Gender Differences, Clinical Correlates, and Longitudinal Outcome of Bipolar Disorder With Comorbid Migraine

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ABSTRACT

Objective: Migraine is a common comorbidity of bipolar disorder and is more prevalent in women than men. We hypothesized comorbid migraine would be associated with features of illness and psychosocial risk factors that would differ by gender and impact outcome.

Method: A retrospective analysis was conducted to assess association between self-reported, physician-diagnosed migraine, clinical variables of interest, and mood outcome in subjects with *DSM-IV* bipolar disorder (N = 412) and healthy controls (N = 157) from the Prechter Longitudinal Study of Bipolar Disorder, 2005–2010. Informed consent was obtained from all participants.

Results: Migraine was more common in subjects with bipolar disorder (31%) than in healthy controls (6%) and had elevated risk in bipolar disorder women compared to men (OR = 3.5; 95% CI, 2.1–5.8). In men, migraine was associated with bipolar II disorder (OR = 9.9; 95% CI, 2.3–41.9) and mixed symptoms (OR = 3.5; 95% CI, 1.0–11.9). In comparison to absence of migraine, presence of migraine was associated with an earlier age at onset of bipolar disorder by 2 years, more severe depression ($\beta = .13$, $P = .03$), and more frequent depression longitudinally ($\beta = .13$, $P = .03$). Migraine was correlated with childhood emotional abuse ($P = .01$), sexual abuse ($P = 4 \times 10^{-3}$), emotional neglect ($P = .01$), and high neuroticism ($P = 2 \times 10^{-3}$). Protective factors included high extraversion ($P = .02$) and high family adaptability at the trend level ($P = .08$).

Conclusions: Migraine is a common comorbidity with bipolar disorder and may impact long-term outcome of bipolar disorder, particularly depression. Clinicians should be alert for migraine comorbidity in women and in men with bipolar II disorder. Effective treatment of migraine may impact mood outcome in bipolar disorder as well as headache outcome. Joint pathophysiologic mechanisms between migraine and bipolar disorder may be important pathways for future study of treatments for both disorders.

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Bipolar disorder is an illness that affects 2.1% of the population[1] and is one of the top 10 contributors of years of life lived with disability for persons aged 15–44 years.[2] In addition, health care for bipolar disorder costs more on a per capita basis than for depression, asthma, coronary artery disease, or diabetes,[3] and comorbid medical conditions negatively affect quality of life and contribute to the burden of illness.[4–6] Migraine is a common comorbidity of bipolar disorder. In population-based studies, the rate of migraine in the general population is 9%–15%,[7–12] whereas the rate of migraine comorbidity with bipolar disorder is 16%–54%.[9,10,13–17]

Migraine is more prevalent in women (15%–20%) than in men (6%),[7,12] and, although bipolar disorder has no gender differential, comorbidities that affect women at a higher rate may be associated with a different course of illness or presentation of bipolar disorder.[18] Women with bipolar disorder are at higher risk for bipolar II disorder, comorbid anxiety disorders, and suicide attempts.[19,20] We hypothesized that individuals with comorbid migraine and bipolar disorder have features of more severe illness, such as earlier age at onset; mixed symptoms; suicidal ideation and psychosis; more frequent, severe, and variable mood during longitudinal follow-up; and more severe psychosocial risk factors, such as trauma and stressful life events. Neuroticism, a tendency to experience negative affect such as depressed mood and anxiety, has been associated with both migraine[21] and bipolar disorder,[22] and we hypothesized that neuroticism would be elevated in those with migraine and bipolar disorder. We hypothesized that the presentation of migraine in bipolar disorder would differ by gender, specifically that women with migraine would be more likely to have bipolar II disorder, rapid cycling, anxiety disorders, and suicide attempts. By identifying risk factors and outcomes associated with comorbid migraine, we highlight the need for attention to the frequent comorbidity of migraine in bipolar disorder and the possibility of treatments that target both illnesses.

METHOD

We retrospectively investigated differences in baseline characteristics and longitudinal outcome in 412 subjects with *DSM-IV* bipolar I and II disorder; schizoaffective disorder, bipolar type; and bipolar disorder not otherwise specified (270 females; 142 males) and 157 healthy control subjects (86 females; 71 males) with and without comorbid migraine. Patients with bipolar disorder and healthy controls with no personal or family history of mood or psychotic disorder were recruited to the Prechter Longitudinal Study of Bipolar Disorder at the University of Michigan between 2005 and 2010. This study was approved by the University of Michigan Institutional Review Board; informed consent was obtained from all participants. Diagnostic interviews were completed with the Diagnostic Interview for Genetic Studies (DIGS),[23] and clinicians rated mood with the Hamilton Depression Rating Scale (HDRS)[24] and the Young Mania Rating Scale.[25] Interviewers included physicians, psychologists, and masters'-level mental health professionals,

Clinical Points

- Migraine is commonly associated with more severe bipolar disorder and worse outcome.
- Women with bipolar disorder and men with bipolar II disorder are particularly vulnerable to migraine.
- A history of abuse and a personality trait of high neuroticism increase vulnerability to migraine, and high family adaptability and extraversion are protective factors.

and a best-estimate procedure by at least 2 of the study clinicians was used to verify diagnoses.[26] The DIGS interview captured history of psychopathology. Medical history was elucidated by the DIGS through a series of questions to determine whether the subject had physician-diagnosed medical conditions, including migraine. If a subject reported a diagnosis of migraine, follow-up questions determined age at onset and an unstructured description of clinical features of migraine. Subjects were measured for height and weight. A subset of subjects also completed questionnaires at baseline, including the Childhood Trauma Questionnaire (CTQ),[27] Life Events Occurrence Survey,[28] Life Events Checklist,[29] Family Adaptability and Cohesion Evaluation Scale II (FACES II),[30] and NEO-Personality Inventory—Revised.[31] The Patient Health Questionnaire-9 (PHQ-9)[32] and the Altman Self-Rating Mania Scale (ASRM)[33] were completed every 2 months for the follow-up period of up to 5 years. Baseline depressive symptoms were reported using the 21 plus atypical items of the HDRS. Values of continuous variables were compared between the euthymic group and the control group, and gender differences in the bipolar disorder group were compared using an independent sample *t* test, with the exception of frequency of mood symptom scores and childhood trauma scale sexual abuse subscale, which were compared using the Mann-Whitney *U* test because of highly skewed distribution. Categorical variables were compared using a χ^2 test. A logistic regression model was constructed with migraine presence as the dependent variable and bipolar disorder, sex, body mass index (BMI), and age as independent variables. A second logistic regression model was constructed in the bipolar disorder sample only, with migraine presence as the dependent variable and sex, rapid cycling, serotonin-norepinephrine reuptake inhibitor (SNRI) use, BMI, bipolar II disorder, and mixed symptoms as independent variables. Mixed symptoms were captured in the DIGS and defined as a history of presence of symptoms of the opposite pole during at least 1 week of a mood episode: subsyndromal manic symptoms during depression (mean ± SD number of symptoms = 3.10 ± 3.38) or subsyndromal depressive symptoms during mania (mean ± SD number of symptoms = 2.81 ± 2.20).[34] Bivariate testing revealed that odds for bipolar II disorder and rapid cycling were increased in men with bipolar disorder. To further investigate this association, a third logistic regression model was constructed for bipolar disorder men only, including migraine presence as the dependent variable, bipolar II disorder, mixed symptoms, SNRI use, BMI, and rapid cycling.

