Factors Associated with Antidepressant Effects of Ketamine: A Reanalysis of Double-Blind Randomized Placebo-Controlled Trial of Intravenous Ketamine for Treatment-Resistant Depression

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ABSTRACT

Introduction Predictors of treatment response to intravenous ketamine remain unclear in patients with treatment-resistant depression (TRD); therefore, this study aimed to clarify these predictors using the US National Institutes of Health database of clinical trials.

Methods Data from a placebo-controlled, double-blind, randomized controlled trial were used to assess the efficacy of intravenous ketamine in adult patients with TRD (NCT01920555). For the analysis, data were used from the participants who had received therapeutic doses of intravenous ketamine (i. e., 0.5 and 1.0 mg/kg). Logistic and multivariable regression analyses were conducted to explore the demographic and clinical factors associated with response to treatment or changes in the Hamilton Depression Rating Scale 6 items (HAM-D-6) total score.

Results This study included 31 patients with TRD (13 women; mean ± standard deviation age, 48.4 ± 10.9 years). Logistic regression analysis showed that the age of onset was positively correlated with treatment response after three days of ketamine administration ($\beta = 0.08$, $p = 0.037$); however, no association was observed between treatment response and age, sex, baseline HAM-D-6 total score, or dissociative score assessed with the Clinician-Administered Dissociative States Scale 40 min after ketamine infusion. Multiple regression analysis showed that no factors were correlated significantly with the percentage change in the HAM-D-6 total score three days after ketamine administration.

Discussion Later disease onset correlates with a better treatment response three days after ketamine infusion in patients with TRD. Glutamatergic signal transmission may be impaired in patients with an earlier onset of depression, resulting in decreased neuroplasticity, which diminishes ketamine response.

Trial Registration Data used in this secondary analysis were obtained from ClinicalTrials.gov, identifier: NCT01920555.

Introduction

Ketamine is a dissociative anesthetic that antagonizes glutamatergic N-methyl-D-aspartate (NMDA) receptors. Clinical trials have consistently demonstrated that ketamine has rapid-acting and robust antidepressant effects in patients with major depressive disorder (MDD) and bipolar depression (BD) [1–4]. However, retrospective chart reviews have reported that only 18 % to 45 % of patients with MDD or BD respond to acute intravenous ketamine therapy in real-world clinical settings [5, 6]. Therefore, predicting patients with MDD or BD who are likely to benefit from intravenous ketamine treatment is clinically relevant.

Several predictors of the efficacy of intravenous ketamine therapy have been reported. Rong et al. (2018) reviewed 12 studies to identify potential predictors of a successful response to intravenous ketamine infusion in patients with treatment-resistant depression (TRD) [7]. In their analysis, patients with MDD and BD with a family history of alcohol use disorder showed a greater improvement in the total scores of the Montgomery-Asberg Depression Scale (MADRS) after ketamine infusion than in patients without these factors [8, 9]. Moreover, higher body mass index was correlated with a greater reduction in the 17-item Hamilton Depression Rating Scale (HAM-D-17) total score at 1 d and 230 min after ketamine infusion in patients with MDD and BD [10]. Other studies have reported the association of following factors with better response to ketamine treatment: lower number of treatment failures and lower baseline severity of illness [11], younger age and no history of neuromodulation treatment [12], lower baseline intelligence quotient [13], lower pretreatment working memory function [14], lower adiponectin [15], higher brain-derived neurotrophic factor (BDNF) after ketamine administration [16], single nucleotide polymorphism (SNP) in the Val/Val BDNF allele at rs6265 [17], and smaller left hippocampal volume [18]. However, these studies had several limitations, such as the study design heterogeneity (e. g., a combination of open-label and randomized placebo-controlled trials, including both MDD and BD). Recently, Alnefeesi et al. (2022) conducted a systematic review and meta-analysis of studies evaluating the real-world clinical effectiveness of ketamine in patients with TRD [19]. They reported that the mean number of failed antidepressants and depressive symptomatology scores at baseline were negatively correlated with remission rates, whereas the mean age was positively correlated with symptom improvement in the meta-regression analysis. However, other clinically relevant variables, such as age at onset and dissociative symptoms, have not been thoroughly investigated. While one study reported that earlier onset age was predictive of favorable treatment response after ketamine administration in patients with TRD [20], the findings from previous studies examining the association between age of onset and response to antidepressant treatment in patients with MDD have been inconsistent [21–28]. In addition, the lack of agreement among previous studies is also the case for the association between dissociative symptoms and treatment response to ketamine infusion [29–33].

