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CLINICAL FEATURES OF BIPOLAR DISORDER COMORBID WITH ANXIETY DISORDERS DIFFER BETWEEN MEN AND WOMEN

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Abstract

Background—Anxiety disorders are commonly comorbid with bipolar disorder (BP) and may worsen course of illness, but differential impact of specific anxiety disorders in men and women remains unknown.

Methods—We measured the impact of comorbid panic disorder (PD), social phobia, specific phobia, and obsessive-compulsive disorder (OCD) in 460 women and 276 men with Bipolar I Disorder (BPI) or schizoaffective disorder, bipolar type from the National Institute of Mental Health Bipolar Genetics Initiative. We compared clinical characteristics in BP with and without each anxiety disorder in men and women separately correcting for family relatedness.

Results—Comorbid PD, OCD, and specific phobia were more common in women with BP than men. Comorbid social phobia correlated with increased risk of alcohol abuse in BP women, but not men. Women with comorbid PD attended fewer years of school. Comorbidity with OCD was associated with earlier age at the onset of BP for both genders. Comorbid PD, OCD, and specific phobia were associated with more antidepressant trials in BP, across both genders, compared to BP patients without these anxiety disorders.

Conclusion—In BP, comorbid anxiety disorders are associated with increased risk for functional impairment, and women had differently associated risks than men. Clinicians should be aware of an increased risk for comorbid PD, OCD, and specific phobia in women with BP, and an increased risk of alcohol abuse in women with BD and comorbid social phobia.

Keywords

psychiatry; panic; obsessive-compulsive; social phobia; specific phobia; depression; mania; alcohol; female

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INTRODUCTION

Anxiety disorders are highly comorbid in bipolar disorder (BP), with studies in the National Institute of Mental Health (NIMH) Bipolar Genetics Initiative sample and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) cohort showing a higher incidence of anxiety disorders in patients with BP than in the general population.[1-6] In BP patients, comorbid anxiety disorders have been associated with higher BP symptom burden and worse severity of illness.[1,4,7,8] In the general population, anxiety disorders are more common in women than men, and have been shown to differentially affect work productivity in women when compared to men.[3] BP affects men and women at an equal rate,[4,9] however, given gender differences in the presentation of anxiety disorders, there may be specific features that characterize the association of anxiety disorders in BP women compared to BP men.

In a cross-sectional analysis of the first 500 patients entered into the STEP-BD cohort, an analysis of gender differences in BP highlighted that women were more likely than men to be diagnosed with posttraumatic stress disorder (PTSD), but not other anxiety disorders.[10] In a study examining the gender differences in the Stanley Foundation Bipolar Treatment Outcome Network, specific phobia, obsessive-compulsive disorder (OCD), and PTSD were more prevalent in women, but not panic disorder (PD), agoraphobia without panic, social phobia, or anxiety not otherwise specified.[11] Women with BP have also been found to exhibit increased risk for alcoholism and chronicity of depression, but whether these clinical correlates of BP in women relate to their increased risk for anxiety remains to be determined.

Recent cross-sectional studies have shown that anxiety disorder comorbidity affects the clinical presentation of BP, but a specific relationship by gender was not explored. Comorbid OCD was associated with a history of shorter periods of euthymia in the STEP-BD.[1] Several studies have reported OCD,[12,13] PD,[1] and social phobia to associate with more suicide attempts in BP,[1,14,15] although rates differ between studies. In the STEP-BD cohort, dimensional anxiety scores including worry, anxiety sensitivity, phobic avoidance, and panic frequency were linked to increased suicidal ideation and behavior.[16] Drug and alcohol dependence are also increased in the population of BP patients with anxiety; in the first 500 STEP-BD patients, having a comorbid anxiety disorder doubled the lifetime risk of alcohol abuse or dependence, and almost doubled the lifetime risk of substance abuse or dependence.[1] In a sample of BP adolescents, the number of comorbid anxiety disorders incrementally increased the risk for substance abuse.[14]

