HHS Public Access

Author manuscript

J Affect Disord. Author manuscript; available in PMC 2018 August 15.

Published in final edited form as:

J Affect Disord. 2017 August 15; 218: 195–200. doi:10.1016/j.jad.2017.04.057.

Anhedonia as a Clinical Correlate of Suicidal Thoughts in Clinical Ketamine Trials

Elizabeth D. Ballard, PhD[a,*], **Kathleen Wills, BS**, **Níall Lally, PhD**[a,b], **Erica M. Richards, MD, PhD**[a], **David A. Luckenbaugh, MA**[a], **Tessa Walls, MS**[a], **Rezvan Ameli, PhD**[a], **Mark J. Niciu, MD, PhD**[a], **Nancy E. Brutsche, MSN**[a], **Lawrence Park, MD**[a], and **Carlos A. Zarate Jr., MD**[a]

[a]Experimental Therapeutics & Pathophysiology Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, 20892, USA

[b]Institute of Cognitive Neuroscience, University College London, London, WC1N 3AR, UK

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.

[*]Correspondence to. Building 10, CRC Room 7-3345, 10 Center Drive, MSC 1282, Bethesda, MD 20892, Tel: +(001) 301-435-9399, fax: +(001) 301-402-9360. Elizabeth.Ballard@nih.gov.

Keywords

suicide; anhedonia; depression; ketamine; RDoC

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., 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.

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

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.

Statistical Analysis

Univariate statistics, specifically t-tests and chi-squares, were used to compare the demographic and clinical characteristics of participants who reported or did not report suicidal ideation at baseline. Patients had to have a score of 2 or more on the SSI5 to be counted as having suicidal ideation. Anhedonia symptoms were measured by the SHAPS

and the BDI anhedonia subscale. Hierarchical linear regressions were used to evaluate the relationship between suicidal ideation and anhedonia (either SHAPS or BDI anhedonia) at baseline and change in suicidal ideation and anhedonia at one day post-ketamine infusion. Change was calculated using a simple difference, not percentage change, due to the distribution of suicidal ideation scores. The current model was a standard linear regression where the initial model was a simple regression (one predictor). The second model forced an additional predictor into the model in a separate block in order to assess change in the first predictor and the degree that the second predictor added to the model. Although the blocks could include groups of variables, in this model the blocks had one variable each. The advantage of this hierarchical (or sequential) approach is the ability to evaluate the initial predictor alone before getting to the full model. These models were run unadjusted and then adjusted for depression at baseline or with change in depressive symptoms. The R^2 change was also examined to quantify how much of the variance in suicidal thoughts was explained by anhedonia when depressive symptoms were placed in the model first. Models evaluating change at one day post-ketamine infusion were limited to participants who reported any level of suicidal thoughts at baseline (SSI5 > 1) and were not randomized to receive riluzole in the open-label trial.

In addition, similar regression analyses were performed for any anhedonia measure that was found to be significantly associated with suicidal ideation; each of the five items from the SSI5 were evaluated to determine if specific suicide-related thoughts were associated with anhedonia. All statistics were conducted using SPSS version 21. Significance was considered at $p < .05$, two-tailed.

Results

One hundred participants were included in this analysis (35 with BD and 65 with MDD). The sample was 52% male, with a mean age of 45.88 (SD = 12.37). At baseline before ketamine infusion, 48 participants (48%) reported any suicidal thoughts, as defined by a score of 2 or more on the SSI5. Demographic and clinical characteristics of the participants by baseline level of suicidal thoughts are presented in Table 1. Patients with suicidal ideation at baseline had a higher frequency of past history of suicide attempts and more current depressive and anhedonia symptoms in contrast to patients without suicidal ideation at baseline.

Results from the hierarchical linear regression analysis are presented in Table 2. At baseline, the SHAPS was associated with suicidal thoughts, as measured by the SSI5, both unadjusted as well as adjusted for depressive symptoms. The BDI anhedonia score was not significantly associated with suicidal thoughts. At one day post-ketamine infusion, change in SHAPS was associated with change in suicidal thoughts, both unadjusted as well as adjusted for change in depressive symptoms. In the hierarchical model, the SHAPS explained an additional 13% of the variance in change in suicidal thoughts beyond what was explained by change in depressive symptoms (when these were entered into the model first). Change in BDI anhedonia score was associated with change in suicidal thoughts, but not when adjusting for depressive symptoms. Comparing the beta weights between this study and the previously published literature, it is possible that a sample size similar to that used by Winer and

colleagues would have made these relationships significant in the current study (Winer et al., 2014). This suggests that differences may be related to issues of sample size.

