Published in final edited form as:

J Clin Psychiatry. 2014 May ; 75(5): 512–519. doi:10.4088/JCP.13m08623.

Gender differences, Clinical Correlates and Longitudinal Outcome of Bipolar Disorder with Co-morbid Migraine

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Abstract

Objective—Migraine is a common co-morbidity of bipolar disorder (BD), and is more prevalent in women than men. We hypothesized co-morbid migraine would be associated with features of illness and psychosocial risk factors which would differ by gender and impact outcome.

Methods—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 BD (N=412) and healthy controls (HC, 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 BD (31%) than HC (6%), and had elevated risk in BD women compared to men (OR 3.5, CI 2.1, 5.8). In men, migraine was associated with BPII (OR 9.9, CI 2.3, 41.9) and mixed symptoms (OR 3.5, CI 1.0, 11.9). Migraine was associated with an earlier age at onset of BD by 2 years, more severe depression ($B = .13$, $p = .03$), and more frequent depression longitudinally ($B = .13$, $p = .03$). Migraine was associated with childhood trauma ($p < .02$) and high neuroticism ($p < .01$), and protective factors included high family adaptability ($p = .05$) and high extraversion ($p = .01$).

Conclusion—Migraine is a common co-morbidity with BD and may impact long-term outcome of BD, particularly depression. Clinicians should be alert for migraine co-morbidity in women, and in men with BPII. Effective treatment of migraine may impact mood outcome in BD as well

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Presented at the American College of Neuropsychopharmacology, Hollywood, Florida December 2–6, 2012.

Disclaimer: E. Saunders, R. Nazir, M. Kamali, K. Ryan, S. Evans, S. Langenecker – none; M. McInnis – Merck Pharmaceuticals (Honoraria for Speaker's bureau); A. Gelenberg – Zynx (consultanship), Pfizer Pharmaceutical (investigator-initiated grant through Penn State), Healthcare Technology Systems, Inc. (major stock ownership).

as headache outcome. Joint pathophysiological mechanisms between migraine and BD may be important pathways for future study of treatments for both disorders.

Introduction

Bipolar disorder (BD) 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 ages 15–44.² In addition, health care for BD 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 BD. In population-based studies, the rate of migraine in the general population is 9–15%,^{7–12} whereas the rate of migraine co-morbidity with BD is 16–54%.^{9,10,13–17}

Migraine is more prevalent in women (15–20%) than men (6%),^{7,12} and though BD has no gender differential, comorbidities that affect women at a higher rate may be associated with a different course of illness or presentation of BD.¹⁸ Women with BD are at higher risk for bipolar II disorder (BPII), co-morbid anxiety disorders, and suicide attempts.^{19,20} We hypothesized that individuals with co-morbid migraine and BD 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 BD,²² and we hypothesized that neuroticism would be elevated in those with migraine and BD. We hypothesized that the presentation of migraine in BD would differ by gender, specifically that women with migraine would be more likely to have BPII, 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 migraines in BD and the possibility of treatments that target both illnesses.

