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Increased Illness Burden in Women with Co-Morbid Bipolar and Premenstrual Dysphoric Disorder: Data from 1,099 Women from STEP-BD Study

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Abstract

Objective—The impact of co-morbid Premenstrual Dysphoric Disorder (PMDD) in women with bipolar disorder (BD) is largely unknown. We compared illness characteristics and female-specific mental health problems between women with BD with and without PMDD.

Method—1,099 women with BD who participated in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) were studied. Psychiatric diagnoses and illness characteristics were assessed using the Mini International Neuropsychiatric Interview. Female-specific mental health was assessed using a self-report questionnaire developed for STEP-BD. PMDD diagnosis was based on DSM-5 criteria.

Results—Women with co-morbid BD and PMDD had earlier onset of bipolar illness ($p < 0.001$) and higher rates of rapid cycling ($p = 0.039$), and increased number of past-year hypo/manic

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Declaration of Interest

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($p=0.003$), and lifetime/past-year depressive episodes ($p<0.05$). Co-morbid PMDD was also associated with higher proportion of panic disorder, post-traumatic stress disorder, generalized anxiety disorder, bulimia nervosa, substance abuse, adult attention deficit disorder (all $p<0.05$). There was a closer gap between BD onset and age of menarche in women with co-morbid PMDD ($p=0.003$). Women with comorbid PMDD reported more severe mood symptoms during the perinatal period and while taking oral contraceptives ($p<0.001$).

Conclusions—The comorbidity between PMDD and BD is associated with worse clinical outcomes and increased illness burden.

Keywords

Age of onset; Bipolar disorder; Burden of illness; Menarche; Premenstrual dysphoric disorder

Introduction

The course of bipolar disorder (BD) in women is characterized by increased risk of mood instability during female-reproductive life events such as the premenstrual, perinatal and perimenopausal periods (1–3). The onset of BD in women peaks between 15–23 years of age, with depressive episodes typically preceding manic episodes(4). Compared to men, women with BD have a higher prevalence of BD type-II, more lifetime number of depressive episodes, rapid cycling, mixed features, and are burdened by more medical and psychiatric comorbidities (5–8). While the vast majority of research in women with BD has been in the area of pregnancy and the postnatal period, much fewer studies have examined the relationship between BD and premenstrual dysphoric disorder (PMDD).

PMDD affects 3–9% of women(9). PMDD has recently been acknowledged in the DSM-5 as an independent psychiatric diagnosis, whereas in the ICD-10 PMDD is diagnosed under “Other specified mood [affective] disorders”(10). A large community-based epidemiological study found that women with a diagnosis of PMDD were 8 times more likely to receive a diagnosis of BD, compared to those without PMDD(9). A longitudinal analysis of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) found that women with BD who reported “premenstrual worsening of mood” had more depressive episodes, more sub-threshold depressive and manic symptoms, and experienced an earlier relapse in the 12-month follow-up(11). Notably, several independent studies found an association between premenstrual, postnatal and perimenopausal worsening of symptoms in women with BD(12–14), suggesting that a subset of women with BD are particularly vulnerable during periods of hormonal fluctuation(15). Here, we studied a sample of 1,099 women with BD who provided detailed information on reproductive life events as part of the STEP-BD study(16).

Aims of the Study

The main objective of this study was to compare illness characteristics, prevalence of co-morbid psychiatric disorders and female-specific mental health problems between women with and without premenstrual dysphoric disorder, *using the DSM-5 definition*. We hypothesized that women with co-morbid bipolar disorder and premenstrual dysphoric

disorder have worse course of illness and higher rates of psychiatric morbidity and female-specific mental health problems.

