



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,

Table 1
Demographic and clinical characteristics and their relationship with attempted suicide.

	Suicide attempts		OR (95% CI)	p-value	BP type	Sex
	None N = 996	1 or more N = 469			interaction p-value ^a	Interaction p-value ^b
Age, yrs., mean (SD)	43.7 (15.8)	40.7 (12.8)	0.99 (0.98, 0.99)	< 0.001	0.20	0.90
Female sex	548 (55.0%)	342 (72.9%)	2.20 (1.73, 2.80)	< 0.001	0.55	–
Obesity ^c	390 (41.9%)	213 (48.6%)	1.32 (1.05, 1.65)	0.02	0.56	0.98
Bipolar I subtype	671 (67.4%)	346 (73.8%)	1.36 (1.07, 1.74)	0.02	–	0.55
Rapid cycling ^d	471 (47.6%)	296 (63.8%)	1.94 (1.55, 2.44)	< 0.001	0.24	0.005
Cycle acceleration ^d	243 (24.6%)	149 (32.3%)	1.46 (1.15, 1.86)	0.002	0.66	0.72
Early age of onset ^e	185 (19.7%)	107 (24.7%)	1.34 (1.02, 1.75)	0.04	0.63	0.14
Any anxiety disorder	579 (58.9%)	345 (74.4%)	2.02 (1.59, 2.58)	< 0.001	0.49	0.34
Increased severity ^f	302 (30.6%)	202 (43.6%)	1.76 (1.40, 2.21)	< 0.001	0.83	0.95
Nicotine dependence ^g	348 (35.8%)	224 (49.1%)	1.73 (1.38, 2.17)	< 0.001	0.60	0.99
Alcohol dep./abuse ^g	346 (35.4%)	221 (48.6%)	1.72 (1.37, 2.16)	< 0.001	0.81	0.30
Other substance abuse ^g	229 (24.4%)	153 (34.0%)	1.59 (1.25, 2.04)	< 0.001	0.41	0.82
Bulimia nervosa	125 (16.4%)	85 (25.1%)	1.71 (1.25, 2.33)	< 0.001	0.20	0.56
Binge eating behavior ^h	223 (27.5%)	128 (36.2%)	1.50 (1.15, 1.95)	0.003	0.23	0.45
Binge eating disorder	190 (23.4%)	111 (31.4%)	1.50 (1.14, 1.98)	0.004	0.33	0.73
Any eating disorder	293 (29.6%)	188 (40.3%)	1.60 (1.27, 2.02)	< 0.001	0.26	0.82

All values are N (%) unless otherwise specified.

^a A significant interaction indicates that the effect of the variable under examination for predicting attempted suicide differs significantly between subgroups with bipolar I vs. II disorder (BP type).

^b A significant interaction indicates that the effect of the variable under examination for predicting attempted suicide differs significantly between men and women.

^c Obesity was defined as having a body mass index (BMI) ≥ 30 kg/m².

^d Refers to having a lifetime history of self-reported rapid cycling or cycle acceleration, the latter defined as de-creases in inter-episode duration over time.

^e Early age of onset was defined as the reported onset of the first lifetime mood episode occurring before age 20 yrs.

^f Refers to self-reported increases in mood episode severity over time.

^g Substance use disorders in our study included DSM-IV-TR-defined alcohol abuse/dependence, nicotine dependence, and other substance abuse/dependence.

^h Binge eating behavior was defined on the basis of affirmative responses to items 5 and 6 on the Eating Disorder Diagnostic Scale.

suggesting that the effects of these variables for predicting attempted suicide did not differ significantly between individuals with BD-I vs. BD-II. There was a significant interaction between lifetime history of rapid cycling and sex when predicting the risk of attempted suicide in the overall cohort. For men, the odds of history of attempted suicide were 3 times higher among those with lifetime rapid cycling history (OR 3.06, 95% CI 2.01–4.68), whereas in women, those with a lifetime

rapid cycling history had odds of attempted suicide nearly 1.5-times more, as compared with persons without a lifetime history of rapid cycling (OR 1.48, 95% CI 1.12–2.00). The interaction between rapid cycling and sex was significant in persons with BD-I ($p = 0.03$), and nearly significant for those with BD-II ($p = 0.06$).

As shown in Table 3, the most influential variables on the risk of attempted suicide were female sex, lifetime history of rapid cycling,

Table 2
Demographic and clinical characteristics and their relationship with attempted suicide, by bipolar subtype.