Methods

We retrospectively investigated differences in baseline characteristics and longitudinal outcome in 412 subjects with BD (270 F; 142 M) and 157 healthy control subjects (86 F; 71 M) with and without comorbid migraine. Patients with BD, and healthy controls with no personal or family history of mood or psychotic disorder were recruited to the Prechter Longitudinal Study of BD at the University of Michigan between 2005 and 2010. This study was approved by the UM IRB. Diagnostic interviews were completed with the Diagnostic Interview for Genetic Studies (DIGS),²³ and clinicians rated mood with the Hamilton Depression Rating Scale,²⁴ and the Young Mania Rating Scale.²⁵ Interviewers included physicians, psychologists, and masters-level mental health professionals, and a best-estimate procedure by at least two of the study clinicians was used to verify diagnoses.²⁶ The DIGS interview captured history of psychopathology. Medical history was elucidated in the DIGS through a series of questions to determine if the subject had a 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 (LEOS);²⁸ Life Events Checklist (LEC);²⁹ Family Adaptability and Cohesion Evaluation Scale II (FACES II);³⁰ and NEO-Personality Index – Revised (NEO-PI-R).³¹ The Patient Health Questionnaire (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 HDRS 21 plus atypical items. Values of continuous variables were compared between euthymic group and the control group and gender differences in the BD group were compared using 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 due to highly skewed distribution. Categorical variables were compared using chi-square test. A logistic regression model was constructed with migraine presence as the dependent variable and BD, sex, body mass index (BMI) and age as independent variables. A second logistic regression model was constructed in the BD sample only, with migraine presence as the dependent variable, and sex, rapid cycling, SNRI use, BMI, BPII 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 one week of a mood episode: subsyndromal manic symptoms during depression (mean number of symptoms: 3.10 $\pm$ 3.38) or subsyndromal depressive symptoms during mania (mean number of symptoms: 2.81 $\pm$ 2.20).³⁴ Because bivariate testing showed odds for BPII and rapid cycling were increased in men with BD, a third logistic regression model was constructed for BD men only, including migraine presence as the dependent variable, BPII, mixed symptoms, serotonin-norepinephrine reuptake inhibitor (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 alpha level for significance was set at .05 and the level for trend toward significance was set at .10.

Results

Demographic and clinical description (Supplementary eTable 1)

Migraine was significantly more likely to be present in the BD as compared to the healthy control group (BD: n=127, 31%; HC: n=10, 6%, $p < 1 \times 10^{-3}$). Migraine comorbidity was much higher in females than males in both the HC and BD groups: ninety percent of migraine sufferers were female in the control group, 83% in the BD group ($p = 1 \times 10^{-6}$). BMI

was higher in the BD group than the control group ($p=1\times 10^{-6}$) and age at interview was also higher in the BD group ($p<1\times 10^{-3}$). Migraine onset occurred at a mean of 18 ± 11 years old in the control group and 22 ± 12 years old in the BD group, however no statistical difference was detected ($p=.30$), potentially due to the small number of those with migraine in the control group. Migraine age at onset in the BD group was on average 6 years after the age at onset of BD (16 ± 7).

Clinical correlates associated with migraine in the BD group

We investigated the strength of bivariate association between clinical characteristics and migraine in the BD group; results are shown in Table 1 for the entire sample and shown in Table 2a for women and Table 2b for men. (Supplementary eTable 3 shows results by gender and BPI/BPII diagnosis). Female sex increased odds of migraine (Table 1, OR 3.5, CI 2.1–5.8), and BMI was marginally associated with migraine ($r=.11$ $p=.05$) but age was not ($r=-.02$, $p=.70$). Age at onset of BD was not associated with migraine ($r=-.05$, $p=.27$). A diagnosis of BPII increased the odds of migraine (OR 2.1, CI 1.2–3.6) when compared to BPI, and in men, the diagnosis of BPII increased the odds of migraine by a greater amount (OR 4.2, CI 1.4–12.4). A history of rapid cycling increased the odds of migraine in men (Table 2b, OR 3.5, CI 1.4–8.8). A history of mixed symptoms increased the odds of migraine in women (Table 2a, OR 1.7, CI 1.0–2.9) and when combined by gender (Table 2, OR 2.0, CI 1.3–3.0). The definition of mixed symptoms included a history of 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 (Table 2a, OR 1.9, CI 1.0–3.7). 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 ($p<.01$). Baseline depressive symptoms were significantly correlated with migraine (Table 2, $r=.26$, $p<1\times 10^{-3}$), but baseline manic symptoms were not (Table 2, $p=.55$).

Bivariate associations in a subgroup of BD subjects showed a positive correlation between migraine and CTQ emotional abuse ($r=.20$, $p=.01$), CTQ sexual abuse ($r=.17$, $p=.4\times 10^{-3}$), CTQ emotional neglect ($r=.19$, $p=.01$), and neuroticism ($r=.22$, $p=2\times 10^{-3}$). There was a negative correlation between migraine and extraversion ($r=-.16$, $p=.02$), and a trend toward negative correlation with FACES II family adaptability score ($r=-.12$, $p=.08$).

