Published in final edited form as:

Psychiatry Res. 2017 November ; 257: 303–308. doi:10.1016/j.psychres.2017.07.065.

Active Suicidal Ideation during Clinical Antidepressant Trials

Elizabeth D. Ballard, PhD^{*}, Sam L. Snider, BA, Allison C. Nugent, PhD, David A. Luckenbaugh, MA, Lawrence Park, MD, and Carlos A. Zarate Jr., MD

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

Abstract

Suicidal patients are often excluded from clinical trials of psychiatric medications and from investigations using neurobiological techniques. To evaluate the presence, impact, and stability of active suicidal ideation (SI) across a range of antidepressant trials, we reviewed 14 clinical trials conducted in patients with either major depressive disorder (MDD) or bipolar disorder (BD) (N=269). Active SI at any time point in the clinical trial was identified and linked to participation in other research procedures. Stability of active SI across subsequent days was evaluated using intraclass correlation coefficients (ICCs) and compared to other depressive symptoms. Across 14 clinical trials, 63 participants (23%) reported active SI at some point during study participation. Of these participants, 33 completed a neuroimaging procedure and 16 completed polysomnography within a week of active SI. When active SI was subsequently assessed, only 39% of patients continued to report active SI after three days of assessment, despite receiving no additional treatment. ICCs were not significant for either SI or pessimism; other depressive symptoms showed stability over time. The results suggest that research can be conducted in depressed patients with active SI if such research coincides with careful observation. Active SI and pessimism may be particularly vulnerable to fluctuation.

Keywords

Suicide; Depression; Clinical Trials; Suicidal Ideation; Safety; Neuroimaging

^{*}Correspondence to: Building 10, CRC Room 7-5341, 10 Center Drive, MSC 1282, Bethesda, MD 20892, Tel.: (001) 301-435-9399; Fax: (001) 301-402-9360.

Conflict of Interest

Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; NCT00024635/04-M-0222/ZIA MH002857), by a NARSAD Independent Investigator Award to Dr. Zarate, and by a Brain and Behavior Mood Disorders Research Award to Dr. Zarate. Dr. Zarate is listed as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (5*S*)-dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders; he has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. The remaining authors have no conflicts of interest to disclose, financial or otherwise.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

Suicide is a public health threat that has surpassed motor vehicle accidents as the leading cause of injury-related death in the US (Centers for Disease Control and Prevention National Center for Injury Prevention and Control, 2013b; Rockett et al., 2012). Indeed, recent evidence suggests that the suicide rate in the US has risen since 1999, with the largest increases occurring since 2006 (Centers for Disease Control and Prevention National Center for Injury Prevention and Control, 2013a; Curtin et al., 2016; National Action Alliance for Suicide Prevention: Research Prioritization Task Force, 2014). Effective treatments for suicidal patients are limited; only one psychiatric medication—clozapine—is FDA-approved for suicidal behavior, and this agent is indicated for use in patients with schizophrenia or schizoaffective disorder (http://clozaril.com/wp-content/themes/eyesite/pi/2016i0627_Clozaril_PI_09302016.pdf). In addition, though not FDA-approved for suicidal thoughts or behavior, some evidence suggests that other treatments may reduce suicide risk, including electroconvulsive therapy (ECT) in individuals with severe depressive and psychotic illness (Prudic and Sackeim, 1999) and lithium in individuals with bipolar disorder (BD) (Baldessarini et al., 1999). Psychotherapeutic approaches such as Dialectical Behavioral Therapy (DBT) and Cognitive Behavioral Therapy (CBT) have also been shown to reduce the incidence of repeat suicide attempts over weeks to months (Brown et al., 2005; Linehan et al., 2006). Overall, however, very few interventions have been shown to reduce suicide risk in the short term (hours to days).

As a result, research into active suicide risk is critically needed. The National Action Alliance for Suicide Prevention published a prioritized research agenda aimed at reducing the US suicide rate by 20% (National Action Alliance for Suicide Prevention, 2012); the agenda included a need to better understand the neurobiological processes that lead individuals to consider suicide in order to identify new feasible treatments. However, while one of the research objectives was to identify “biomarkers that point to promising treatments and/or predict treatment response” related to suicide risk (National Action Alliance for Suicide Prevention: Research Prioritization Task Force, 2014), a subsequent portfolio analysis revealed no published studies in the literature that could address this aim (National Action Alliance for Suicide Prevention: Research Prioritization Task Force, 2015).