Materials and Methods

Participants

Study participants were over 15 years of age and met DSM-IV criteria for bipolar I or bipolar II disorder. To determine a clinical diagnosis, the Mini International Neuropsychiatric Interview (MINI) Plus Version 4.4(17) and the Affective Disorder Evaluation (ADE), were administered. The ADE is a comprehensive standardized clinical interview, which assesses psychiatric history, current state, diagnosis, most severe episodes, mood symptom pattern, childhood, social and family history, past treatment and medical history. The ADE contains the mood and psychosis modules derived from the Structured Clinical Interview for DSM-IV (SCID)(18), and provides a continuous score, which can be used to diagnose bipolar disorder and its subtypes. A final, categorical diagnosis was produced using a consensus of continuous scores on the ADE and categorical MINI diagnosis (19). Inclusion into the STEP-BD study was offered by psychiatrists to all diagnostically eligible patients in STEP-BD clinics, who met the following criteria: (1) a diagnosis of bipolar disorder I, II, not otherwise specified or cyclothymia through both the MINI and the ADE; (2) age 15+; (3) informed consent to enter into the STEP-BD registry. Exclusion criteria consisted of (1) incapability or lack of will to continue with study assessments; (2) incapability of following informed consent procedures; (3) patients not being part of the outpatient program (20). Participants were excluded from the current analysis if they had met criteria for bipolar NOS, cyclothymia or schizoaffective disorder, bipolar subtype. Detailed information about the STEP-BD study is available (16). Information about past and current premenstrual symptoms was obtained through a self-report questionnaire developed from STEP-BD, which participants completed upon their entrance to the study(11). The self-report reproductive questionnaire included information about mood symptoms during reproductive events, including 14 premenstrual symptoms (crying easily, food craving, bloating, breast tenderness, feeling overwhelmed or out of control, abdominal pain, lack of energy, decreased interest in activities, irritability/anger, anxiety/tension, mood swings, depression, insomnia/hypersomnia, difficulties concentrating), symptoms experienced while taking oral contraceptives, during pregnancy and the postpartum period. It also asked detailed information about participants' early menstrual history, focusing on cycles which occurred during the first 5 years following menarche, and preceded any pregnancy or oral contraceptive consumption. As part of the reproductive questionnaire, participants self-reported having missed their menstrual period for longer than two months, other than being pregnant (11). Research ethics approval was obtained for the study from the Massachusetts General Hospital Institutional Review Board. All participants provided written signed informed consent prior to study entry, after receiving a complete description of the study. For participants aged 15–17, written informed consent was obtained from a parent or legal guardian, while written assent was obtained from the participants. The study was registered at ClinicalTrials.gov Identifier: NCT00012558.

In the present study, we used the new DSM-5 classification criteria to define PMDD diagnosis: at least 5 symptoms during the premenstrual period, including (1) at least one of the four core symptoms of premenstrual syndrome (PMS) (anxiety/tension, mood swings, depression, irritability/anger); (2) other PMS symptoms (crying easily, food cravings, bloating, abdominal pain, breast tenderness, lack of energy, decreased interest in activities, insomnia/hypersomnia, feeling overwhelmed/out of control, and difficulties concentrating), (3) reporting that the premenstrual symptoms interfered with work, school, activities and/or interpersonal relationships.

Site Selection

Sites for the STEP-BD study were chosen from formal applications, where sites provided information on their capability to provide clinical services, care and resources to patients with bipolar disorder including the following: availability of staff and clinical services; computer and telecommunication infrastructure appropriate for secure web data entry. The initial screening selected sites in the United States which had specialty bipolar disorder programs, caring for at least 100 current patients. Of these, the final sites were selected based on experience in conducting research in patients with bipolar disorder, geographic and demographic balance and diversity criteria, for instance excluding sites that were solely fee-for-service or solely Veteran's Hospital clinics. Prior to initiating the study, selected sites implemented study procedures in the clinic by contracting with the coordinating center. Staff in selected sites were stringently certified in outcome assessment, data entry and medical education in bipolar disorder prior to initiating the study, gathering data, seeing and treating patients within STEP-BD. The following sites ultimately participated in STEP-BD: Baylor College of Medicine, Case Western Reserve University, Cornell University/New York Presbyterian Hospital, Howard University, Massachusetts General Hospital, New York University/Bellevue Hospital Center, Portland Veteran's Administration Medical Center, Stanford University School of Medicine, University of Colorado Health Sciences Center, University of Louisville Medical School, University of Massachusetts Medical School, University of Missouri at Kansas City, University of Oklahoma Health Sciences Center, University of Pennsylvania Medical Center, University of Pittsburgh Medical Center/Western Psychiatric Institute, and University of Texas at San Antonio; Medical University of South Carolina, University of Arizona, University of California-San Diego, University of Maryland, State University of New York at Buffalo, and Rush–Presbyterian St. Luke's Medical Center.