Due to the demonstrated relationship between the SHAPS and the SSI5, additional hierarchical linear regression analyses between the SHAPS and the first five items of the SSI were examined in an exploratory analysis (Table 3). At baseline, SHAPS score was significantly correlated with the “reduced wish to live” as well as the “few reasons for living/ increased reasons for dying” items. When adjusting for depressive symptoms, only the “reduced wish to live” item remained significant. After ketamine infusion, change in SHAPS score was correlated with change in all five SSI items. After adjusting for change in depressive symptoms, the “wish to die”, “reasons for living”, “reasons for dying”, and “passive suicidal thoughts” items were still associated with change in SHAPS score.

In order to examine the timing of change in symptoms, we conducted a post-hoc analysis to examine whether change in SHAPS score and change in depressive symptoms at the 230-minute post-ketamine infusion time point were associated with change in suicidal ideation (as measured by the SSI5) at one day post-ketamine infusion. Change in SHAPS score at 230 minutes (Standardized Beta = .55, $p < .001$) and change in depressive symptoms at 230 minutes (Standardized Beta = .66, $p < .001$) were each significantly associated with change in suicidal ideation at day one. When both change in depressive symptoms and change in anhedonia levels at 230 minutes were entered into the same model, only change in depressive symptoms significantly predicted change in suicidal ideation one day post-ketamine infusion (Standardized Beta = .46, $p = .01$ for depression, Standardized Beta = .25, $p = .16$ for anhedonia).

Discussion

In this evaluation of clinical ketamine trials in individuals with treatment-resistant MDD or BD, reductions in suicidal thoughts were associated with reductions in anhedonia that occurred independently of reductions in depressive symptoms. As measured by an anhedonia-specific measure—the SHAPS—changes in anhedonia accounted for an additional 13% of the variance in change in suicidal thoughts, and this impact was seen beyond the effects of depressive symptoms. Given that previous work by Ballard and colleagues suggested that depressive symptoms account for about 19% of the change in suicidal ideation after ketamine administration (Ballard et al., 2014a), this analysis offers another possible explanation for ketamine’s ability to reduce suicidal thoughts, namely by reducing anhedonia.

It is also interesting to note that exploratory analyses suggested that, while it appeared that decreased wish to live was associated with anhedonia at baseline, reduced levels of anhedonia at one day post-ketamine administration were associated with reduced wish to die, increased reasons for living, fewer reasons for dying, and fewer passive suicidal thoughts. Results highlight the potential importance of anhedonia in assessing suicidal thoughts and suicide risk, and may benefit from further analyses of other suicide risk factors, such as impulsivity, hopelessness, or distress. The SHAPS may also be a particularly helpful tool for understanding the relationship between suicidal thoughts and anhedonia, given that

it is unaffected by demographics and has established internal consistency and validation in MDD clinical trials (Rizvi et al., 2016). At the same time, it is important to note that suicidal ideation was the outcome of interest; while suicidal ideation is often a precursor to suicide attempts or death, many patients ideate without engaging in suicidal behavior (Kuo et al., 2001). Further investigation is needed to assess whether reductions in suicidal ideation after interventions such as ketamine ultimately lead to reduced risk for suicidal behavior.

These results diverge somewhat from previously published investigations of suicide and anhedonia, which may be due to differences in design and patient population. In the analysis by Winer and colleagues, the BDI anhedonia subscale at baseline was found to predict suicidal thoughts when controlling for cognitive and affective symptoms of depression (Winer et al., 2014). In contrast, in the present analysis, the BDI anhedonia subscale was not associated with suicidal ideation. This could have been due to differences in sample size (and perhaps patient selection and study duration) given beta-weights between the current analysis and Winer et al.'s results were comparable. While the average time frame of analysis in the study by Winer and colleagues was six weeks, clinical measurements in the ketamine trials spanned only one day. It may be that measures such as the SHAPS are particularly suited to measuring state changes over the course of minutes to hours, as experienced by some patients after ketamine. It also may be that the rapid-acting effects of ketamine are more associated with experiences of pleasure, as measured by the SHAPS, rather than overall lack of interest, which may be better assessed by the BDI anhedonia subscale. At the same time, the results underscore the need for future research, using a variety of methods, to investigate the relationship between anhedonia symptoms and suicidal thoughts.