Mood outcomes were characterized by severity, variability, and frequency of clinically significant symptoms of depression or mania through the duration of follow-up, which differed for each participant. The severity of depression outcome was defined for each individual by the maximum PHQ-9 score over follow-up; the severity of mania outcome was defined for each individual by the maximum ASRM score over follow-up. The variability of the depression outcome was defined for each individual by the standard deviation in PHQ-9 scores over the duration of follow-up; the variability of the mania outcome was defined by the standard deviation in ASRM scores over the duration of follow-up. The frequency of clinically significant depressive or manic symptoms was defined as the proportion of the follow-up period that the individual had a PHQ-9 or ASRM score over 5. Multivariable linear regression models were created to determine predictors of mood outcome. The α level for significance was set at .05, and the level for trend toward significance was set at .10.

RESULTS

Demographic and Clinical Description

Migraine was significantly more likely to be present in the bipolar disorder as compared to the healthy control group (bipolar disorder: n = 127 [31%]; healthy controls: n = 10 [6%]; $P \leq 1 \times 10^{-3}$) (Supplementary eTable 1). Migraine comorbidity was much higher in females than males in both the healthy control and bipolar disorder groups: 90% of migraine sufferers were female in the control group, 83% in the bipolar disorder group ($P = 1 \pm 10^{-6}$). Body mass index was higher in the bipolar disorder group than the control group ($P = 1 \pm 10^{-6}$), and age at interview was also higher in the bipolar disorder group ($P < 1 \pm 10^{-3}$). Migraine onset occurred at a mean ± SD of 18 ± 11 years old in the control group and 22 ± 12 years old in the bipolar disorder group; however, no statistical difference was detected ($P = .30$), potentially because of the small number of those with migraine in the control group. Migraine age at onset in the bipolar disorder group was, on average, 6 years after the mean ± SD age at onset of bipolar disorder (16 ± 7 years).

Clinical Correlates Associated With Migraine in the Bipolar Disorder Group

We investigated the strength of bivariate association between clinical characteristics and migraine in the bipolar disorder group; results are shown in Table 1 for the entire sample and shown in Table 2 for women and for men. (Supplementary eTables 2–5 shows results by gender and bipolar I/II disorder diagnosis.) Female sex increased odds of migraine (OR = 3.5, 95% CI, 2.1–5.8), and BMI was marginally associated with migraine ($r = 0.11$ $P = .07$), but age was not ($r = -0.02$, $P = .70$) (Table 1). Age at onset of bipolar disorder was not associated with migraine ($r = -0.05$, $P = .27$). A diagnosis of bipolar II disorder increased the odds of migraine (OR = 2.1; 95% CI, 1.2–3.6) when compared to bipolar I disorder. A history of mixed symptoms increased the odds of migraine (OR = 2.0; 95% CI, 1.3–3.0) (Table 1). The definition of mixed symptoms included a history of

Table 1. Baseline Demographics and Clinical Characteristics in Bipolar Disorder Group: Comparing Those With and Without Migraine

Characteristic	No Migraine (n = 285)	Migraine (n = 127)	*r*/OR[a]	*P*/95% CI
Female, n (%)	165 (58)	105 (83)	3.5	2.1–5.8
BMI, mean (SD)	28.6 (6.0)	30.2 (7.8)	0.11	.07
Age, mean (SD), y	38 (14)	39 (12)	−0.02	.70
Age at onset of bipolar disorder, mean (SD), y	18.5 (8.2)	16.2 (6.9)	−0.05	.27
Bipolar I disorder, n (%)	223 (78)	83 (65)	Reference[b]	Reference[b]
Bipolar II disorder, n (%)	37 (13)	29 (23)	2.1	1.2–3.6
Schizoaffective disorder, bipolar type, n (%)	7 (3)	6 (5)	NA	NA
Bipolar disorder NOS, n (%)	18 (6)	9 (7)	NA	NA
Rapid cycling, n (%)	89 (31)	52 (41)	1.5	1.0–2.4
History of mixed symptoms, n (%)	102 (36)	63 (50)	2.0	1.3–3.0
History of mixed episodes, n (%)	68 (24)	40 (31)	1.6	1.0–2.5
History of psychosis, n (%)	159 (56)	63 (50)	0.75	0.5–1.2
History of suicide attempt, n (%)	110 (39)	57 (45)	1.3	0.8–1.9
Anxiety disorder, n (%)	104 (37)	52 (41)	1.2	0.8–1.9
Drug use disorder, n (%)	51 (18)	28 (22)	1.3	0.8–2.2
Alcohol use disorder, n (%)	127 (45)	58 (46)	1.1	0.7–1.6
No. of manic episodes, median (IQR)	2 (4)	2 (7)	−0.06	.41
No. of depressive episodes, median (IQR)	5 (16)	10 (30)	0.22	< .01
No. of hypomanic episodes, median (IQR)	3.5 (20)	12 (40)	0.17	.01
	(n = 147)	(n = 70)	*r*[c]	*P*
Depression, mean (SD)[d]	11.28 (9.90)	17.38 (12.92)	0.26	1×10^{-3}
Mania, mean (SD)[e]	2.88 (4.89)	3.29 (3.98)	0.04	.55
CTQ emotional abuse, mean (SD)	11.41 (5.86)	13.76 (6.14)	0.18	.01
CTQ physical abuse, mean (SD)	7.86 (4.10)	8.61 (4.67)	0.08	.23
CTQ sexual abuse, median (IQR)	5 (4)	6 (11)	0.17	4×10^{-3}
CTQ emotional neglect, mean (SD)	11.84 (5.61)	14.03 (6.08)	0.18	.01
CTQ physical neglect, mean (SD)	8.65 (2.47)	8.81 (2.73)	0.03	.67
FACES II cohesion, mean (SD)	3.94 (2.11)	3.63 (1.97)	−0.07	.30
FACES II adaptability, mean (SD)	3.91 (2.05)	3.40 (1.94)	−0.12	.08
LEOS undesirable events, mean (SD)	2.12 (2.52)	1.99 (1.97)	−0.03	.69
LEC life events scale, mean (SD)	4.54 (3.32)	5.03 (3.73)	0.07	.33
NEO Personality Inventory-Revised, mean (SD)[f]				
Neuroticism	60.21 (13.58)	66.40 (12.62)	0.22	2×10^{-3}
Extraversion	50.28 (11.62)	46.31 (11.84)	−0.16	.02
Openness	56.73 (12.24)	58.59 (13.30)	0.07	.31
Agreeableness	49.07 (12.78)	47.33 (12.77)	−0.06	.35
Conscientiousness	43.47 (13.90)	42.77 (13.41)	−0.02	.73