The relationship between comorbid anxiety disorders and BP has also been examined in prospective studies. In a study of 138 patients after a 3-year follow-up period, comorbid social phobia predicted a longer duration of mood symptoms, and greater illness severity when compared with the group of BP patients without anxiety.[17] A prospective study that followed the first 1,000 patients enrolled into the STEP-BD program for 1 year showed a loss of 29–30 days well for PD; and a loss of 34–44 days for social phobia and OCD.[7] A report of the Collaborative Depression Study describes the relationship between clinical outcome and anxiety disorder diagnoses and anxiety symptom clusters in 335 BP patients followed for 18.0 years. OCD was found to predict time in depressive episodes, whereas PD and phobias did not.[8]

The NIMH Bipolar Genetics Initiative dataset is a large, well-characterized dataset consisting of families and individuals with BP that includes prevalence of PD, OCD, social phobia, and specific phobia.[5] In a subset of BP families from this database, a specific genetic linkage pattern was described for PD.[18,19] Further, studies showed an association

between rapid mood switching and PD in families in this sample.[20,21] A recent study by Goes et al.[22] reports on the clinical characteristics and familial aggregation of anxiety disorders including PD, OCD, social phobia, and specific phobia in MDD (Major Depression Disorder) and BP families from sample, showing fewer years of education in PD, earlier age of first depression, higher number of depressive episodes, and an increased risk of suicide attempt across anxiety disorders. In that study, comorbid OCD associated with greater severity, the earliest age of onset for depression, the earliest age of treatment, and the highest number of depressive episodes.[22]

To further characterize the clinical features of BP and comorbid anxiety disorders in men and women, we queried the clinical features of patients with and without specific anxiety disorders in a sample of 736 participants diagnosed with BP I and schizoaffective disorder, BP type derived from the NIMH Bipolar Genetics Initiative. We examined clinical variables reflecting functional and clinical severity by gender, then identified the association of the clinical variable to the risk for each anxiety disorder (PD, OCD, social phobia, specific phobia) in men and women separately. With the exception of OCD, anxiety disorders are more common in women in the general population, and we hypothesized that BP in women would be associated with higher rates of comorbid anxiety disorders and that this anxiety would associate with more impairment in women than men.

METHODS

Gender differences in the prevalence and clinical correlates of four anxiety disorders (PD, OCD, social phobia, and specific phobia) were investigated in 736 individuals with BP, type I or schizoaffective disorder, bipolar type from the NIMH Bipolar Genetics Initiative. This population was recruited for a study of genetics, and clinical data were gathered using the Diagnostic Interview for Genetic Studies (DIGS).[23] In addition to the interview, medical records were obtained from inpatient and outpatient treatment whenever possible. A detailed description of methods of assessment and evaluation have been documented elsewhere.[24] Data were not collected on GAD (Generalized Anxiety Disorder), PTSD, agoraphobia without panic, and separation anxiety disorder. The prevalence of PD, OCD, social phobia, and specific phobia anxiety disorders and the number of comorbid anxiety disorders were compared between men and women using χ^2 analysis. Clinical variables were compared between genders using *t*-tests or Mann-Whitney U tests for continuous variables or χ^2 tests for dichotomous variables, as appropriate. Dichotomous clinical variables included alcohol abuse, alcohol dependence, marital status, sex, and suicide attempts (yes/no). Continuous clinical variables included age of BP onset, years of school, number of hospitalizations, number of manias, number of depressions, severity of depression, severity of mania, number of antidepressants tried, number of mood stabilizers tried, number of antipsychotics tried, number of sedative/hypnotics tried, and number of stimulants tried. The number of hypomanias was not included due to paucity of data. Quantification of severity was determined for the most severe, or most extreme, mood episode by the interviewer. Anchors for severity included (1) no impairment, (2) improvement in functioning, (3) impairment in functioning, or (4) incapacitation. Improvement in functioning was defined as an improvement in occupational or social functioning; improvement can be associated with hypomania. Impairment was defined as decreased functioning but not meeting criteria for incapacitation; incapacitation was defined as an inability to function at home, school, or work for 2 days in a row, hospitalization, ECT treatment, the presence of psychotic symptoms, or complete inability to carry on a conversation. Logistic regression models were built using the Generalized Estimating Equation (GEE) to control for familial relatedness.[25] Each model was controlled for age at interview. Separate models were built for PD, OCD, social phobia, and specific phobia. The comparison group included subjects without each specified anxiety disorder, but included those with other anxiety disorders. The