There are a number of benefits to linking suicidal thoughts with anhedonia, specifically within an NIMH RDoC framework (https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml). First, there is a burgeoning literature on the neurobiology of anhedonia, including linkage to specific neural circuits and neurotransmitters as well as animal models. Given that the neuroimaging literature around suicidal thoughts is comparatively sparse and that animal models of suicide are non-existent (Cox Lippard et al., 2014), this connection to anhedonia can highlight key target areas for future evaluation of treatments for suicidal ideation. For example, anhedonia is often subcategorized into consummatory (hedonic pleasure) and motivational (reward/cost/anticipation) components. Preclinical evidence shows that dopamine is involved with the motivational component (Treadway and Zald, 2011). Specifically, preclinical studies in mice found that increased levels of dopamine after the sucrose-water test (Kaczmarek and Kiefer, 2000), as well as neuroleptic drug administration (Pecina et al., 1997), did not alter the liking response or explain the consummatory component of anhedonia, suggesting no specific link between dopamine and motivational anhedonia. Furthermore, it has been proposed that regions of the medial prefrontal cortex—for instance, the orbitofrontal cortex (OFC) and anterior cingulate cortex, which input into the ventral striatum—are involved in the consummatory aspects of anhedonia (Treadway and Zald, 2011). Thus, given that specific neural circuits may be associated with distinct aspects of anhedonia, future research could evaluate whether suicidal thoughts are particularly associated with deficits in wanting (motivational) as compared to liking (consummatory). Uncovering such an association between regions and

linked circuits in the brain may suggest directions for future biological research on suicidal thoughts and behaviors.

In addition, understanding the link between suicidal thoughts and anhedonia may also provide further insights into ketamine's treatment effects. Positron emission tomography (PET) imaging studies found that glucose metabolism in the infralimbic cortex was associated with suicidal ideation but not depression, both at baseline and after ketamine infusion (Ballard et al., 2014b). Moreover, the anti-anhedonic effects of ketamine have been linked to increased glucose metabolism in the dorsal anterior cingulate cortex (dACC) and putamen in patients with BD (Lally et al., 2014), and with increased glucose metabolism in the dACC and decreased OFC metabolism in MDD patients (Lally et al., 2015). Prospective studies can determine whether there are distinct neural signatures for ketamine's antidepressant, anti-suicidal, and anti-anhedonic effects, or whether there is substantial overlap. Given that our understanding of ketamine's mechanism of action is still evolving (Zanos et al., 2016), evidence from neuroimaging modalities can be linked with other potential ketamine metabolites or biomarkers to both better understand the antidepressant effects of ketamine and the biological foundations of these clinical symptoms.

Despite these interesting findings, this study is associated with several limitations that highlight the need for prospective evaluation. First, patient samples were limited to individuals with treatment-resistant MDD or BD, further limiting extrapolations from the small sample size. Second, both suicidal ideation and anhedonia can exist outside of a major depressive episode; therefore, additional research may be indicated for patients across a spectrum of suicidal, anhedonic, and depressive symptoms. Third, acutely suicidal patients were excluded from one of the clinical trials (before medication taper); the results might have differed if the analysis had included patients at imminent suicide risk or who had higher scores on the SSI5. Also, measuring rapid changes in suicidal ideation is a relatively new field; we chose to use the SSI5 because previous analyses by our group had shown increased sensitivity to change over the total SSI (Ballard et al., 2015), but further psychometric validation of scales used in ketamine research are needed. Fourth, the SHAPS does not clearly distinguish between motivational (anticipation) and consummatory (liking) components of anhedonia. Other measures such as the Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2006), which distinguishes between consummatory and motivational anhedonia, could be useful in linking suicidal thoughts to specific aspects of anhedonia. Fifth, all anhedonia measures relied on self-reported variables, although a clinician version of the SHAPS has been developed (Ameli et al., 2014). Finally, it is possible that tasks of reward responsiveness (Dillon et al., 2014) could be used to more directly connect these symptoms to specific neural circuits. These include implicit suicide risk (Nock et al., 2010) as well as the dot-probe task; indeed, a recent meta-analysis of studies using the dot-probe task concluded that depressed patients have an attentional bias away from positive information (Winer and Salem, 2016).