[a]Spearman *r* reported for number of manic, hypomanic, and depressive episodes and CTQ sexual abuse and migraine; OR (95% CI) reported for categorical variables.
[b]Pearson χ^2 comparisons done for bipolar II disorder using bipolar I disorder as the reference group.
[c]Pearson *r* reported for correlation between normally distributed continuous variables and migraine.
[d]Baseline depression symptoms were measured with the Hamilton Depression Rating Scale.
[e]Baseline manic symptoms were measured with the Young Mania Rating Scale.
[f]From the 5-factor model NEO-Personality Index-Revised.
Abbreviations: BMI = body mass index, CTQ = Childhood Trauma Questionnaire, FACES II = Family Adaptability and Cohesion Evaluation Scale II, IQR = interquartile range, LEC = Life Events Checklist, LEOS = Life Events Occurrence Survey, NA = not applicable, NOS = not otherwise specified.

subsyndromal mixed episodes, whereas a history of mixed episodes included only mixed episodes as defined by *DSM-IV* criteria. Drug use disorder increased the odds of migraine in women. The odds of mixed episodes, psychosis, suicide attempt, anxiety disorder, or alcohol use disorder were not increased in the migraine group ($P > .05$). The number of depressive and hypomanic episodes reported at baseline were correlated with migraine ($P \leq .01$). Baseline depressive symptoms were significantly correlated with migraine ($r = 0.26$, $P = 1 \times 10^{-3}$), but baseline manic symptoms were not ($P = .55$) (Table 1).

Bivariate associations in a subgroup of bipolar disorder subjects showed a positive correlation between migraine and CTQ emotional abuse ($r = 0.18$, $P = .01$), CTQ sexual abuse ($r = 0.17$, $P = 4 \times 10^{-3}$), CTQ emotional neglect ($r = 0.18$, $P = .01$), and neuroticism ($r = 0.22$, $P = 2 \times 10^{-3}$). There was a negative correlation between migraine and extraversion ($r = -0.16$, $P = .02$) and a trend toward negative correlation with FACES II family adaptability score ($r = -0.12$, $P = .08$).

Clinical Characteristics by Gender

There was no significant difference between rates of migraine in the bipolar II disorder versus bipolar I disorder group in the women (OR = 1.6; 95% CI, 0.8–3.0) (Table 2). Group differences between women with bipolar disorder and migraine and without migraine included a marginally higher rate of mixed symptoms (OR = 1.7; 95% CI, 1.0–2.9), drug use disorder (OR = 1.9; 95% CI, 1.0–3.7), and baseline report of more lifetime depressive ($r = 0.19$, $P < .01$) and hypomanic episodes ($r = 0.13$, $P = .04$). Comparisons of psychosocial factors included higher depressive symptoms in women ($r = 0.22$, $P = .01$), higher median level of sexual abuse ($r = 0.18$, $P = .03$), higher level of emotional neglect ($r = 0.18$, $P = .03$), and higher mean neuroticism ($r = 0.18$, $P = .03$).

Table 2. Clinical Characteristics in Bipolar Disorder Group by Gender: Comparing Women and Men With and Without Migraine

