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Clinical, psychological and environmental predictors of prospective suicide events in patients with Bipolar Disorder

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ABSTRACT

Patients with Bipolar Disorder (BD) have high rates of suicide compared to the general population. The present study investigates the predictive power of baseline clinical, psychological and environmental characteristics as risk factors of prospective suicide events (attempts and completions). Data was collected from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study. 3083 bipolar patients were included in this report, among these 140 (4.6%) had a suicide event (8 died by suicide and 132 attempted suicide). Evaluation and assessment forms were used to collect clinical, psychological and socio-demographic information. Chi-square and independent *t*-tests were used to evaluate baseline characteristics. Potential prospective predictors were selected on the basis of prior literature and using a screening analysis of all risk factors that were associated with a history of suicide attempt at baseline and were tested using a Cox regression analysis. The strongest predictor of a suicide event was a history of suicide attempt (hazard ratio = 2.60, p-value < 0.001) in line with prior literature. Additional predictors were: younger age, a high total score on the personality disorder questionnaire and a high percentage of days spent depressed in the year prior to study entry. In conclusion, the present findings may help clinicians to identify patients at high risk for suicidal behavior upon presentation for treatment.

1. Introduction

Bipolar Disorder (BD) is characterized by a high risk of suicide attempts and completions, resulting in a 15-fold higher risk compared to that in the general population (Harris and Barraclough, 1997). Approximately 10% of BD patients die from completed suicide (Harris and Barraclough, 1997). Studies show rates of attempted suicide up to 30% among BD patients (Novick et al., 2010), and rates of suicidal ideation up to 56% for those with an adult first episode, and ~74% among patients with a pediatric first episode (Carter et al., 2003). To date, retrospective and cross sectional studies have proposed many risk factors for suicidal behavior in BD patients. These include demographic factors (female gender (Nivoli et al., 2011), age of first depressive episode (Song et al., 2012)), comorbidities (such as anxiety disorders (Baldassano, 2006), borderline personality (Neves et al., 2009), substance abuse (Finseth et al., 2012) or eating disorder (McElroy et al., 2011)), clinical features (feelings of hopelessness (Acosta et al., 2012; Johnson et al., 2005), number of mood episodes, history of suicide attempt and mixed-state or rapid cycling BD (Baldassano, 2006)), heritability, such as family history of suicide attempt (Goldstein et al., 2012), social withdrawal, stressful life events (Papolos et al., 2005). Prospective studies have shown that suicide attempts in BD patients can be predicted by: long duration of untreated illness (Altamura et al., 2010), cigarette smoking (Ostacher et al., 2009), rapid cycling (Garcia-Amador et al., 2009), early onset of Bipolar Disorder (Coryell et al., 2012), previous suicide attempt(s) (Nordstrom et al., 1995), index of depression severity (Angst et al., 2002), alcohol or other substance abuse (Preuss et al., 2003) and feelings of hopelessness (Maser et al., 2002). The majority of studies to date has examined small sample sizes, often concentrating on single, or few, predictors. Such models, although informative, remain insufficient in predicting individual course of suicidality.

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is the largest cohort study to date on BD, and followed 4361 BD patients (Bowden et al., 2012; Sachs et al., 2003). To date, published studies have explored risk factors of suicide in the first sub-samples only. In the first 1000 patients, higher number of psychiatric medications prior to study entry predicted future suicide attempts (Martinez et al., 2005), while in the first 1500 participants, previous suicide attempts and time spent depressed

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were predictors of suicide attempts or completion, in a 2-year period (Marangell et al., 2006). One study examined the effect of lithium on suicide events in the complete sample, but found no protective effect (Marangell et al., 2008). The present study aims to investigate the predictive power of baseline clinical, psychological and environmental characteristics as risk factors of prospective suicide events (attempts or completions) in the STEP-BD cohort. The selection of variables was based on prior research evidence of association with suicide and using a screening analysis of all risk factors that were associated with a history of suicide attempt at baseline. We employed multivariate models allowing for the evaluation of unique predictors of suicide. This method may bring forward distinct characteristics that can be used to identify patients at high risk for suicidal behavior upon presentation for treatment.

2. Methods

2.1. Participants and study overview

STEP-BD is a prospective study, aiming to develop knowledge on risk factors and treatment effectiveness for the management of Bipolar Disorder and evaluate the longitudinal outcome of patients with this disorder. Patients gave both oral and written consent for participation, in accordance with declaration of Helsinki. The study design was approved by the Human Subjects Panel from each site. Exclusion criteria were being unable or unwilling to follow the assessments, refuse to give consent or be below 15 years of age. Patients were followed by trained psychiatrists and treated according to the evidenced based current therapy guidelines (Sachs et al., 2003). Overall, 4360 patients were included in the STEP-BD; we used data from the STEP-BD Standard Care Pathway (SCP) for this report ($n = 4107$). Patients in the SCP could belong to any spectrum of BD presented for clinical care, and received pharmacological interventions as clinically indicated by the principles of evidence-based treatment and published guidelines, updated annually in the STEP-BD Clinicians Handbook. The protocol promoted the application of evidence-based treatments at regular clinical sessions during treatment, according to the needs of the patient and did not follow compliance to a specific treatment algorithm. This naturalistic study used ongoing assessments of treatment and outcome information.

