekly schedule followed by maintenance of the antidepressant response with once weekly ketamine infusions.

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Appendix A

Table A1.
Demographic and Clinical Characteristics

	Single infusion (N=115)			**Repeat infusions (N=63)**		
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**
Age (years)	43.78	14.45	19 – 76	43.25	13.67	19 – 70
Weight (kg)	77.77	18.98	47 – 127	76.87	18.58	47 – 127
BMI	26.69	5.56	16.3 – 43.1	26.55	5.41	16.3 – 43.1
Dose (mg) [1, 2]	47.07	26.79	15 – 240	53.15	40.79	17 – 205
Dose/kg (mg) [1, 2]	0.62	0.38	0.16 – 3.02	0.70	0.43	0.32 – 2.58
QIDS-SR						
Baseline	18.63	3.70	11 – 26	19.19	3.71	11 – 26
Total medications	2.2	1.8	0 – 7	2.3	1.6	0 – 7
	N	**%**		**N**	**%**	
Time of post-infusion assessment (TPIA)			Infusion Schedule			
Day 3	74	64.3	Twice weekly	41	65.1	
Day 7	41	35.7	Once weekly	22	34.9	
Gender (m/f)	52/63	45.2/54.8		26/37	41.3/58.7	
Diagnosis						
MDD	88	76.5		49	77.8	
AD	54	47.0		29	46.0	
BD	26	22.6		14	22.2	
PTSD	13	11.3		7	11.1	
Pain	7	6.1		5	7.9	
Medication						
Benzodiazepine*	44	38.3		23	36.5	
SSRI	38	33.0		22	34.9	
Anticonvulsant	37	32.2		22	34.9	
SNRI	27	23.5		14	22.2	
Antipsychotic	26	22.6		15	23.8	
AAD	25	21.7		13	20.6	
Psychostimulant	20	17.4		11	17.5	

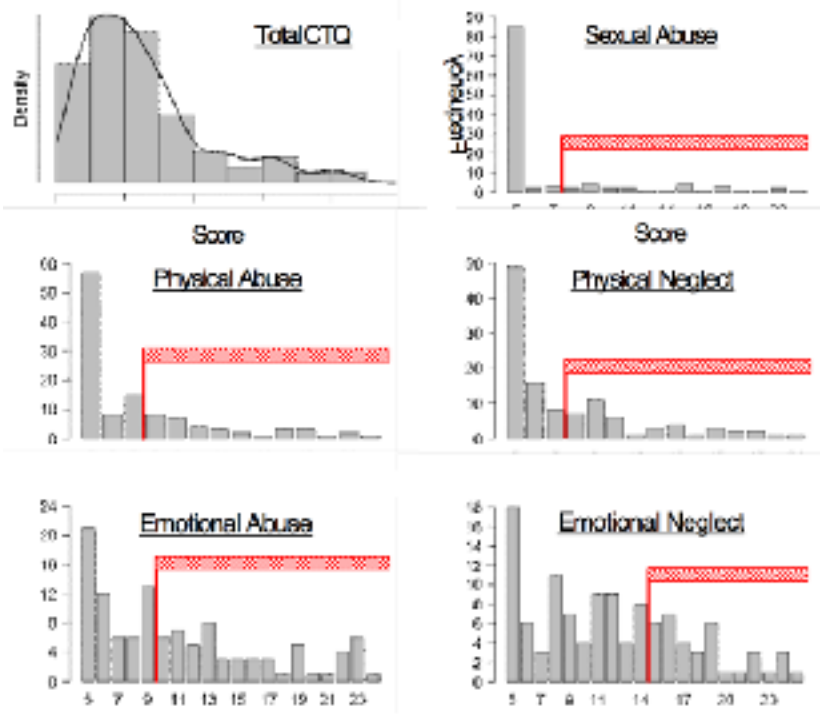
Hypnotic	12	10.4	8	12.7
Opioid	9	7.8	8	12.7
Lithium	9	7.8	4	6.3
TCA	6	5.2	4	6.3
Anxiolytic	5	4.4	2	3.2

[1] Variables that were normalized with an inverse transformation prior to data analysis.
QIDS: Quick Inventory of Depression Symptomatology – Self-Report; MDD: major depressive disorder; AD: anxiety disorder; BD: bipolar disorder; PTSD: post-traumatic stress disorder; SSRI: selective serotonin reuptake inhibitor; SNRI serotonin - norepinephrine reuptake inhibitor; AAD: atypical antidepressant; TCA: tricylic antidepressant.
* Benzodiazepine medications were withheld the day of infusion

Appendix B

Figure B1.

