Research paper

Distinct trajectories of antidepressant response to intravenous ketamine☆

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ARTICLE INFO

ABSTRACT

Background: The N-methyl-D-aspartate receptor antagonist ketamine is potentially effective in treatment resistant depression. However, its antidepressant efficacy is highly variable, and there is little information about predictors of response.
Methods: We employed growth mixture modeling (GMM) analysis to examine specific response trajectories to intravenous (IV) ketamine (three infusions; mean dose 0.63 mg/kg, SD 0.28, range 0.30 – 2.98 mg/kg over 40 min) in 328 depressed adult outpatients referred to a community clinic. The Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) assessed depression severity at baseline and before each infusion, up to three infusions for four total observations.
Results: GMM revealed three QIDS-SR response trajectories. There were two groups of severely depressed patients, with contrasting responses to ketamine. One group (n=135, baseline QIDS-SR=18.8) had a robust antidepressant response (final QIDS-SR=7.3); the other group (n=97, QIDS-SR=19.8) was less responsive (final QIDS-SR=15.6). A third group (n=96) was less severely depressed at baseline (QIDS-SR=11.7), with intermediate antidepressant response (final QIDS-SR=6.6). Comparisons of demographic and clinical characteristics between groups with severe baseline depression revealed higher childhood physical abuse in the group with robust ketamine response (p=0.01).
Limitations: This was a retrospective analysis on a naturalistic sample. Patients were unblinded and more heterogenous than those included in most controlled clinical trial samples. Information pertaining to traumatic events occurring after childhood and pre-existing or concurrent medical conditions that may have affected outcomes was not available.
Conclusions: Overall, ketamine's effect in patients with severe baseline depression and history of childhood maltreatment may be consistent with ketamine-induced blockade of behavioral sensitization.

1. Introduction

Approximately one-third of patients with major depressive disorder (MDD) do not respond to conventional antidepressant treatments and are considered to have treatment-resistant depression (TRD) (Nemeroff, 2007). TRD is associated with a 29% increase in all-cause mortality (Li et al., 2019), most notably from increased rates of suicide and accidents (Reutfors et al., 2018), and twice the economic burden (Johnston,

Powell, Anderson, Szabo, & Cline, 2019) of non-TRD MDD. Repeated intravenous (IV) infusions of subanesthetic doses of the N-methyl-D-aspartate receptor (NMDAR) channel blocker ketamine are safe and effective in patients with TRD (aan het Rot et al., 2010; Murrough et al., 2013; Singh et al., 2016; Zarate et al., 2006). The antidepressant effect of a single infusion of ketamine can begin as early as a few hours after a single infusion and last for at least one week (Zarate et al., 2006). Repeated infusions prolong and enhance ketamine's antidepressant

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effect (O'Brien, Lijffijt, Wells, Swann, & Mathew, 2019; Singh et al., 2016; Vande Voort et al., 2016). However, a substantial proportion of TRD patients have suboptimal responses to ketamine, thus making it important to evaluate predictors of treatment outcomes (O'Brien et al., 2019; Rong et al., 2018). Insight into trajectories of treatment response would improve clinical decision making, facilitate better treatment outcomes, and enhance therapeutics for patients with TRD.

A history of trauma reduces response to conventional antidepressant medications in depressed patients (Nanni, Uher, & Danese, 2012). We previously reported that IV ketamine treatment, when added to conventional antidepressants, was more likely to result in response and remission in a community-based sample of depressed patients with severe compared to mild childhood physical abuse and neglect, suggesting that ketamine may block persisting neurobiological effects of childhood trauma (O'Brien et al., 2019). To examine treatment trajectories and to further examine the role of childhood maltreatment, we conducted a hypothesis-free, data-driven latent-class analysis to (i) identify specific trajectories of treatment response to repeated ketamine infusions, and (ii) examine childhood maltreatment in addition to other demographic and clinical factors associated with the identified trajectories (Ram & Grimm, 2009).

2. Methods

2.1. Study Sample and Procedures

Clinical and demographic data was collected from a community IV ketamine clinic from April 2016 to January 2020 as part of routine clinical care. Researchers received a de-identified database for which the Baylor College of Medicine Institutional Review Board (IRB) provided a waiver of consent. The dataset included 407 patients who received treatment through the clinic. Patients were excluded from the dataset for the current analyses if they (i) had not completed a QIDS-SR assessment at pre-treatment baseline, (ii) had only received one ketamine infusion, or (iii) were younger than age 17. The final study dataset consisted of 328 patients who were referred for ketamine treatment. Patients received ketamine infusions at varying intervals depending on patient preference. The Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) (Rush et al., 2003; Trivedi et al., 2004) was administered before each infusion. Ongoing medication treatments spanned a range of classes. The total number of infusions and duration of treatment were determined individually by the patient and treatment provider.

2.2. Administration of IV ketamine

Ketamine infusions took place in a private room equipped for vital sign monitoring. Infusions were administered over 40 – 60 minutes by a board-certified anesthesiologist (AW). The initial dose of ketamine was weight-based using a 0.50 mg/kg ketamine calculation and other clinically relevant factors. Dosage was maintained or adjusted over the course of treatment for each individual patient to reach a dose in which the patient reported a mild dissociative effect (Pennybaker, Niciu, Luckenbaugh, & Zarate, 2017) and was tolerated. For nausea, patients were given ondansetron as needed.