	Women				Men			
Characteristic	No Migraine (n = 165)	Migraine (n = 105)	r/OR[a]	P/95% CI	No Migraine (n = 112)	Migraine (n = 21)	r/OR[a]	P/95% CI
Bipolar I disorder, n (%)	123 (75)	69 (66)	Reference[b]	Reference[b]	100 (89)	14 (67)	Reference[b]	Reference[b]
Bipolar II disorder, n (%)	25 (15)	22 (21)	1.6	0.8–3.0	12 (11)	7 (33)	4.2	1.4–12.4
Rapid cycling, n (%)	58 (35)	40 (38)	1.1	0.7–1.9	31 (28)	12 (57)	3.5	1.4–8.8
Mixed symptoms, n (%)	67 (41)	53 (51)	1.7	1.0–2.9	35 (31)	10 (48)	2.0	0.8–5.3
Mixed episodes, n (%)	41 (25)	33 (31)	1.5	0.9–2.6	27 (24)	7 (33)	1.6	0.6–4.4
Psychosis, n (%)	86 (52)	52 (50)	.90	0.5–1.5	73 (65)	11 (52)	0.6	0.2–1.4
Suicide attempts, n (%)	75 (46)	51 (49)	1.1	0.7–1.8	35 (31)	6 (29)	0.9	0.3–2.4
Anxiety disorder, n (%)	73 (44)	43 (41)	0.9	0.5–1.4	31 (28)	9 (43)	2.0	0.8–5.1
Alcohol use disorder, n (%)	63 (38)	49 (47)	1.4	0.9–2.3	64 (57)	9 (43)	0.6	0.2–1.5
Drug use disorder, n (%)	22 (13)	24 (23)	1.9	1.0–3.7	29 (26)	4 (19)	0.7	0.2–2.2
No. of manic episodes, median (IQR)	2 (5)	2 (8)	−0.01	.94	3 (4)	1.5 (5)	−0.10	.24
No. of depressive episodes, median (IQR)	5.5 (17)	10 (25)	0.19	< .01	4 (12)	6.5 (66)	0.19	.03
No. of hypomanic episodes, median (IQR)	4 (20)	12 (40)	0.13	.04	3 (29)	17.5 (31)	0.14	.09
	(n = 95)	(n = 57)	r[c]	P	(n = 52)	(n = 13)	r[c]	P
Baseline depression, mean (SD)[d]	12.24 (10.32)	17.57 (13.39)	0.22	.01	9.67 (9.02)	16.54 (11.13)	0.29	.02
Baseline mania, mean (SD)[e]	2.52 (3.74)	3.23 (4.06)	0.09	.27	3.56 (6.48)	3.54 (3.71)	−0.01	.99
CTQ emotional abuse, mean (SD)	12.44 (6.32)	14.3 (6.14)	0.14	.08	9.52 (4.36)	11.38 (5.75)	0.16	.20
CTQ physical abuse, mean (SD)	8.00 (4.53)	8.68 (4.66)	0.07	.37	7.62 (3.20)	8.31 (4.91)	0.08	.54
CTQ sexual abuse, median (IQR)	5 (4)	7 (12)	0.18	.03	5 (4)	5 (10)	0.06	.62
CTQ emotional neglect, mean (SD)	12.27 (5.96)	14.49 (6.05)	0.18	.03	11.06 (4.87)	12.00 (6.03)	0.08	.55
CTQ physical neglect, mean (SD)	8.72 (2.6)	8.81 (2.63)	0.02	.84	8.54 (2.19)	8.85 (3.26)	0.05	.69
FACES II cohesion, mean (SD)	3.75 (2.10)	3.58 (2.03)	−0.04	.63	4.29 (2.10)	3.85 (1.78)	−0.09	.49
FACES II adaptability, mean (SD)	3.71 (2.11)	3.39 (2.03)	−0.07	.36	4.29 (1.90)	3.46 (1.51)	−0.18	.15
LEOS undesirable events, mean (SD)	2.19 (2.49)	2.05 (1.92)	−0.03	.72	2.00 (2.58)	1.69 (2.21)	−0.05	.70
LEC life events scale, mean (SD)	4.63 (3.43)	4.72 (3.50)	0.01	.88	4.37 (3.14)	6.39 (4.48)	0.23	.06
NEO Personality Inventory-Revised, mean (SD)[f]								
Neuroticism	60.61 (14.02)	65.79 (13.09)	0.18	.03	59.48 (12.86)	69.08 (10.32)	0.30	.02
Extraversion	49.57 (11.52)	46.49 (12.22)	−0.13	.12	51.58 (11.78)	45.43 (10.37)	−0.21	.10
Openness	57.78 (12.36)	58.37 (13.90)	0.02	.79	54.81 (11.89)	59.54 (10.71)	0.16	.20
Agreeableness	48.75 (12.70)	47.02 (13.05)	−0.07	.42	49.65 (12.96)	48.69 (11.85)	−0.03	.81
Conscientiousness	43.05 (13.88)	42.02 (12.73)	−0.04	.65	44.23 (14.03)	46.08 (16.25)	0.05	.69

[a]Spearman *r* reported for number of manic, hypomanic, and depressive episodes and CTQ sexual abuse and migraine; OR (95% CI) reported for categorical variables.
[b]Pearson χ^2 comparisons done for bipolar II disorder using bipolar I disorder as the reference group.
[c]Pearson *r* reported for correlation between normally distributed continuous variables and migraine.
[d]Baseline depression symptoms were measured with the Hamilton Depression Rating Scale.
[e]Baseline manic symptoms were measured with the Young Mania Rating Scale.
[f]From the 5-factor model NEO-Personality Index-Revised.
Abbreviations: CTQ = Childhood Trauma Questionnaire, FACES II = Family Adaptability and Cohesion Evaluation Scale II, IQR = interquartile range, LEC = Life Events Checklist, LEOS = Life Events Occurrence Survey.

Group differences in the men included a higher rate of migraine in those with bipolar II disorder compared to bipolar I disorder (OR = 4.2; 95% CI, 1.4–12.4) and higher rates of rapid cycling (OR = 3.5; 95% CI, 1.4–8.8). Baseline reports of lifetime history of depressive episodes ($r = 0.19$, $P = .03$) and hypomanic episodes showed a trend for difference ($r = 0.14$, $P = .09$). Psychosocial characteristics that differed between men with and without migraine included more depressive symptoms in the migraine group ($r = 0.29$, $P = .02$), a trend for association with more life events ($r = 0.23$, $P = .06$), and higher neuroticism ($r = 0.30$, $P = .02$).

Use of Medication in Those With and Without Migraine

We investigated the prevalence of history of lifetime use of medications for migraine in the groups with and without migraine, particularly because some of the common treatments for migraine include antidepressants, which have been suggested to change clinical characteristics of bipolar disorder, including inducing rapid cycling.[35] Valproic acid, topiramate, gabapentin, selective serotonin reuptake inhibitors (SSRIs), SNRIs, and tricyclic antidepressants (TCAs) were all more commonly taken by those in the migraine group ($P < .02$) (Supplementary eTable 6). Monoamine oxidase inhibitors were taken by only 5 subjects in the cohort, 4 without migraine and 1 with migraine.

Lifetime history of SNRI use was associated with rapid cycling ($r = 0.15$, $P = 3 \times 10^{-3}$), while TCA use showed a trend ($r = 0.10$, $P = .05$) and SSRI use was not associated ($r = 0.05$, $P = .30$). When investigated by diagnosis, correlation between SNRI use and rapid cycling was strongest in schizoaffective disorder, bipolar type (n = 14, $r = 0.576$, $P = .03$), followed by bipolar I disorder (n = 312, $r = 0.161$, $P = .004$). Rapid cycling and SNRI use were not correlated in bipolar II disorder (n = 66, $r = 0.013$, $P = .91$) or bipolar disorder not otherwise specified (n = 27, $r = 0.090$, $P = .65$). Serotonin-norepinephrine reuptake inhibitor use was then incorporated into multivariable models that included rapid cycling.

