



Active suicidal ideation during clinical antidepressant trials

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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.

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,

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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 and 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.

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