Clinical characteristics by gender (Table 2a and Table 2b)

There was no significant difference between rates of migraine in the BPII vs BPI group in the women (OR 1.6, 95% CI 0.8–3.0). Group differences between women with BD 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 ($r=0.18$, $p=.03$).

Group differences in the men included a higher rate of migraine in those with BPII compared to BPI (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 ($r=0.3$, $p=.02$).

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 BD, including inducing rapid cycling.³⁵ Valproic acid, topiramate, gabapentin, selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA) were all more commonly taken by those in the migraine group ($p<.02$) (Supplementary eTable 2). 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 ($r=.15$, $p=3\times 10^{-3}$), while TCA showed a trend ($r=.10$, $p=.05$) and SSRI use was not associated ($r=.05$, $p=.30$). When investigated by diagnosis, correlation between SNRI use and rapid cycling was strongest in SAB ($n=14$, $r=.576$, $p=.03$), followed by BPI ($n=312$, $r=.161$, $p=.004$). Rapid cycling and SNRI use were not correlated in BPII ($n=66$, $r=.013$, $p=.91$) or BPNOS ($n=27$, $r=.090$, $p=.65$). SNRI use was then incorporated into multivariable models that included rapid cycling.

Multivariable models of baseline risk factors for migraine (Table 3)

BD increased the odds of migraine by 6.0 (CI 3.0, 12.2) when corrected for age, sex and BMI. In those with BD, female sex increased odds of migraine (OR 3.0, CI 1.6, 5.6) and rapid cycling was significant at a trend level (OR 1.7, CI .99, 2.9) when controlled for SNRI use. BMI, BPII and mixed symptoms were eliminated from the final model. In men with BD, BPII (OR 9.9, CI 2.3, 41.9) and mixed symptoms (OR 3.5, CI 1.0, 11.9) were independently associated with migraine after controlling for SNRI use. BMI and rapid cycling were eliminated from the final model.

Longitudinal outcome (Table 4)

Bivariate comparisons of longitudinal follow-up of subjects showed that subjects with BD 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 (Figure 1). Subjects with migraine also had more variability in manic symptoms than those without migraine ($p>.01$) (Figure 1). There were no gender differences in these outcome variables ($p>.05$). In multivariable analysis, migraine was a significant predictor of depression severity ($B=.13$, $p=.03$) and depression frequency ($B=.13$, $p=.03$) over follow-up when controlled for age, BMI and sex and baseline mood symptoms. Migraine did not predict

manic severity ($p=0.19$), variability ($p=0.11$) or frequency ($p=0.61$), or depression variability ($p=0.49$).

Conclusion

We found that migraine was highly prevalent in BD and, as in the general population, especially in women with BD. Those with BD and migraine showed a younger age at onset of BD, 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, BP-II 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 co-morbidity with migraine headache in patients with BD.^{9,10,13–17} We found that in our BD sample, as in both general and clinical populations, migraine were more common in women,^{10,36,37} though at least one 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 BP-II disorder.^{13,16,37} Our results showed that in this sample the risk of migraine in those with BP-II was not independent of the association with female sex. Because both BP-II and migraine are more common in women, we could hypothesize the increase in prevalence of migraine in BP-II may be due to a gender effect, or the increased prevalence of migraine in females may be due to the increased risk for a BP-II illness. However, risk for migraine headache was particularly high in men with BP-II, and mixed symptoms were associated with migraine headache in men with BD independent of association with BP-II. 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 BD clinical populations that show that worse severity of BD as evidenced by earlier age at onset, greater psychosocial impairment, and worse depression in those with migraine headache.^{13,17,40} We found that outcome was not gender-dependent, despite gender difference in prevalence of migraine. Younger age at onset of BD, despite the age at onset for migraine headache being after the age of onset of BD, may hint at underlying common pathology between migraine and BD that manifests first as mood symptoms and second as migraine.