Research in individuals with active suicidal ideation (SI) poses a number of difficulties, including issues of informed consent, environmental safety during procedures, potential delays in care, and the need for appropriate follow-up care (Pearson et al., 2001). As a result, individuals with SI are often excluded from clinical trials in mood disorders, which frequently do not provide a clear operational definition of suicide risk (Zimmerman et al., 2002). In their recent review of clinical trials in depression, Zimmerman and colleagues noted that 75% of the studies excluded patients for “clinically significant SI,” and that trials had become more restrictive over the most recent years of study. In fact, studies published between 2010–2014 were *more* likely to exclude patients with either active SI or a past history of suicide attempts than investigations from the previous decade (Zimmerman et al., 2015). Thus, while neurobiological research with actively suicidal individuals is required to advance the treatment of suicidal patients, such research with suicidal patients has concomitantly been conducted less frequently. Furthermore, few details exist regarding the

specific meaning of the phrase “clinically significant SI,” and whether or not SI should be ascertained by clinician judgement or specific clinical rating scales.

Here, we reviewed the research participation of patients with active SI across a series of clinical trials with antidepressants or mood stabilizers conducted within the Intramural Program of the National Institute of Mental Health (NIMH). Clinically significant SI was defined using a commonly used clinical rating scale: the suicide item from the Montgomery-Asberg Depression Rating Scale (MADRS). It should be noted from the outset that we chose to focus specifically on assessing suicidal thoughts because a number of the clinical trials used here had excluded patients with “clinically significant SI” from clinical trials. However, many other factors may be associated with increased suicide risk, including proxies such as hopelessness (Beck et al., 1985) or psychological pain (Mee et al., 2011), as well as underlying factors such as difficulties with impulsivity or emotion regulation (Turecki et al., 2012). Despite this distinction, we believe these data on the presence and fluctuation of active SI in clinical trials for depression can inform the feasibility and design of future research with suicidal individuals.

Specifically, the study sought to: 1) identify the prevalence of active SI at any time during these clinical trials; 2) assess how many patients were withdrawn from studies after an instance of active SI (a variable that has implications for study monitoring); 3) investigate how many participants completed a neurobiological procedure—specifically a sleep study (polysomnography (PSG)) or a neuroimaging procedure (functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), or positron emission tomography (PET))—within a week of active SI (specifically because these procedures can help identify potential biomarkers of acute suicide risk); and 4) investigate the stability of active SI over the subsequent three days in order to compare the stability of SI to other depressive symptoms (a variable with important implications for when and how patients are excluded from investigation).

2. Methods

2.1 Clinical trials

All participant data were collected across 14 inpatient and outpatient clinical trials conducted in individuals with major depressive disorder (MDD) or BD that took place at the NIMH Intramural Research Program between 2001 and 2014. All patients were assessed and screened for study participation under a single screening protocol (NCT00024635) and then went on to sign consent forms for specific clinical trials. All protocols were approved by an Institutional Review Board (IRB) at the National Institutes of Health (NIH), and all participants gave informed consent twice: at screening and at the time of entry into their clinical trial. Additional data regarding the clinical trials and about patient selection were previously published (Nugent et al., 2016). Diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (First et al., 2001) as well as clinical judgment. A number of the trials included additional research procedures, including PSG, MEG, fMRI, and PET.

The clinical trials had different exclusion criteria related to suicide risk at baseline. Three trials had no suicide-specific exclusions. Seven trials excluded individuals considered to

have “serious suicide risk,” but this risk was not operationally defined and was left to clinician judgement. Other trials excluded particular levels of SI. For instance, one trial excluded individuals with a score of 3 or more on the Hamilton Depression Rating Scale (HAM-D) suicide item; one trial excluded individuals with a score of 4 or more on the MADRS suicide item; some trials excluded individuals with a history of suicide attempts (ranging from a past history of suicide attempt in the last six months to the past three years). It should be noted that excluding patients with suicidal thoughts at baseline did not preclude patients from reporting active SI during the trial. Additional data regarding study withdrawals across these clinical trials have been published (Nugent et al., 2016).

2.2 Clinical care and safety procedures

While patients were drawn from disparate protocols, certain clinical care and safety standards were in place for all studies. Specifically, during their respective protocols, participants were queried about suicidal thoughts; this occurred at minimum on a daily basis if they were inpatients or at each clinic visit if they were outpatients. Participants were also instructed to report any suicidal thoughts to clinical staff. These independent ratings were part of general nursing and physician assessments and were not included as part of the research ratings.

