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Research paper

Disentangling the association of depression on the anti-fatigue effects of ketamine

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ABSTRACT

Background: Fatigue and depression are closely associated. The purpose of this secondary analysis was to understand the relationships between depression and improvements in specific depression domains on the anti-fatigue effects of ketamine, which we previously reported.

Methods: This secondary analysis re-evaluated data collected longitudinally from 39 patients with treatment-resistant Major Depressive Disorder (MDD) enrolled in a double-blind, randomized, placebo-controlled, crossover trial using a single intravenous infusion of ketamine hydrochloride (0.5 mg/kg over 40 minutes) or placebo. A mediation model assessed the effect of depression on the anti-fatigue effects of a single dose of intravenous ketamine versus placebo at Day 1 post-infusion. Fatigue was measured using the National Institutes of Health–Brief Fatigue Inventory (NIH-BFI), and depression was assessed by the Montgomery–Åsberg Depression Rating Scale (MADRS).

Results: Compared to placebo, ketamine significantly improved fatigue ($p = .0003$) as measured by the NIH-BFI, but the anti-fatigue effects of ketamine disappeared ($p = .47$) when controlling for depression as measured by MADRS total score. In this study sample, the anti-fatigue effects of ketamine were mostly accounted for by the changes in amotivation and depressed mood scores.

Conclusions: In this study, ketamine did not have a unique effect on fatigue outside of its general antidepressant effects in patients with treatment-resistant depression. Specifically, the anti-fatigue effects of ketamine observed in this study seem to be explained by the effects of ketamine on two symptom domains of depression: amotivation and depressed mood. The study findings suggest that the anti-fatigue effects of ketamine should be assessed by fatigue-specific measures other than the NIH-BFI or future studies should enroll fatigued patients without depression.

Fatigue and depression are complex constructs, but their association is well documented (Bakshi et al., 2000; Jacobsen et al., 2003; Brown and Kroenke, 2009). Both significantly influence the capacity to perform everyday actions and endorse greater functional disability (Lin et al., 2013; Milanovic et al., 2018). They have been strongly correlated in multiple reports (Bakshi et al., 2000; Jacobsen et al., 2003; Brown and Kroenke, 2009). However, some evidence suggests that depression and fatigue are distinct constructs, for example, it was observed that fatigue symptoms persist even after the remission of depression (Ferguson et al., 2014). Nevertheless, separating fatigue from depression, especially when evaluating for treatment outcomes, continues to be a challenge because of the limits of available tools to distinguish one construct from the other.

Amotivation is a common symptom of depression, as well as in fatigue (Hegerl and Ulke, 2016). There is a dearth of information related to the relationship of amotivation and fatigue, especially in the clinical population. Most of the studies investigating the association of amotivation and fatigue used pre-clinical models. Amotivation is associated with a constellation of negative symptoms such as apathy characterized by reduced interest in participation in purposeful behavior, lack of initiative, problems in initiation or sustaining an activity to completion, lack of concern or indifference, and a flattening of affect (Pluck and Brown, 2002). A previous study proposed a shared biological mechanism to explain amotivation and fatigue in a subset of depressed patients (Raison and Miller, 2011). Further investigations to explore this relationship are warranted.

Previous work from our team observed that a single dose of ketamine (0.5 mg/kg intravenous dose) had rapid and sustained anti-fatigue effects 40 minutes after infusion, which lasted until 2 days post infusion (Saligan et al., 2016). In fact, the effect size of the ketamine-placebo difference was greatest at day 2 ($d = 0.59$). What is unknown is whether the anti-fatigue effects of ketamine are markedly linked by the association of depression with fatigue. Knowing the extent of the association of depression on the anti-fatigue effects of ketamine is important, in order to identify potential shared or distinct biological pathways that distinguish fatigue from depression. Currently, the

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etiology of fatigue is unknown.

Our research team is pursuing prospects to identify potential therapeutic targets for both debilitating conditions of fatigue and depression. Moreover, because they seem to be clinically interrelated, it is of more importance to find a way to understand the influence of one over the other, especially in evaluating treatment outcomes. For this purpose, we have incorporated independent measures of fatigue and depression in our clinical trials. We developed the National Institutes of Health–Brief Fatigue Inventory (NIH-BFI) as a distinct measure of fatigue within the context of depression (Saligan et al., 2015), and administered the Montgomery–Asberg Depression Rating Scale (MADRS), a commonly used unidimensional measure of depressive symptoms (Montgomery and Asberg, 1979). Our published reports on the antidepressant and anti-fatigue effects of ketamine provide the unique possibility of advancing our understanding on how fatigue and depression are closely related (Zarate et al., 2006; Saligan et al., 2016). More importantly, new data collected from the National Institute of Mental Health ketamine clinical trials meant to assess ketamine's mechanism of action are poised to identify which improvements in specific domains of depression are related to the anti-fatigue effects of ketamine (Ballard et al., 2018).

This study investigated the association of depression on the rapid anti-fatigue effects of a single intravenous dose of ketamine. Further, the study identified the improvements of specific symptom domains of depression that are related to the anti-fatigue effects of ketamine. Findings from this study can advance our understanding of the tapestry of symptoms that can co-occur or are closely bound to this multidimensional fatigue construct. This information is clinically useful to refine the conceptual definition of fatigue, and to identify shared and distinct biologic pathways to develop optimal therapy.

