Distinct trajectories of antidepressant response to intravenous ketamine

Brittany O’Brien a,b,*, Marijn Lijffijt a,b, Jaehoon Lee b,c, Ye Sil Kim c, Allison Wells e,f, Nicholas Murphy b,d, Nithya Ramakrishnan b, Alan C. Swann a,b, Sanjay J. Mathew a,b,d

a Michael E. DeBakey VA Medical Center, 2002 Holcombe Boulevard, Houston, TX, 77030, USA
b Baylor College of Medicine, Menninger Department of Psychiatry and Behavioral Sciences, 1977 Butler Boulevard, Houston, TX, 77030, USA
c The Menninger Clinic, 12301 S Main Street, Houston, TX, 77035, USA
d Lone Star Infusion, PLLC, 14740 Barryknoll Lane, Houston, TX, 77079, USA
e Baylor College of Medicine, Department of Anesthesiology, One Baylor Plaza, Houston, TX, 77030, USA
f The Menninger Clinic, 12301 S Main Street, Houston, TX, 77035, USA

Keywords: Ketamine, Depression, Response trajectory, Childhood trauma, Behavioral sensitization, Naturalistic

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 heterogeneous 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 (van 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 effect (O’Brien, Lijffijt, Wells, Swann, & Mathew, 2019; Singh et al., 2016; Vande Voort et al., 2016). However, a substantial proportion of TRD

* Brittany O’Brien and Marijn Lijffijt contributed equally to this work
* Corresponding author at: Baylor College of Medicine, Menninger Department of Psychiatry and Behavioral Sciences, 1977 Butler Boulevard, Houston, TX, 77030, USA
E-mail address: brittany.o.brien@bcm.edu (B. O’Brien).

https://doi.org/10.1016/j.jad.2021.03.006
Received 27 January 2021; Received in revised form 25 February 2021; Accepted 2 March 2021
Available online 9 March 2021
0165-0327/© 2021 Elsevier B.V. All rights reserved.
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, Uber, & 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 with 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 accessed 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, Nicu, Luckenbaugh, & Zarate, 2017) and was tolerated. For nausea, patients were given ondansetron as needed. 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, 2007; 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 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 Mplus 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).

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 > 0.70), 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=0.039), but this 1-point difference does not appear clinically meaningful. The difference between SD-RI and SD-MI groups increased as a function of ketamine infusions, with larger group differences at clinical 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 infusion. 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, comorbid diagnoses, 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 disorders (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±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 categories 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. Trajectory 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 depression (QIDS-SR=11.7) and moderate (5.1 points, 44%) improvement over three successive ketamine infusions. While distinct improvement trajectories have been previously found in MDD patients using antidepressants (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, 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 & Jezioriski, 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
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.

Author statement

Contributions: Conceptualization (O’Brien B, Lijffijt M) Dataset (Wells A) Methodology (Lee J, Lijffijt M, Swann AS) Formal Analysis (Lee J, Kim YS) Writing – Original Draft (O’Brien B, Lijffijt M, Swann AS) Writing Review & Editing (Murphy N, Ramakrishnan N, Mathew SJ) All authors contributed to and have approved the final manuscript.

Funding source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability: The data that support the findings of this study are...
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

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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.

<table>
<thead>
<tr>
<th>Type</th>
<th>Method</th>
<th>BIC</th>
<th>Entropy</th>
<th>LMR aLRT (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear growth</td>
<td>1-class</td>
<td>5477</td>
<td>1.000</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>2-class</td>
<td>5469</td>
<td>0.776</td>
<td>.071</td>
</tr>
<tr>
<td></td>
<td>3-class</td>
<td>5474</td>
<td>0.648</td>
<td>.577</td>
</tr>
<tr>
<td></td>
<td>4-class</td>
<td>5475</td>
<td>0.687</td>
<td>.608</td>
</tr>
<tr>
<td>Quadratic growth</td>
<td>1-class</td>
<td>5424</td>
<td>1.000</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>2-class</td>
<td>5414</td>
<td>0.779</td>
<td>.022</td>
</tr>
<tr>
<td></td>
<td>3-class</td>
<td>5405</td>
<td>0.714</td>
<td>.240</td>
</tr>
<tr>
<td></td>
<td>4-class</td>
<td>5414</td>
<td>0.694</td>
<td>.603</td>
</tr>
</tbody>
</table>

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


Declaration of Competing Interest

Drs. Mathew, O’Brien and Swann are supported through the use of facilities and resources at the Michael E. DeBakey VA Medical Center, Houston, Texas. Drs. Lee, Mathew and Murphy receive support from The Menninger Clinic, Houston, Texas. Dr. Mathew has served as a consultant to Alkermes, Allergan, Axsome Therapeutics, Lexio Biosciences, Engrail, Greenbio Biosciences, Janssen, Neurocrine, Perception Neuroscience, Praxis Precision Medicines, Sage Therapeutics, and Signant Health. He has received research support from Biohaven Pharmaceuticals and VistAGen Therapeutics.

All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

None.

References