When active suicidal thoughts were reported, the treatment team conducted an immediate and comprehensive clinical assessment of risk and symptom severity. Based on this assessment and on patient observation, a determination was made regarding whether it was safe for participants to continue in study activities. If continued study participation represented a significant safety risk, the participant was withdrawn from the study and appropriate clinical treatment was initiated. If continued study participation was not deemed to represent a significant safety risk, the participant remained in the study but with increased safety monitoring and additional safeguards. Participants were also in consistent contact with an independent human subjects protection unit that interviewed patients throughout their participation and could make recommendations to the research team regarding whether any particular patient needed to be withdrawn due to worsening symptoms.

2.3 Measures

The primary outcome measure used in the present analysis was the MADRS (Montgomery and Asberg, 1979), which includes one item that assesses suicide risk. This item has been correlated with suicidal behavior at six month follow-up (Montgomery et al., 1983). A score of 4 on the MADRS suicide item is described as “probably better off dead. Suicidal thoughts are common and suicide is considered as a possible solution, but without specific plans or intention”. This score is considered to reflect clinically significant SI, as compared to a score of 2, defined as “weary of life, only fleeting suicidal thoughts,” which is thought to represent more passive suicidal thoughts. A score of 4 on the MADRS suicide item was used as an inclusion criterion for an SI-focused study of the glutamatergic modulator ketamine (Murrough et al., 2015). In one of the clinical trials, the HAM-D (Hamilton, 1960) was used as an outcome measure; for these patients, a score of 3 or more on the HAM-D suicide item (“suicide ideas or gestures”) was considered to represent clinically significant SI for analytic purposes. Other items from the MADRS were used as comparison measures in stability

analyses; these included reported sadness, pessimism, inner tension, decreased concentration, and an inability to feel (items 2, 3, 6, 8, and 9 on the MADRS, respectively); it should be noted that these items rely on patient report rather than clinical observation (i.e. reported sadness as compared to apparent sadness). Items related to appetite and sleep patterns were not included due to concerns that those symptoms would not show enough variability over daily assessments.

2.4 Procedures

Research databases were evaluated for demographic data and mood rating scores. Participants who reported active SI were identified regardless of whether the SI occurred during the screening phase or during active study participation. Study completions and withdrawals at the time of active SI were also evaluated. Clinical ratings were also linked in time to other research procedures, specifically a sleep EEG (polysomnography) as well as neuroimaging procedures (fMRI, PET, and MEG). Individuals who completed one of these procedures within a week of reporting active SI were identified. It should be noted that, for safety monitoring and as part of clinical practice for these procedures, all neuroimaging scans were attended by a clinical provider in addition to the technicians.

2.5 Stability of SI

In a subset of the clinical trials—specifically, trials investigating a rapid-acting antidepressant in treatment-resistant MDD or BD—participants received daily mood ratings. For these trials, we identified the first instance of active SI after drug/placebo administration (i.e. because of the agent's rapid-acting effects, we selected the first instance of SI after the initial antidepressant effects of the experimental agent had dissipated). Once these instances of active SI were identified, we evaluated the next three subsequent days of mood ratings to evaluate the stability of symptoms. During these three days, no new treatments were initiated as part of the clinical trials. Other items from the MADRS, including sadness, inner tension, concentration, inability to feel, and pessimism were also included as comparators to depressive symptoms that may change over time.

2.6 Statistical analysis

Demographic and clinical characteristics between individuals who did and did not have active SI during their research participation were compared using chi-square and *t*-tests. With regard to the rapid-acting antidepressant trials, intraclass correlation coefficients (ICCs) were calculated with both fixed (item) and random (individual) effects, with absolute agreement and a 95% confidence interval. In order to maximize variability, we focused on ICCs between Day 2 and Day 3 (post-administration of an experimental medication), as there would be little variability in active SI on Day 1 of any assessment. IBM SPSS version 21 (Armonk, N.Y.) was used for all statistical analyses and significance was considered at $p < .05$, two-tailed.