1. Methods

1.1. Design and subjects

This is a secondary analysis of data collected from an original study (NCT00088699) (Nugent et al., 2018). This study was a double-blind, randomized, placebo-controlled, crossover clinical study exploring the efficacy of ketamine as an intervention in reducing depressive symptoms in patients with Major Depressive Disorder (MDD). This analysis includes the 35 MDD patients described in the Nugent et al., publication as well as four additional participants who were collected for additional biomarker/sleep analyses (Nugent et al., 2018). Informed consent was obtained for all study participants. The study was conducted at the NIH Clinical Center, Bethesda, Maryland. Participants with treatment-resistant MDD (DSM-IV criteria) received a single infusion of ketamine hydrochloride intravenously at a dose of 0.5 mg/kg over 40 minutes or placebo on 2 experimental days separated by 2 weeks.

Men and women, ages 18–65 years with diagnosis of recurrent MDD without psychotic features as diagnosed using the Structured Clinical Interview for Axis I DSM-IV Disorders-Patient Version (First et al., 1997), and with an age of onset ≤ 40 years were eligible participants. Potential participants were enrolled if they had a score of ≥ 20 on the MADRS (Montgomery and Asberg, 1979) at screening and before each infusion. In addition, each subject had to have failed to respond to at least one prior adequate antidepressant trial, as assessed by the Antidepressant Treatment History Form, and to be experiencing a current major depressive episode of at least four weeks duration (Sackeim, 2001). Subjects were either un-medicated or tapered off medications for a minimum of two weeks before randomization (5 weeks for fluoxetine, 3 weeks for aripiprazole). Individuals with a DSM-IV diagnosis of drug or alcohol dependence or abuse within the past three months, serious or unstable illness, or uncorrected hypo- or hyperthyroidism were excluded. Additional study details have been previously published (Nugent et al., 2018).

1.2. Measures

Fatigue was assessed using the seven-item, clinician-administered NIH-BFI validated to measure fatigue separate from depression in the context of depressive disorders (Saligan et al., 2015). All items were scored using a descending order of Likert-type of response from none or normal to worst symptoms. Concentration difficulties and lassitude were scored from 0 to 6, while fatigability, work and activities, retardation were scored from 0 to 4. Irritability was scored from 0 to 8, and general somatic symptoms were rated from 0 to 2. All items except for retardation asked the responder to recall their experiences in the past week, while retardation was rated in real time by the clinician conducting the interview. Total NIH-BFI scores ranged from 0 to 34, where a higher NIH-BFI score suggests severity of fatigue symptoms. Depression was assessed using the 10-item MADRS. The MADRS is a reliable and valid unidimensional instrument to assess six core depressive symptoms such as apparent sadness, reported sadness, inner tension, lassitude, inability to feel, and pessimistic thoughts (Montgomery and Asberg, 1979). All MADRS items were also scored using a descending order of Likert-type of response from 0 (none or normal) to 6 (worst symptom). Similarly, MADRS rates the participant's experience over the past week. The MADRS total score ranges from 0 to 60 points, with higher total scores suggesting greater depressive symptoms. Both measures were administered by clinical interview from trained clinical research staff. Both questionnaires were administered in the mornings at baseline and Day 1 (24 h) post-ketamine infusion.

Specific symptom domains were assessed using previous results from an Exploratory Factor Analysis (EFA) of the MADRS, the Hamilton Depression Rating Scale (HAMD), the Snaith–Hamilton Pleasure Rating Scale (SHAPS), and the Beck Depression Inventory (BDI) (Ballard et al., 2018). EFA depression subscales included Depressed Mood, Tension, Negative Cognition, Impaired Sleep, Suicidal Thoughts, Reduced Appetite, and Amotivation. Ratings for the eighth available subscale, anhedonia, was obtained from only about half of the sample and was therefore excluded from analysis. Ratings from eight assessments were used in this analysis (-60 minutes before ketamine infusion, then 40 minutes, 80 minutes, 120 minutes, 230 minutes, Day 1, Day 2, Day 3 after ketamine infusion), but Day 1 was selected as the timepoint of interest as it correlates with peak ketamine response.

1.3. Data analyses

Descriptive statistics characterized the demographic and clinical attributes of the study participants. A mediation model was generated to determine whether the effect of ketamine on depression symptoms accounted for its effect on fatigue. Because a proposed mediator variable must be correlated with treatment (Kraemer et al., 2002), we confirmed, as previously reported (Nugent et al., 2018), a significant effect of ketamine versus placebo on MADRS total score. Next, we evaluated the effect of ketamine versus placebo on the NIH-BFI total score. Finally, we entered the MADRS total score (the putative mediator) into the model and documented whether it was statistically significant and whether the effect of ketamine versus placebo remained statistically significant in its presence. This process was repeated in further analyses using the EFA depression subscales as potential mediators.

General linear mixed models were used. A repeated effect of (categorical) time was entered for each drug nested within subject, with an unstructured covariance matrix. A random intercept for each subject was used to account for nesting of drug within subject. Degrees of freedom were calculated using the Kenward–Roger approximation. Baseline assessments were modeled, and the effect of ketamine was estimated using a contrast between the baseline – Day 1 difference for each drug. Cohen's *d* effect size was calculated using the estimated difference, standard error, and degrees of freedom from this contrast. Infusion was entered as a covariate. Both drug and putative mediator