Subject response distributions of total CTQ and CTQ subscales. Clinically significant maltreatment cut-offs for each of the subscales are indicated by the red shaded areas. The number and percentage of subjects are as displayed in Table S1. There is no cut-off available for total CTQ.



Appendix C

Table C1.

RM-GLM outcomes of effects of ketamine single infusion on treatment response as a function of CTQ maltreatment load controlling for demographic and treatment variables

	F(1,109)	p	μ^2_p
Main effects			

Time	*12.32*	*< .001*	*0.102*
Gender	3.77	.055	0.042
Age	*4.79*	*.031*	*0.042*
TPIA	2.94	.09	0.026
Load	0.11	.74	0.001
Interaction effects			
Time x load	**7.96**	**.006**	**0.068**
Time x TPIA	3.05	.084	0.027
Time x gender	0.16	.69	0.001
Time x age	0.03	.86	<0.001
Gender x TPIA	0.18	.74	0.001
Time x gender x TPIA	0.36	.55	0.003

RM-GLM analysis that included CTQ maltreatment load, age, gender, time of post-infusion assessment (TPAI; day 3 or day 7) and dose as independent variables showed that QIDS-SR scores decreased with increased age ($r = -0.20$, $p = .032$), and that QIDS-SR across baseline and post-infusion assessment was higher for women (QIDS-SR = 16.60 ± 3.85) than for men (QIDS-SR = 14.99 ± 3.75). The time by load interaction remained significant.

X^2 tests or t-tests revealed that response and remission rates were not related to age, dose, gender or TPIA.

Appendix D

Influence of Diagnosis and Psychopharmacological Treatment on Maltreatment Effects

Possible effects of diagnosis or medication on time by maltreatment interactions were tested with RM-GLM with baseline and follow-up QIDS-SR as dependent variables, and load as continuous independent variable instead of grouping variable to avoid empty or low populated cells. Each diagnosis or medication was tested separately. Diagnoses and medications did not affect the time by load interaction for single infusion, although for repeated infusion the interaction was no longer significant with the inclusion of antipsychotic, hypnotics or atypical antidepressant medication. No main effects of interactions were revealed for any of the diagnoses or medications.

Table D1.
Time by maltreatment load interaction for single and for repeat ketamine infusion when correcting for diagnosis or concurrent pharmacological treatment.

	Single infusion		**Repeat infusion**	
	F	**p**	**F**	**P**
MDD	11.74	<.001	4.77	.001
BD	11.73	<.001	2.00	.095
AD	12.03	<.001	4.60	<.001
PTSD	12.96	<.001	4.64	.001

Pain	11.83	<.001	4.63	.001
SSRI	12.15	<.001	3.75	.006
SNRI	10.30	.002	3.69	.006
Antipsychotic	12.84	<.001	1.51	.199
anticonvulsant	12.42	<.001	3.57	.008
Stimulant	12.69	<.001	2.94	.021
Benzo	12.20	<.001	3.96	.004
Hypnotic	10.96	.001	2.32	.057
Atypical AD	11.84	<.001	1.89	.114

Appendix E

A RM-GLM analysis that included demographic (age, gender) and treatment (dose, treatment schedule) characteristics as independent variables revealed no significant effects of gender, age, dose and treatment schedule. X^2 tests and t-tests showed that response and remission status were not or minimally related to age, dose, gender or TPIA.

Appendix F

To calculate BF for interaction terms, we provide an example from the text of the interaction between time and maltreatment load. BF is extracted from the output in JASP [25]. Comparing the interaction model (combination of time main effects model + load main effects model + time x load interaction, BF = $4.215X10^{+46}$) with the main effects model (time + load main effects, BF = $6.419X10^{+45}$) showed that the interaction model was preferred over the main effects model by BF = 6.57 ($1/[6.419X10^{+45}/4.215X10^{+46}]$).

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