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Brief Report

Sex differences in the risk of rapid cycling and other indicators of adverse illness course in patients with bipolar I and II disorder

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Objectives: To examine the independent effects of sex on the risk of rapid cycling and other indicators of adverse illness course in patients with bipolar I disorder (BP-I) or bipolar II disorder (BP-II).

Methods: We analyzed data from the first 1,225 patients enrolled in the Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder. Demographic and clinical variables were ascertained using standardized questionnaires; height and weight were assessed to determine body mass index (BMI). Rates of rapid cycling, cycle acceleration, and increased severity of mood episodes over time were compared between women and men overall and within subgroups defined by bipolar disorder subtype (BP-I or BP-II). Multiple logistic regression analysis was used to assess the independent effect of sex on the risk of these indicators of adverse illness course.

Results: Women had significantly higher rates of rapid cycling than men. Overall rates of rapid cycling were higher in patients with BP-II than BP-I; and sex differences in the rate of rapid cycling were more pronounced in patients with BP-II than BP-I, although the power to detect statistically significant differences was reduced due to the lower sample size of subjects with BP-II. Female sex was a significant predictor of rapid cycling, cycle acceleration, and increased severity of mood episodes over time after adjusting for age, bipolar disorder subtype, BMI, having any comorbid psychiatric disorder, and current antidepressant use.

Conclusions: Female sex was associated with significantly higher risk of rapid cycling, cycle acceleration, and increased severity of mood episodes over time in a sample of 1,225 patients with bipolar disorders.

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There is evidence for sex differences in a number of important clinical features of bipolar disorder. Clinical data have suggested that women with bipolar disorder, in comparison to men with bipolar disorder, have higher rates of associated illness features of bipolar II disorder (BP-II), rapid cycling and antidepressant-associated rapid cycling, and higher rates of comorbid anxiety and

eating disorders—two conditions that predict rapid cycling and a more severe bipolar course of illness (1–6).

However, a meta-analysis that evaluated 10 studies published between 1977 and 1988 concluded that rapid cycling was moderately but inconsistently associated with female sex (7), and some recent studies have not confirmed earlier observations of higher rates of rapid cycling and illness course in women with bipolar disorder (8–11). As such, there is still considerable uncertainty regarding the relationship between sex and risk of rapid cycling and other indicators of adverse illness course in patients with bipolar disorders, independent of known risk factors. Additionally, very few studies have examined these sex differences by bipolar disorder subtype.

To address these uncertainties, we conducted an analysis of data from the Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder. Our objective was to examine the relationship between sex and the lifetime risk of rapid cycling and other markers of adverse illness course in a large, well-characterized cohort of patients with bipolar I disorder (BP-I) or BP-II.

Methods

The Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder (referred to hereafter as the Bipolar Biobank) was initiated in 2009 as a collaboration between the Mayo Clinic, the Lindner Center of HOPE/University of Cincinnati, and the University of Minnesota to identify novel biomarkers for bipolar disorder disease risk and treatment response. Details regarding the Bipolar Biobank procedures for subject recruitment, the obtaining of informed consent, clinical phenotyping, and biospecimen collection and processing have been published elsewhere (12).

Data for this study were derived from the first 1,225 patients enrolled in the Bipolar Biobank. Eligible participants were adults (age $\geq$ 18 years) with clinical diagnoses of BP-I or BP-II who were able to provide valid informed consent. Actively psychotic or suicidal patients were excluded from participation.