comparison groups were chosen this way to allow for detection of differences specific to each anxiety disorder studied. Predictors that showed significance difference between groups were included in a refined model, and goodness of fit was tested using the Quasi Likelihood under Independence (QIC) Model Criterion to determine the best fitting model. Models for PD, OCD, social phobia, and specific phobia were then created for males and females separately to determine the effect of sex on features of BP with and without anxiety disorders. Because there were only nine males with comorbid OCD in this sample, the number of clinical predictors was greater than the number of subjects resulting in insufficient statistical power; thus, the comparison of models by sex is not included for OCD.

RESULTS

CHARACTERISTICS OF THE POPULATION

This population of 736 individuals from the NIMH Bipolar Genetics Initiative represented 473 families. Almost two thirds of the sample was female (62.5%); the average age at interview was 42 ± 12 years, and the average age did not significantly differ between men and women. One third of the population ($N = 242$) had one or more of the four comorbid anxiety disorders—OCD, PD with and without agoraphobia, social phobia, or specific phobia. One quarter of the population had one of these anxiety disorders, and 10% had more than one. Female subjects with BP were more likely than males to have one, two, three, or four comorbid anxiety disorders ($\chi^2 = 16.9$, $df = 4$, $P = .002$). Table 1 summarizes the clinical characteristics of the population by gender. A number of other clinical characteristics also differed by gender: alcohol dependence was more common in men than women, whereas suicide attempts, number of depressive episodes, number of antidepressant treatments, and number of sedative/hypnotic treatments were greater in women than men.

PANIC DISORDER

The prevalence of comorbid PD in the total sample was 25%. Three-quarters of the subjects with BP and PD were women, and the prevalence of comorbid PD was 30% in women and 17% in men ($\chi^2 = 14.5$, df 1, $P = 1.4 \times 10^{-4}$). The average age at onset of PD was 24 ± 12 years in the combined sample, and did not differ between men and women (Table 1). Women are more likely to have comorbid PD than men ($OR = 1.8$, $P = .006$, 95% CI: 1.2–2.6). Women with BP and PD were more likely to have fewer years of schooling and to have used more antidepressants than women with BP without PD, although this was not true for men with BP and PD (Table 2). BP subjects with PD were more likely to have less severe mania than those subjects with BP without PD (Table 2).

Results of comparisons between BP with PD and BP without PD were similar in men and women for alcohol abuse, alcohol dependence, marital status, suicide attempts, age of BP onset, number of hospitalizations, number of manias, number of depressions, severity of depression, number of mood stabilizers tried, number of antipsychotics tried, number of sedative/hypnotics tried, or number of stimulants tried.

OBSESSIVE-COMPULSIVE DISORDER

The prevalence of comorbid OCD in the sample was 6%, and 80% of the subjects with BP and OCD were women. The prevalence of OCD was significantly greater in women (7%) than in men (3%; $\chi^2 = 4.9$, $df = 1$, $P = .027$). The average age at onset of OCD was 16.2 ± 6.5 years for men and 23.0 ± 13.4 years for women, which were significantly different (Table 1). For both male and female patients, comorbid OCD was associated with lower age at onset of BP and more antidepressant treatment than in those without OCD (Table 2).