Psychosocial factors that correlated with migraine headache in our BD sample included childhood emotional, sexual abuse and emotional neglect, found most strongly in women with BD 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 two 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 BD. Genetic factors influence susceptibility to both illnesses, and those with BD and migraine may have a shared pathology.^{36,46} Abnormal activation cytokine-based inflammatory mechanisms has recently been reported in BD^{47,48} and in migraine headache,⁴⁹ and there is evidence for abnormal metabolism of arachidonic acid (AA) in both disorders.^{50–53} In addition, the effectiveness of anti-epileptic treatments for both BD and migraine headache provides an indication that there is a link in pathophysiological processes between the two 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 BD who are followed through a longitudinal study, and this group may not represent the most severe end of the BD spectrum. Strengths include a relatively large sample of well-characterized subjects with BD followed longitudinally.

Migraine is commonly comorbid with BD, is associated with a more severe clinical picture of BD, and is associated with worse outcomes measured prospectively. Women are particularly vulnerable to migraine, as are those with BP-II, though men with BP-II 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 BD, as well as effects of treatments on conditions may lead to improved outcomes for people with BD and migraine comorbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of financial support: The Heinz C. Prechter Bipolar Research Fund – University of Michigan. The project described was supported by the National Center for Research Resources, Grant KL2 RR033180 (EFHS), and is now at the National Center for Advancing Translational Sciences, Grant KL2 TR000126. The content is solely the

responsibility of the authors and does not necessarily represent the official views of the NIH. The sponsors of this research did not have direct influence over the collection, analysis or interpretation of data.

Acknowledgement of assistance: We would like to thank the participants in the Prechter Longitudinal Study of Bipolar Disorder and the dedicated research team of the Prechter Bipolar Group, without whom this work would not be possible.

The Heinz C. Prechter Bipolar Research Fund supported the collection of the data for the Prechter Longitudinal Study of Bipolar Disorder and the Prechter Bipolar Genetic Repository. The data reside at the University of Michigan, and can be requested through inquiries addressed to Dr. Melvin G. McInnis, MD, Department of Psychiatry, University of Michigan School of Medicine, Ann Arbor, MI, 48109.

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Clinical Points

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

Figure 1.

Depression severity over longitudinal follow-up differed between the migraine and non-migraine groups, but mania severity did not differ

Depression severity was assessed using the PHQ-9 and mania severity was assessed using the Altman Self-Rating Mania Scale (ASRM); Y-axis reflects group mean scores $\pm$ standard deviation on these measures. Models comparing depression and mania severity accounted for age, BMI, sex, BPI vs. BPIL.