	Bipolar I disorder Suicide attempts		OR (95% CI)	p-value	Bipolar II disorder Suicide attempts		OR (95% CI)	p-value
	None N = 671	1 or more N = 346			None N = 325	1 or more N = 123		
Age, yrs., mean (SD)	44.3 (16.0)	40.6 (12.9)	0.98 (0.98, 0.99)	< 0.001	42.3 (15.4)	41.0 (12.6)	0.99 (0.98, 1.01)	0.41
Female sex	352 (52.5%)	244 (70.5%)	2.17 (1.64, 2.86)	< 0.001	196 (60.3%)	98 (79.7%)	2.58 (1.58, 4.22)	< 0.001
Obesity ^a	266 (42.4%)	153 (48.1%)	1.26 (0.96, 1.65)	0.10	124 (40.7%)	60 (50.0%)	1.46 (0.96, 2.23)	0.08
Rapid cycling ^{b,*}	288 (43.2%)	214 (62.4%)	2.18 (1.67, 2.85)	< 0.001	183 (56.7%)	82 (67.8%)	1.61 (1.04, 2.50)	0.03
Cycle acceleration ^b	152 (22.9%)	107 (31.4%)	1.54 (1.15, 2.06)	0.004	91 (28.3%)	42 (35.0%)	1.37 (0.87, 2.14)	0.17
Any anxiety disorder	388 (58.9%)	256 (74.6%)	2.06 (1.54, 2.74)	< 0.001	191 (59.0%)	89 (73.6%)	1.94 (1.22, 3.07)	0.005
Early age of onset ^c	134 (21.1%)	85 (26.7%)	1.37 (1.00, 1.87)	0.05	51 (16.8%)	22 (19.1%)	1.17 (0.67, 2.03)	0.58
Increased severity ^d	183 (27.5%)	143 (41.9%)	1.91 (1.45, 2.51)	< 0.001	119 (37.0%)	59 (48.4%)	1.60 (1.05, 2.43)	0.03
Nicotine dependence ^e	234 (35.7%)	168 (49.9%)	1.79 (1.37, 2.34)	< 0.001	114 (36.2%)	56 (47.1%)	1.57 (1.02, 2.40)	0.04
Alcohol dep./abuse ^e	237 (36.0%)	163 (48.7%)	1.69 (1.29, 2.20)	0.001	109 (34.3%)	58 (48.3%)	1.79 (1.17, 2.75)	0.007
Other substance abuse ^e	150 (24.1%)	107 (32.3%)	1.50 (1.12, 2.02)	0.007	79 (25.1%)	46 (38.7%)	1.88 (1.20, 2.95)	0.006
Bulimia nervosa	82 (17.2%)	55 (23.4%)	1.48 (1.01, 2.17)	< 0.05	43 (15.1%)	30 (28.9%)	2.27 (1.33, 3.88)	0.003
Binge eating behavior ^f	136 (26.8%)	79 (32.9%)	1.34 (0.96, 1.87)	0.09	87 (28.5%)	49 (43.0%)	1.90 (1.21, 2.95)	0.005
Binge eating disorder	112 (22.1%)	67 (28.0%)	1.37 (0.97, 1.95)	0.08	78 (25.6%)	44 (38.6%)	1.83 (1.16, 2.89)	0.01
Any eating disorder	184 (27.5%)	126 (36.5%)	1.51 (1.15, 2.00)	0.003	109 (33.9%)	62 (50.8%)	2.02 (1.32, 3.08)	0.001

All values are N (%) unless otherwise specified.

^a Obesity was defined as having a body mass index (BMI) ≥ 30 kg/m².

^b Refers to having a lifetime history of self-reported rapid cycling or cycle acceleration, the latter defined as decreases in inter-episode duration over time.

^c Early age of onset was defined as the reported onset of the first lifetime mood episode occurring before age 20 yrs.

^d Refers to self-reported increases in mood episode severity over time.

^e Substance use disorders in our study included DSM-IV-TR-defined alcohol abuse/dependence, nicotine dependence, and other substance abuse/dependence.

^f Binge eating behavior was defined on the basis of affirmative responses to items 5 and 6 of the Eating Disorder Diagnostic Scale.

* Rapid cycling x sex interaction was significant ($p = 0.03$) for participants with bipolar I disorder, and was nearly significant ($p = 0.06$) for those with bipolar II disorder.

Table 3
Relative influence (RI) of demographic and clinical characteristics on the risk for attempted suicide, overall and by bipolar subtype.

Variable	Overall RI (%)	Bipolar I disorder RI (%)	Bipolar II disorder RI (%)
Sex	11.11	9.17	9.60
Rapid cycling	10.96	13.29	9.61
Nicotine dependence ^a	9.90	12.73	6.79
Increased severity ^b	9.82	10.05	9.40
Bipolar subtype	8.19	–	–
Early age of onset ^c	7.49	9.08	3.54
Any anxiety disorder	7.35	9.10	6.15
Binge eating disorder	6.16	4.80	10.33
Alcohol dep./abuse ^a	5.78	4.69	9.48
Binge eating behavior ^d	5.77	6.07	9.12
Other substance abuse ^a	4.88	5.00	6.43
Obesity ^e	4.51	5.87	6.36
Age > 42yrs. at enrollment	4.32	5.90	6.65
Cycle acceleration ^f	3.76	4.27	6.55

^a Substance use disorders in our study included DSM-IV-TR-defined alcohol abuse/dependence, nicotine dependence, and other sub-stance abuse/dependence.