To fill this gap in the literature and examine the factors associated with treatment response, we conducted a post-hoc analysis of data from a placebo-controlled, double-blind, randomized controlled trial that assessed the acute efficacy of ketamine infusion versus an active placebo in patients with TRD. We hypothesized that dissociative symptoms and age of onset would be related to treatment response in this homogeneous diagnostic group.

Methods

We conducted a post-hoc analysis of the data from a clinical trial (NCT01920555). A detailed explanation of this trial is described elsewhere [2]. Briefly, all enrolled patients experienced a current depressive episode lasting at least eight weeks and were diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision. The Structured Clinical Interview for the DSM-IV Patient Edition supported the diagnosis of MDD. Additionally, all patients had TRD, which was defined as a subjectively unsatisfactory response (i. e., less than 50 % improvement in depression symptoms) to at least two adequate treatment courses during the current depressive episode, including the current antidepressants. At both the screening and baseline visits, all patients were required to have a MADRS [34] total score of ≥ 20. In total, 99 eligible patients were randomly assigned to one of five 40-min infusion groups in a 1:1:1:1:1 ratio: a single dose of ketamine 0.1 mg/kg (n = 18), ketamine 0.2 mg/kg (n = 20), ketamine 0.5 mg/kg (n = 22), ketamine 1.0 mg/kg (n = 20), and midazolam 0.045 mg/kg (active placebo) (n = 19). The primary endpoint assessments were performed over 3 days, and all patients were followed for 30 days. At each visit, the study clinicians used the Hamilton Depression Rating Scale 6 items (HAM-D-6) as the primary outcome in all patients (i. e., days 0, 1, 3, 5, 7, 14, and 30). All patients also underwent assessment using the HAM-D-17 at baseline. The Clinician-Administered Dissociative States Scale (CADSS) [35] was used to assess dissociative symptoms 5 min before and 40, 80, and 120 min after ketamine infusion. Data used in this post-hoc analysis were derived from patients who received a single therapeutic dose of ketamine infusion (i. e., 0.5 or 1.0 mg/kg) and received an assessment with the HAM-D-17 [36, 37] at baseline and HAM-D-6 at both baseline and day 3. We selected these two dose groups because the original study demonstrated significantly superior antidepressant efficacy in the 0.5 and 1.0 mg/kg groups than that of the active placebo. The treatment response in the current study was defined as a ≥ 50 % reduction in the HAM-D-6 total score [38, 39] on day 3 than that of the baseline score, which was consistent with the original trial. A local institutional review board approved the protocols, and all patients provided written informed consent to participate in this trial. Ethical approval was not sought for this study, which used anonymous data.

Logistic regression analysis was conducted to examine factors associated with treatment response on day 3; the following explanatory variables were included: age, age of onset, sex, HAM-D-6 total scores at baseline, and CADSS total scores 40 min after ketamine infusion. Moreover, multiple regression analysis was performed using the same explanatory variables to examine the factors associated with the percentage change in HAM-D-6 total scores on day 3 from baseline. $P < 0.05$ was considered statistically significant (two-tailed). Statistical analyses were performed using R, version 4.1.0.

Results

Among the patients who participated in the original clinical trial, 31 (ketamine 0.5 mg/kg, n = 17; 1.0 mg/kg, n = 14; 13 women; mean age 48.4 years) were included in this post-hoc analysis. The demographic and clinical characteristics of the participants are summarized in ▶ **Table 1**.

Logistic regression analysis revealed a positive correlation between the age of onset and the treatment response on day 3 ($\beta = 0.08$, $p = 0.037$), as shown in ▶ **Table 2**. However, treatment response to ketamine was not significantly related to age, sex, baseline HAM-D-6 total score, and CADSS total score 40 min after ketamine infusion. Multiple regression analysis showed that no factors significantly correlated with the rate of change in the HAM-D-6

▶ **Table 1** Demographic and clinical characteristics of patients.

Characteristics (N = 31)	Mean ± SD or N (%)
Age (year)	48.4 ± 10.9
Age of onset (year)	22.6 ± 12.4
Duration of illness (year)	25.8 ± 15.3
Number of hospitalizations	0.2 ± 0.4
Number of nonresponding antidepressants	3.0 ± 1.2
HAM-D-6 total score at baseline	12.7 ± 1.8
HAM-D-6 total score on day 3	6.8 ± 4.3
Change in HAM-D-6 total score on day 3	−6.0 ± 4.3
HAM-D-17 sleep symptoms at baseline	4.6 ± 1.9
HAM-D-17 core emotional symptoms at baseline	8.2 ± 2.2
HAM-D-17 atypical symptoms at baseline	4.4 ± 1.9
CADSS total score at baseline	0.0 ± 0.2
CADSS total score at 40 min	18.8 ± 15.3
CADSS total score at 80 min	0.2 ± 0.4
CADSS total score at 120 min	0.1 ± 0.3
CADSS amnesia symptoms at 40 min	2.5 ± 2.5
CADSS depersonalization symptoms at 40 min	5.8 ± 5.3
CADSS derealization symptoms at 40 min	9.0 ± 7.3
Sex, Male	18 (58.1)
Past treatment with TMS	1 (0.03)
Concurrent psychotherapy	13 (41.9)
Treatment responder	14 (45.2)

Abbreviations: CADSS, Clinician-Administered Dissociative States Scale; HAM-D-6, Hamilton Rating Scale for Depression, 6-item version; HAM-D-17, Hamilton Rating Scale for Depression, 17-item version; SD, standard deviation; TMS, Transcranial Magnetic Stimulation.