Other clinical covariates including alcohol abuse, alcohol dependence, marital status, suicide attempts, years of school, number of hospitalizations, number of manias, number of depressions, severity of depression, severity of mania, number of mood stabilizers tried, number of antipsychotics tried, number of sedative/hypnotics tried, and number of stimulants tried were not significantly different between those with BP and comorbid OCD and BP without OCD. We choose not to do an analysis of BP comorbid with OCD by gender because only a few men with comorbid BP and OCD were observed in our sample.

SOCIAL PHOBIA

Comorbid social phobia was prevalent at a rate of 8%, and 63% of those with social phobia and BP were women. The prevalence of social phobia did not differ significantly between men and women ($\chi^2 = .033$, $df = 1$, $P = .856$). The average age at onset of social phobia was 13 ± 8 years and did not differ significantly between men and women (Table 1). Women with BP and social phobia were four times more likely than women without comorbid social phobia to have comorbid alcohol abuse. Men with social phobia were not more likely to have alcohol abuse than men without comorbid social phobia. Other clinical characteristics including alcohol dependence, marital status, suicide attempts, age of BP onset, years of school, number of hospitalizations, number of manias, number of depressions, severity of depression, severity of mania, number of antidepressants tried, number of mood stabilizers tried, number of antipsychotics tried, number of sedative/hypnotics tried, and number of stimulants tried were not significantly different between those with BP and social phobia and those without social phobia, and results of these comparisons did not significantly differ between men and women.

SPECIFIC PHOBIA

Comorbid specific phobia was prevalent at a rate of 8%, and 81% of the subjects with BP and specific phobia were women. Prevalence of comorbid specific phobia differed significantly between women (10%) and men (4%; $\chi^2 = 8.6$, $df = 1$, $P = .005$). The average age at onset of specific phobia was 11 ± 8 years, and was significantly less in men (7.3 ± 4.4) than in women (12.0 ± 8.8). Women with comorbid specific phobia were more likely to have had more treatment with antidepressants and were less likely to have had sedative hypnotics than BP subjects without social phobia (Table 2). Other clinical characteristics including alcohol abuse, alcohol dependence, marital status, suicide attempts, age of BP onset, years of school, number of hospitalizations, number of manias, number of depressions, severity of depression, severity of mania, number of mood stabilizers tried, number of antipsychotics tried, number of sedative/hypnotics tried, and number of stimulants tried were not significantly different between those with BP and specific phobia and those without specific phobia, and did not significantly differ between men and women.

DISCUSSION

We examined differences in the prevalence of comorbid PD, OCD, social phobia, and specific phobia between men and women with BP, and compared differences in clinical features of BP with and without each comorbid anxiety disorder in men and women. Female gender increased the odds of having comorbid PD, OCD, and specific phobia, but not social phobia, consistent with increased rates of anxiety disorders in women in the general population.[3,26] Studies of gender differences in BP have shown variable results with regard to increased rates of anxiety disorders; Altshuler et al.[11] showed elevated rates in women of specific phobia and OCD but not PD or social phobia; and Baldassano et al.[10] showed no increase in PD, social phobia, or OCD in women. One difference in our study is that the sample consisted of families with BP; PD and OCD were shown in this sample to aggregate

in families,[22] and women with familial BP may be more prone to comorbid anxiety disorders.

Increased rates of anxiety disorders in BP may be linked to an underlying predilection for trait anxiety, since high neuroticism has been linked to BP and predisposes to anxiety, particularly in women.[27-30] Neuroticism also predisposes to depression, however, we did not find an increase in number or severity of depressive episodes in this sample, consistent with the STEP-BD data.[10] This may be due to the retrospective nature of our data and quantifying depression by the number of episodes, as a prospective study has shown that women had no more episodes than men but had more depressive symptoms on follow-up.[11] However, although we also did not find a difference in severity of the worst depressive or manic episode by gender, this measurement does not give an indication of chronicity of the symptoms, and it is possible that such a measure would show a difference by gender.