Statistical Analysis

Statistical analysis was performed using IBM SPSS statistical software, version 22.0.0.0 for Macintosh(21). The distribution of the data was evaluated using the Shapiro test for normality, and Levene's test for equality of variances. We used independent t-tests to compare continuous variables between women with and without PMDD for normally distributed variables. For non-parametric variables, we used the Mann Whitney U test to compare continuous variables between groups. To compare categorical variables between women with and without PMDD, including demographics and illness comorbidities we performed chi-square tests, and calculated odds ratios. We conducted a log rank test to compare age of onset for bipolar disorder between women with and without PMDD, and to

evaluate the gap between menarche and onset of bipolar disorder. We created Kaplan-Meier survival curves, and compared these using the log-rank test, to determine whether these were statistically different. To test whether history of PMDD had an independent effect on risk of psychiatric comorbidities, rapid cycling, number of episodes and antidepressant-induced mania, we performed binomial and multinomial logistic regression analyses. Binomial logistic regressions were used for binary outcomes (psychiatric comorbidity, rapid cycling, and antidepressant-induced mania). Each regression included age of onset of BD and PMDD diagnosis. Multinomial logistic regressions were used to analyze non-binary outcomes: total number of episodes (lifetime and past-year), and number of hypo/manic and depressive episodes (lifetime and past-year). The STEP-BD study collected information on number of episodes categorically. Lifetime and past year total number of episodes was described in categories: (0, 1, 2, 3, 4, 5–12, 13–52, 53+). Data concerning lifetime number of hypo/manic and depressive episodes were collected in the following categories: (0, 1, 2, 3–4, 5–9, 10–20, 20–50, too many to count). Finally, data concerning past-year number of depressive and hypo/manic episodes were collected as a continuous measure. Due the use of these discrepant categories, we standardized this information into a smaller number of categories which were more comparable between lifetime and past-year number of episodes. Total number of past-year and lifetime episodes were categorized according to number of episodes (0, 1, 2–12, 13 +), as were past-year and lifetime hypo/manic and depressive episodes (0, 1, 2–9, 10+). In these multinomial regressions, we controlled for age of onset and lifetime comorbidities which were significantly associated with PMDD. All tests were performed using $\alpha=0.05$ as the level of significance.

Results

Demographics

We studied 1,099 women with a diagnosis of bipolar I or bipolar II disorder who completed the self-report reproductive questionnaire (11). There were no differences in age, race, marital status or employment status between women with or without PMDD ($p>0.05$, Table 1). Women with co-morbid PMDD had achieved a lesser level of education than women with no PMDD ($p=0.03$).

Illness Characteristics

Women with and without PMDD were equally likely to have bipolar I or II disorder, and did not differ in terms of first episode polarity (Table 2). Women with PMDD had an earlier age of onset compared to women without PMDD (14.6 ± 6.4 vs. 16.7 ± 7.6 , $p<0.001$, Figure 1a), including earlier onset of both hypo/manic and depressive episodes ($p<0.001$). In unadjusted analyses, women with PMDD were more likely to report rapid cycling (OR=1.94, 95%CI: 1.44, 2.62), antidepressant-induced mania (OR=1.31, 95% CI: 1.02, 1.69), as well as greater number of depressive and hypo/manic episodes both lifetime and in the past year ($p<0.01$). However, after controlling for age of onset and psychiatric comorbidities, presence of PMDD was still associated with higher risk of rapid cycling (OR = 1.43, 95%CI: 1.02, 2.01), but the differences in antidepressant-induced mania and total number of lifetime and past-year mood episodes were no longer significant. Women with co-morbid PMDD had higher

number of past-year hypo/manic ($p=0.003$), and lifetime/past-year depressive episodes ($p<0.05$).

Psychiatric Comorbidities

Women with co-morbid PMDD were more likely to have a lifetime history of an anxiety disorder (OR=2.10, 95%CI: 1.61, 2.72, Figure 2). More specifically, women with PMDD were more likely to have a diagnosis of generalized anxiety disorder (GAD) (OR=1.88, 95%CI:1.43, 2.49), panic disorder with (OR=2.03, 95%CI: 1.47, 2.79) and without agoraphobia (OR=1.81, 95%CI: 1.18, 2.79), but not history of lifetime agoraphobia only (OR=1.12, 95%CI: 0.72, 1.74). There were no differences in diagnosis of obsessive compulsive disorder (OCD) (OR=1.28, 95%CI: 0.89, 1.84) or social phobia (OR=1.30, 95%CI: 0.98, 1.72) between the groups.