2.3. Behavior-symptom Measures

Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR): The QIDS-SR is a 16-item self-report scale assessing the severity of depressive symptoms using total score and scores on symptom domains related to diagnosis of major depressive episodes (Diagnostic and Statistical Manual of Mental Disorders-5th edition (American Psychiatric Association, 2013)). Individual items on the QIDS-SR have been grouped into 3 empirically defined clusters of symptoms: Core Emotional (low mood, loss of interest, feelings of worthlessness, low energy/fatigability, difficulty concentrating), Sleep (difficulty falling asleep, difficulty

staying asleep, early awakening) and Atypical symptoms (psychomotor agitation, psychomotor retardation, suicidal ideation, hypersomnia) (Chekroud et al., 2017). The QIDS-SR is reliable and sensitive to change. The internal consistency is satisfactory (Cronbach's alpha=0.86), and there is a high correlation between QIDS-SR total score and total score on other depression scales (r around 0.80) (Rush et al., 2003; Trivedi et al., 2004).

Childhood Trauma Questionnaire (CTQ): The CTQ is a 28-item self-report scale measuring childhood maltreatment. Validated in clinical and non-clinical samples, the CTQ has robust psychometric properties (internal consistency>0.78; test-retest reliability r=0.88). (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997; Bernstein et al., 1994; Bernstein & Fink, 1998). Twenty-five items assess the presence of childhood abuse or neglect across 5 domains: sexual, physical and emotional abuse, and physical and emotional neglect. Three items assess minimization and denial. Each item is scored on a 5-point Likert scale, in reference to "When you were growing up". Scores range from 5 to 25 on each of the 5 abuse and neglect subscales with higher scores indicating more severe maltreatment. A maltreatment load score (from 0–5) was calculated to denote the total number of domains in which a patient scored above a previously established threshold cut score for clinically significant maltreatment (O'Brien et al., 2019). A higher load score indicates more extensive clinically significant childhood maltreatment. The CTQ was administered during the initial clinic visit before the first infusion.

2.4. Data analysis

We conducted growth mixture modeling (GMM; (Ram & Grimm, 2009)) analyses to (i) identify the number of patient groups that demonstrate different patterns of change in depression severity during ketamine treatment and (ii) examine demographic and clinical factors potentially related to those identified trajectories of depression severity. The first four QIDS-SR assessments related to the first three consecutive ketamine infusions were analyzed for modeling efficiency and accuracy; Missing data due to dropout after the first two assessments (fewer than 4 clinic visits) were handled via full information maximum likelihood (FIML) estimation (Little & Rubin, 1987). Patients received ketamine infusions at varying intervals depending on patient preference.

First, we applied GMM to evaluate a series of models to determine (a) the number of latent classes, each representing a group of patients with a similar change in QIDS-SR and (b) the shape (linear vs. non-linear) of this change. As shown in Fig. 1, the models included first-order latent variables of depression that were measured as total score and by sleep, core emotional, and "atypical" symptoms domains from four QIDS-SR assessments (Chekroud et al., 2017). Longitudinal measurement invariance was confirmed ensuring that progress in the observed symptoms can be attributed to actual change in depression severity (Dimitrov, 2010). The depression latent variables were then loaded on the second-order latent variables — *Intercept, Linear Slope*, and/or *Non-linear Slope* — that determined the shape of change in depression severity over time. Finally, the change factors were loaded on a third-order class latent variable that indicated the existence of different patient groups demonstrating specific, linear or non-linear trajectories of depression severity. We compared eight models including 1- to 4-class models of linear change and 1- to 4-class models of quadratic change (Ram & Grimm, 2009). In addition to interpretability and theoretical conformity of each model, analyses included: Bayesian Information Criterion (BIC; (Sclove, 1987) with lower values suggesting better fitting models (B. Muthén, 2003; Nylund, Asparouhov, & Muthén, 2007); entropy, summarizing the extent to which a model generates classification errors (Jedidi, Ramaswamy, & Desarbo, 1993), with larger values approaching 1 reflecting fewer classification errors; and Lo-Mendell-Rubin adjusted likelihood-ratio test (LMR aLRT; (Lo, Mendell, & Rubin, 2001)) for a model with c (linear and/or non-linear) classes with a significant *p*-value suggesting that the model should be rejected in favor of a model with $c + 1$ classes. In addition, we used
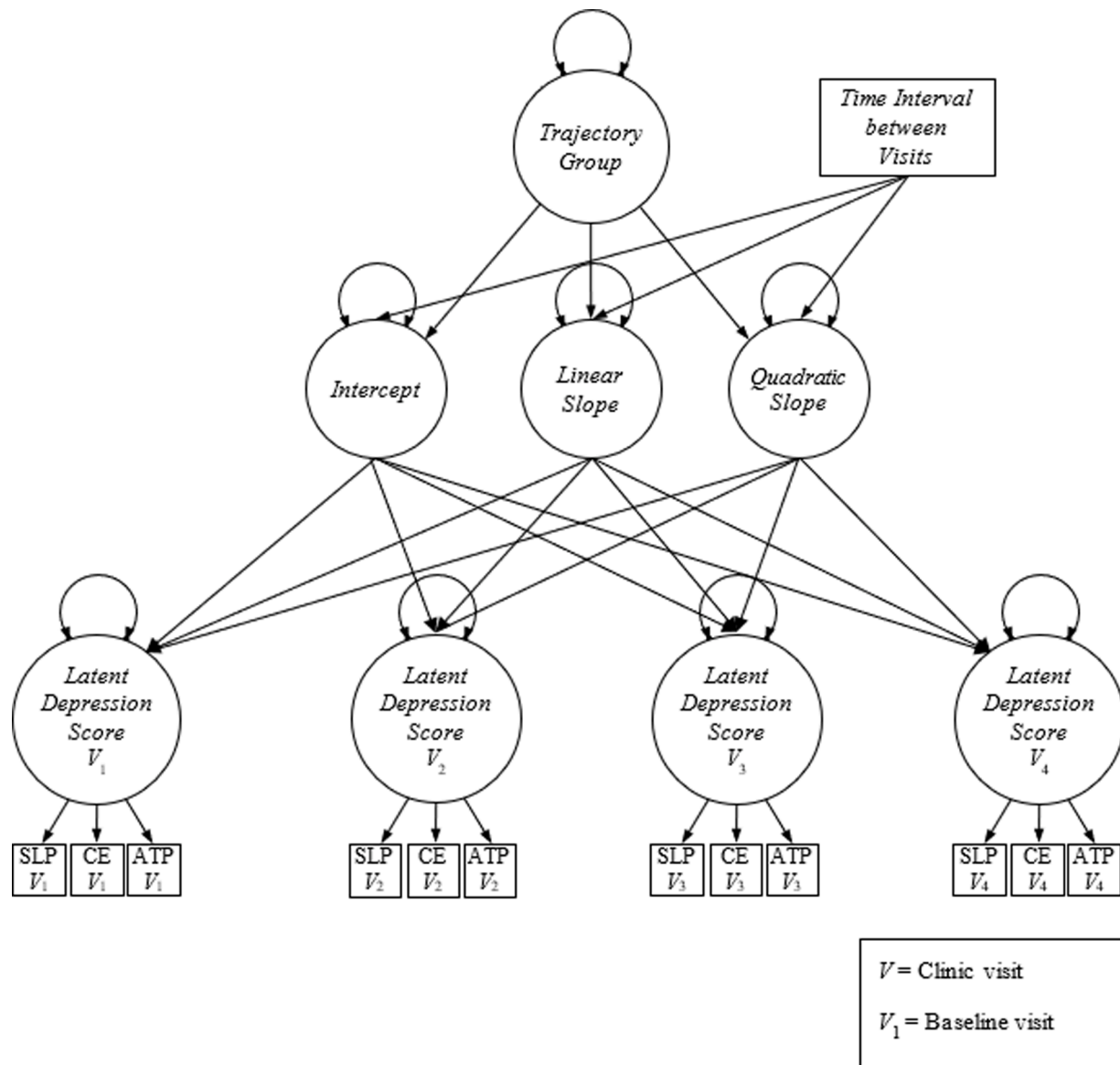
Fig. 1. Fitted growth mixture models for trajectory groups of latent depression. This figure shows the manner in which each trajectory group is 1) defined by time characteristics including intercept and linear/nonlinear slopes, which 2) result in changes in latent depression scores across clinic visits. The latent depression score is comprised of the QIDS-SR sleep, core emotional, and atypical symptom clusters.