3. Results

Data collected from 269 depressed participants across 14 clinical trials were included. For individuals who participated in multiple trials, only data from the first trial was used in the

analysis in order to isolate one instance of SI per individual, given that repeated instances of active SI might have impacted whether individuals continued or discontinued research participation. Figure 1 depicts the research participation of these patients—including withdrawals from their respective studies—as well as the number with active SI. Sixty-three participants (23%) reported active SI at some point during their clinical trial. Table 1 lists the demographic and clinical differences between participants who did and did not report active SI during a trial. Participants who reported active SI were more likely to be diagnosed with BD, to have a past history of suicide attempt, and to be enrolled in a trial requiring treatment-resistant depression (TRD, failure to respond to at least one adequate antidepressant trial) as an inclusion criterion ($p < .05$). At baseline, these participants had higher scores on the MADRS suicide item as well as higher MADRS scores overall (with the suicide item removed) ($p < .01$). No differences in age, gender, or other clinical characteristics were observed between the two groups. Participants with active SI showed a nominally earlier age of onset ($p = .054$) and were less likely to complete their study protocol ($p = .09$), but these findings did not reach statistical significance.

As a further investigation of study withdrawals, we evaluated whether participants were withdrawn from their study protocol at the time of their active SI. Of the 63 patients with active SI, 42 completed the study protocol (67%). No differences in demographic characteristics, clinical characteristics, or baseline MADRS scores were observed between those participants with SI who completed their study protocol and those who did not. Of the patients who withdrew, 12/21 (57%) were withdrawn at the time of their active SI ratings. Reasons for patient withdrawal that occurred at a different time point from active SI (9/21, or 43% of the remaining patients) included medical complications, family concerns, and a lack of response to study medication. None of the patients attempted suicide during their participation in the protocol, but one subject did attempt suicide while still under the care of the psychiatric inpatient unit.

The date of active SI was then linked to the date of other neurobiological procedures. Sixteen (25%) participants completed PSG within a week of reporting active SI. Thirty-three (52%) participants completed a neuroimaging procedure (PET, fMRI, MEG) within a week of reporting active SI. No significant difference in study withdrawal rates were observed between those participants who completed the neurobiological research procedures and those who did not ($p > .20$).

For the stability analysis, data from 17 participants who reported active SI during a rapid-acting antidepressant clinical trial were included. As stated in the methods, active SI was only included in the analysis after the initial effects of the experimental medication had dissipated. Nine (53%) of the 17 had a neurobiological research procedure on same day that they experienced active SI. Additional assessments were included up to three days after the initial report of active SI. By Day 4 (three days after the first instance of active SI), only 39% of the same subjects continued to report clinically significant SI. The percentage of participants whose levels of active SI increased, decreased, or remained the same is presented in Figure 2a. Figure 2b depicts participants who completed a neurobiological research procedure on the same day they first reported active SI. Results of the stability analysis showed that the ICCs between Day 2 and Day 3 were not significant for either SI or

pessimism, suggesting greater variability over time. All of the other depressive symptoms, including depressed mood, inner tension, concentration, and ability to feel had significant ICCs, suggesting stability in symptoms over time. Results from the ICC analysis are presented in Table 2.

4. Discussion

Results from 14 clinical antidepressant trials conducted in individuals with mood disorders suggest that active SI was relatively common, occurring in almost a quarter of participants. When active suicidal thoughts occurred, some participants were withdrawn from their respective studies for more proactive treatment, but others were able to complete neurobiological procedures, such as imaging or sleep studies, with no significant impact on study completion or patient safety. In fact, for those who continued in their respective study, SI decreased in most patients in the subsequent three days, even when subjects were asked to undergo research procedures. A sub-analysis of daily assessment of suicidal thoughts suggested that, compared to other depressive symptoms, active SI and pessimism may be particularly vulnerable to changes over time. Taken together, these results suggest that clinical research with actively suicidal patients can be done as long as careful observation and follow-up assessments are in place.

Results from this analysis are somewhat contrary to trends in the current antidepressant trials literature. As noted by Zimmerman and colleagues, recent antidepressant trials may be becoming increasingly more restrictive in excluding patients with suicidal thoughts or behaviors (Zimmerman et al., 2015). It should be noted, however, that the setting in which most of the trials included in the present analysis occurred is somewhat unique; most participants were psychiatric inpatients who could be monitored closely over the course of their respective trials. As length of stay on inpatient units has decreased over the decades, it is possible that a shift from inpatient to outpatient clinical trials has had an impact on the severity of patients permitted in such research. In addition, a substantial proportion of patients were enrolled in trials of rapid-acting treatments (for instance, ketamine and scopolamine); thus, the rapidity of those agents' antidepressant effects allowed for shorter trial lengths than typical antidepressants, which may also have facilitated close observation of these patients. Even so, the findings suggest that depressed patients do report clinically significant suicidal thoughts during clinical trials. Regardless of whether these patients are ultimately withdrawn from a study, careful suicide risk monitoring is an integral part of antidepressant clinical trials. Given that suicidal thoughts are relatively common in depressed clinical samples—indeed, some studies using measures such as the Scale for Suicide Ideation (SSI) have estimated rates as high as 58% (Sokero et al., 2003)—including patients with suicidal thoughts may not only be appropriate, but even necessary, for generalizing findings to patients seen across clinical settings.

