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Symptomatology and predictors of antidepressant efficacy in extended responders to a single ketamine infusion

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ABSTRACT

Background: Antidepressant response to a single subanesthetic dose infusion of the glutamatergic modulator ketamine is transient in most depressed patients; however, a minority continue to experience an extended response. This study examined depressive symptoms and potential clinical predictors of extended response to ketamine in subjects with mood disorders.

Methods: Subjects were diagnosed with either major depressive disorder (MDD) or bipolar depression. All subjects were treatment-resistant and experiencing a major depressive episode of at least moderate severity. MDD subjects were unmedicated and those with bipolar depression were receiving therapeutic-dose lithium or valproate. All subjects received a single 0.5 mg/kg ketamine infusion. Data were collected pre-infusion (baseline) and at days one, 14, and 28 post-infusion.

Results: Twelve of 93 (12.9%) participants continued to meet response criteria (50% reduction in Montgomery-Asberg Depression Rating Scale (MADRS) score) at two weeks. All depressive symptoms assessed by the MADRS were improved at two weeks in ketamine responders except for sleep duration/depth. A positive family history of alcohol use disorder in a first-degree relative (FHP) and greater dissociation during the infusion were associated with better antidepressant response at two weeks. Improved measures of apparent sadness, reported sadness, inability to feel, and difficulty concentrating at day 1 correlated most strongly with antidepressant effects at two weeks.

Limitations: Post-hoc design, small sample size, diagnostic heterogeneity.

Conclusions: Static (FHP) and dynamic (improved depressive symptoms) factors may be clinically useful in predicting whether a patient will have an extended response to ketamine.

1. Introduction

Worldwide, major depressive disorder (MDD) is associated with high rates of morbidity and disability. The disorder is thought to affect 4.3% of the world's population (Vos et al., 2012), and lifetime prevalence is estimated at 14.6% (Bromet et al., 2011). Most currently available antidepressant treatments can take two to four weeks to elicit an initial response, and treatment often requires several months for a full response. Indeed, in the real-world effectiveness Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, only 36.8% of patients experienced a remission of their depressive symptoms in response to a standard course of the selective serotonin reuptake inhibitor citalopram (Rush et al., 2006). The same study found that one-third of patients did not achieve remission even after four different antidepressant treatment trials with agents of different classes. Taken together, the evidence underscores the significant need for more rapid-acting and effective antidepressants, presumably with alternative mechanisms of action.

Aberrant glutamatergic neurotransmission has been implicated in both preclinical models of depression and in MDD (Niciu et al., 2014b; Shors et al., 1989). As a result, glutamatergic agents have been investigated as novel antidepressants (Niciu et al., 2014a; Skolnick et al., 1996). Multiple clinical trials have demonstrated that subanesthetic dose ketamine has robust and rapid antidepressant efficacy in both treatment-refractory MDD and in bipolar depression (Coyle and Laws, 2015; Lee et al., 2015). However, the antidepressant effects of a single ketamine infusion are transient in most patients (Coyle and Laws, 2015); as an example, only 50% of ketamine responders continue to respond at two days post-infusion (Newport et al., 2015).

Multiple studies have attempted to extend antidepressant response

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to ketamine. For instance, the glutamatergic modulator riluzole was tested in two randomized, double-blind, placebo-controlled trials but the effect did not separate from placebo (Ibrahim et al., 2012; Mathew et al., 2010). D-cycloserine, a partial agonist at the glycine co-agonist site of the NMDA receptor, has also been studied in relapse prevention and was found to be effective in a small (n=12) proof-of-concept study in bipolar depression (Kantrowitz et al., 2015). Nevertheless, the most promising antidepressant maintenance strategy currently under investigation appears to be repeated-dose ketamine infusions; yet, to date, only a few such studies have been conducted (aan het Rot et al., 2010; Cusin et al., 2016; Diamond et al., 2014; Murrough et al., 2013; Rasmussen et al., 2013; Singh et al., 2016). These multiple infusion studies have observed extended time-to-relapse (Rasmussen et al., 2013) as well as an increased number of responders (Diamond et al., 2014; Murrough et al., 2013; Rasmussen et al., 2013). Early response to ketamine was also found to predict extended response; one study noted an average time to relapse of 18 days after the last infusion and approximately one-third of the 17 phase I responders maintained antidepressant response at the end of a naturalistic follow-up period (83 days) (Murrough et al., 2013). Given these observations, identifying clinical and/or sociodemographic correlates of extended response in single-infusion ketamine studies is critical as it may facilitate better research design and data interpretation in future multiple-infusion protocols.

Relatedly, efforts are underway to identify biomarkers of ketamine response (for a review, see (Iadarola et al., 2015)). Areas of investigation include brain-derived neurotrophic factor (BDNF) (Haile et al., 2014; Laje et al., 2012; Machado-Vieira et al., 2009), Shank3 (Ortiz et al., 2015), D-serine (Moaddel et al., 2015), interleukin-6 (Yang et al., 2015), vascular endothelial growth factor receptor 1 (VEGF-1) (Permoda-Osip et al., 2014), and vitamin B12 (Lundin et al., 2014; Permoda-Osip et al., 2014). While these studies are promising, many of the findings need to be replicated.