hierarchical linear modeling to compare the slopes of linear or nonlinear change in overall depression score between classes.

Once the number and membership of classes were established, the second step compared patient-specific variables across classes. These variables (Table 1) included demographic characteristics, concomitant medications, psychiatric diagnoses (such as major depressive disorder, bipolar disorder, anxiety disorders), and childhood maltreatment history measured by the CTQ (physical, sexual, and emotional abuse, and physical and emotional neglect), as potential antecedents for different trajectories of depression severity. Class means of each variable were derived via posterior probability-based multiple imputations; the between-class equality of the means was assessed by Wald chi-square test (Asparouhov, 2007). The time interval between clinic visits was accounted for by regressing the change latent variables on this covariate. All analyses were performed using M*plus* 8.0 (Muthén & Muthén, n.d.) and R 3.6.1(R Core Team, 2019).

3. Results

3.1. Subjects

Demographic and clinical characteristics are described in Table 1. Patients had a mean baseline QIDS-SR score=17.03; SD=4.71, reflecting a severe level of depression (QIDS-SR mild depression score range=6-10; moderate=11-15; severe=16-20; very severe=21-27). Most subjects reported a mood disorder, primarily major depressive disorder (MDD; 80.2%). Over half the patients in the sample reported an anxiety disorder (AD; 54.3%). Patients most commonly reported taking a serotonin reuptake inhibitor (SSRI; n=100 [30.5%]) followed by an anticonvulsant and/or a benzodiazepine (both n=86 [26.2%]) during treatment. Mean ketamine dose at baseline was 0.57 mg/kg (SD=0.25; range=0.32 – 3.02).

Table 1
Sample characteristics at baseline (N=328).

	N (%)	M	SD/%
Age	328	43.59	13.85
Gender			
Female	166		50.6%
Body Mass Index	321	27.15	6.02
Weight (lb)	321	177.25	45.93
QIDS-SR	328	17.03	4.71
Ketamine dose (mg/kg)			
1st visit	321*	0.57	0.25
2nd visit	320	0.64	0.30
3rd visit	280	0.71	0.36
Medications			
SSRI	100		30.5%
Anticonvulsant	86		26.2%
Benzodiazepine	86		26.2%
SNRI	68		20.7%
Atypical Antidepressant	67		20.4%
Antipsychotic	66		20.1%
Stimulant	55		16.8%
Hypnotic	32		9.8%
Opioid	25		7.6%
Lithium	19		5.8%
Anxiolytic	17		5.2%
TCA	11		3.4%
Other	8		2.4%
Total Medications		1.95	1.72
Diagnosis and comorbid disorders			
Major depressive disorder	263		80.2%
Bipolar depression	59		18.0%
Anxiety disorder	178		54.3%
PTSD	49		14.9%
OCD	18		5.5%
Pain	19		5.8%
Attention-deficit disorder	22		6.7%
CTQ childhood maltreatment	206		
Physical abuse (8)		7.72	4.40
Sexual abuse (8) [†]		7.24	4.62
Emotional abuse (10) [†]		11.30	5.47
Physical neglect (8) [†]		7.53	3.50
Emotional neglect (15) [†]		12.28	5.55
CTQ maltreatment load (mean)		1.81	1.66
CTQ maltreatment load (category)			
0		64	31.1%
1		38	18.4%
2		39	18.9%
3		26	12.6%
4		19	9.2%
5		20	9.7%

