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Research paper

Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials

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ABSTRACT

Background: Identifying clinical correlates associated with reduced suicidal ideation may highlight new avenues for the treatment of suicidal thoughts. Anhedonia occurs across psychiatric diagnoses and has been associated with specific neural circuits in response to rapid-acting treatments, such as ketamine. This analysis sought to evaluate whether reductions in suicidal ideation after ketamine administration were related to reduced levels of anhedonia, independent of depressive symptoms.

Methods: This post-hoc analysis included treatment-resistant patients with either major depressive disorder (MDD) or bipolar disorder (BD) from several clinical trials of ketamine. Anhedonia was assessed using a subscale of the Beck Depression Inventory (BDI) and the Snaith-Hamilton Pleasure Scale (SHAPS). The outcome of interest was suicidal ideation, as measured by a subscale of the Scale for Suicide Ideation (SSI5), one day post-ketamine administration.

Results: Anhedonia, as measured by the SHAPS, was associated with suicidal thoughts independent of depressive symptoms both before and after ketamine administration. One day post-ketamine administration, improvements on the SHAPS accounted for an additional 13% of the variance in suicidal thought reduction, beyond the influence of depressive symptoms. The BDI anhedonia subscale was not significantly associated with suicidal thoughts after adjusting for depressive symptoms.

Limitations: Data were limited to patients experiencing a major depressive episode and may not be generalizable to patients experiencing an active suicidal crisis.

Conclusions: Suicidal thoughts may be related to symptoms of anhedonia independent of other depressive symptoms. These results have implications for the potential mechanisms of action of ketamine on suicidal thoughts.

1. Introduction

Each year, approximately 800,000 individuals worldwide die by suicide (World Health Organization, 2014). Better treatment of suicidal thoughts—which have a worldwide lifetime prevalence of almost 10% (Nock et al., 2008)—is a critical target in preventing suicide deaths. In the United States alone, eight million adults consider suicide annually (Crosby et al., 2011), and hundreds of thousands of individuals seek treatment for suicide or self-harm each year (Ting et al., 2012). Although psychotherapy treatments such as cognitive-behavioral therapy (CBT) (Brown et al., 2005) and dialectical behavioral therapy (Linehan et al., 2006) have been shown to reduce suicidal behavior, only one medication, clozapine, is FDA-approved for suicide risk; however, clozapine use is limited to individuals with schizophrenia or schizoaffective disorders. In their Prioritized Research Agenda for Suicide Prevention, the National Action Alliance for Suicide Prevention has called for more research into suicidal thoughts, including how people become suicidal, and into potential avenues for treatment (National Action Alliance for Suicide Prevention: Research Prioritization Task Force, 2014).

A wealth of research into risk factors for the development of suicidal thoughts exists (Nock et al., 2008; Rudd et al., 1996; Van Orden et al.,

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2010); however, relatively few symptoms have been systematically investigated as clinical correlates in the *reduction* of suicidal thoughts. While it is certainly possible that particular clinical symptoms may mediate both increases and decreases in levels of suicidal ideation, an urgent need exists to identify symptoms that, when treated, reduce suicidal thoughts.

Anhedonia—loosely described as a lack of interest in or an inability to experience pleasure—is experienced across psychiatric diagnoses, including affective disorders and schizophrenia. Interestingly, anhedonia has been associated with specific brain regions and appears to occur independently from other depressive symptoms (Lally et al., 2015; Watson et al., 1995). In this regard, anhedonia is a promising modifiable risk factor and treatment target for suicidal patients, as it has been shown to predict death by suicide in the next year in patients with affective disorders (Fawcett et al., 1990). Loss of interest, a proxy for anhedonia, may also increase in the months before suicidal behavior, as demonstrated in a STEP-BD sample of patients with bipolar disorder (BD) (Ballard et al., 2016). A recent study by Winer and colleagues similarly found that anhedonia independently predicted suicidal ideation in an inpatient sample of adults even when controlling for cognitive and affective depressive symptoms (Winer et al., 2014); specifically, reductions in anhedonia symptoms were associated with fewer suicidal thoughts at discharge from the hospital setting, highlighting the potential role of anhedonia as a treatment target. Similar results were found in a sample of college students (Winer et al., 2016). However, additional controlled investigations exploring the relationship between suicide and anhedonia are needed, given that there is presently no rapid-acting treatment for either. Clinical trials of ketamine, a glutamatergic modulator currently being evaluated as a rapid-acting antidepressant, provide an ideal opportunity for such investigation.

