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Research paper

Characterizing the course of suicidal ideation response to ketamine

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ABSTRACT

Background: : No pharmacological treatments exist for active suicidal ideation (SI), but the glutamatergic modulator ketamine elicits rapid changes in SI. We developed data-driven subgroups of SI trajectories after ketamine administration, then evaluated clinical, demographic, and neurobiological factors that might predict SI response to ketamine.

Methods: : Data were pooled from five clinical ketamine trials. Treatment-resistant inpatients (n = 128) with DSM-IV-TR-diagnosed major depressive disorder (MDD) or bipolar depression received one subanesthetic (0.5 mg/kg) ketamine infusion over 40 min. Composite SI variable scores were analyzed using growth mixture modeling to generate SI response classes, and class membership predictors were evaluated using multinomial logistic regressions. Putative predictors included demographic variables and various peripheral plasma markers.

Results: : The best-fitting growth mixture model comprised three classes: Non-Responders (29%), Responders (44%), and Remitters (27%). For Responders and Remitters, maximal improvements were achieved by Day 1. Improvements in SI occurred independently of improvements in a composite Depressed Mood variable for Responders, and partially independently for Remitters. Indicators of chronic SI and self-injury were associated with belonging to the Non-Responder group. Higher levels of baseline plasma interleukin-5 (IL-5) were linked to Remitters rather than Responders.

Limitations: : Subjects were not selected for active suicidal thoughts; findings only extend to Day 3; and plasma, rather than CSF, markers were used.

Conclusion: : The results underscore the heterogeneity of SI response to ketamine and its potential independence from changes in Depressed Mood. Individuals reporting symptoms suggesting a longstanding history of chronic SI were less likely to respond or remit post-ketamine.

1. Introduction

Suicide poses a serious threat to public health. Worldwide, suicide accounts for approximately 1 million deaths, and 10 million suicide attempts are reported annually (World Health Organization, 2014). In the United States, the national suicide rate has increased by approximately 28% over the last 15 years (Curtin et al., 2016). At the same time, relatively few interventions for suicide risk exist. While treatments such as clozapine and lithium have demonstrated effects on suicidal behavior over weeks to months, these effects may be limited to specific diagnoses (Cipriani et al., 2005; Griffiths et al., 2014). Currently, no FDA-approved medications exist to treat suicidal ideation (SI), leaving those who experience a suicidal crisis with limited options for a reprieve of symptoms. Consequently, a critical need exists for rapid-acting treatments that can be used in emergency settings.

A promising off-label agent for this purpose is the rapid-acting antidepressant ketamine, which past studies have suggested reduces suicidal thoughts (Diazgranados et al., 2010a; Murrough et al., 2015; Price et al., 2009). A recent meta-analysis of 167 patients with a range of mood disorder diagnoses found that ketamine reduced suicidal thoughts compared to placebo as rapidly as within a few hours, with effects lasting as long as seven days (Wilkinson et al., 2017). These results are reinforced by newer findings of reduced active suicidal ideation post-ketamine compared to a midazolam control

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(Grunebaum et al., 2018). As the efficacy literature develops in the era of personalized medicine, two important issues must be addressed. First, little is known about the acute course of SI following ketamine. The speed with which antidepressant response occurs, and how much improvement can be expected on average, has been documented for single administrations of ketamine (Mathew et al., 2012; Sanacora et al., 2017); in the limited available literature, researchers have emulated previous studies examining antidepressant effect, where a cutoff of 50% improvement demarcated response (Nierenberg and DeCecco, 2001). Nevertheless, it remains unknown whether this categorization accurately reflects the phenomenon of suicidal thoughts. Empirically-derived approaches to the description of SI trajectory after ketamine may be useful in operationalizing "response" in future clinical trials.

Second, identifying demographic, clinical, or biological predictors of SI response to ketamine would allow researchers and clinicians to determine who is most likely to exhibit an SI response to ketamine. A broad literature describes clinical and demographic predictors for suicide risk (Franklin et al., 2017), and a smaller literature connects suicidal thoughts and behaviors to plasma markers such as brain-derived neurotrophic factor (BDNF) and cytokines (Bay-Richter et al., 2015; Falcone et al., 2010; Isung et al., 2012; Serafini et al., 2017; Serafini et al., 2013). However, no biomarkers have been shown to predict SI/behavior response to intervention, a finding reinforced by the National Action Alliance for Suicide Prevention's Research Prioritization Task Force's Portfolio Analysis (National Action Alliance for Suicide Prevention: Research Prioritization Task Force, 2015). Notably, predictor analyses have the potential to reveal insights into personalized treatments for suicidal individuals, as well as the neurobiology of SI response. With respect to antidepressant response, for example, this approach yielded the observation that individuals with a family history of alcohol dependence may be more likely to exhibit an antidepressant response to ketamine (Krystal et al., 2003; Niciu et al., 2014; Permoda-Osip et al., 2014).