Table 3. Multivariable Models of Correlates of Migraine

Variable	Bivariate, $r(P)$/ OR (95% CI)	Multivariable, Logistic Regression, OR (95% CI)		
		Bipolar Disorder/ Healthy Controls[a]	Bipolar Disorder Only[b]	Bipolar Disorder, Men[c]
Bipolar disorder	NA	6.0 (3.0–12.2)	NA	NA
Female	3.5 (2.1–5.8)	3.9 (2.3–6.8)	3.0 (1.6–5.6)	…
Body mass index	0.11 (.05)	1.04 (1.0–1.1)		
Age	−0.02 (.70)	…	…	…
Bipolar disorder age at onset	−0.05 (.27)	…	…	…
Bipolar II disorder	2.1 (1.2–3.6)	…		…
Bipolar II disorder, men	4.2 (1.4–12.4)	…	…	9.9 (2.3–41.9)
Rapid cycling	1.5 (0.99–2.4)	…	1.7 (0.99–2.9)	
Rapid cycling, men	3.5 (1.4–8.8)	…	…	…
Mixed symptoms	2.0 (1.3–3.0)	…		3.5 (1.0–11.9)
Mixed episodes	1.6 (0.97–2.5)	…	…	…
Psychosis	0.75 (0.49–1.2)	…	…	…
Suicide attempt	1.3 (0.83–1.9)	…	…	…
Anxiety disorder	1.2 (0.79–1.9)	…	…	…
Drug use disorder	1.3 (0.77–2.2)	…	…	…
Alcohol use disorder	1.1 (0.69–1.6)	…	…	…

[a]Controlled for age.
[b]Controlled for serotonin-norepinephrine reuptake inhibitor use; body mass index, bipolar II disorder, and mixed symptoms eliminated from model by backward selection.
[c]Controlled for serotonin-norepinephrine reuptake inhibitor use; body mass index and rapid cycling eliminated from model by backward selection.
Abbreviation: NA = not applicable.
Symbol: … = variable not included in the model.

Table 4. Mood Outcome in Bipolar Disorder Group: Comparing Those With and Without Migraine[a]

Variable	No Migraine (n = 168), Mean (SD)	Migraine (n = 87), Mean (SD)	P	Multivariable, $\beta(P)$[b]
Depression severity	14.4 (7.2)	18.3 (6.3)	3×10^{-5}	.13 (.03)
Mania severity	7.6 (4.2)	8.9 (4.6)	.03	.08 (.19)
Depression variability	4.0 (2.3)	4.6 (2.2)	.04	.04 (.49)
Mania variability	2.3 (1.3)	2.8 (1.6)	.01	.10 (.11)
	Median (IQR)	Median (IQR)	P	β (P)
Depression frequency	0.57 (0.74)	0.83 (0.48)	$<1\times10^{-3}$	.13 (.03)
Mania frequency	0.14 (0.42)	0.17 (0.40)	.73	−.03 (.61)
Mixed frequency	0.00 (0.20)	0.09 (0.20)	.06	.01 (.91)

[a]Depression symptoms were assessed in longitudinal follow-up using the Patient Health Questionnaire, and mania symptoms were assessed using the Altman Self-Rating Mania Scale.
[b]Linear regression models included age, body mass index, sex, migraine, and baseline mood symptoms.
Abbreviation: IQR=interquartile range.

Multivariable Models of Baseline Risk Factors for Migraine

Bipolar disorder increased the odds of migraine by 6.0 (95% CI, 3.0–12.2) when corrected for age, sex, and BMI (Table 3). In those with bipolar disorder, female sex increased odds of migraine (OR = 3.0; 95% CI, 1.6–5.6), and rapid cycling was significant at a trend level (OR = 1.7; 95% CI, 0.99–2.9) when controlled for SNRI use. Body mass index, bipolar II disorder, and mixed symptoms were eliminated from the final model. In men with bipolar disorder, bipolar II disorder (OR = 9.9; 95% CI, 2.3–41.9) and mixed symptoms (OR = 3.5; 95% CI, 1.0–11.9) were independently associated with migraine after controlling for SNRI use. Body mass index and rapid cycling were eliminated from the final model.

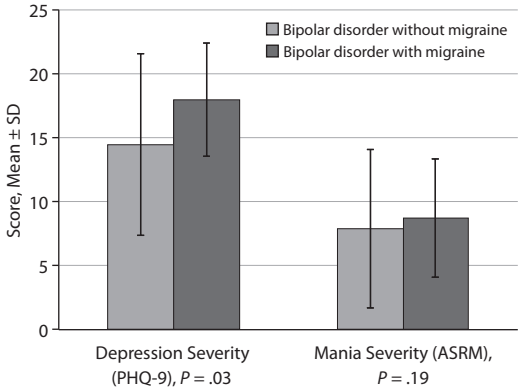
Longitudinal Outcome

Bivariate comparisons of longitudinal follow-up of subjects showed that subjects with bipolar disorder and migraine had more severe and frequent depressive symptoms ($P < .01$) and more severe manic symptoms ($P = .03$) than those without migraine in group comparisons (Table 4). Subjects with migraine also had more variability in manic symptoms than those without migraine ($P = .01$) (Table 4). There were no gender differences in these outcome variables ($P > .05$). In multivariable analysis, migraine was a significant predictor of depression severity ($\beta = .13$, $P = .03$) and depression frequency ($\beta = .13$, $P = .03$) over follow-up when controlled for age, BMI, sex, and baseline mood symptoms (Figure 1). Migraine did not predict manic severity ($P = .19$), variability ($P = .11$), or frequency ($P = .61$) or depression variability ($P = .49$).

DISCUSSION

We found that migraine was highly prevalent in bipolar disorder and, as in the general population, especially in women with bipolar disorder. Those with bipolar disorder and migraine showed a younger age at onset of bipolar

Figure 1. Depression Severity Over Longitudinal Follow-Up Differed Between the Migraine and Nonmigraine Groups, but Mania Severity Did Not Differ[a]



[a]Depression severity was assessed using the PHQ-9, and mania severity was assessed using the ASRM; y-axis reflects group mean ± SD scores on these measures. Models comparing depression and mania severity accounted for age, body mass index, sex, and bipolar I vs II disorder.
Abbreviations: ASRM = Altman Self-Rating Mania Scale, PHQ-9 = Patient Health Questionnaire-9.

disorder and a more severe pattern of depression outcome retrospectively and prospectively. Additional factors that were associated with vulnerability to migraine included childhood abuse and neuroticism, and protective factors included family adaptability and extraversion. In this cohort, bipolar II disorder was not associated with migraine independent of gender. Gender differences emerged in clinical correlates of migraine, including that men with migraines reported more mixed symptoms than men without migraines.