Table 1

Baseline Demographics & Clinical Characteristics in BD 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	0.07
Age, mean (SD)	38 (14)	39 (12)	–0.02	0.70
BD age at onset, mean (SD)	18.5 (8.2)	16.2 (6.9)	–0.05	0.27
BPI, n(%)	223 (78)	83 (65)	ref ^b	ref ^b
BPII, n(%)	37 (13)	29 (23)	2.1	1.2–3.6
SABP, n (%)	7 (3)	6 (5)	N/A	N/A
BPNOS, n (%)	18 (6)	9 (7)	N/A	N/A
Rapid Cycling, n(%)	89 (31)	52 (41)	1.5	1.0–2.4
History of Mixed symptoms, n(%)	102 (40)	63 (56)	2.0	1.3–3.0
History of Mixed episodes	68 (26)	40 (36)	1.6	1.0–2.5
History of Psychosis, n(%)	159 (59)	63 (52)	0.75	0.5–1.2
History of Suicide Attempt, n(%)	110 (39)	57 (43)	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
Manic episodes, median (IQR)	2 (4)	2 (7)	–0.06	0.41
Depression episodes, median (IQR)	5 (16)	10 (30)	0.22	<0.01
Hypomanic episodes, median (IQR)	3.5 (20)	12 (40)	0.17	0.01
	(n=147)	n=(70)	r (mig)	p
Baseline depression, mean (SD)	11.28 (9.90)	17.38 (12.92)	0.26	1×10 ^{–3}
Baseline mania, mean (SD)	2.88 (4.89)	3.29 (3.98)	0.04	0.55
CTQ emotional abuse, mean (SD)	11.41 (5.86)	13.76 (6.14)	0.18	0.01
CTQ physical abuse, mean (SD)	7.86 (4.10)	8.61 (4.67)	0.08	0.23
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	0.01
CTQ physical neglect, mean (SD)	8.65 (2.47)	8.81 (2.73)	0.03	0.67
FACES II cohesion, mean (SD)	3.94 (2.11)	3.63 (1.97)	–0.07	0.30
FACES II adaptability, mean (SD)	3.91 (2.05)	3.40 (1.94)	–0.12	0.08
LEOS Undesirable events, mean (SD)	2.12 (2.52)	1.99 (1.97)	–0.03	0.69
LEC life events scale, mean (SD)	4.54 (3.32)	5.03 (3.73)	0.07	0.33
Neuroticism, mean (SD)	60.21 (13.58)	66.40 (12.62)	0.22	2×10 ^{–3}
Extraversion, mean (SD)	50.28 (11.62)	46.31 (11.84)	–0.16	0.02
Openness, mean (SD)	56.73 (12.24)	58.59 (13.30)	0.07	0.31

Characteristic	No migraine	Migraine		
	(n=285)	(n=127)	r/OR ^a	p/95% CI
Agreeableness, mean (SD)	49.07 (12.78)	47.33 (12.77)	-0.06	0.35
Conscientiousness, mean (SD)	43.47 (13.90)	42.77 (13.41)	-0.02	0.73

Abbreviations: Body Mass Index (BMI); Bipolar I Disorder (BPI); Bipolar II Disorder (BPII); Schizoaffective Disorder, Bipolar Type (SABP); Bipolar Disorder NOS (BPNOS); 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 r (mig) = Pearson's r reported for correlation between normally distributed continuous variables and migraine, Spearman's r reported for mania, hypomania, depression number of episodes and CTQ sexual abuse and migraine; OR (95% CI) reported for categorical variables.

^b Pearson's chi-square comparisons done for BPII using BPI as the reference group

Table 2a

Clinical Characteristics in BD Group by Gender: Comparing Women With And Without Migraine

Characteristic	No migraine (n=165)	Migraine (n=105)	r/OR ^a	p/95% CI
BPI, n(%)	123 (83)	69 (76)	Ref ^b	Ref ^b
BP II, n(%)	25 (17)	22 (24)	1.6	0.8–3.0
Rapid cycling, n(%)	58 (35)	40 (38)	1.1	0.7–1.9
Mixed Symptoms, n(%)	67 (44)	53 (58)	1.7	1.0–2.9
Mixed Episodes, n(%)	41 (27)	33 (36)	1.5	0.9–2.6
Psychosis, n(%)	86 (55)	52 (53)	.90	0.5–1.5
Suicide attempts, n(%)	75 (46)	51 (49)	1.1	0.7–1.8
Anxiety disorder, n(%)	73 (44)	43 (41)	0.9	0.5–1.4
Alcohol use disorder, n(%)	63 (38)	49 (47)	1.4	0.9–2.3
Drug use disorder, n(%)	22 (13)	24 (23)	1.9	1.0–3.7
Manic episodes, median (IQR)	2 (5)	2 (8)	–0.01	0.94
Depressive episodes, median (IQR)	5.5 (17)	10 (25)	0.19	<0.01
Hypomanic episodes, median (IQR)	4 (20)	12 (40)	0.13	0.04
	(n=95)	n=(57)	r (mig)	p
Baseline depression, mean (SD)	12.24 (10.32)	17.57 (13.39)	0.22	0.01
Baseline mania, mean (SD)	2.52 (3.74)	3.23 (4.06)	0.09	0.27
CTQ emotional abuse, mean (SD)	12.44 (6.32)	14.3 (6.14)	0.14	0.08
CTQ physical abuse, mean (SD)	8.00 (4.53)	8.68 (4.66)	0.07	0.37
CTQ sexual abuse, median (IQR)	5 (4)	7 (12)	0.18	0.03
CTQ emotional neglect, mean (SD)	12.27 (5.96)	14.49 (6.05)	0.18	0.03
CTQ physical neglect, mean (SD)	8.72 (2.6)	8.81 (2.63)	0.02	0.84
FACES II cohesion, mean (SD)	3.75 (2.10)	3.58 (2.03)	–0.04	0.63
FACES II adaptability, mean (SD)	3.71 (2.11)	3.39 (2.03)	–0.07	0.36
LEOS Undesirable events, mean (SD)	2.19 (2.49)	2.05 (1.92)	–0.03	0.72
LEC life events scale, mean (SD)	4.63 (3.43)	4.72 (3.50)	0.01	0.88
Neuroticism, mean (SD)	60.61 (14.02)	65.79 (13.09)	0.18	0.03
Extraversion, mean (SD)	49.57 (11.52)	46.49 (12.22)	–0.13	0.12
Openness, mean (SD)	57.78 (12.36)	58.37 (13.90)	0.02	0.79
Agreeableness, mean (SD)	48.75 (12.70)	47.02 (13.05)	–0.07	0.42
Conscientiousness, mean (SD)	43.05 (13.88)	42.02 (12.73)	–0.04	0.65