In this study, neurobiological research procedures were conducted in a subsample of individuals reporting active suicidal thoughts. These procedures did not appear to have a negative impact on patient outcomes, although larger randomized trials would be needed to determine potential causal effects. Much of the preexisting neurobiological literature on suicide risk evaluates individuals with a lifetime history of suicide attempts, given that past

suicidal behavior is the most significant predictor of future suicidal behavior (Suominen et al., 2004). Both fMRI and PET studies have demonstrated that particular findings can predict both past and future suicide attempts (Dombrovski et al., 2013; Oquendo et al., 2016). One fMRI study found that deficits in reward processing were associated with a lifetime history of suicide attempts in older adults (Dombrovski et al., 2013), and a PET study found that serotonin1A binding in the raphe nuclei was associated with more lethal suicide attempts (Oquendo et al., 2016). In addition, a recent multimodal imaging study found that changes in functional connectivity in regions underlying emotion regulation were associated with history of suicide attempts in adolescents with BD (Johnston et al., 2017).

More recently, a growing literature has suggested that insomnia and other sleep difficulties are associated with long-term risk of death by suicide. Our present finding adds to the existing literature suggesting that research, in the appropriate setting, can be conducted with individuals with current suicidal thoughts, a population not often included in research. As new treatments are evaluated that may specifically target suicidal thoughts—for instance, ketamine (Ballard et al., 2014a; Murrough et al., 2015)—the need to understand the neurobiological circuitry underlying suicidal thoughts is only likely to increase, as is the possibility of integrating neurobiological techniques into clinical trials with acutely suicidal individuals. Two recent examples from the ketamine literature underscore this point. First, results from a PET imaging study demonstrated that glucose metabolism in the infralimbic cortex is associated with both suicidal ideation and its reduction after ketamine, but similar findings were not found for depression (Ballard et al., 2014b). Another study found that nocturnal wakefulness, as defined by PSG, was associated with next day suicidal thoughts (Ballard et al., 2016), and that reductions in suicidal thoughts after ketamine were associated with concomitant improvements in wakefulness (Vande Voort et al., 2016). A similar experimental medicine approach for suicidal thoughts could be used to build on this literature in an effort to identify new biomarkers of response and also help identify new treatment strategies for acutely suicidal individuals as they present to psychiatric emergency settings.

The findings concerning the stability of SI warrant further study, due to the small sample size, short follow-up (three days), and post-hoc nature of the analysis. Our results suggest that SI and pessimism may be particularly transient or waxing/waning phenomena, as compared to other depressive symptoms such as depressed mood. A number of factors could be related to this result, including extrinsic motivators or reinforcers that may affect patient self-report of suicidal thoughts. For example, participants could be concerned that reporting suicidal thoughts may lead to withdrawal from a clinical trial, increased observation status, and/or decreased privileges on an inpatient unit. At the same time, it is possible that suicidal thoughts, as distinct from symptoms such as mood or anhedonia, may be particularly transient and more reactive to environmental events. This would have implications for measuring suicide risk, because repeated assessment may be necessary to obtain a comprehensive picture of suicidal thoughts over time. These fluctuations could also impact trial inclusion/exclusion, because assessment with the MADRS suicide item may exclude a patient from a trial on one day, but include that patient on another. These measures may also affect randomized clinical trials due to high placebo response or regression to the mean. Again, further assessments are needed in larger clinical datasets over longer timeframes to

understand whether SI functions similarly to other depressive symptoms, as well as to assess the impact of rapid changes in SI on how patients are included in research and how clinical trials could best be designed to investigate suicide risk.