With the exception of anhedonia (Lally et al., 2014), fatigue (Saligan et al., 2016), and suicidal ideation (DiazGranados et al., 2010b; Reinstatler and Youssef, 2015), the literature looking at specific depressive symptom improvement after ketamine has been limited. In MDD patients who remit with citalopram, residual depressive symptoms, most commonly sleep and appetite disturbance, persist (Nierenberg et al., 2010). Few baseline sociodemographic variables have been investigated with regard to their association with antidepressant response to ketamine past one week. Interestingly, studies have found that family history of an alcohol use disorder in a first-degree relative (FHP) correlated with increased antidepressant effects of ketamine in treatment-resistant individuals with either MDD (Niciu et al., 2014c, 2014d; Phelps et al., 2009) or bipolar depression (Luckenbaugh et al., 2012; Permoda-Osip et al., 2014). In addition, patients with such a history had fewer depressive symptoms for up to four weeks post-infusion (Niciu et al., 2014d). Higher body mass index (BMI) was also found to correlate with greater improvement in depressive symptoms at 230 minutes and one day post-infusion, and no lifetime history of suicide attempt(s) correlated with antidepressant efficacy at one week post-infusion (Niciu et al., 2014c). Another study found that dimensional anxious depression (as defined as a Hamilton Depression Rating Scale (HAM-D) anxiety/somatization factor score ≥7) at baseline also correlated with improvement in depressive symptoms in individuals with treatment-resistant MDD (Ionescu et al., 2014). Finally, greater intra-infusion dissociation (as measured by the Clinician Administered Dissociative States Scale (CADSS)) was found to be correlated with increased antidepressant effects at 230 minutes and at one week post-infusion (Luckenbaugh et al., 2014).

Given the depressive symptoms noted above that have been associated with antidepressant response to ketamine at one week (accounting for significant amounts of the effect variance in prior studies at this time point), we hypothesized that FHP status, anxious depression, no lifetime history of suicide attempt(s), and greater dissociation would correlate with continued antidepressant effects at two weeks, and that all depressive symptoms assessed by the MADRS would be decreased two weeks after ketamine infusion in ketamine responders. We further sought to ascertain whether early symptom improvement would correlate with greater antidepressant effects at two weeks, hypothesizing that improvement in each individual MADRS symptom would correlate with overall antidepressant efficacy at two weeks.

2. Methods

2.1. Participant selection

We examined data previously collected from four independent inpatient studies conducted by our group on the experimental use of ketamine in treatment-resistant MDD and bipolar I/II depression without psychotic features. The studies were conducted between October 2006 and June 2015. The primary results of three of the four studies have been previously published (Diazgranados et al., 2010a; DiazGranados et al., 2010b; Ibrahim et al., 2012; Zarate et al., 2012). Two papers reported the results of a double-blind, placebo-controlled study of a single subanesthetic dose of ketamine in current bipolar depression ("ketamine bipolar"; NCT#00088699, NIH Protocol #04-M-0222, substudy 2) (Diazgranados et al., 2010a; Zarate et al., 2012). One study examined the use of flexible-dose oral riluzole (100–200 mg/day) versus placebo for 28 days following open-label ketamine infusion in treatment-resistant MDD ("ketamine riluzole"; NCT#00088699, NIH Protocol #04-M-0222, substudy 3) (Ibrahim et al., 2012); subjects from both the placebo and riluzole arms were included in this analysis. Results from an additional, ongoing study of ketamine in treatment-resistant depression are unpublished (NCT#00088699, NIH Protocol #04-M-0222, substudy 4).

All participants were between the ages of 18 and 65 years old and admitted to the National Institute of Mental Health's Mood and Anxiety Disorders research unit in Bethesda, Maryland. All participants provided written informed consent as approved by the National Institutes of Health Combined Central Nervous System Institutional Review Board. All neuropsychiatric diagnoses were based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (DSM-IV-TR) criteria as confirmed by both a clinical interview performed by a licensed independent psychiatric practitioner and the Structured Clinical Interview for Axis I DSM-IV Disorders, Patient Version (SCID-I/P) (First et al., 2002); the DSM-5 was not used, given that three of the four studies included in this analysis were completed before the DSM-5 was released. All participants were experiencing a major depressive episode of at least moderate severity (defined as a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥20 (Diazgranados et al., 2010a; Zarate et al., 2012) or ≥22 (Ibrahim et al., 2012)) at screening and prior to infusions. Subjects were also required to not have responded to at least one adequate antidepressant dose/duration trial, have no active substance use diagnosis for at least three months prior to inpatient admission, and have no unstable medical problems.

2.2. Study design

After signing protocol-specific consent forms, all MDD subjects were tapered off their current psychotropic medication regimen and remained medication-free for at least two weeks (five weeks for fluoxetine) prior to infusion. Participants with bipolar I/II depression were tapered off all psychotropic medications except lithium or valproate; these subjects were then initiated and/or maintained on therapeutic levels of lithium or valproate for at least four weeks. All participants received a single subanesthetic (0.5 mg/kg) infusion of ketamine hydrochloride over 40 minutes. In the "ketamine riluzole" open-label study, subjects received ketamine and were then rando-