Note: * weight was missing from 7 patients which resulted in the calculation of
ketamine dose as a function of weight (mg/kg) of 321 patients

[†] previously established threshold cut score of clinically significant trauma
(Walker et al., 1999)

3.2. Trajectories of depression severity

The GMM results revealed three distinct non-linear trajectories of
depression severity over the course of ketamine treatment. This 3-class
model of non-linear change yielded the best absolute fit (i.e., smallest
BIC value), satisfactory classification accuracy (i.e., entropy>.70), and
better fit than the models with two or four classes (i.e., LMR aLRT p>.05)
Model fit values and results of test for the number of growth classes are
presented in the Appendix (A1).

Fig. 2 and Table 2 display the QIDS-SR scores in the 3 patient groups.
Two groups were marked by high baseline depression severity. One
high-depression group (n=135, 41.3% of the sample) experienced rapid
and significant improvement (61%, black line in Fig. 2). The other high-
depression group (n=97, 30 % of the sample) experienced minimal
improvement (21%, blue line in Fig. 2). We refer to these groups as the
Severe Depression-Rapid Improvement (SD-RI) and *Severe Depression-
Minimal Improvement* (*SD-MI*) groups, respectively. The smallest group
(n=96, 28.7% of the sample) had significantly lower baseline depression

scores than the other two groups. Depression scores in this group
improved slowly during ketamine treatment (44%, red line in Fig. 2).
We refer to this group as the *Moderate Depression-Gradual Improvement*
(*MD-GI*) group. Table 3 shows that the SD-MI group had significantly
higher depression scores at baseline compared to the SD-RI group
(p=.039), but this 1-point difference does not appear clinically mean-
ingful. The difference between SD-RI and SD-MI groups increased as a
function of ketamine infusions, with larger group differences at clinic
visits 3 and 4 (about 6- and 8-point differences on the QIDS-SR,
respectively), with effect sizes increasing to 1.2 at Visit 3 and 2.3 at
Visit 4. This finding was also supported by significant slope-by-class
interactions in hierarchical linear modeling (linear slope SD-RI=-0.32,
linear slope SD-MI=-0.22, linear slope MD-GI=-0.08; all p<.05).

Table 3 shows post-hoc comparisons between the two severe
depression groups, which indicates that the rapid improvement in the
SD-RI group is related to stronger improvements for core emotional and
"atypical" domains, both representing syndromal depressive symptoms,
which began to separate from their baseline values after the first infu-
sion. Sleep showed a similar improvement for the two severe depression
groups, suggesting that ketamine has lower efficacy to improve sleep or
that the treatment response for sleep fits a separate class model.
Observed scores of sleep, core emotional, and "atypical" symptoms
across the four visits by trajectory group are depicted in the Appendix
(A2).

3.3. Antecedents of depression change trajectories

Table 4 presents descriptive statistics for the three patient groups,
including demographics, concomitant medications, psychiatric di-
agnoses, and childhood maltreatment scores.

Demographics: the *MD-GI* group included more men than women,
differing from the severe-depression groups (p<.05). The groups were
comparable for age, BMI, and weight (all p>.05).

Ketamine Dose: Displayed in Table 4, the average weight-based dose
of ketamine that patients received differed between the MD-GI group
and the two more severely depressed groups after the first infusion. The
two more severely depressed groups did not differ (p=.22).