Our results are consistent with population-based studies that find increased comorbidity with migraine headache in patients with bipolar disorder.[9,10,13–17] We found that in our bipolar disorder sample, as in both general and clinical populations, migraines were more common in women,[10,36,37] although at least 1 study has shown equal prevalence.[17] One study of familial transmission of migraine headache showed no genetic contribution to sex differences, and the authors hypothesized that susceptibility to environmental factors may play a larger role than genetics in the gender differential.[36]

Consistent with a number of studies, in our cohort, migraine was more common in those with bipolar II disorder than in those with bipolar I disorder.[13,16,37] Our results showed that in this sample the risk of migraine in those with bipolar II disorder was not independent of the association with female sex. Because both bipolar II disorder and migraine are more common in women, we could hypothesize the increase in prevalence of migraine in bipolar II disorder may be due to a gender effect, or the increased prevalence of migraine in females may be due to the increased risk for a bipolar II disorder illness. However, risk for migraine headache was particularly high in men with bipolar II disorder, and mixed symptoms were associated with migraine headache in men with bipolar disorder independent of association with bipolar II disorder. An association between migraine headache and rapid cycling in men was not significant after accounting for use of SNRI antidepressants, which may increase rapid cycling.[38,39] The association between lifetime use of SNRI antidepressants and lifetime history of rapid cycling is notable; however, this study is not designed to distinguish the nature of this association or to determine causality. Further investigation into a longitudinal association between SNRI use and rapid cycling would be warranted.

Our findings are consistent with other studies of migraine headache in clinical populations of bipolar disorder that show greater severity of bipolar disorder in those with migraine headache, as evidenced by earlier age at onset, greater psychosocial impairment, and worse depression.[13,17,40] We found that outcome was not gender dependent, despite a gender difference in prevalence of migraine. Younger age at onset of bipolar disorder, despite the age at onset for migraine headache being after the age at onset of bipolar disorder, may hint at underlying common pathology between migraine and bipolar disorder that manifests first as mood symptoms and second as migraine.

Psychosocial factors that correlated with migraine headache in our bipolar disorder sample included childhood emotional abuse, sexual abuse, and emotional neglect, found most strongly in women with bipolar disorder and migraine. Childhood maltreatment, trauma, and abuse have been found to play a role in developing migraine headache and converting episodic to daily migraine.[6,41,42] Neuroticism was strongly associated with migraine in both genders, and as neuroticism measures propensity to experience negative affect and stress, those with high neuroticism are less likely to be able to be adaptable and flexible in coping styles.[43–45]

In converse, we found 2 factors that were protective against migraine, family adaptability and extraversion. Family adaptability indicates a level of flexibility and support that is likely to reduce stress in the home, and it may be through this reduction of stress that is protective against migraine. Likewise, those who are extroverted are more likely to have a greater social support network, which tends to reduce stress.

Numerous factors are likely to contribute to the co-occurrence of migraine and bipolar disorder. Genetic factors influence susceptibility to both illnesses, and those with bipolar disorder and migraine may have a shared pathology.[36,46] Abnormal activation of cytokine-based inflammatory mechanisms has recently been reported in bipolar disorder[47,48] and in migraine headache,[49] and there is evidence for abnormal metabolism of arachidonic acid in both disorders.[50–53] In addition, the effectiveness of antiepileptic treatments for both bipolar disorder and migraine headache provides an indication that there is a link in pathophysiologic processes between the 2 disorders.[54–57]

Our results must be viewed in light of a number of limitations, including that we had only subjective report of diagnosis of migraine, and, furthermore, we have no detail of the outcome of migraine headache in this population. An additional limitation is that this is a group of patients with bipolar disorder who are followed through a longitudinal

study, and this group may not represent the most severe end of the bipolar disorder spectrum. Strengths include a relatively large sample of well-characterized subjects with bipolar disorder followed longitudinally.

Migraine is commonly comorbid with bipolar disorder, is associated with a more severe clinical picture of bipolar disorder, and is associated with worse outcomes measured prospectively. Women are particularly vulnerable to migraine, as are those with bipolar II disorder, although men with bipolar II disorder have a very high rate of migraine. A history of abuse and a personality trait of high neuroticism increase vulnerability to migraine, and high family adaptability and extraversion are protective factors. Further study into the common mechanism underlying migraine headache and bipolar disorder, as well as effects of treatments on conditions, may lead to improved outcomes for people with bipolar disorder and migraine comorbidity.

Drug names: gabapentin (Neurontin, Gralise, and others), topiramate (Topamax and others), valproic acid (Depakene and others).

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Gender Differences, Clinical Correlates, and Longitudinal Outcome of Bipolar Disorder With Comorbid Migraine

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Supplementary eTable 1. Demographics: Control and BD groups

Characteristic	Control (n=156)	BD (N=412)	p
Migraine, n(%)	10 (6)	127 (31)	$<1x10^{-3}$
Female, n(%)	86 (55)	270 (66)	.03
Female with migraine	9 (90)	105 (83)	$1x10^{-6}$
(n,% of migraine)			
Age, mean (SD)	33 (14)	40 (13)	$<1x10^{-3}$
BMI, mean (SD)	25.5 (5.7)	29.1 (6.7)	$1x10^{-6}$
Migraine AAO[a], mean (SD)	18.20 (10.7)	22.35 (12.2)	.30

[a]AAO: Age at onset

Supplementary eTable 2. Clinical Characteristics in BD Group by Gender and BD diagnosis: Comparing BPI women With And Without Migraine

Characteristic	No migraine	Migraine	
	(n=123)	(n= 69)	p[a]
Rapid cycling, n(%)	47 (38)	25 (36)	0.79
Mixed Symptoms, n(%)	53 (46)	34 (56)	0.22
Mixed Episodes, n(%)	38 (33)	26 (43)	0.21
Psychosis, n(%)	78 (68)	40 (61)	0.33
Suicide attempts, n(%)	52 (43)	36 (52)	0.22
Anxiety disorder, n(%)	50 (41)	27 (39)	0.84
Alcohol use disorder, n(%)	49 (40)	31 (45)	0.49
Drug use disorder, n(%)	8 (7)	12 (17)	0.02
Manic episodes, median (IQR)	3 (5)	3 (12)	0.27
Depressive episodes, median (IQR)	5 (16)	10 (27)	<0.01
Hypomanic episodes, median (IQR)	4 (20)	6 (24)	0.47
	(n=67)	n=(37)	p
AAO, mean (SD)	17.61 (6.57)	15.92 (7.55)	0.24
BMI, mean (SD)	28.63 (7.59)	31.45 (9.31)	0.11
Baseline depression, mean (SD)	12.73 (11.11)	17.81 (14.26)	0.06
Baseline mania, mean (SD)	2.75 (3.84)	3.03 (3.99)	0.73
CTQ emotional abuse, mean (SD)	12.61 (6.13)	14.11 (6.22)	0.24
CTQ physical abuse, mean (SD)	8.24 (4.75)	9.08 (4.93)	0.40
CTQ sexual abuse, median (IQR)	5 (4)	7 (14)	0.05
CTQ emotional neglect, mean (SD)	12.43 (5.94)	14.38 (5.89)	0.11
CTQ physical neglect, mean (SD)	8.84 (2.79)	8.76 (2.73)	0.89
FACES II cohesion, mean (SD)	3.97 (2.15)	3.32 (1.99)	0.14
FACES II adaptability, mean (SD)	3.81 (2.16)	3.19 (2.00)	0.16
LEOS Undesirable events, mean (SD)	2.27 (2.45)	2.14 (2.04)	0.78
LEC life events scale, mean (SD)	4.06 (3.09)	4.38 (2.92)	0.61
Neuroticism, mean (SD)	60.18 (14.65)	62.81 (12.74)	0.36
Extraversion, mean (SD)	50.18 (11.49)	46.86 (12.66)	0.18
Openness, mean (SD)	58.25 (12.27)	56.51 (14.68)	0.52
Agreeableness, mean (SD)	49.58 (12.29)	44.78 (12.14)	0.06
Conscientiousness, mean (SD)	43.03 (14.43)	41.70 (11.52)	0.63