Women with co-morbid PMDD were more likely to have a lifetime history of alcohol abuse (OR=1.74, 95%CI: 1.34, 2.26) or dependence (OR=1.60, 95%CI:1.22, 2.12), as well as lifetime substance abuse (OR=1.49, 95%CI:1.11, 1.99) or dependence (OR=1.47, 95%CI: 1.08, 2.01). Furthermore, lifetime history of bulimia nervosa was more prevalent among women with PMDD (OR=2.43, 95%CI: 1.64, 3.60), but not anorexia (OR=1.25, 95%CI: 0.74, 2.10). Finally, women with co-morbid PMDD were also more likely to have a history of post-traumatic stress disorder (PTSD) (OR=1.94, 95%CI: 1.47, 2.57) and adult attention deficit and hyperactivity disorder (ADHD) (OR=1.76, 95%CI: 1.18, 2.62).

After controlling for age of BD onset, presence of PMDD was still associated with greater likelihood of co-morbid panic disorder without agoraphobia (OR= 1.74, 95%CI: 1.13, 2.69); panic disorder with agoraphobia (OR= 1.92, 95%CI: 1.39, 2.65); PTSD (OR=1.79, 95%CI: 1.34, 2.38), GAD (OR=1.79, 95%CI:1.35, 2.38); alcohol dependence (OR= 1.52, 95%CI: 1.14, 2.01); alcohol abuse (OR= 1.74, 95%CI: 1.34, 2.27); drug abuse (OR=1.42, 95%CI: 1.05, 1.91); adult ADHD (OR=1.53, 95%CI:1.02, 2.31) and bulimia nervosa (OR= 2.41, 95%CI: 1.57, 3.71). The only comorbidity that did not survive this adjustment for age of onset was drug dependence (OR= 1.35, 95%CI:0.98, 1.85).

Female-specific Mental Health

Women with co-morbid PMDD reported earlier age of menarche ($p=0.015$). Notably, there was shorter span of time between the age of menarche and the onset of BD in women with PMDD ($p<0.003$, Table 2, Figure 1b). As far as a possible link with other periods of intense hormonal fluctuation, women with PMDD were more likely to report severe mood symptoms during pregnancy (OR=2.38, 95%CI: 1.73, 3.28) or in the postnatal period (OR=1.92, 95%CI: 1.35, 2.72) compared to women without PMDD. Finally, women with PMDD were more likely to report severe mood symptoms while taking oral contraceptives (OR=2.60, 95%CI: 1.97, 3.43). Women with and without PMDD were equally likely to report a history of having missed their menstrual period for more than 2 months, excluding pregnancies (OR=0.93, 95%CI: 0.73, 1.18).

Discussion

Illness Characteristics

One of the most important findings of this study is that women with co-morbid PMDD had an earlier age of onset of BD. Given that earlier age at onset has been widely associated with worse clinical and functional outcomes in BD, this suggests that the comorbidity with PMDD is associated with increased illness burden. We also found that women with PMDD have higher rates of rapid cycling and more past-year hypo/manic and past-year/lifetime depressive episodes. While the literature is inconsistent in terms of increased risk of rapid cycling, with both positive (22) and negative (12) findings, our results are consistent with a previous report of an earlier age onset in women with BD and premenstrual syndrome (23). Our study suggests that women with co-morbid PMDD may represent a subtype of individuals with higher sensitivity to mood instability associated with fluctuation of endogenous hormones (13,15). A recent study of 158 women with BD found that an earlier age of onset was associated with mood worsening during reproductive life events, and that earlier onset of depressive episodes was linked to more mood instability during use of oral contraceptives (13).

Psychiatric Comorbidities

We found that women with co-morbid PMDD had higher rates of other psychiatric disorders, including panic disorder, GAD, PTSD, lifetime alcohol and drug abuse, bulimia and adult ADHD (Figure 2).