▶ **Table 2** Logistic regression analysis to predict responses on day 3

	β	Std error	t-value	p-value
(Intercept)	−3.85	4.37	−0.88	0.38
Age (year)	0.05	0.04	1.22	0.22
Age of onset (year)	0.08	0.04	2.09	**0.04**
Sex, Male	−0.88	0.93	−0.95	0.34
HAM-D-6 total score at baseline	−0.02	0.25	−0.09	0.93
CADSS total score at 40 min	−0.01	0.03	−0.19	0.85

Bold letters indicate $p < 0.05$. Abbreviations: CADSS, Clinician-Administered Dissociative States Scale; HAM-D-6, Hamilton Rating Scale for Depression, 6-item version; Std error, standard error.

total score on day 3 (▶ **Table 3**). All variance inflation factors of the explanatory variables included in these analyses were below five, suggesting the absence of multicollinearity among these variables.

Discussion

In this post-hoc analysis, we examined the clinical variables associated with the treatment response to intravenous ketamine therapy in patients with TRD. Our study used data from a placebo-controlled, double-blind, randomized controlled trial that assessed the acute efficacy of ketamine infusion compared to an active placebo. In patients who received 0.5 mg/kg or 1.0 mg/kg ketamine infusion, the age of onset was positively correlated with treatment response according to the HAM-D-6 total score change 3 d after ketamine infusion. That is, a later onset of illness was associated with a better treatment response. This finding suggests that the onset of depression may reflect the treatment response of patients with TRD to intravenous ketamine therapy.

▶ **Table 3** Multivariable regression analysis to predict the rate of change in the HAM-D-6 total score on day 3 from baseline

	β	Std error	t-value	p-value
(Intercept)	−0.19	0.62	−0.30	0.77
Age (year)	−0.01	0.01	−2.1	0.83
Age of onset (year)	0.01	0.01	1.95	0.06
Sex, Male	0.01	0.13	0.05	0.96
HAM-D-6 total score at baseline	0.00	0.04	−0.01	0.99
CADSS total score at 40 min	0.00	0.00	0.05	0.96

Abbreviations: CADSS, Clinician-Administered Dissociative States Scale; HAM-D-6, Hamilton Rating Scale for Depression, 6-item version; Std error, standard error.

The findings of previous studies were inconsistent regarding the associations between age of onset and response to antidepressant treatment in patients with MDD [21–28]. In contrast to our result, Chen and colleagues (2021) demonstrated that earlier age of onset was one of the predictors of good treatment response 2 d after a single 0.5 mg/kg intravenous ketamine administration in 73 patients with TRD [20]. The discrepancy between their findings and our result may partly be due to the differences in the study design. Chen et al. included patients who were resistant to treatment for both MDD and BD, and conducted a regression tree analysis using binary classification. They demonstrated that an earlier age of onset was predictive of good treatment response among patients who had a current depressive episode for 24 months or less and a baseline HAM-D-17 total score of 23 or less; however, the present age was not included as a covariate in their analysis. Thus, to clarify the relationship between age at onset and treatment response after ketamine infusion, future studies should adjust for the age in a uniform diagnostic group.

The worse treatment response associated with an earlier onset of illness may be because MDD with an earlier age of onset may be related to chronic depression. According to the DSM-5, chronic depression is defined as depression that has persisted for at least two years, [40]. Compared to non-chronic depression, chronic depression is associated with an earlier age of onset and more frequent episodes of depression [41, 42]. Moreover, patients with chronic depression often do not respond to pharmacotherapy and psychotherapy [43–45] and need higher dosages to achieve improvement [44]. In the present study, it may be possible that MDD patients with an earlier age of onset had characteristics of chronic depression and were more resistant to ketamine treatment than other MDD patients.