^b Refers to self-reported increases in mood episode severity over time.

^c Early age of onset was defined as the reported onset of the first life-time mood episode occurring before age 20 yrs.

^d Binge eating behavior was defined on the basis of affirmative responses to items 5 and 6 of the Eating Disorder Diagnostic Scale.

^e Obesity was defined as having a body mass index (BMI) ≥ 30 kg/m².

^f Refers to having a lifetime history of cycle acceleration, defined as decreases in inter-episode duration over time.

comorbid nicotine dependence, increased mood episode severity over time, and bipolar disorder subtype in the overall cohort. There were generally similar findings for BD-I and BD-II subjects separately

4. Discussion

In this large cross-sectional cohort of adults with BD-I or BD-II, nearly one-third of patients reported having at least one lifetime suicide attempt. Rates of lifetime attempted suicide were higher in women than men, and in patients with BD-I than BD-II. Lifetime attempted suicide was associated with female sex, bipolar I subtype, binge eating behavior, psychiatric and substance use disorder comorbidities, a lifetime history of rapid cycling and other indicators of adverse illness course (including cycle acceleration and increased mood episode severity over time), and early age of bipolar illness onset in the entire cohort. There was some variation in the rank-ordering of demographic and clinical risk factors in terms of their relative influence on the risk of attempted suicide between patients with BD-I and BD-II. However, these differences were modest, and there was substantial overlap of suicide risk factors between BD-I and BD-II subgroups. Notably, rapid cycling was a particularly strong risk factor for attempted suicide in men with BD-I.

Our results are broadly consistent with a systematic review of 141 observational studies of risk factors for suicide in patients with bipolar disorders (Schaffer et al., 2015b). In that report, female sex, younger age of illness onset, and psychiatric comorbidity were each significantly associated with the risk of suicide attempts or death by suicide; however, in contrast with our findings, the majority of reviewed studies identified no significant differences in the rate of attempted suicide by bipolar subtype. Similar findings of non-statistically significant differences in suicide attempts by bipolar subtype were reported in another meta-analysis of 101 observational studies (Tondo et al., 2016). In our study, the absolute difference in lifetime suicide attempt rates between BD-I and BD-II subgroups was modest (3.8%). In the context of the broader literature, our findings suggest that where significant differences in lifetime suicide attempt rates exist between BD-I and BD-II patients, these differences are likely to be small.

Our study was focused on finding differences in the influence of demographic and clinical factors on the risk of attempted suicide

between BD-I and BD-II subgroups. Very few studies have focused on examining such differences. Our findings are in agreement with those of a recently published cross-sectional study by Goffin and colleagues of 494 adults with BD-I and BD-II that showed similar rates of attempted suicide between these two groups (with slightly higher rates observed in BD-I patients), and strong associations between alcohol and other substance use disorder comorbidities with lifetime attempted suicide in both BD-I and BD-II subgroups (Goffin et al., 2016). Findings of a strong association between alcohol and substance use disorders regardless of bipolar subtype contrast with those of a smaller cross-sectional study of 138 adults with BD-I or BD-II (Sublette et al., 2009). In that report, substance use disorders were associated with suicide attempts in BD-I but not BD-II patients, although a small number of BD-II subjects ($n = 42$) may have resulted in limited statistical power for detecting such an association. Our report extends the existing literature by documenting a significant association between nicotine dependence and lifetime attempted suicide in BD-I and BD-II subgroups (Ducasse et al., 2015).

We were interested in examining the effects of comorbid eating disorders and anxiety disorders on the risk of attempted suicide in BD-I and BD-II subgroups, given the known associations between these comorbidities and attempted or completed suicide broadly (Kanwar et al., 2013; Preti et al., 2011), and in patients with bipolar disorders specifically (Schaffer et al., 2015c; McElroy et al., 2016, 2011). In the Goffin study, attempted suicide rates were significantly higher in persons with comorbid eating disorders and anxiety disorders than those without these comorbid disorders in BD-I but not BD-II patients (Goffin et al., 2016). By contrast, comorbid eating disorders and anxiety disorders were associated with lifetime attempted suicide in both BD-I and BD-II subgroups in our cohort.