Medications: More patients in the *SD-MI* group reported taking anti-
convulsants (34.0%) and opioid medications (11.3%) than patients in
MD-GI group (anti-convulsant=18.8%; opioids=3.1%) (adjusted
p<.05), potentially reflecting a more severe illness-course for patients in
the *SD-MI* group than in the *MD-GI* group. The groups did not differ in
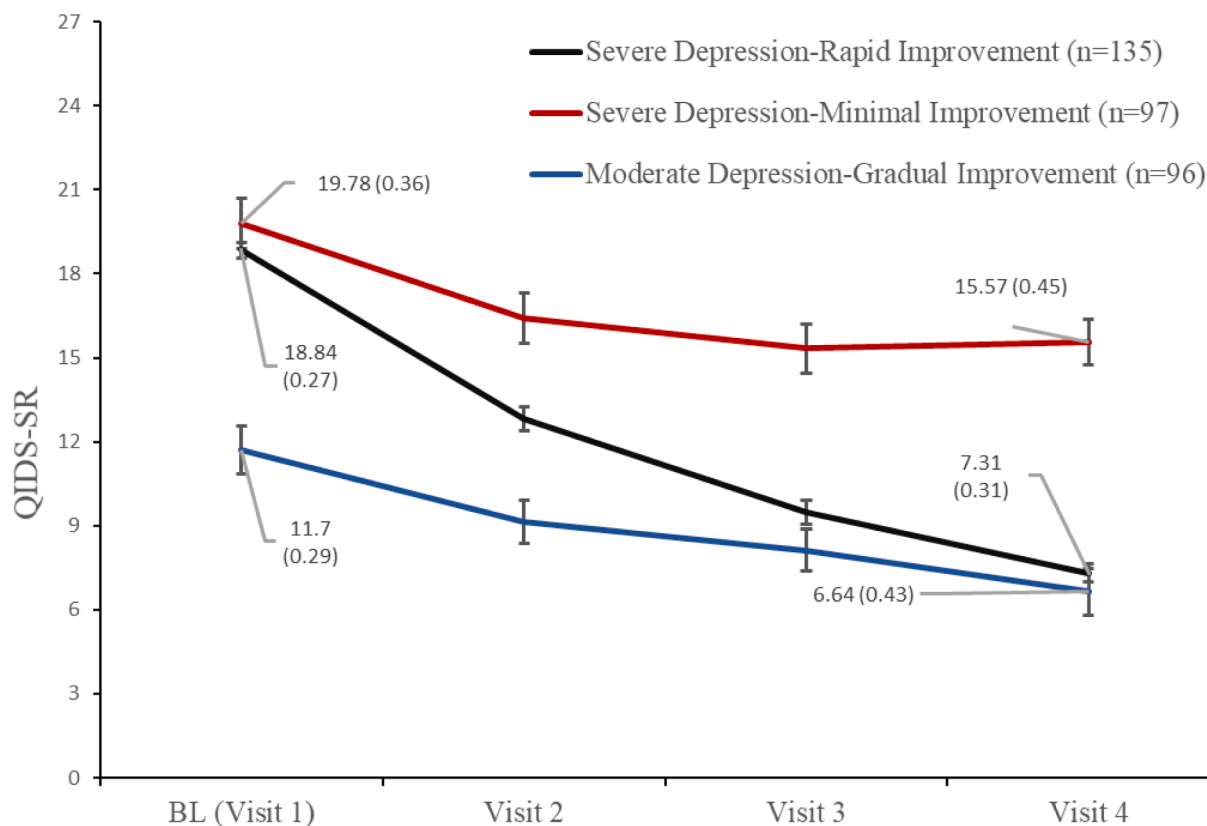other medications.

Diagnoses: SD-RI self-reported a diagnosis of attention-deficit disor-
ders (9.6%) more frequently than *MD-GI* (2.1%). There were no other
differences in diagnosis or comorbid disorders.

History of childhood maltreatment: Table 4 shows the CTQ childhood
maltreatment scores. CTQ scores differed between the two severe
depression groups. The patients in the *SD-RI* group had significantly
higher scores for physical abuse ($M \pm SE$=8.75 ± 0.58) than those in *SD-
MI* (6.97 ± 0.42) and *MD-GI* groups (6.97 ± 0.44) (adjusted p<.01).
Table 4 also displays CTQ maltreatment load score, representing the
cumulative number of clinically significant CTQ maltreatment cate-
gories that have previously shown to impact ketamine treatment
response (O'Brien et al, 2019). Groups did not differ on load (see
Table 4; both p>.05).

4. Discussion

GMM revealed three mutually exclusive response trajectories among
patients receiving IV ketamine treatment in a community setting. Tra-
jectory groups included two with relatively severe baseline depression:
one with baseline QIDS-SR of 19.8 and modest (4.2, 21%) improvement,
and another with baseline QIDS-SR of 18.8 and substantial (11.5, 61%)
improvement; an additional group had relatively mild baseline depres-
sion (QIDS-SR=11.7) and moderate (5.1 points, 44%) improvement over

Fig. 2. Treatment response trajectory groups with QIDS-SR scores over time. This figure shows QIDS-SR scores across treatment visits for the three trajectory groups, including mean QIDS-SR scores and Standard Errors (in parentheses) for baseline and final scores. The statistical breakdown of the groups over time is detailed in Table 3. Each time point demonstrated significant separation among the three groups using an adjusted alpha value of at least .05, except for the comparison of the SD-RI and MD-GI groups at visit 4, which was not significantly different.

three successive ketamine infusions. While distinct improvement trajectories have been previously found in MDD patients using antidepressants (Uher et al., 2010; Smagula, et al., 2015), psychotherapy (Stulz et al, 2010) and even neurostimulation paradigms such as tDCS (Goerigk et al., 2020) and rTMS (Kaster et al., 2019), this is to our knowledge the first report of distinct response trajectory groups following treatment with IV ketamine in a primary mood disorder group.

Three or more distinct treatment response trajectories appears to be a general finding across treatments. A study of a diverse group of psychiatric inpatients receiving psychological and pharmacological interventions found two groups with high "mental illness" scores (derived from measurements of depression severity, anxiety, psychological flexibility, emotion regulation and disability scales) that had either rapid improvement or minimal improvement, and a group with a moderate "mental illness" score with minimal improvement, over 6 weeks of treatment (Oh et al., 2020). The composition, symptom measurements, and treatments used differed from the current study, but despite these differences the most severely ill patients fell into two groups with highly divergent treatment response trajectories. This pattern of contrasting treatment response in identifiable subgroups of severely depressed patients illustrates the potential value of identifying pretreatment characteristics of severely ill patients that predict treatment response or nonresponse.

Childhood physical abuse was the only pretreatment characteristic measured in the current study that differed between the high depression groups with contrasting response to treatment. Demographic variables and other clinical variables did not differentiate the groups. These outcomes suggest that patients with relatively severe depression combined with a childhood history of more severe physical abuse could benefit

substantially from ketamine. This prospect of a more responsive patient population potentially provides the means of stratifying TRD patients for larger ketamine clinical trials. However, other variables, not measured here, may be related to a better treatment response, for example enhanced interleukin-6 (Yang et al, 2015) or an increased intensity of ketamine-induced dissociation (Pennybaker, Niciu, Luckenbaugh & Zarate, 2017).