Abbreviations: Childhood Trauma Questionnaire (CTQ); Life Events Occurrence Survey (LEOS); Life Events Checklist (LEC); Family Adaptability and Cohesion Evaluation Scale II (FACES II); Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness from the Five Factor model NEO-Personality Index – Revised (NEO-PI-R). Baseline depression symptoms were measured with the Hamilton Depression Rating Scale (HDRS-29), baseline manic symptoms were measured with the Young Mania Rating Scale (YMRS).

[a] comparisons between groups done using independent sample t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables (manic, depressive, and hypomanic episodes, CTQ sexual abuse); Pearson Chi-square used for categorical variables.

Supplementary eTable 3. Clinical Characteristics in BD Group by Gender and BD diagnosis: Comparing BPI Men With And Without Migraine

BPI MEN: Characteristic	(n=100)	(n=14)	p[a]
Rapid Cycling, n(%)	26 (26)	9 (64)	<0.01
Mixed Symptoms, n(%)	32 (36)	8 (62)	0.07
Mixed Episodes, n(%)	25 (28)	5 (39)	0.52
Psychosis, n(%)	67 (71)	11 (79)	0.75
Suicide Attempts, n(%)	25 (25)	4 (29)	0.76
Anxiety Disorder, n(%)	27 (27)	5 (36)	0.53
Alcohol Use Disorder, n(%)	56 (56)	5 (36)	0.15
Drug Use Disorder, n(%)	26 (26)	3 (21)	0.71
Manic episodes, median (IQR)	3 (5)	4 (11)	0.56
Depressive episodes, median (IQR)	4 (12)	6.5 (50)	0.20
Hypomanic episodes, median (IQR)	1 (22)	17.5 (48)	0.08
	(n=45)	n=(9)	p
AAO, mean (SD)	21.07 (11.05)	14.44 (3.81)	0.08
BMI, mean (SD)	30.19 (5.73)	29.89 (8.44)	0.90
Baseline depression, mean (SD)	9.29 (8.73)	16.89 (11.63)	0.30
Baseline mania, mean (SD)	3.62 (6.73)	3.89 (4.22)	0.91
CTQ emotional abuse, mean (SD)	9.67 (4.59)	10.89 (6.13)	0.49
CTQ physical abuse, mean (SD)	7.82 (3.30)	8.67 (5.75)	0.54
CTQ sexual abuse, median (IQR)	5 (5)	5 (10)	0.90
CTQ emotional neglect, mean (SD)	11.00 (5.01)	11.89 (6.37)	0.65
CTQ physical neglect, mean (SD)	8.67 (2.31)	8.89 (3.89)	0.82
FACES II cohesion, mean (SD)	4.20 (2.07)	3.67 (1.66)	0.47
FACES II adaptability, mean (SD)	4.29 (1.87)	3.22 (1.30)	0.11
LEOS Undesirable events, mean (SD)	1.87 (2.28)	2.00 (2.50)	0.88
LEC life events scale, mean (SD)	4.51 (3.27)	6.33 (4.21)	0.15
Neuroticism, mean (SD)	59.18 (12.68)	67.89 (11.71)	0.06
Extraversion, mean (SD)	50.96 (11.52)	43.78 (12.14)	0.10
Openness, mean (SD)	54.49 (11.39)	58.11 (8.18)	0.37
Agreeableness, mean (SD)	50.82 (11.89)	49.33 (13.23)	0.74
Conscientiousness, mean (SD)	44.91 (13.52)	47.67 (19.29)	0.61

Abbreviations: Childhood Trauma Questionnaire (CTQ); Life Events Occurrence Survey (LEOS); Life Events Checklist (LEC); Family Adaptability and Cohesion Evaluation Scale II (FACES II); Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness from the Five Factor model NEO-Personality Index – Revised (NEO-PI-R). Baseline depression symptoms were measured with the Hamilton Depression Rating Scale (HDRS-29), baseline manic symptoms were measured with the Young Mania Rating Scale (YMRS).

[a] comparisons between groups done using independent sample t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables (manic, depressive, and hypomanic episodes, CTQ sexual abuse); Pearson Chi-square used for categorical variables.

Supplementary eTable 4. Clinical Characteristics in BD Group by Gender and BD diagnosis: Comparing BPII Women With And Without Migraine