Suicide attempt rates differ by specific eating disorders (Kanwar et al., 2013), and the prevalence of specific eating disorders may vary by bipolar subtype (McElroy et al., 2005). We thus examined the associations between specific eating disorders and binge eating behavior, a possible indicator of impulsivity and suicidal behavior in patients with eating disorders (Foulon et al., 2007), on the risk of attempted suicide in BD-I and BD-II patients. In our study, bulimia nervosa was associated with attempted suicide in both BD-I and BD-II patients; binge eating disorder and binge eating behavior were both significantly associated with attempted suicide in BD-II patients, whereas weaker, trend-level associations between binge eating disorder and binge eating behavior and attempted suicide were observed in BD-I patients.

In our study, obesity had a very weak but statistically significant association with attempted suicide in the cohort as a whole. However, there was no significant obesity x bipolar subtype interaction effect. A relationship between obesity and heightened risk for suicide has been reported previously (Pompili et al., 2006). However, the relationship between obesity and death by suicide is complex. A recent meta-analysis of 38 observational studies suggested an inverse association between BMI and completed suicide (Perera et al., 2016), though a qualitative review of the same evidence highlighted methodological limitations and conflicting results across individual studies, making it difficult to draw firm conclusions regarding an association between BMI and suicide. Obesity was significantly associated with greater depressive symptom burden and lifetime suicide attempt risk among 1600 patients with bipolar disorders who participated in Wave 1 and Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions with diagnosed bipolar disorder (Goldstein et al., 2013). However, these differences were no longer statistically significant after adjusting for demographic variables. Obesity was independently associated with twice the risk of lifetime suicide attempts, as compared with non-obese persons, in a smaller cohort study of 255 outpatients with bipolar disorders (Gomes et al., 2010). Additional studies on a possible moderating role of obesity on risk of attempted suicide in patients with BD-I and BD-II are needed.

Our analyses also focused on the impact of self-reported markers of adverse bipolar illness course (lifetime rapid cycling, cycle acceleration

and increased mood episode severity over time) on the risk of lifetime attempted suicide. In our study, all three markers of adverse bipolar illness course were associated with lifetime suicide attempt(s). In general, the observed effect sizes were stronger in BD-I than BD-II subjects. However, formal testing of interactions between these markers and bipolar subtype yielded non-significant findings. Our results are broadly consistent with those of Goffin and colleagues, who reported an association between having more frequent (≥ 10) lifetime mood episodes and suicide attempts in both BD-I and BD-II patients (Goffin et al., 2016). In the Goffin study, however, rapid cycling was not associated with attempted suicide in both BD-I and BD-II patients. To our knowledge, ours is the first study to investigate the relationship between lifetime suicide attempt history and self-reported cycle acceleration and increased mood episode severity over time in BD-I and BD-II patients. Additional studies of a possible moderating role of these and other markers of adverse bipolar illness course on the risk of attempted suicide in patients with BD-I and BD-II are needed.

Our main interest was to provide a broad, quantitative comparison of the RI of specific clinical and demographic factors on the risk of attempted suicide between BD-I and BD-II patients, using a gradient-boosted machines model (GBM). Using this approach, we found some differences in the rank-ordering of the most influential variables on attempted suicide between BD-I and BD-II groups, but these differences were small and of questionable significance in terms of risk prediction. Our results were in accord with the observed lack of significant interactions between individual variables and bipolar subtype using conventional logistic regression modeling in our study, and the results of a secondary analysis of data from the Jorvi Bipolar Study in which risk factors for suicide attempts were found to be non-identical, but highly-overlapping between BD-I and BD-II groups (Valtonen et al., 2005).

There are limitations to our approach to consider. Because current suicidality and psychosis (an index of illness severity) are likely to relate to past suicidality, some bias may have been introduced by initially excluding actively psychotic or suicidal patients who required acute hospitalization from Biobank participation. Patients were eligible for Biobank participation after resolution of these concerns, which may have reduced the propensity for selection bias. However, the number of subjects that were excluded for these reasons was unavailable, thus limiting our ability to ascertain the magnitude of a possible effect. Although we examined the predictive effects of a large number of variables on the risk of attempted suicide, we did not collect data on other known risk factors for attempted suicide in bipolar patients, such as residual depressive symptom burden and family history of completed or attempted suicide. The interpretability of our findings may be limited by the cross-sectional design of our study, and our reliance on self-report for defining suicide attempt status and a number of predictor variables—including markers of adverse bipolar illness course such as rapid cycling, cycle acceleration and increased mood episode severity over time. In particular, the retrospective ascertainment of these clinical variables may limit their reliability. Cohort members were recruited from a mood disorders specialty clinic nested within an academic department of psychiatry, which may limit the generalizability of our findings. These limitations are balanced by notable strengths that included a robust sample size and detailed clinical phenotyping of all cohort members.

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