Women in this sample demonstrated an elevated rate of alcohol abuse with respect to the general population, consistent with a number of studies.[10,31,32] In addition, women with comorbid social phobia demonstrated a four-fold increased risk for alcohol abuse, whereas risk was not increased by social phobia for men. The impulsivity seen in manic and hypomanic episodes may increase the likelihood of binge drinking in women with BP and social phobia, who may be particularly likely to use alcohol to facilitate social interaction. Understanding the interaction of these comorbidities will underscore the need for clinicians to be attentive to the possibility of binge drinking in women with BP and social phobia, increasing the likelihood of early intervention.

We find that patients with comorbid PD have fewer years of school, and this difference is significant in women but not men. Educational impairment in women with BP with comorbid PD could be driven by the onset of PD, since the age of onset of PD was in the early 20s; symptoms experienced prior to the onset of the full disorder could contribute to dropping out more frequently from school. Female patients with PD have been shown to have more respiratory symptoms than men, have abnormal respiratory physiology, and are more sensitive to CO_2 induction of panic attacks.[33,34] The type of PD found in women with BP may differ in severity from men and lead to more functional impairment.

OCD was associated with an earlier age at onset of BP, raising the concern that OCD itself or its treatment (e.g. with selective serotonin reuptake inhibitors) might induce mania in individuals with a BP diathesis. However, the average age at the onset of OCD was 2 years after the average age at onset of BP for the combined sample, so that most subjects in this sample would not have been treated for OCD prior to developing BP. The age of onset was significantly higher in women, and lower in men, however, the sample size for men with comorbid OCD was small and this difference could be skewed. In addition, comorbidity with OCD did not affect the age at the first treatment, which did not differ between men and women, thus it is unlikely the pharmacological intervention for OCD could have induced BP. Another possibility is that BP with comorbid OCD may be a unique, earlier occurring subtype with a common or overlapping biological etiology. For instance, striatal hyperactivity has been demonstrated in both OCD and BP raising the possibility of a common etiological basis.[35,36]

Comorbid social phobia and specific phobia preceded BP in subjects with both disorders, but was not associated with a lower age of onset of BP. Comorbid specific phobia was found to be present much earlier in men than women, but there were no other clinical characteristics that were more severe in the male patients with BP and specific phobia than

in the female patients. In fact, women with BP and specific phobia had a history of more treatments with antidepressants and sedative/hypnotics than men.

Despite the early age of onset of social phobia (13 years in our sample of BPI), age at the first psychiatric treatment was not significantly different between the individuals with social phobia and those without, indicating that social phobia was untreated prior to the development of mood symptoms, and that BP was not antidepressant driven. Comorbid social phobia was the only anxiety comorbidity investigated that did not have a predominance of antidepressant use in females, perhaps reflecting the equal gender distribution of comorbid social phobia. Given the prevalent comorbidity of social phobia and BP, and the fact that there were on average 9 years between the onset of social phobia and BP, these data would suggest the importance of heightened awareness of early social phobia in both men and women with BP.

Several anxiety comorbidities were associated with increased number of antidepressants trials including OCD, specific phobia, and PD, and results in PD and specific phobia were driven by increased antidepressant use in women. Data from the STEP-BD cohort showed no overall difference in antidepressant use in women when compared to men,[10] however in an analysis that combined genders, comorbid PD and social anxiety disorder increased the likelihood that subjects were taking antidepressants at the start of the study.[37] Interestingly, in that study cohort, the odds ratio of antidepressant use for OCD was not significantly higher than for those without OCD. The increased number of antidepressants over a lifetime in women with comorbid PD and specific phobia, and in men and women with comorbid OCD may be an indicator of severity, may signal that anxiety was not responsive to antidepressants, or that certain antidepressants were associated with intolerable side effects, including switching to hypomanic or manic states. Preliminary research suggests that comorbid anxiety disorders may render BP refractory to treatment, possibly due to the hypomanic switches induced when serotonergic medications are prescribed for anxiety symptoms.[38]