This analysis is associated with several limitations. First, and as noted above, one limitation is the specialized setting in which the research occurred. Patients were often included in clinical trials on a research inpatient unit with high staff to patient ratios and opportunities for careful assessment during research. Second, acute suicide risk was an exclusionary factor upon entry for a number of these trials, specifically because many of the trials involved a medication taper, and emphasis was thus placed on not exposing suicidal patients to undue risk by withdrawing them from their medications. As a result, the participants in this analysis are not directly comparable to actively suicidal patients who may be seen in psychiatric emergency departments. Third, even when we collapsed the data across 14 clinical trials, overall sample sizes were small, particularly in analyses of clinical stability over time. Finally, while the MADRS suicide item is often used in clinical trials as an inclusionary/exclusionary criterion because it identifies clinically significant suicidal thoughts, it has not been linked to later suicide attempts or death. Large-scale analyses of clinical data are needed to further explore findings related to the fluctuations of clinical symptoms, potentially using multi-item suicide assessments such as the SSI (Beck et al., 1979) and the Columbia Suicide-Severity Rating Scale (C-SSRS) (Posner et al., 2011), both of which have been shown to predict later suicidal behavior; such studies may potentially be feasible if data from large health care systems, such as the Veteran's Administration (VA), are analyzed. Such measures may also assess specific suicide-related cognition, including suicidal intent, suicidal plan, wish to live, and wish to die, all of which may also impact suicide risk and stability over time.

In sum, our results indicate that a substantial proportion of participants in clinical antidepressant trials reported active suicidal thoughts; nevertheless, many were still able to participate in research procedures such as neuroimaging or sleep studies. Given that there is an important and burgeoning pharmacological (Murrough et al., 2015) and psychotherapeutic (Brown et al., 2005; Comtois et al., 2011; Linehan et al., 2006; O'Connor et al., 2015) literature of clinical trials for acutely suicidal individuals, the results of the current study further support the feasibility and need for neurobiological research with suicidal individuals. Working with individuals and organizations that are already conducting research with high risk individuals, such as the VA, may offer a prime opportunity to integrate neurobiological methods into ongoing clinical trials. Further investigation and research in this area is needed to ensure that such research is conducted safely and ethically.

Acknowledgments

The authors thank the 7SE research unit and staff for their support. Ioline Henter (NIMH) provided invaluable editorial assistance.

Funding Information

Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; NCT00024635/04-M-0222/ZIA MH002857), by a NARSAD Independent Investigator Award to Dr. Zarate, and by a Brain and Behavior Mood Disorders Research Award to Dr. Zarate. The NIMH, NARSAD, and the Brain & Behavior Research Foundation had no further role in

study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

References

- Baldessarini RJ, Tondo L, Hennen J. Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. *J Clin Psychiatry*. 1999; 60(Suppl 2):77–84. discussion 111–116.
- Ballard ED, Ionescu DF, Vande Voort JL, Niciu MJ, Richards EM, Luckenbaugh DA, Brutsche NE, Ameli R, Furey ML, Zarate CA Jr. Improvement in suicidal ideation after ketamine infusion: Relationship to reductions in depression and anxiety. *J Psychiatr Res*. 2014a; 58:161–166. [PubMed: 25169854]
- Ballard ED, Lally N, Nugent AC, Furey ML, Luckenbaugh DA, Zarate CA Jr. Neural correlates of suicidal ideation and its reduction in depression. *Int J Neuropsychopharmacol*. 2014b; 18:pyu069. [PubMed: 25550331]
- Ballard ED, Vande Voort JL, Bernert RA, Luckenbaugh DA, Richards EM, Niciu MJ, Furey ML, Duncan WCJ, Zarate CA Jr. Nocturnal wakefulness is associated with next-day suicidal ideation in major depressive disorder. *J Clin Psychiatry*. 2016; 77:825–831. [PubMed: 27337418]
- Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *J Consult Clin Psychol*. 1979; 47:343–352. [PubMed: 469082]
- Beck AT, Steer RA, Kovacs M, Garrison B. Hopelessness and eventual suicide: a 10-year prospective study of patients hospitalized with suicidal ideation. *Am J Psychiatry*. 1985; 142:559–563. [PubMed: 3985195]
- Brown GK, Ten Have T, Henriques GR, Xie SX, Hollander JE, Beck AT. Cognitive therapy for the prevention of suicide attempts: a randomized controlled trial. *JAMA*. 2005; 294:563–570. [PubMed: 16077050]
- Centers for Disease Control and Prevention National Center for Injury Prevention and Control. National Violent Death Reporting System. 2013a.
- Centers for Disease Control and Prevention National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS). 2013b.
- Comtois KA, Jobes DA, SSOC, Atkins DC, Janis K, CEC, Landes SJ, Holen A, Yuodelis-Flores C. Collaborative assessment and management of suicidality (CAMS): feasibility trial for next-day appointment services. *Depress Anxiety*. 2011; 28:963–972. [PubMed: 21948348]
- Curtin, SC., Warner, M., Hedegaard, H. Increase in Suicide in the United States, 1999–2014: NCHS Data Brief. Hyattsville, MD: 2016.
- Dombrovski AY, Szanto K, Clark L, Reynolds CF, Siegle GJ. Reward signals, attempted suicide, and impulsivity in late-life depression. *JAMA Psychiatry*. 2013; 70:1. [PubMed: 23925710]
- First, MB., Spitzer, RL., Gibbon, M., Williams, JB. Structured Clinical Interview for DSM-IV TR Axis I Disorders, Research Version, Patient Edition. New York State Psychiatric Institute, Biometrics Research; New York: 2001.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960; 23:56–62. [PubMed: 14399272]
- Johnston JA, Wang F, Liu J, Blond BN, Wallace A, Liu J, Spencer L, Cox Lippard ET, Purves KL, Landeros-Weisenberger A, Hermes E, Pittman B, Zhang S, King R, Martin A, Oquendo MA, Blumberg HP. Multimodal neuroimaging of frontolimbic structure and function associated with suicide attempts in adolescents and young adults with bipolar disorder. *Am J Psychiatry*. 2017 Jan 31. [Epub ahead of print].
- Linehan MM, Comtois KA, Murray AM, Brown MZ, Gallop RJ, Heard HL, Korslund KE, Tutek DA, Reynolds SK, Lindenboim N. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. *Arch Gen Psychiatry*. 2006; 63:757–766. [PubMed: 16818865]
- Mee S, Bunney BG, Bunney WE, Hetrick W, Potkin SG, Reist C. Assessment of psychological pain in major depressive episodes. *J Psychiatr Res*. 2011; 45:1504–1510. [PubMed: 21831397]

- Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979; 134:382–389. [PubMed: 444788]
- Montgomery SA, Roy D, Montgomery DB. The prevention of recurrent suicidal acts. *Br J Clin Pharmacol*. 1983; 15(Suppl 2):183s–188s. [PubMed: 6824553]
- Murrough JW, Soleimani L, DeWilde KE, Collins KA, Lapidus KA, Iacoviello BM, Lener M, Kautz M, Kim J, Stern JB, Price RB, Perez AM, Brallier JW, Rodriguez GJ, Goodman WK, Iosifescu DV, Charney DS. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. *Psychol Med*. 2015; 45:3571–3580. [PubMed: 26266877]
- National Action Alliance for Suicide Prevention. U.S. Department of Health and Human Services (HHS) 2012 National Strategy for Suicide Prevention: Goals and Objectives for Action. Office of the Surgeon General and National Action Alliance for Suicide Prevention; Washington, DC: 2012.
- National Action Alliance for Suicide Prevention: Research Prioritization Task Force. A prioritized research agenda for suicide prevention: An action plan to save lives. National Institute of Mental Health and the Research Prioritization Task Force; Rockville, MD: 2014.
- National Action Alliance for Suicide Prevention: Research Prioritization Task Force. National Suicide Prevention Research Efforts: 2008–2013 Portfolio Analyses. Rockville, MD: 2015.
- Nugent AC, Iadarola ND, Miller FG, Luckenbaugh DA, Zarate CA Jr. Safety of research into severe and treatment-resistant mood disorders: analysis of outcome data from 12 years of clinical trials at the US National Institute of Mental Health. *Lancet Psychiatry*. 2016; 3:436–442. [PubMed: 26971192]
- O'Connor SS, Comtois KA, Wang J, Russo J, Peterson R, Lapping-Carr L, Zatzick D. The development and implementation of a brief intervention for medically admitted suicide attempt survivors. *Gen Hosp Psychiatry*. 2015; 37:427–433. [PubMed: 25983187]
- Oquendo MA, Galfalvy H, Sullivan GM, Miller JM, Milak MM, Sublette ME, Cisneros-Trujillo S, Burke AK, Parsey RV, Mann JJ. Positron Emission Tomographic Imaging of the Serotonergic System and Prediction of Risk and Lethality of Future Suicidal Behavior. *JAMA Psychiatry*. 2016; 73:1048–1055. [PubMed: 27463606]
- Pearson JL, Stanley B, King CA, Fisher CB. Intervention research with persons at high risk for suicidality: safety and ethical considerations. *J Clin Psychiatry*. 2001; 62(Suppl 25):17–26.
- Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011; 168:1266–1277. [PubMed: 22193671]
- Prudic J, Sackeim HA. Electroconvulsive therapy and suicide risk. *J Clin Psychiatry*. 1999; 60(Suppl 2):104–110. discussion 111–106. [PubMed: 10073397]
- Rockett IR, Regier MD, Kapusta ND, Coben JH, Miller TR, Hanzlick RL, Todd KH, Sattin RW, Kennedy LW, Kleinig J, Smith GS. Leading causes of unintentional and intentional injury mortality: United States, 2000–2009. *Am J Public Health*. 2012; 102:e84–92. [PubMed: 22994256]
- Sokero TP, Melartin TK, Rytsala HJ, Leskela US, Lestela-Mielonen PS, Isometsa ET. Suicidal ideation and attempts among psychiatric patients with major depressive disorder. *J Clin Psychiatry*. 2003; 64:1094–1100. [PubMed: 14628986]
- Suominen K, Isometsa E, Suokas J, Haukka J, Achte K, Lonnqvist J. Completed suicide after a suicide attempt: a 37-year follow-up study. *Am J Psychiatry*. 2004; 161:562–563. [PubMed: 14992984]
- Turecki G, Ernst C, Jollant F, Lanbonte B, Mechawar N. The neurodevelopmental origins of suicidal behavior. *Trends Neurosci*. 2012; 35:14–23. [PubMed: 22177979]
- Vande Voort JL, Ballard ED, Luckenbaugh DA, Bernert RA, Richards EM, Niciu MJ, Park LT, Machado-Vieira R, Duncan WCJ, Zarate CA Jr. Antisuicidal response following ketamine infusion is associated with decreased nighttime wakefulness in major depressive disorder and bipolar disorder. *J Clin Psychiatry*. 2016 Dec 6. [Epub ahead of print].
- Zimmerman M, Clark HL, Multach MD, Walsh E, Rosenstein LK, Gazarian D. Have Treatment Studies of Depression Become Even Less Generalizable? A Review of the Inclusion and Exclusion Criteria Used in Placebo-Controlled Antidepressant Efficacy Trials Published During the Past 20 Years. *Mayo Clin Proc*. 2015; 90:1180–1186. [PubMed: 26276679]