	No migraine	Migraine	
Characteristic	(n=25)	(n=22)	p[a]
Rapid cycling, n(%)	7 (28)	11 (50)	0.12
Mixed Symptoms, n(%)	9 (38)	9 (47)	0.52
Mixed Episodes, n(%)	2 (8)	2 (11)	0.81
Psychosis, n(%)	3 (13)	5 (25)	0.28
Suicide attempts, n(%)	12 (50)	8 (38)	0.42
Anxiety disorder, n(%)	17 (68)	10 (46)	0.12
Alcohol use disorder, n(%)	8 (32)	9 (41)	0.53
Drug use disorder, n(%)	4 (16)	5(23)	0.56
Depressive episodes, median (IQR)	9 (45)	10 (21)	
Hypomanic episodes, median (IQR)	8 (28)	20 (38)	
	(n=16)	n=(15)	p
AAO, mean (SD)	17.19 (7.14)	14.53 (6.24)	0.28
BMI, mean (SD)	28.16 (6.99)	28.97 (2.86)	0.67
Baseline depression, mean (SD)	12.50 (8.66)	18.93 (10.64)	0.79
Baseline mania, mean (SD)	1.25 (2.08)	4.20 (4.54)	0.03
CTQ emotional abuse, mean (SD)	10.81 (6.73)	13.53 (5.34)	0.22
CTQ physical abuse, mean (SD)	7.63 (4.52)	7.27 (3.56)	0.81
CTQ sexual abuse, median (IQR)	5.5 (6)	6 (7)	0.68
CTQ emotional neglect, mean (SD)	10.44 (5.75)	15.13 (6.44)	0.04
CTQ physical neglect, mean (SD)	8.00 (1.75)	8.80 (2.51)	0.31
FACES II cohesion, mean (SD)	3.25 (1.92)	4.00 (2.10)	0.31
FACES II adaptability, mean (SD)	3.25 (1.95)	3.53 (1.96)	0.69
LEOS Undesirable events, mean (SD)	0.94 (0.93)	1.60 (1.50)	0.16
LEC life events scale, mean (SD)	5.00 (3.83)	4.60 (4.10)	0.78
Neuroticism, mean (SD)	62.38 (12.64)	71.73 (11.13)	0.04
Extraversion, mean (SD)	47.13 (10.60)	44.47 (9.87)	0.48
Openness, mean (SD)	54.38 (11.46)	59.13 (11.08)	0.25
Agreeableness, mean (SD)	45.63 (14.31)	55.33 (12.78)	0.06
Conscientiousness, mean (SD)	41.00 (12.14)	43.07 (15.57)	0.68

Abbreviations: Childhood Trauma Questionnaire (CTQ); Life Events Occurrence Survey (LEOS); Life Events Checklist (LEC); Family Adaptability and Cohesion Evaluation Scale II (FACES II); Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness from the Five Factor model NEO-Personality Index – Revised (NEO-PI-R). Baseline depression symptoms were measured with the Hamilton Depression Rating Scale (HDRS-29), baseline manic symptoms were measured with the Young Mania Rating Scale (YMRS).

[a] comparisons between groups done using independent sample t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous

variables (depressive, and hypomanic episodes, CTQ sexual abuse); Pearson Chi-square used for categorical variables.

Supplementary eTable 5. Clinical Characteristics in BD Group by Gender and BD diagnosis: Comparing BPII Men With And Without Migraine

Characteristic	(n=12)	(n=7)	p[a]
Rapid Cycling, n(%)	4 (33)	3 (43)	1.00
Mixed Symptoms, n(%)	3 (27)	2 (29)	1.00
Mixed Episodes, n(%)	2 (18)	2 (29)	0.61
Psychosis, n(%)	2 (18)	0	0.50
Suicide Attempts, n(%)	4 (36)	2 (29)	0.73
Anxiety Disorder, n(%)	3 (25)	4 (57)	0.16
Alcohol Use Disorder, n(%)	3 (25)	4 (57)	0.16
Drug Use Disorder, n(%)	1 (8)	1 (14)	1.00
Depressive episodes, median (IQR)	5 (27)	20 (37)	0.10
Hypomanic episodes, median (IQR)	20 (37)	20 (24)	0.53
	(n=5)	n=(3)	p
AAO, mean (SD)	16.40 (5.13)	20.00 (4.00)	0.34
BMI, mean (SD)	27.42 (3.19)	25.47 (0.67)	0.35
Baseline depression, mean (SD)	6.60 (5.86)	18.00 (13.00)	0.13
Baseline mania, mean (SD)	3.80 (5.85)	1.67 (1.53)	0.57
CTQ emotional abuse, mean (SD)	8.20 (2.78)	10.00 (2.65)	0.40
CTQ physical abuse, mean (SD)	5.60 (0.89)	6.33 (1.53)	0.41
CTQ sexual abuse, median (IQR)	0 (0)	7 (0)	0.14
CTQ emotional neglect, mean (SD)	10.40 (4.04)	11.33 (7.10)	0.82
CTQ physical neglect, mean (SD)	7.80 (1.10)	8.33 (1.53)	0.58
FACES II cohesion, mean (SD)	5.60 (2.30)	3.67 (2.31)	0.29
FACES II adaptability, mean (SD)	5.20 (2.05)	3.67 (2.31)	0.36
LEOS Undesirable events, mean (SD)	1.00 (1.00)	1.33 (1.53)	0.72
LEC life events scale, mean (SD)	3.80 (2.39)	7.67 (6.43)	0.25
Neuroticism, mean (SD)	58.20 (14.41)	74.33 (5.51)	0.12
Extraversion, mean (SD)	59.00 (13.77)	50.33 (2.52)	0.34
Openness, mean (SD)	62.40 (15.24)	60.67 (19.09)	0.89
Agreeableness, mean (SD)	43.00 (20.68)	44.33 (9.24)	0.92
Conscientiousness, mean (SD)	46.00 (16.75)	41.67 (7.51)	0.69

Abbreviations: Childhood Trauma Questionnaire (CTQ); Life Events Occurrence Survey (LEOS); Life Events Checklist (LEC); Family Adaptability and Cohesion Evaluation Scale II (FACES II); Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness from the Five Factor model NEO-Personality Index – Revised (NEO-PI-R). Baseline depression symptoms were measured with the Hamilton Depression Rating Scale (HDRS-29), baseline manic symptoms were measured with the Young Mania Rating Scale (YMRS).

[a] comparisons between groups done using independent sample t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous

variables (depressive, and hypomanic episodes, CTQ sexual abuse); Pearson Chi-square used for categorical variables.

Supplementary eTable 6. Medication use in BD group: Comparing Those With And Without Migraine

Medication	No migraine (n=285)	Migraine (n=127)	p
Valproic Acid, n(%)	120 (24)	55 (37)	$2x10^{-3}$
Topiramate, n(%)	23 (5)	23 (16)	$6x10^{-6}$
Gabapentin, n(%)	37 (8)	26 (18)	$2.5x10^{-4}$
SSRI, n(%)	178 (63)	94 (74)	0.02
SNRI[a], n(%)	68 (24)	44 (35)	0.02
TCA, n(%)	40 (14)	38 (30)	$<1x10^{-3}$
MAOI, n(%)	4 (1)	1 (1)	0.51 (exact)

[a]AD tested for associated with RC: SNRI associated with RC in both groups ($p<3x10^{-3}$), TCA and SSRI are not ($p>.36$).