Abbreviations: Bipolar I Disorder (BPI); Bipolar II Disorder (BP II); 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 r (mig) = Pearson's r reported for correlation between normally distributed continuous variables and migraine, Spearman's r reported for mania, hypomania, depression number of episodes and CTQ sexual abuse and migraine; OR (95% CI) reported for categorical variables.

^b Pearson's chi-square comparisons done for BPII using BPI as the reference group

Table 2b

Clinical Characteristics in BD Group by Gender: Comparing Men With And Without Migraine

Characteristic	No migraine (n=112)	Migraine (n=21)	r/OR ^a	p/95% CI
BPI, n (%)	100 (89)	14 (67)	ref ^b	ref ^b
BPII, n (%)	12 (11)	7 (33)	4.2	1.4–12.4
Rapid Cycling, n(%)	31 (26)	12 (55)	3.5	1.4–8.8
Mixed Symptoms, n(%)	35 (33)	10 (50)	2.0	0.8–5.3
Mixed Episodes, n(%)	27 (26)	7 (35)	1.6	0.6–4.4
Psychosis, n(%)	73 (65)	11 (50)	0.6	0.2–1.4
Suicide Attempts, n(%)	35 (30)	6 (27)	0.9	0.3–2.4
Anxiety Disorder, n(%)	31 (26)	9 (41)	2.0	0.8–5.1
Alcohol Use Disorder, n(%)	64 (53)	9 (41)	0.6	0.2–1.5
Drug Use Disorder, n(%)	29 (24)	4 (18)	0.7	0.2–2.2
Manic episodes, median (IQR)	3 (4)	1.5 (5)	–0.10	0.24
Depressive episodes, median (IQR)	4 (12)	6.5 (66)	0.19	0.03
Hypomanic episodes, median (IQR)	3 (29)	17.5 (31)	0.14	0.09
	(n=52)	n=(13)	r (mig)	p
Baseline depression, mean (SD)	9.67 (9.02)	16.54 (11.13)	0.29	0.02
Baseline mania, mean (SD)	3.56 (6.48)	3.54 (3.71)	–0.01	0.99
CTQ emotional abuse, mean (SD)	9.52 (4.36)	11.38 (5.75)	0.16	0.20
CTQ physical abuse, mean (SD)	7.62 (3.20)	8.31 (4.91)	0.08	0.54
CTQ sexual abuse, median (IQR)	5 (4)	5 (10)	0.06	0.62
CTQ emotional neglect, mean (SD)	11.06 (4.87)	12.00 (6.03)	0.08	0.55
CTQ physical neglect, mean (SD)	8.54 (2.19)	8.85 (3.26)	0.05	0.69
FACES II cohesion, mean (SD)	4.29 (2.10)	3.85 (1.78)	–0.09	0.49
FACES II adaptability, mean (SD)	4.29 (1.90)	3.46 (1.51)	–0.18	0.15
LEOS Undesirable events, mean (SD)	2.00 (2.58)	1.69 (2.21)	–0.05	0.70
LEC life events scale, mean (SD)	4.37 (3.14)	6.39 (4.48)	0.23	0.06
Neuroticism, mean (SD)	59.48 (12.86)	69.08 (10.32)	0.30	0.02
Extraversion, mean (SD)	51.58 (11.78)	45.43 (10.37)	–0.21	0.10
Openness, mean (SD)	54.81 (11.89)	59.54 (10.71)	0.16	0.20
Agreeableness, mean (SD)	49.65 (12.96)	48.69 (11.85)	–0.03	0.81
Conscientiousness, mean (SD)	44.23 (14.03)	46.08 (16.25)	0.05	0.69

