



Research paper

The relative influence of individual risk factors for attempted suicide in patients with bipolar I versus bipolar II disorder



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ABSTRACT

Objectives: To compare the relative influence (RI) of individual predictors for lifetime attempted suicide between adults with bipolar I (BBD-I) and bipolar II disorder (BBD-II).

Methods: We conducted an analysis of data from 1465 enrollees in the Mayo Clinic Bipolar Disorder Biobank. Demographic and clinical variables and history of attempted suicide were ascertained using standardized questionnaires. Height and weight were assessed to determine body mass index (BMI); obesity was defined as BMI ≥ 30 kg/m². The frequencies of these variables were compared between persons with and without self-reported lifetime suicide attempts both overall, and within BD-I and BD-II subgroups. Gradient boosting machine (GBM) models were used to quantify the RI of study variables on the risk of lifetime attempted suicide.

Results: Nearly one-third of patients reported having a lifetime suicide attempt. Attempted suicide rates were higher in patients with BD-I than BD-II, but absolute differences were small. Lifetime attempted suicide was associated with female sex, BD-I subtype, psychiatric and substance use comorbidities, binge eating behavior, lifetime history of rapid cycling, other indicators of adverse illness course, and early age of bipolar illness onset in the entire cohort. Differences in the rank-ordering of RI for predictors of attempted suicide between BD-I and BD-II patients were modest. Rapid cycling was a strong risk factor for attempted suicide, particularly in men with BD-I.

Limitations: Actively psychotic or suicidal patients needing psychiatric hospitalization were initially excluded, but were approached after these acute psychiatric problems resolved.

Conclusions: The prevalence of lifetime attempted suicide was significantly higher in BD-I than BD-II in this large, cross-sectional cohort. Predictors of attempted suicide were similar in BD-I and BD-II subgroups.

1. Introduction

Rates of attempted suicide are strikingly high in patients with bipolar disorders. An estimated 0.9% of bipolar disorder patients attempt suicide each year (Beyer and Weisler, 2016), and 25% attempt suicide during their lifetime (Schaffer et al., 2015a). The importance of attempted suicide in patients with bipolar disorder rests in the fact that it is a robust predictor of eventual death by suicide (Antypa et al., 2013; Isometsa et al., 2014; Tsai et al., 2002)—a leading cause of premature mortality in patients with bipolar disorder (Hayes et al., 2015; Ösby et al., 2001). In a 20-year prospective study of 6891 psychiatric outpatients, up to 14% of all completed suicides were accounted for by suicide in bipolar patients, and bipolar disorder diagnosis was associated with the highest risk of eventual suicide among all psychiatric diagnoses (Brown et al., 2000).

A number of risk factors for attempted suicide in bipolar patients have been identified. Among these risk factors, depressive polarity in the current or most recent mood episode has had the strongest association with suicide attempts in persons with bipolar disorders (Schaffer et al., 2015b). The strong and consistent association between depression and attempted suicide in bipolar patients raises the possibility that the risk of attempted suicide may differ significantly between persons with bipolar I (BD-I) and bipolar II (BD-II) disorder. Longitudinal studies have shown that while adults with BD-I spend nearly half of total follow-up days symptomatically depressed (Judd et al., 2002), patients with BD-II spend an even higher proportion of days depressed (Judd et al., 2003). We and others have shown that, relative to patients with BD-I, those with BD-II are at higher risk of having a variety of adverse bipolar illness characteristics that are tied to heightened risk of attempted or completed suicide, such as rapid cycling and comorbid

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psychiatric and substance use disorders (Erol et al., 2015; Kupka et al., 2003; Vieta et al., 2000). These factors raise the hypothesis that lifetime suicide attempts may be more common in patients with BD-II than BD-I.

Studies that have compared the rates of attempted suicide between BD-I and BD-II subgroups have yielded variable results, with some reporting higher rates in patients with BD-I (Antypa et al., 2013; Bega et al., 2012; Joyce et al., 2010), some finding higher rates in patients with BD-II (Holma et al., 2014; Song et al., 2012; Tondo et al., 1999), and others finding no significant differences in the rates of attempted suicide between the two groups (Dennehy et al., 2011; Finseth et al., 2012; Galfalvy et al., 2006; Leverich et al., 2003; Valtonen et al., 2006). Very few studies have focused on identifying and comparing the most influential risk factors for attempted suicide between BD-I and BD-II patients (Goffin et al., 2016; Sublette et al., 2009; Valtonen et al., 2005). We conducted an analysis of data from the Mayo Clinic Bipolar Disorders Biobank (referred to hereafter as the Bipolar Biobank) to quantify the relative influence (RI) of individual risk factors for lifetime attempted suicide, both overall and separately within subgroups of patients with BD-I and BD-II.

2. Method

The Bipolar Biobank was initiated in 2009 as a collaboration between Mayo Clinic, the Lindner Center of HOPE/University of Cincinnati, and the University of Minnesota to identify biomarkers for disease risk and treatment response in patients with bipolar disorders. Details regarding Bipolar Biobank procedures for participant recruitment, informed consent, clinical phenotyping, and biological specimen sampling, processing and storage have been published previously (Frye et al., 2015).

We analyzed data from 1465 Bipolar Biobank enrollees. Eligible participants were adults (aged ≥ 18 years) with clinical diagnoses of BD-I or BD-II who were able to provide valid informed consent. Patients who were actively psychotic or actively suicidal and needing psychiatric hospitalization were not approached initially for participation in the Bipolar Biobank; however, patients who were initially excluded for these reasons were approached after these acute psychiatric problems resolved.