The goals of this study were to elucidate trajectories of SI response and identify predictors of that response, with the ultimate goal of adding to the growing literature surrounding ketamine's specific effects on SI. In particular, we sought to determine whether the heterogeneous patterns of change in SI after ketamine administration were better explained by a model with two or more latent groups of trajectories rather than a single average trajectory, using secondary analyses from previously published clinical trials. These classes were then used to evaluate potential clinical, demographic, and plasma biomarker predictors of SI response to ketamine in order to generate hypotheses.

2. Methods

Data from five independent studies of ketamine in treatment-resistant major depressive disorder (MDD) and bipolar I or II depression without psychotic features were combined; details regarding the patient population have been published previously (Diazgranados et al., 2010b; Ibrahim et al., 2012; Nugent et al., 2018; Zarate et al., 2012; Zarate et al., 2006). A total of 128 patients (ages 19 to 66 (M = 43.83, SD = 12.12); 58 males and 70 females; see Table 1) were admitted for study to the Mood and Anxiety Disorders research unit at the National Institutes of Health (NIH), Bethesda, MD, USA. Participants were screened and deemed eligible for further evaluation upon meeting research criteria, which included meeting criteria for a major depressive episode of at least moderate severity (≥ 18 on the Hamilton Depression Rating Scale (HAM-D) (Zarate et al., 2006) or ≥ 20 (Diazgranados et al., 2010b; Nugent et al., 2018; Zarate et al., 2012) on the Montgomery-Asberg Depression Rating Scale (MADRS). Once at the NIH, patient diagnosis was established using the Structured Clinical Interview for Axis I Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (First et al., 2002) and corroborated by a team of clinicians using all available information. All subjects were in good physical health, as determined by medical history, physical examination, and laboratory tests. Exclusion criteria included pregnancy, breastfeeding, or illicit comorbid substance abuse with the previous three months. Written informed consent was obtained from all participants, and the NIH combined Neuroscience Institute Review Board approved the studies.

Table 1
Demographics of sample used in growth mixture model and predictor analysis.

	Growth mixture model Sample (N = 128)		Predictor analysis sample (N = 107)	
	M	***SD***	***M***	***SD***
Age (years)	43.83	12.12	43.07	12.18
Body mass index	29.55	6.79	29.04	6.35
Length of Illness (years)	25.01	12.49	24.78	12.67
Clinical ratings				
MADRS	33.47	4.68	33.47	4.68
Suicidal ideation score	0.35	0.18	0.36	0.18
Depressed mood score	0.59	0.10	0.60	0.10
	n	***%***	***n***	***%***
Sex (Male)	58	45	50	47
Race (White)	105	83	93	88
Diagnosis				
Major depressive disorder	86	67	65	61
Bipolar disorder	42	33	42	39
History of suicide attempt	48	38	42	39
History of psychiatric hospitalization	80	63	70	65

Note: Suicidal Ideation and Depressed Mood scores are composite scores on a scale of 0 (no symptoms) to 1 (most severe symptoms). The Depressed Mood factor comprises items from the Beck Depression Inventory (BDI; Item 1), the Montgomery–Asberg Depression Rating Scale (MADRS; Items 1, 2, 6, 8), and the Hamilton Depression Rating Scale (HAMD; Items 1, 2, 16). The Suicidal Thoughts factor includes items from the MADRS (Item 10) and BDI (Items 2 and 9).

2.1. Design

As noted above, subject data were obtained from one of five studies; one of these examined ketamine's antidepressant effects in MDD (Zarate et al., 2006), two examined the use of ketamine to treat bipolar depression (Diazgranados et al., 2010b; Zarate et al., 2012), one examined the use of riluzole to extend ketamine's antidepressant effects (Ibrahim et al., 2012), and one explored ketamine's mechanism of action (Nugent et al., 2018) (Clinical Trials Identifier: NCT0088699; NIH Protocol 04-M-0222, substudies 1, 2, 3, and 4, respectively). All patients received a single subanesthetic (0.5 mg/kg) intravenous infusion of ketamine hydrochloride over 40 min. Patients enrolled in the MDD ketamine crossover and ketamine-riluzole studies were free of all psychotropic medications for at least two weeks (five weeks for fluoxetine) prior to the first infusion. The two bipolar studies were both randomized, double-blind, placebo-controlled crossover studies where subjects were maintained on therapeutic levels of either lithium or valproate for at least two weeks prior to the first infusion. The current analyses included the ketamine-only condition (all bipolar patients and all MDD patients with the exception of those randomized to add-on riluzole), at baseline, Day 1, Day 2, and Day 3. It should be noted that many participants were taking numerous medications at the time of their admission to the NIH; participants subsequently completed a screening phase, medication taper, and medication washout period, which could range from weeks to months before entry into the present study and ketamine administration. Therefore, we make a distinction between variables that were collected upon admission to the NIH (which were included as potential clinical and sociodemographic predictors of SI response) and baseline (which were ratings administered just before ketamine infusion, as part of these randomized control trials).