In conclusion, this post-hoc analysis, which drew data from several clinical trials of ketamine in individuals with treatment-resistant MDD or BD, found an association between reductions in suicidal thoughts and anhedonia that occurred independently of depressive symptoms. Moving forward, translational approaches can be used to link these results to

what is known about the neurobiology of anhedonia, offering new perspectives for suicide research. The results also suggest that future suicide research would benefit from continuing to use anhedonia measures, such as the SHAPS or TEPS, as well as reward paradigms. These techniques could help to both conceptualize the symptom of anhedonia as well as serve as potential predictors or clinical correlates of suicide risk. Perhaps more importantly, the results underscore the possibility that therapies already available for anhedonia—such as CBT and BAT (Craske et al., 2016)—may be used to treat patients with suicidal ideation by decreasing anhedonia symptoms and improving neural responses in the reward system (Treadway and Zald, 2011). Additional analyses using rapid-acting interventions, such as ketamine, can help further our understanding of the neurobiology of both suicidal thoughts and anhedonia, leading to innovative treatments.

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Highlights

- Ketamine has been associated with rapid reductions in suicidal thoughts.
- Ketamine has also been associated with reductions in anhedonia.
- Ketamine's anti-suicidal effects may be due to its ability to reduce anhedonia.
- Anhedonia may be an important research and treatment target for suicidal thoughts.

Table 1

Association between Suicidal Ideation at Baseline and Demographic and Clinical Characteristics

	No Suicidal Ideation (SSI5 < 2) N (%)	Suicidal Ideation (SSI5 > 2) N(%)	X^2	p
Male gender	26(50%)	26(54%)	.17	.68
Past psychiatric hospitalization	30(64%)	32(80%)	2.76	.10
Past suicide attempt	15(29%)	28(61%)	10.17	.001
	Mean (SD)	Mean (SD)	t	p
Age	44.9(12.50)	27.57(11.78)	1.10	.28
Length of Illness	24.77(13.46)	29.59(12.04)	1.96	.07
Depression				
HAM-D without suicide or work/activity items	16.44(3.16)	18.67(3.52)	3.33	.001
BDI without suicide or anhedonia items	20.25(6.00)	24.33(7.01)	3.14	.002
Anhedonia				
SHAPS	36.02(6.04)	40.50(7.28)	3.36	.001
BDI Anhedonia Subscale	4.87(1.77)	5.67(1.87)	2.20	.03

BDI: Beck Depression Inventory; HAM-D: Hamilton Rating Scale for Depression; SHAPS: Snaith-Hamilton Pleasure Scale; SSI5: Sum of first five items from Scale for Suicide Ideation

Table 2

Hierarchical Linear Regression Analysis of Suicidal Ideation and Anhedonia Measures at Baseline and One Day Post-Ketamine Infusion

	SSI5				
	Unadjusted		**Adjusting for depressive symptoms/change in depressive symptoms[b]**		**R^2 change of anhedonia measure beyond measures of depressive symptoms[c]**
	Beta[a]	**p**	**Beta**	**p**	
Baseline					
SHAPS	.28	.005*	.21	.03*	.04
BDI Anhedonia	.13	.20	.05	.64	.002
Symptom Change One Day Post-Ketamine					
SHAPS	.63	<.001*	.40	.003*	.13
BDI Anhedonia	.58	<.001*	.23	.15	.03

BDI: Beck Depression Inventory; SHAPS: Snaith-Hamilton Pleasure Scale; SSI5: Sum of first five items from Scale for Suicide Ideation

*p < .05;

[a]Standardized Beta;

[b]Model 1 where depressive symptoms were added into the model second.

[c]Model 2 where depressive symptoms were added into the model first

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Table 3

Hierarchical Linear Regression Analysis of SHAPS and Individual SSI Items at Baseline and One Day Post-Ketamine Infusion

	Single Items from SSI5			
	Unadjusted		Adjusting for depressive symptoms/change in depressive symptoms	
	Beta[a]	p	Beta	p
Reduced Wish to Live				
Baseline	.31	.002*	.30	.004*
Symptom Change One Day Post-Ketamine	.41	.01*	.30	.09
Wish to Die				
Baseline	.20	.05	.12	.21
Symptom Change One Day Post-Ketamine	.59	<.001*	.40	.008*
Few Reasons to Live/Increased Reasons to Die				
Baseline	.24	.02*	.19	.06
Symptom Change One Day Post-Ketamine	.56	<.001*	.34	.02*
Desire to make a Suicide Attempt				
Baseline	.02	.82	−.29	.77
Symptom Change One Day Post-Ketamine	.46	.005*	.29	.08
Passive Suicidal Feelings				
Baseline	.19	.06	.22	.03*
Symptom Change One Day Post-Ketamine	.54	.001*	.37	.02*

SHAPS: Snaith-Hamilton Pleasure Scale; SSI5: Sum of first five items from Scale for Suicide Ideation

*p < .05;

[a]Standardized Beta