Our study is limited by the cross-sectional nature of the evaluations, the limited information we have on treatment, and lack of information on several important anxiety disorders including PTSD, GAD, agoraphobia without panic, and separation anxiety disorder. For this reason, we were unable to compare those with anxiety to those without anxiety disorder at all; to account for this, we compared BP with and without each disorder individually. Because these disorders may be present in the “non-anxiety” group in these data, the comparisons between the anxiety disorder groups and the group without each of the studied anxiety disorders may be attenuated. PTSD and GAD in particular have been associated with worsened course of illness and severity of BP;[7,17] thus, individuals with PTSD and GAD who were accounted for in the “non-anxiety” group might have a more severe BP, which lessens the differences in comparison with the anxiety disorder group. Our results therefore can be interpreted to be specific to the comorbid anxiety disorders studied here.

In addition, all of the data were gathered retrospectively, and recollection bias could impact the recall of symptoms that occurred many years ago. Whenever possible, information from medical records was used to corroborate recall, however, this was not possible in all cases.

Future investigation should include measures of neuroticism in studies to evaluate the interaction between gender, personality features, and development of mood and anxiety disorders. Additionally, longitudinal studies of youth at risk for BP will begin to disentangle the possible interplay between mood and anxiety symptoms over the course of development in girls and boys. In clinical samples of anxious youth, separation anxiety disorder tends to precede the development of PD,[39] the most prevalent comorbid anxiety disorder in our

sample of adult subjects with BP. In addition, early onset anxiety symptoms may commingle across the anxiety disorders, such that children with separation anxiety disorder, GAD, PD, or OCD are likely to develop any of the others at a 2-year follow-up.[40] Given the age at interview of subjects included in our study, it is possible that early childhood anxiety symptoms may have been lost due to recollection bias.

Our work highlights the risk for comorbid anxiety disorders in women with BP, and the finding that a number of measures of severity are differentially affected in women with anxiety comorbities than those without. Taken together, these findings support early attention to anxiety disorders in the treatment of women with BP to improve clinical care.

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TABLE 1

Clinical characteristics of the sample by gender; comparisons between males and females

	Total *N* = 736	Female *N* = 460 (62.5%)	Male *N* = 276 (37.5%)
Number of comorbid anxiety disorders *N* (% of total) *			
0	494 (67%)	286 (39%)	208 (28%)
1	165 (22%)	115 (25%)	50 (18%)
2	58 (8%)	42 (9%)	16 (6%)
3	15 (2%)	14 (3%)	1 (.4%)
4	4 (.5%)	3 (.7%)	1 (.4%)
Age at interview (y)	42.6 ± 12.4	42.9 ± 12.0	42.1 ± 13.1
Age at onset BP (y)	20.0 ± 8.8	19.6 ± 8.8	20.7 ± 8.9
Age at first treatment (y)	22.8 ± 9.0	22.9 ± 8.7	23.0 ± 9.8
Age at onset PD	24.4 ± 11.8	24.8 ± 12.1	23.3 ± 10.7
Age at onset OCD *	21.5 ± 12.5	23.0 ± 13.4	16.2 ± 6.5
Age at onset Social Phobia	12.9 ± 7.9	12.0 ± 8.6	14.6 ± 6.5
Age at onset Specific phobia *	11.0 ± 8.3	12.0 ± 8.8	7.3 ± 4.4
Alcohol abuse	45 (6.5%)	31 (6.7%)	18 (6.5%)
Alcohol dependence **	221 (30.7%)	107 (23.3%)	116 (42.0%)
Married	319 (43.9%)	202 (43.9%)	121 (43.8%)
Number of years of school	14 ± 3	14.2 ± 2.6	14.5 ± 2.9
Suicide attempt **	310 (43.1%)	225 (48.9%)	89 (32.2%)
Severity of mania	2.8 ± .55	2.8 ± .58	2.8 ± .50
Severity of depression	1.8 ± .46	1.8 ± .43	1.8 ± .50
Number of manias	11.0 ± 27.3	11.2 ± 29.4	10.3 ± 22.4
Number of depressions *	13.7 ± 31.4	15.5 ± 34.8	10.3 ± 23.3
Number of psych hospitalizations	5.3 ± 8.3	5.5 ± 9.4	5.0 ± 6.1
Number of antidepressants **	3.1 ± 2.7	3.4 ± 2.8	2.6 ± 2.4
Number of mood stabilizers	1.6 ± .88	1.6 ± .91	1.6 ± .83
Number of antipsychotics	1.6 ± 1.8	1.7 ± 1.8	1.6 ± 1.7
Number of sedative/hypnotics **	1.6 ± 1.9	1.8 ± 2.0	1.3 ± 1.7
Number of stimulants	.09 ± .31	.08 ± .28	.11 ± .35