The relationship between severity of childhood abuse and ketamine's antidepressant treatment response obtained in the current data-driven study is consistent with results of our hypothesis-driven study in a smaller and overlapping sample of patients (n=63). Patients in our previous study showed a more pronounced antidepressant response and a higher chance to reach remission if they reported severe compared to milder childhood history of sexual abuse, physical abuse, and cumulative clinically significant maltreatment on multiple domains (maltreatment load) (O'Brien et al., 2019). In the current study, we replicated these findings, demonstrating that, in a larger sample of depressed patients, more severe, self-reported childhood maltreatment related to a stronger decrease in depressive symptoms after repeated IV ketamine infusions. Although the outcomes of the two studies differ in relationships to specific types of childhood trauma, both suggest that childhood trauma may predict favorable responses to ketamine in severely-depressed patients with treatment-resistant depression.

As a severe, uncontrollable, or inescapable stressor, childhood maltreatment can induce behavioral sensitization, marked by increased neurophysiological and behavioral responses to subsequent milder stressors and to addictive stimuli (Peter W. Kalivas & Stewart, 1991; McLaughlin et al., 2014). This has been demonstrated in humans (Boileau et al., 2006; Booij et al., 2016) and may contribute to complications of psychiatric illness, including suicidal behavior (Björkenstam,
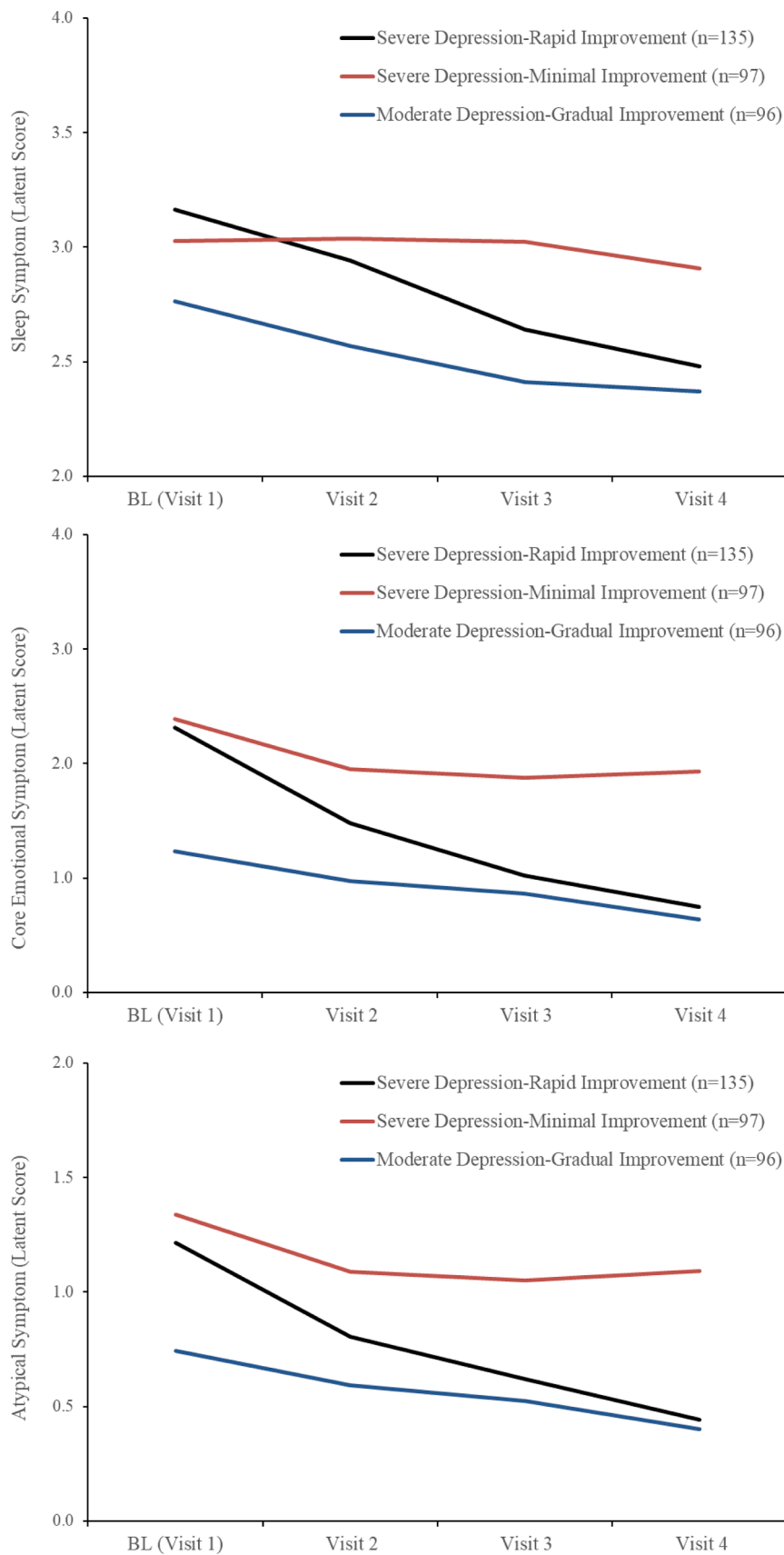
Fig. 2. (*continued*).