The Bipolar Biobank protocol included a detailed baseline evaluation, conducted over several visits. The Structured Clinical Interview for the DSM-IV (SCID) was completed for all participants to confirm the clinical diagnosis of bipolar disorder, and to establish illness characteristics (such as bipolar disorder subtype and age at onset) and comorbid Axis I disorder diagnoses. The baseline evaluation also included completion of structured patient-rated and clinician-administered questionnaires to determine demographic variables (age at Bipolar Biobank enrollment, sex, race, Hispanic ethnicity, employment status, and education level) and additional bipolar illness characteristics. The latter included lifetime history of rapid cycling (at least four mood episodes in a given calendar year), cycle acceleration (self-reported decrease in inter-episode duration over time), changes in the severity of mood episodes over time (self-reported increase or decrease in episode severity), lifetime psychosis, lifetime suicidality, comorbid psychiatric and substance use disorder diagnoses, and level of inter-episode functioning. Psychosis was positive if the patient had a lifetime history of hallucinations or delusions during a depressive or manic episode. Suicidality was positive if the patient had one or more lifetime suicide attempts requiring medical intervention, and was further classified according to lifetime number of attempts. Age of bipolar disorder onset was collected using pre-defined age strata (<20, 20–49, 50–64, and 65–79 years). Height and body weight measurements were obtained at the time of enrollment to calculate body mass index (BMI; kg/m^2).

Frequency distributions and summary statistics were computed as proportions for categorical variables and as means with standard deviations (SDs) for continuous measures. Demographic and clinical variables, and frequencies of lifetime rapid cycling, cycle acceleration, and increasing mood episode severity over time, were compared between women and men overall, and within subgroups defined by bipolar disorder subtype (BP-I or BP-II) using chi-square/Fisher's exact tests for categorical data and *t*-tests/Wilcoxon rank sum tests for continuous data. The independent effects of sex on the risk of rapid cycling, cycle acceleration, and increasing mood episode severity over time were examined using multiple logistic regression models adjusted for age at enrollment, bipolar disorder subtype, BMI at enrollment, presence of any comorbid psychiatric or substance use disorder diagnosis, and current antidepressant use. Covariates were selected based on prior evidence for their association with rapid cycling or worse bipolar disorder illness course (2, 13–17).

Results

Demographic characteristics by sex and bipolar disorder subtype are presented in Table 1. A total of 1,225 persons with bipolar disorder were enrolled at the time of analysis (60.7% women), including 863 subjects with BP-I (58.3% women) and 362 with BP-II (66.6% women). The sample

Table 1. Demographic characteristics by sex and bipolar disorder subtype

	Total			Bipolar I disorder			Bipolar II disorder		
	Male (n = 481) n (%)	Female (n = 744) n (%)	p-value	Male (n = 360) n (%)	Female (n = 503) n (%)	p-value	Male (n = 121) n (%)	Female (n = 241) n (%)	p-value
Total, n (%)	481 (39.3)	744 (60.7)	0.007[a]	360 (41.7)	503 (58.3)	–	121 (33.4)	241 (66.6)	–
Race[a]									
Caucasian	421 (90.0)	663 (90.7)	0.67	312 (89.1)	445 (90.5)	0.54	109 (92.4)	218 (91.2)	0.71
African American	12 (2.6)	19 (2.6)		10 (2.9)	12 (2.4)		2 (1.7)	7 (2.9)	
Asian	5 (1.1)	11 (1.5)		5 (1.4)	10 (2.0)		0 (0.0)	1 (0.4)	
Other/mixed[b]	30 (6.4)	38 (5.2)		23 (6.6)	25 (5.1)		7 (5.9)	13 (5.4)	
Hispanic ethnicity	14 (3.0)	16 (2.2)	0.38	10 (2.9)	11 (2.3)	0.57	4 (3.5)	5 (2.1)	0.482
Marital status									
Married[c]	223 (49.0)	339 (47.9)	0.71	157 (46.0)	216 (45.2)	0.06	66 (57.9)	123 (53.5)	0.44
Unmarried	232 (51.0)	369 (52.1)		184 (54.0)	262 (54.8)		48 (42.1)	107 (46.5)	
Employment status[d]									
Full-time	136 (32.8)	157 (23.3)	0.002	91 (29.4)	100 (22.0)	0.049	45 (42.9)	57 (25.9)	0.009
Part-time	69 (16.6)	142 (21.0)		50 (16.1)	92 (20.2)		19 (18.1)	50 (22.7)	
Unemployed	210 (50.6)	376 (55.7)		169 (54.5)	263 (57.8)		41 (39.0)	113 (51.4)	
Education level									
High school or less	66 (14.7)	113 (16.1)	0.51	49 (14.6)	75 (15.9)	0.62	17 (14.9)	38 (16.6)	0.70
Higher than high school	384 (85.3)	588 (83.9)		287 (85.4)	397 (84.1)		97 (85.1)	191 (83.4)	
Comorbid mental health condition	422 (88.7)	648 (88.4)	0.89	313 (88.2)	440 (88.7)	0.81	109 (90.1)	208 (87.8)	0.51
Comorbid substance use disorder	261 (55.4)	325 (45.0)	0.0004	192 (54.6)	228 (46.4)	0.02	69 (57.0)	97 (40.3)	0.004
Age at enrollment, years, mean ± SD	43.1 ± 15.8	42.2 ± 14.4	0.5	43.4 ± 15.8	42.5 ± 14.6	0.54	42.2 ± 15.6	41.5 ± 14.0	0.87