As another explanation for the association between an earlier onset of illness and a worse treatment response is that an earlier age at onset is associated with a longer duration of illness in MDD [27, 46, 47]. Previous studies have found that a longer duration of illness is associated with a lower treatment response to antidepressant treatment in patients with MDD [21, 48, 49]. Thus, the higher resistance to ketamine treatment in early-onset patients with TRD in the present study may possibly be attributed to the longer duration of illness. Preclinical and clinical evidence support impaired glutamatergic pathways in patients with MDD [50, 51]. Some postmortem studies have reported that compared to controls, patients with MDD have decreased expression of glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor subunit in the perirhinal cortex [52], cornu ammonis (CA)1, and dentate gyrus [53]. Moreover, animal studies have demonstrated that exposure to chronic stress causes a reduction in AMPA receptor subunit expression in these brain regions [54]. Furthermore, the number of apical dendrite spines of CA1 and CA3 pyramidal cells was progressively reduced over 3 w in a depression model consisting of chronically and unpredictably stressed mice [55]. The antidepressant effects of ketamine are assumed to occur via the activation of AMPA receptors and synaptogenic signaling pathways [51]. The long course of the disease may have impaired glutamatergic signaling transmission, disturbed neuroplasticity, and developed ketamine resistance. However, the relationship between illness duration and AMPA receptor expression in patients with MDD has not been clarified, since no technique to measure AMPA receptors in living humans is available. Recently, [^{11}C] K-2, the first positron emission tomography tracer that specifically binds to AMPA receptors, was developed [56–59]. Future studies are warranted to investigate the relationship between the treatment response to ketamine and AMPA receptor expression before and after ketamine infusion in the context of neural plasticity.

This study found no association between the total CADSS score 40 min after ketamine administration and treatment response 3 d after ketamine infusion. The relationship between the dissociative side effects of ketamine and antidepressant effects has been examined in several previous studies, but their findings are inconsistent [29, 30]. For example, in a single-blind study of 10 patients with MDD, no association was found between the maximum change in the CADSS total score and the change in the HAM-D-17 total score at any time point after administering a single dose of ketamine at a subanesthetic dose [32]. However, Luckenbaugh et al. (2014) studied 108 patients with TRD and found that a higher CADSS total score 40 min after ketamine administration was correlated with a percentage decrease in the HAM-D-17 total score 7 d and 230 min after ketamine infusion [33]. Later, Phillips et al. (2019) conducted a randomized, double-blind crossover trial in which participants received a single dose of 0.5 mg/kg ketamine infusion over 40 min. They found that the increase in the CADSS total score 40 min after ketamine administration correlated with the MADRS total score reduction at 24 h post-infusion [31]. The discrepancy between these findings and our result may possibly be due to the small sample size and lack of power of the present study. Additionally, the CADSS may not have fully captured the dissociative symptoms of ketamine because it was initially developed to assess dissociative symptoms of post-traumatic stress disorder [35]. To elucidate the relationship between treatment response and dissociative symptoms after ketamine administration, further studies should include larger sample sizes and utilize more sensitive and specific rating scales that measure dissociative symptoms after ketamine administration.

The strengths of this study were that the original trial had a robust study design, and the study participants consisted of a uniform diagnostic group (i. e., TRD), resulting in high-quality data. However, our study had several limitations. First, this was a post-hoc analysis and was not originally designed to investigate the predictors of treatment response after ketamine infusion. Second, the sample size was small. Third, the study evaluated depressive symptoms only 3 d after ketamine administration and did not assess them at other time points. Fourth, the data on the duration of the index episode were not available; therefore we could not analyze the effect of this factor on the treatment outcome. Finally, previous studies reported that a positive family history of alcohol use disorder and body mass index were associated with treatment response to ketamine; however, these factors were not assessed in the current study.

Conclusions

A later onset of illness was associated with a better treatment response 3 d after 0.5 mg/kg or 1.0 mg/kg ketamine infusion in patients with TRD. This finding suggests that patients with early-onset TRD may be biologically distinct from those with late-onset TRD, and ketamine treatment may be more beneficial in patients with late-onset TRD. The long course of the disease may impair glutamatergic signal transmission and neuroplasticity; however, the relationship between neuroplasticity and treatment response to ketamine infusion is not fully understood. Further studies are needed to predict the response to intravenous ketamine and elucidate the mechanism underlying the antidepressant effect of ketamine.

Additional Information

Data used in this study were obtained from controlled access datasets distributed by The National Institute of Mental Health (NIMH)-supported National Database for Clinical Trials. The original dataset is available at the NIMH Data Archive (https://nda.nih.gov/). The identification number of the NIMH data repository study is #2166. NCT01920555 was supported by the NIMH contract HHSN271201100006I to the Massachusetts General Hospital. The primary purpose of the present study was to examine the factors associated with treatment response to intravenous ketamine in patients with TRD. This article reflects the authors' views and may not reflect the opinions or views of the NCT01920555 study investigators or the NIMH.

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Conflict of Interest

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