Table 2
QIDS-SR total depression scores over time for each of the three trajectory groups

	SD-RI(n=135)		SD-MI(n=97)		MD-GI(n=96)		Overall difference		Pairwise Comparisons		
	M	SE	MN	SE	M	SE	F	p	SD-RIvs SD-MI	SD-RIvs MD-GI	SD-MIvs MD-GI
BL (Visit 1)	18.84	0.27	19.78	0.36	11.70	0.291	429.76	< .001	*	**	**
Visit 2	12.83	0.42	16.41	0.53	9.13	0.445	112.08	< .001	**	**	**
Visit 3	9.47	0.43	15.34	0.52	8.13	0.432	123.84	< .001	**	*	**
Visit 4	7.31	0.31	15.57	0.45	6.64	0.432	270.11	< .001	**	NS	**

Note. * adjusted $p < .05$, ** adjusted $p < .01$.

Table 3
Post-hoc comparisons of depression scores between SD-RI and SD-MI group

	SD-RI		SD-MI		Class difference		
	M	SD	M	SD	t	p	d
Total Depression							
BL (Visit 1)	18.84	3.15	19.78	3.57	−2.07	**.039**	0.282
Visit 2	12.83	4.84	16.41	5.27	−5.28	**< .001**	0.713
Visit 3	9.47	4.59	15.34	4.87	−8.74	**< .001**	1.247
Visit 4	7.31	3.18	15.57	3.96	−14.94	**< .001**	2.337
Sleep							
BL (Visit 1)	3.16	0.90	3.03	0.93	1.14	.257	0.152
Visit 2	2.94	0.91	3.04	1.02	−0.73	.464	0.100
Visit 3	2.66	0.88	3.00	1.01	−2.56	**.011**	0.368
Visit 4	2.49	0.80	2.87	0.88	−2.96	**.004**	0.455
Core emotional							
BL (Visit 1)	2.32	0.36	2.39	0.42	−1.43	.153	0.194
Visit 2	1.48	0.72	1.95	0.69	−5.04	**< .001**	0.667
Visit 3	1.03	0.65	1.85	0.62	−9.05	**< .001**	1.276
Visit 4	0.74	0.44	1.89	0.46	−16.72	**< .001**	2.566
Atypical							
BL (Visit 1)	1.22	0.52	1.34	0.63	−1.55	.122	0.214
Visit 2	0.80	0.47	1.09	0.55	−4.11	**< .001**	0.562
Visit 3	0.61	0.43	1.05	0.58	−5.95	**< .001**	0.881
Visit 4	0.45	0.33	1.07	0.54	−8.77	**< .001**	1.431

Note. Adjusted *p* values less than .05 are in boldface.

Hjern, Björkenstam, & Kosidou, 2018) and complex course with treatment resistance (Lijffijt, O'Brien, Salas, Mathew, & Swann, 2018). Extensive animal data shows that NMDAR inhibition by ketamine or similar compounds blocks development and expression of behavioral sensitization to stressors and addictive stimuli (P. W. Kalivas, 1995; Wolf, 1998; Wolf & Jeziorski, 1993; Wolf, White, & Hu, 1994). Effects of ketamine on sensitization are rapid (Gaytan, Swann, & Dafny, 2002) and ketamine has been shown clinically to reduce trauma-related symptoms and PTSD (Albott et al., 2018; Feder et al., 2014; McGhee, Maani, Garza, Gaylord, & Black, 2008) although not all studies have reported this effect (McGhee et al., 2014). Further, neurophysiological effects of NMDAR inhibition appear to be associated with reduced expression of apparent stress-sensitization in PTSD (Lijffijt et al, 2019). These effects may result from complex adaptive responses among subtypes of amino acid receptors in neurons and glia (P. W. Kalivas, 1995; Wolf, 1998; Wolf & Jeziorski, 1993; Wolf et al., 1994). Ketamine and its congeners may represent a new class of antidepressant treatments (Krystal, Abdallah, Sanacora, Charney, & Duman, 2019) that act via combined long- and short-term behavior regulation (Lijffijt et al., 2018).

Finally, the ketamine dose was significantly lower for the MD-GI group than the high depression groups. Ketamine doses did not differ between the two severely ill groups. The absence of this difference indicates that the improvement in the rapid response group was not due to a higher dose.

5. Limitations

Data for this study was obtained from a treatment-seeking community-based sample that was more heterogeneous in terms of diagnosis and concurrent treatments than clinical trial samples. All patients knew that they received ketamine, which could bias outcomes positively relative to blinded clinical trials. Further, the statistical strategy in this study was data-driven, rather than hypothesis-driven. The generalizability provided by this naturalistic strategy entails certain additional limitations:

1) Depression severity was assessed after multiple days when patients came in for their next infusion. The number of days between infusions (and thus also between assessments) was a covariate in the analyses, and it is therefore not known whether treatment schedule impacted response.
2) We did not have information about substance use disorders, stressors and traumatic events occurring after childhood, and pre-existing or concurrent medical conditions.
3) We did not obtain neurophysiological, biochemical, or neuroimaging measures related to depression or its treatment, nor measures potentially related to behavioral sensitization.

6. Conclusions

This study, using a hypothesis-free, data-driven approach and a naturalistic, community-based sample, demonstrated three distinct trajectories of ketamine response in TRD. Two trajectory groups included severely ill patients, with contrasting responses to ketamine in those with and without childhood physical abuse. The results are potentially consistent with ketamine-associated improvement of early trauma-related sensitization in TRD and preclinical studies demonstrating inhibition of behavioral sensitization by NMDAR inhibitors. Behavioral mechanisms mediating response to ketamine, and development of clinically accessible measures identifying these mechanisms, merit further study.