SD = standard deviation.
[a]Comparison of bipolar disorder type by gender.
[b]Caucasian versus all others collapsed comparison for p-values.
[c]Includes 'living with someone in a marriage-like relationship'.
[d]Some categories include individuals who selected multiple statuses. Dominant status was chosen.

was predominantly middle-aged, Caucasian, and educated beyond the level of high school graduate. No statistically significant differences in age at study enrollment, race, education level, marital or employment status, or presence of at least one comorbid mental health disorder diagnosis were observed between men and women. Men had significantly higher rates of substance use disorders than women in the overall sample, and in patients with BP-I and BP-II.

Differences in bipolar illness course by sex and bipolar disorder subtype based on univariate analyses are presented in Table 2. Women had significantly higher rates of rapid cycling [odds ratio (OR) = 1.36, p = 0.009] and self-reported cycle acceleration than men (OR = 1.64, p < 0.0001). Significant sex differences in rates of rapid cycling were observed in patients with BP-I (OR = 1.33, p = 0.04), but not BP-II (OR = 1.36, p = 0.18), whereas significant sex differences in self-reported cycle acceleration were observed regardless of bipolar disorder subtype. Women reported significantly higher rates of increased episode severity over time than did men in the overall sample (OR = 1.55, p = 0.0002), and in patients with BP-I, but not BP-II. Significantly higher rates of lifetime suicide attempts were observed in women than men, regardless of the bipolar subtype. There were no statistically significant sex differences with respect to age of bipolar disorder onset or lifetime occurrence of psychotic episodes (data not shown).

In multivariable analyses, female sex was associated with a significantly higher risk of rapid cycling [OR = 1.35, 95% confidence interval (CI): 1.05–1.73], self-reported cycle acceleration (OR = 1.58, 95% CI: 1.22–2.05), and increased mood episode severity over time (OR = 1.53, 95% CI: 1.19–1.96), in models adjusted for age and BMI at enrollment, bipolar disorder type, comorbid psychiatric disorder, and antidepressant use. The main results (women at higher risk for each outcome) were unchanged in multivariable sensitivity analyses that also adjusted for categorical age at bipolar illness onset (data not shown).

Discussion

To our knowledge, the present study represents the largest study to examine sex differences in the lifetime risk of rapid cycling and other indicators of adverse illness course in patients with BP-I or BP-II. The odds of rapid cycling were higher for women than for men, after adjusting for other risk factors. The adjusted odds of self-reported cycle acceleration and increased mood episode severity over time were also higher for women than for men. Although our overall sample size was large, our BP-II sample was much smaller than our BP-I sample, which may have limited our ability to detect subtle but important sex differences of interest in patients with BP-II. Our study employed a cross-sectional design, and there was no longitudinal follow-up. Instead, we used retrospective data collection methods to define rapid cycling and other bipolar disorder illness course measures. Although our multivariable modeling procedures accounted for important risk factors for rapid cycling and adverse illness course, we cannot exclude the possibility of residual confounding by other risk factors such as clinical or subclinical hypothyroidism.