Abbreviations: Bipolar I Disorder (BPI); Bipolar II Disorder (BP II); 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 r (mig) = Pearson's r reported for correlation between normally distributed continuous variables and migraine, Spearman's r reported for mania, hypomania, depression number of episodes and CTQ sexual abuse and migraine; OR (95% CI) reported for categorical variables.

^b Pearson's chi-square comparisons done for BPII using BPI as the reference group

Table 3

Multivariable models of correlates of migraine

	Bivariate	Multivariable	Multivariable	Multivariable
	r(p)/OR (95% CI)	BD/HC, β(p)^a	BD only, β(p)^b	BD men, β(p)^c
BD	N/A	6.0 (3.0–12.2)	N/A	N/A
Female	3.5 (2.1–5.8)	3.9 (2.3–6.8)	3.0 (1.6–5.6)	---
BMI	.11 (0.05)	1.04 (1.0–1.1)	<i>b</i>	<i>c</i>
Age	-.02 (.70)	---	---	---
BD age at onset	-.05 (.27)	---	---	---
BPII	2.1 (1.2–3.6)	---	<i>b</i>	---
BPII-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)	<i>c</i>
Rapid Cycling, men	3.5 (1.4–8.8)	---	---	---
Mixed symptoms	2.0 (1.3–3.0)	---	<i>b</i>	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 (SNRI) use; body mass index (BMI), BPII, and mixed symptoms eliminated from model by backward selection. “---” indicates variables that were not included in the model.^c controlled for SNRI use; BMI, rapid cycling eliminated from model by backward selection. “---” indicates variables that were not included in the model.

Table 4

Mood Outcome in BD group: Comparing Those With And Without Migraine

	No migraine	Migraine		
	N=168	n=87		Multivariable ^a
	Mean (SD)	Mean (SD)	p	β(p)
Depression severity	14.4 (7.2)	18.3 (6.3)	3×10^{-5}	0.13 (0.03)
Mania severity	7.6 (4.2)	8.9 (4.6)	0.03	0.08 (0.19)
Depression variability	4.0 (2.3)	4.6 (2.2)	0.04	0.04 (0.49)
Mania variability	2.3 (1.3)	2.8 (1.6)	0.01	0.10 (0.11)
	Median (IQR)	Median (IQR)	p	β(p)
Depression frequency	0.57 (0.74)	0.83 (0.48)	$<1 \times 10^{-3}$	0.13 (0.03)
Mania frequency	0.14 (0.42)	0.17 (0.40)	0.73	-0.03 (0.61)
Mixed frequency	0.00 (0.20)	0.09 (0.20)	0.06	0.01 (0.91)

Depression symptoms were assessed in longitudinal follow-up using the PHQ-9 and mania symptoms were assessed using the Altman Self-Rating Mania Scale (ASRM).

^aLinear regression models included age, BMI, sex, migraine, baseline mood symptoms