Table 4

Descriptive statistics and comparisons of identified classes

	SD-RI(*n*=135)		SD-MI(*n*=97)		MD-GI (*n*=96)		Overall difference		Pairwise difference		
	M / N	*SE / %*	*M / N*	*SE / %*	*M / N*	*SE / %*	X^2 / F	*p*	SD-RI vs SD-MI	SD-RI vs MD-GI	SD-MI vs MD-GI
Age	44.08	1.22	42.04	1.31	44.46	1.46	1.90	.387			
Gender											
Female	80	59.3%	47	48.5%	39	40.6%	8.33	**.016**	NS	**	NS
BMI	27.29	0.52	27.08	0.60	27.03	0.64	0.12	.941			
Weight (lb)	180.75	4.35	175.31	4.11	174.32	4.68	1.24	.539			
Medication											
SSRI	42	31.1%	34	35.1%	24	25.0%	2.44	.295			
SNRI	29	21.5%	14	14.4%	25	26.0%	4.43	.109			
Atypical Antidepressant	34	25.2%	18	18.6%	15	15.6%	3.45	.179			
TCA	5	3.7%	4	4.1%	2	2.1%	0.85	.654			
Antipsychotic	29	21.5%	19	19.6%	18	18.8%	0.28	.868			
Anti-convulsant	35	25.9%	33	34.0%	18	18.8%	6.02	**.049**	NS	NS	*
Lithium	7	5.2%	7	7.2%	5	5.2%	0.45	.798			
Stimulant	26	19.3%	15	15.5%	14	14.6%	1.02	.600			
Anxiolytic	6	4.4%	7	7.2%	4	4.2%	0.97	.615			
Benzo	43	31.9%	23	23.7%	20	20.8%	3.94	.139			
Opioid	11	8.1%	11	11.3%	3	3.1%	6.21	**.045**	NS	NS	*
Hypnotic	16	11.9%	8	8.2%	8	8.3%	1.09	.581			
Other	4	3.0%	2	2.1%	2	2.1%	0.25	.883			
Diagnosis and comorbid disorders											
Major depressive disorder	107	79.3%	81	83.5%	75	78.1%	1.08	.584			
Bipolar depression	30	22.2%	15	15.5%	14	14.6%	2.71	.259			
Anxiety	74	54.8%	54	55.7%	50	52.1%	0.28	.871			
Obsessive compulsive disorder	5	3.7%	7	7.2%	6	6.2%	1.60	.449			
PTSD	26	19.3%	11	11.3%	12	12.5%	3.26	.196			
Pain	11	8.1%	5	5.2%	3	3.1%	2.91	.234			
Attention-deficit disorder	13	9.6%	7	7.2%	2	2.1%	7.90	**.019**	NS	*	NS
Ketamine dosage (mg/kg)											
Visit 1	0.57	0.02	0.61	0.04	0.53	0.01	5.82	.054			
Visit 2	0.64	0.02	0.71	0.04	0.58	0.02	9.64	**.008**	NS	*	**
Visit 3	0.71	0.03	0.77	0.05	0.63	0.02	8.70	**.013**	NS	*	**
CTQ											
Physical abuse	8.75 ‡	0.58	6.97	0.42	6.97	0.44	7.50	**.024**	*	*	NS
Sexual abuse	7.61	0.53	6.93	0.56	7.00	0.56	0.95	.622			
Emotional abuse	11.89 ‡	0.57	11.46‡	0.75	10.24‡	0.66	3.63	.163			
Physical neglect	7.90	0.40	6.93	0.36	7.60	0.49	3.43	.180			
Emotional neglect	12.64	0.60	12.15	0.71	11.86	0.71	0.75	.688			
CTQ maltreatment load (average)	1.88	0.18	1.56	0.20	1.98	0.229	2.35	.310			
CTQ maltreatment load (category)							10.74	.378			
0	21	15.6%	23	23.7%	18	18.8%					
1	21	15.6%	11	11.3%	6	6.3%					
2	13	9.6%	14	14.4%	12	12.5%					
3	14	10.4%	6	6.2%	7	7.3%					
4	6	4.4%	4	4.1%	8	8.3%					
5	9	6.7%	5	5.2%	6	6.3%					

Note. *p* values less than .05 are in boldface. NS, adjusted *p* > .05, * adjusted *p* < .05, ** adjusted *p* < .01; ‡ indicates score is clinically significant for trauma in this domain.

Author statement

Submission declaration

All authors confirm that the work presented here has not been published previously and is not currently being considered for publication elsewhere in press or submitted elsewhere.

Funding sources

Data availability statement

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

Appendix

A1. Model fit values and results of test for the number of growth classes.

Model	BIC	Entropy	LMR aLRT (*p*)
Linear growth			
1-class	5477	1.000	**< .001**
2-class	5469	0.776	.071
3-class	5474	0.648	.377

(*continued*)

4-class	5475	0.687	.608
Quadratic growth			
1-class	5424	1.000	**< .001**
2-class	5414	0.779	**.022**
3-class	5405	0.714	.240
4-class	5414	0.694	.603

Note. BIC = Bayesian information criterion. LMR aLRT = Lo-Mendell-Rubin adjusted likelihood-ratio test. *p* values less than .05 are in boldface

A2. Sleep, core emotional, and atypical symptom cluster trajectories (BL=QIDS-SR baseline assessment at Visit1 before the first infusion)

CRediT authorship contribution statement

Brittany O'Brien: . **Marijn Lijffijt:** . **Jaehoon Lee:** . **Ye Sil Kim:** . **Allison Wells:** Data curation. **Nicholas Murphy:** . **Nithya Ramakrishnan:** . **Alan C. Swann:** . **Sanjay J. Mathew:** .

Declaration of Competing Interest

Acknowledgment

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