Results of prior studies on the association between sex and rapid cycling are mixed (8–11, 18–25). Earlier studies did not control for most confounders, and were smaller (sample sizes varied between 42 and 434 persons) (18, 20–22, 24, 25). More recent studies were larger, and controlled for possible confounding factors including age, bipolar disorder subtype, comorbid medical disorders, comorbid psychiatric disorders, substance use, and antidepressant use. (8–11). Among them, the largest prospective study included 1,191 patients with bipolar disorder, and reported no significant difference in rates of rapid cycling between men and women over one year of follow-up (8). In that study, the observed rate of rapid cycling was much lower in the follow-up year (5% of patients) than in the year before study entry (32%). Similar findings were reported by others (24, 26). These results support the notion that rapid cycling may be a transitory phenomenon in the course of bipolar illness (27), which may explain some of the contradictory findings between studies. Our study, in contrast, investigated lifetime risk of rapid cycling. Therefore, potential bias owing to transience of rapid cycling status is less of a concern here.

There is still controversy regarding the effect of the interaction between sex and bipolar disorder subtype on the risk of rapid cycling (27). Female preponderance for rapid cycling was stronger for BP-I in some studies (19, 28, 29), although rapid cycling in BP-II is also strongly related to female sex (27). Overall, higher rapid cycling rates have been reported in BP-II than BP-I (2). In line with previous studies, we observed higher rates of rapid cycling in patients with BP-II than BP-I in our sample. Although sex differences in the rates of rapid cycling were pronounced in both patients with BP-I (51.7% versus 44.6% for women versus men, respectively; OR = 1.33) and those with BP-II (60.0% versus 52.5%, respectively; OR = 1.36), these differences were statistically significant only

Table 2. Bipolar illness onset and course characteristics and current medications by sex and bipolar disorder subtype

	Total			Bipolar I disorder			Bipolar II disorder		
	Male n (%)	Female n (%)	p-value	Male n (%)	Female n (%)	p-value	Male n (%)	Female n (%)	p-value
Rapid cycling[a]	221 (46.6)	398 (54.5)	0.009	158 (44.6)	257 (51.7)	0.04	63 (52.5)	141 (60.0)	0.18
Cycle acceleration[b]	96 (20.3)	218 (30.3)	0.0001	63 (17.8)	146 (29.9)	<0.0001	33 (27.5)	72 (31.2)	0.48
Increased severity	186 (39.2)	363 (50.1)	0.0002	133 (37.7)	242 (49.1)	0.001	53 (43.8)	121 (52.2)	0.14
Psychosis	202 (42.9)	304 (41.9)	0.74	189 (54.0)	274 (55.8)	0.60	13 (10.7)	30 (12.8)	0.57
Age at onset, years									
19 or younger	96 (21.5)	136 (19.8)	0.42	77 (23.2)	103 (22.0)	0.44	19 (16.7)	33 (15.1)	0.11
20–49	299 (67.0)	488 (70.9)		221 (66.6)	331 (70.6)		78 (68.4)	157 (71.7)	
50–64	43 (9.6)	57 (8.3)		29 (8.7)	28 (6.0)		14 (12.3)	29 (13.2)	
65–79	8 (1.8)	7 (1.0)		5 (1.5)	7 (1.5)		3 (2.6)	0 (0)	
Lifetime suicide attempt(s)									
0	365 (76.5)	441 (60.7)	<0.0001	264 (74.0)	283 (57.3)	<0.0001	101 (84.2)	158 (67.8)	0.001
1	57 (12.0)	140 (19.3)		47 (13.2)	105 (21.2)		10 (8.3)	35 (15.0)	
2 or more	55 (11.5)	146 (20.1)		46 (12.9)	106 (21.5)		9 (7.5)	40 (17.2)	
Inter-episode functioning									
Well or adequately	259 (53.9)	383 (53.1)	0.30	186 (52.7)	268 (54.6)	0.31	72 (60.3)	115 (47.7)	0.16
Some/great difficulty	150 (31.2)	220 (32.6)		114 (31.7)	139 (28.3)		36 (29.8)	81 (33.6)	
Continuous symptoms/poor functioning	62 (12.9)	119 (14.3)		50 (13.9)	84 (17.1)		12 (9.9)	35 (14.5)	
Current medications									
Any pharmaco-therapy	427 (92.8)	687 (95.8)	0.03	321 (92.5)	463 (94.7)	0.20	106 (93.8)	224 (98.3)	0.03
Any mood stabilizer	317 (75.8)	482 (77.9)	0.45	244 (74.9)	327 (75.2)	0.92	73 (79.4)	155 (84.2)	0.31
Any antidepressant	197 (41.0)	375 (50.4)	0.0003	132 (36.7)	239 (47.5)	0.003	65 (53.7)	136 (56.4)	0.15