Clinical intravenous administration of sub-anesthetic doses of ketamine has been associated with rapid (within hours) reductions in suicidal thoughts across several investigations (Diazgranados et al., 2010; Larkin and Beautrais, 2011; Murrough et al., 2015; Price et al., 2009; Zarate et al., 2012). These reductions in suicidal ideation remained significant when controlling for the effects of ketamine on other depressive symptoms (Ballard et al., 2014a). Ketamine has also been evaluated in relation to anhedonia in treatment-refractory major depressive disorder (MDD) (DeWilde et al., 2015; Lally et al., 2014). Moreover, recent findings suggest that the effects of ketamine on anhedonia also occur independently of depressive symptoms in BD (Lally et al., 2014). Building on this research, we hypothesized that reductions in suicidal thoughts in response to ketamine would be related to ketamine's anti-anhedonic effects. Such findings would underscore the importance of studying anhedonia as it relates to suicide, both as a treatment target and as a way to understand the neurobiological underpinnings of suicide risk. Importantly, psychotherapeutic techniques such as Behavioral Activation Therapy (BAT) have been associated with changes in reward processing (Dichter et al., 2009), which may also provide additional potential treatment options for suicidal patients.

The current analysis reviews results from several ketamine clinical trials in order to evaluate the relationship between suicidal thoughts and anhedonia after ketamine infusion. Because of ketamine's rapid antidepressant effects, we were able to focus on changes in suicidal ideation and anhedonia within one day post-infusion. Specifically, we hypothesized that the relationship between anhedonia and suicidal thoughts would be significant even when adjusting for other depressive symptoms, both at baseline and after one day of treatment. As an exploratory analysis, we evaluated whether anhedonia symptoms correlated with specific suicide-related thoughts, such as wish to live and reasons for living. The analysis sought to highlight the potential role of anhedonia as a treatment target in reducing suicidal thoughts, with an emphasis on hypothesis generation for future studies investigating the effects of anhedonia symptoms on suicide risk.

2. Methods

Data were drawn from three independent clinical trials of ketamine (all substudies of NCT00088699), including two placebo-controlled trials of ketamine and one open-label trial in which participants were randomized to receive add-on riluzole after ketamine infusion (Ibrahim et al., 2012; Zarate et al., 2012). Eligible participants were 18–65 years old, and all had been diagnosed with treatment-resistant MDD or BD without psychotic features, as determined by the Structured Clinical Interview for Axis I Diagnostic and Statistical Manual (DSM)–IV Disorders, patient version (SCID-P) (First et al., 2001). Patients were experiencing a major depressive episode of at least moderate severity (objectively defined as ≥18 on the 21-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) or ≥20 or ≥22 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) at screening and at the start of each infusion, respectively). None of the participants were receiving psychotropic medications at the time of ketamine infusion, with the exception of BD patients, who were maintained on a mood stabilizer (lithium or valproate). Participants were excluded from the trial if they had been diagnosed with an active substance use disorder (except nicotine and caffeine) in the three months prior to screening. Clinically significant suicidal thoughts at baseline (before medication taper) were an exclusion criterion for one of the clinical trials. Written informed consent was obtained from all participants as approved by the NIH Combined Central Nervous System (CNS) Institutional Review Board.

A subanesthetic dose of ketamine was administered intravenously (.5 mg/kg over 40 min) as part of each clinical trial. Participants received psychiatric assessments through clinician-administered and self-reported measures 60 min before and the day following ketamine infusion, as described below.

2.1. Measures

The *Snaith-Hamilton Pleasure Scale (SHAPS)* (Snaith et al., 1995) is a self-report scale of anhedonia symptoms. Participants are asked to evaluate how much they would enjoy participating in specific activities. An example question is “I would enjoy being with my family or close friends”; the participant is asked to respond whether they agree or disagree with each statement on a four-point Likert scale.

The *Beck Depression Inventory (BDI)* (Beck et al., 1961) is a widely used self-report measure of depressive symptoms. Three items from the BDI—the Loss of Interest, Loss of Pleasure, and Loss of Interest in Sex items—have been used to create an anhedonia subscale (Joiner et al., 2003). This subscale was used to measure anhedonia in Winer and colleagues’ 2014 analysis of anhedonia and suicide (Winer et al., 2014).

The *Scale for Suicide Ideation (SSI)* (Beck et al., 1979) is a clinician-administered measure of suicidal ideation. The first five items are administered to every patient; if a patient reaches a certain score on those items, the remaining 19 items are administered. These items assess measures such as reduced wish to live, wish to die, reasons for living/dying, desire to make a suicide attempt, and passive suicidal thoughts. Because the full SSI was not administered to each participant, only the first five items (SSI5) were included in this analysis, in line with previous analyses suggesting that the use of the abbreviated versus total SSI in clinical trials of treatments such as ketamine may be able to capture rapid changes in symptoms over minutes to hours (Ballard et al., 2015).

The *Hamilton Depression Rating Scale (HAM-D)* (Hamilton, 1960) is a clinician-administered measure of depressive symptoms. The HAM-D was included in this analysis to control for depressive symptoms. When the HAM-D was used as a covariate, items related to suicide and anhedonia were excluded to reduce collinearity.