Bipolar Biobank procedures included a detailed evaluation at baseline, conducted over several visits. BD-I or BD-II diagnoses, age of bipolar symptom onset, and comorbid Axis I psychiatric diagnoses were established using the Structured Clinical Interview for the DSM-IV (SCID) (First et al., 2002). For comorbid substance use disorders, these assessments covered DSM-IV-TR diagnoses of alcohol and other substance abuse or dependence, as well as nicotine dependence (American Psychiatric Association, 2000).

The baseline assessment also included structured patient-rated and clinician-administered questionnaires to ascertain demographic variables (age at Bipolar Biobank enrollment, sex, race, Hispanic ethnicity, employment status, and education level), clinical variables (including comorbid anxiety, nicotine dependence, alcohol and other substance abuse/dependence, and eating disorders; and comorbid binge-eating behaviors) and self-reported bipolar illness characteristics, including lifetime history of rapid cycling, cycle acceleration (defined as decreases in inter-episode duration over time), increased mood episode severity over time, lifetime psychosis during depressive or manic episodes, and lifetime number of suicide attempts. Age of onset of bipolar disorder was collected using pre-defined age strata (< 20, 20–49, 50–64, and 65–79 years). Early age of onset was defined as the self-reported onset of the first lifetime mood episode occurring before age 20 years. Binge eating behavior was defined on the basis of affirmative responses to items 5 and 6 of the Eating Disorder Diagnostic Scale (EDDS) which assess experiences of losing control while eating an unusually large amount of food (Stice et al., 2000). Height and body weight were measured at the time of enrollment to calculate body mass index (BMI, kg/m^2). Obesity was defined as having a BMI $\geq 30 \text{ kg}/\text{m}^2$.

Frequency distributions and summary statistics were computed as proportions for categorical variables and as means with standard deviations for continuous variables. Demographic and clinical variables were compared between persons with and those without at least one self-reported lifetime suicide attempt using logistic regression. Interactions between these variables and bipolar disorder subtype (BD-I vs. BD-II) and sex were also tested. Gradient boosting machine (GBM) models were used to quantify the relative influence (RI) of study variables on the risk of lifetime attempted suicide in presence of the other variables, both overall and by bipolar subtype. GBM modeling is a non-parametric machine learning approach centered on enhancing prediction by combining information from multiple variables that may not be significant individually, but together may be highly informative (Atkinson et al., 2012). GBM has important advantages over conventional logistic regression, including the ability to fit complex (non-linear) relationships, reduced sensitivity to the effects of outliers, and no need for prior variable transformations (Elith et al., 2008). Specifically, GBM modeling was used to build multivariable prediction models by incorporating all of the variables without variable selection. The RI of a given variable is a measure of its importance, relative to that of other variables, in the model prediction process. Each variable's RI is estimated in the context of a model that includes all of the other variables. Therefore, the measure of the effect of each variable is adjusted for the effects of the other variables. For this analysis, the RI value of a given variable was expressed as the percentage of the total risk that was explained by the modeled predictors. The GBM models were fit with 8000 trees and 5 cross validation folds, with a learning rate of 1000 and allowing up to 3-way interactions. The GBM approach does not assess whether independent effects are significant in a traditional statistical sense, i.e., using p-values. Therefore, we also modeled the effects of the same demographic and clinical variables on the risk of lifetime attempted suicide using traditional logistic regression models. To assess whether the effects of a particular variable differed across groups, we used interaction terms for bipolar disorder subtype and sex. Statistical analyses were performed using the R free statistical software (<http://cran.r-project.org>) and the *gbm* package.

3. Results

Demographic and clinical characteristics by suicide attempt status, overall and by bipolar subtype, are presented in Tables 1, 2, respectively. A total of 1465 individuals were enrolled at time of analysis, including 1017 (69.4%) persons with BD-I and 448 (30.6%) with BD-II. The cohort was predominantly female (60.8%), middle-aged (mean age 42 yrs.), and Caucasian (91.4%). Of the 1465 participants, a total of 469 (32.0%) reported having at least one lifetime suicide attempt. Lifetime suicide attempt rates were higher in women than men (38.4% vs. 22.1%, $p < 0.0001$), and in BD-I than BD-II patients (34.0% vs. 27.5%, $p = 0.02$).

As shown in Table 1, female sex; bipolar I subtype; binge eating behavior; comorbid anxiety disorders, alcohol abuse/dependence, nicotine dependence, other substance abuse/dependence, and eating disorders; lifetime history of rapid cycling, cycle acceleration, and increased mood episode severity over time; and early age of onset were associated with lifetime suicide attempt in the entire cohort. In general, these same factors were also associated with lifetime suicide attempt separately within subgroups of participants with BD-I and BD-II (Table 2). However, significant evidence of association of attempted suicide with mean age at cohort entry, early age of onset, and cycle acceleration was only observed in the subset of persons with BD-I. Binge eating behavior and comorbid binge eating disorder were significantly associated with attempted suicide only in the subset of persons with BD-II disorder, although comorbid bulimia nervosa was a significant predictor of attempted suicide in persons with BD-I and BD-II.

There were no significant interactions between any of the predictors of attempted suicide from Table 1 and bipolar disorder subtype,

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