Zimmerman M, Mattia JJ, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry*. 2002; 159:469–473. [PubMed: 11870014]

Highlights

- Suicide research is critically needed.
- Suicidal patients are often excluded from antidepressant clinical trials.
- In 14 clinical trials, 23% of patients reported active suicidal thoughts.
- Many suicidal patients were able to complete neurobiological procedures.
- Suicidal thoughts may be vulnerable to fluctuation.

Figure 1.
Process of evaluating active suicidal ideation (SI) during clinical trials for depression

Figure 2.

(a) Stability of active suicidal ideation (SI) after three days of assessment in participants with SI at Day 1 (n = 17). **(b)** Stability of active SI after three days of assessment for participants who completed neurobiological research procedures on Day 1 (n = 9). *Data are drawn from rapid-acting antidepressant clinical trials only.

Table 1

Demographics of Participants in Clinical Antidepressant Trials

	No active SI during research participation (n = 206)	Active SI during research participation (n = 63)		
	Mean(SD)	Mean(SD)	<i>t</i>	<i>p</i>
Age	43.54(11.69)	45.54(12.98)	1.16	.25
Age of Onset	21.65(10.95)	18.56(11.07)	1.94	.054
MADRS Score at Baseline (suicide item removed)	28.74(6.37)	32.02(6.32)	3.16	.002
MADRS Suicide Item at Baseline	1.25(0.89)	2.95(1.09)	11.92	<.001
	N(%)	N(%)	χ^2	<i>p</i>
Gender			2.56	.11
Male	94(46)	36(57)		
Female	112(54)	27(43)		
Diagnoses			8.13	.02
Bipolar I	19(9)	12(19)		
Bipolar II	13(6)	8(13)		
MDD	174(84)	43(68)		
History of Suicide Attempt	32(16)	26(41)	15.54	<.001
Comorbid Diagnosis	122(59)	32(51)	1.40	.24
History of Abuse	85(41)	23(37)	0.53	.47
Substance Abuse History	77(37)	29(46)	1.95	.16
TRD Protocol	154(75)	56(89)	5.63	.02
Completed Study	159(77)	42(67)	2.82	.09

SI: suicidal ideation; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: major depressive disorder; TRD: treatment-resistant depression

Table 2

Intraclass Correlation Coefficients (ICCs) on Days 2 and 3 After Acute SI

	ICC	p
SI	.24	.11
Concentration	.86	<.001
Mood	.79	<.001
Inability to Feel	.77	<.001
Inner Tension	.53	.008
Pessimism	.05	.43

SI: suicidal ideation