2.2. Assessments

Several measures were used to investigate patients' clinical status. The diagnosis of Bipolar Disorder, and its characteristics were assessed with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and Affective Disorder Evaluation (ADE) form (Sachs, 2004), which was assessed upon study entry together with a socio-demographic form (Sachs, 2004). The ADE was an assessment tool that used versions of the mood and psychosis modules from the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition, for use by practicing clinicians. The ADE also included systematic assessment of lifetime and recent course of illness, including history of suicide attempt. The ADE form was also used to assess the presence of suicide ideation at baseline; suicide ideation was defined as the following: patients had to express symptoms, for the past 7 days, answering to the question "rate associated symptoms for the past week" in a range from −2 (less likely) to +2 (very likely) in ¼ points increment depending on how much they had thought about suicide; based on previous suggestions (Marangell et al., 2006) we defined values from −2 to 0 as "no suicide ideation" and values from 0 to 2 as "positive suicide ideation". The Young mania rating scale (YMRS) (Young et al., 1978) was used to assess severity of mania symptoms while depression severity was measured using the Montgomery and Asberg (1979) Depression Rating Scale (MADRS). Exposure to lithium or SSRI treatment prior the time point of the suicide event was recorded using the Clinical Monitoring Form, a standardized form designed as a routine progress note during the STEP-BD trial. The 60-item Neuroticism Extroversion Openness Five Factor Inventory (NEO-FFI) was used to evaluate the personality traits defined in five basic dimensions (Costa et al., 1992; McCrae and John, 1992). Hopelessness was measured using Beck's hopelessness scale, a 20-item true/false questionnaire assessing the patient's feelings of hope toward different aspects of life, such as future, work and accomplishment (Beck et al., 1974). The 15-item Family History questionnaire assessed the presence of psychiatric illnesses in the family members of the patient (Sachs, 2004). The Life Experiences Survey (LES), a 50-item survey, investigated the impact of single life events on the person's life (Sarason et al., 1978); negative values from 0 (no impact) to −3 (extremely negative impact) corresponded to "negative life events" (values were recoded to non-negative integers for analyses); values from 0 to +3 (extremely positive) represented the "positive life events". The Personality Diagnostic Questionnaire (PDQ) was used to assess personality disorders according to DSM-IV; it consists of a set of 99 true/false statements and the total score reflects a general index of personality disorder (Fossati et al., 1998). The Quality of Life Enjoyment and Satisfaction short Form (QLES-SF) evaluated the amount of satisfaction felt by the patients in the past week prior administration; higher scores indicate greater satisfaction (Endicott et al., 1993).

2.3. Suicide outcome

The main suicide outcome of this report was a prospective "suicide event" (defined as attempt or completion and referred to as such from this point). Suicide events were assessed through the Serious Adverse Events (SAE) form and/or Care Utilization form (CU) as suggested previously (Marangell et al., 2006, 2008). The SAE form was assessed by the clinician during all visits. Questions used to assess suicidality in the present report were "did the patient die by suicide?" and "was there any suicide attempt?". An independent safety officer and SAE committee of the STEP-BD reviewed all potential suicide events to ensure accurate classification. The Care Utilization (CU) was a semi-structured interview (clinician-rated form), administered every 3 months during the first year and every 6 months after that, in which the patient was asked to answer questions on the use of services, as well as on suicidal acts, such as "did you attempt suicide in the last 3 months?". Suicide attempts were defined as self-injurious behaviors with intent for serious harm and/or lethality. A suicide event was coded as present if a suicide attempt or completion was documented in the SAE and/or CU forms, and absent if no evidence of suicidal behavior was present in the two forms.

2.4. Statistical analysis

Predictors were selected on the basis of prior literature and using a screening analysis of all risk factors that were associated with a history of suicide attempt at baseline in the present sample. Chi-square and independent-sample *t*-tests were used to identify differences between baseline characteristic in patients without and with a history of suicide attempt (Table 1).

For the prospective analysis, risk factors were subsequently divided in three clusters; (i) clinical factors: age of onset of the first manic or depressive episode, number of mania/depressive episodes, bipolar subtype, YMRS total score, MADRS total score, SSRI and lithium use, percentage of days depressed or anxious in the

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