* $P < .05$

** $P < .01$.

TABLE 2

Odds ratios for predictors of comorbid anxiety disorders in BP. All analyses corrected for age at interview and family relatedness

		Panic		OCD	Social phobia		Specific phobia	
	N		*N*		*N*		*N*	
N (% of total sample)	186	(25%)	42	(6%)	55	(8%)	59	(8%)
F (% of all F)	138	(30%) **	33	(7%) *	35	(8%)	47	(10%) **
M (% of all M)	48	(17%)	9	(3%)	20	(7%)	12	(4%)
	OR	95%CI	OR	95% CI	OR	95% CI	OR	95% CI
Female	**1.8**	**1.2–2.6**	1.9	.87–4.2	.98	.55–1.8	**2.7**	**1.4–5.0**
Alcohol abuse	1.6	.86–3.1	2.4	.97–5.9	**2.8**	**1.3–6.0**	.65	.18–2.4
Male	.79	.17–3.7	***		1.4	.30–6.2	1.5	.24–9.8
Female	1.8	.82–3.9			**4.1**	**1.7–9.9**	.31	.04–2.7
Schooling	**.90**	**.83–.96**	.92	.82–1.0	.99	.89–1.1	.93	.84–1.0
Male	.92	.97–1.2	***		.98	.82–1.2	1.0	.79–1.3
Female	**.89**	**.82–.97**			1.0	.84–1.2	.93	.83–1.1
Age at onset BP	.98	.95–1.0	**.94**	**.90–.99**	.98	.94–1.0	1.0	.95–1.1
Male	.97	.93–1.0	***		1.0	.98–1.0	.99	.87–1.1
Female	.99	.96–1.0			.97	.93–1.0	1.0	.96–1.1
Severity of mania	**.64**	**.42–.97**	.88	.57–1.3	.74	.44–1.3	.74	.34–1.4
Male	.78	.47–1.3	***		2.7	.66–11.1	.62	.26–1.5
Female	.78	.55–1.1			.72	.39–1.3	.65	.40–1.1
Antidepressant treatments	**1.1**	**1.1–1.2**	**1.1**	**1.0–1.3**	1.0	.91–1.2	**1.2**	**1.1–1.3**
Male	1.1	.97–1.2	***		1.1	.84–1.4	1.1	.79–1.5
Female	**1.1**	**1.1–1.2**			1.2	.96–1.4	**1.2**	**1.1–1.4**
Sedative/hypnotic treatments	1.1	.96–1.2	.93	.77–1.1	1.1	.48–2.5	**.76**	**.62–.94**
Male	1.1	.96–1.3			1.1	.80–1.5	.68	.41–1.1
Female	1.0	.91–1.2			1.0	.79–1.2	**.78**	**.62–.97**

Note: Bold = $P < 0.028$.

* $P < .05$

** $P < .01$

*** analysis by sex not valid in OCD due to small number of men in the sample.