[a]Refers to any lifetime history of rapid cycling defined as at least four mood episodes/year.
[b]Refers to patient reported decreasing inter-episode duration.

in the larger subset of patients with BP-I; likely, we were under-powered to detect such a difference in the smaller sample of patients with BP-II.

Our bipolar disorder questionnaires included items that assessed lifetime self-reported cycle acceleration and increased episode severity over time, which are important self-reported measures of adverse illness course (30). In our sample, women reported more cycle acceleration and higher rates of increased episode severity over time than men. Whereas significant sex differences in cycle acceleration were observed regardless of bipolar disorder subtype, a significant sex difference in increased episode severity over time was observed in patients with BP-I but not BP-II. Others have reported a significant association between cycle acceleration and female sex (30–32), which may be tied to higher risk of rapid cycling in women than men. To our knowledge, this is the first study to investigate sex differences with regard to increased self-reported episode severity over time.

We explored potential sex differences in several risk factors for rapid cycling and adverse bipolar illness course. It has been suggested that rapid cycling patients tend to have a younger age of illness onset (26); however, we did not find any significant differences between men and women with respect to self-reported age of bipolar disorder onset, in line with other clinical studies (9, 10, 33–35). Unfortunately, Bipolar Biobank data on the age of illness onset were categorized into strata, not given as a continuous variable, which is a limitation of our study. We found no significant sex differences in lifetime occurrence of psychotic episodes. Our results contrast with those of prior studies that reported higher rates of lifetime psychosis among men (36, 37) or among women (38) with bipolar disorders. No studies, including ours, have compared the number of psychotic episodes in male and female bipolar disorder patients. Higher suicide attempt rates in women with bipolar disorder have been reported previously (39, 40), and our findings were confirmatory in both the overall sample and in patients with BP-I and BP-II separately. Still, not all studies have found significant sex differences with regard to suicidal behaviors in patients with bipolar disorders (10, 23).

Antidepressants have been inconsistently associated with increased risk of precipitating polar mood switching and rapid cycling (41, 42). Some prospective studies have linked antidepressant use and rapid cycling (8), while others have failed to demonstrate an association between antidepressant use and onset of rapid cycling or the resolution of rapid cycling in association with antidepressant discontinuation (26). Given that a significantly higher proportion of women were taking antidepressants than men in our cohort and that antidepressants may cause destabilization of mood in at least some patients with bipolar disorders, our multivariable analyses were adjusted for current antidepressant use.

In conclusion, female sex was associated with significantly higher risk of rapid cycling, cycle acceleration, and increased severity of mood episodes over time in a sample of 1,225 patients with bipolar disorders, independent of several known risk factors. Larger prospective studies of men and women with bipolar I or II disorders are needed to more clearly define the longitudinal impact of sex on bipolar illness course, and to examine potential sex-specific moderators of adverse disease course.

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Disclosures

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