Our results are inconsistent with a small study of 92 women with BD that did not find differences in comorbidity of GAD, panic disorder, agoraphobia, anorexia, bulimia, alcohol or substance abuse (12). Also contrary to our study, this latter study reported higher rates of OCD in women with BD and co-morbid PMDD (12). The association of premenstrual symptoms and substance use has been previously reported in a cohort of women with PMS (24), and in a community-based cohort where illicit substance use preceded the onset of PMS (25). A novel finding in our sample is that women with co-morbid PMDD were more likely to be diagnosed with adult ADHD. Though previous studies have pointed to cognitive deficits associated with PMDD (e.g. 26), this association, to our knowledge, has not been reported in any population.

Eating disorders are highly prevalent among women with BD. Bulimia nervosa has a 15% prevalence among individuals with BD, while a further 12% report binge eating disorder, and 0.2% report anorexia nervosa (27), compared to the 0.9% and 1.5% lifetime prevalence of anorexia and bulimia nervosa in the US, respectively(28). Interestingly, a recent large epidemiological study (N=8,694) found that women with PMDD were 8× more likely to receive a diagnosis of bulimia nervosa (29).

Female-specific Mental Health

A novel finding of our study was that women with co-morbid PMDD had an earlier age at menarche, and, perhaps more importantly, the age of onset of BD was closer to the menarche in women with PMDD compared to those without PMDD. Previous smaller studies have

supported an association between onset of BD and menarche (30), and in case our result is replicated in an independent large study this may open a venue for research on the role of hormones/puberty on the onset of BD.

We also found that women with co-morbid PMDD reported greater mood instability during pregnancy, postnatal period and use of hormonal contraceptives, which suggests that these women may represent a particular subtype with increased vulnerability to mood worsening during periods of intense hormonal fluctuation. Previously, Payne and colleagues did not find an association between premenstrual symptoms and postpartum symptoms in women with bipolar I disorder, though this association was present in women with major depressive disorder(31). More recently, Fornaro & Perugi(12) found that history of postnatal depression was associated with diagnosis of PMDD among women with BD, consistent with Perich et al.(13) who also found a link between postnatal mood episodes and premenstrual symptom worsening in women with BD. Our finding that women with co-morbid PMDD are more likely to report severe mood symptoms while using hormonal contraceptives is a novel finding. The literature on the impact of hormonal contraceptives in women with BD is scant and inconsistent. For instance, Freeman et al.(32) did not find an association between contraceptive agents and mood worsening in a sample of 50 women with BD, while Perich et al.(13) found that 35% of women with BD reported worsening of mood symptoms associated with contraceptive use. Finally, we have recently published clinical cases of women with co-morbid BD and PMDD who responded well to hormonal contraceptives adjunctive to mood stabilizers for treatment of PMDD (33,34).

Strengths and Limitations

One of the strengths of this study is the sample size (n=1,099). To our knowledge, this is the largest study investigating the burden of illness in women with co-morbid BD and PMDD. Another strength was the careful clinical characterization of the study population that allowed us to investigate the rates of other co-morbid psychiatric disorders. Also, the use of a detailed questionnaire of reproductive life events allowed us to define the PMDD cases based on the DSM-5 criteria. In terms of limitations, this study was a post-hoc analysis and was not originally designed to investigate the impact of co-morbid PMDD in women with BD. Mood symptoms and history of past manic and depressive episodes were obtained through self-report and were, therefore, subject to recall bias. Moreover, our study design did not enable us to confirm the presence of premenstrual symptoms through prospective symptom charting, as per the current standards of PMDD diagnosis. However, the DSM-5 criteria allow the diagnosis of “provisional PMDD” before the prospective evaluation of symptoms is completed, and it is very unlikely that any study with a sample size in the range of thousands will be able to conduct daily prospective symptom charting. In fact, the challenge of prospective data collection in large cohorts of women with PMDD is well documented, where less than half of women tend to complete the prospective charting required for a formal diagnosis (35). Additionally, the STEP-BD study collected information on number of episodes categorically, where lifetime and past-year total number of episodes and lifetime number of manic and depressive episodes were collected using different categorization, whereas data concerning past-year number of depressive and manic episodes were collected as a continuous measure. This discrepancy may explain why we found

differences between women with and without PMDD in past-year hypo/manic episodes and lifetime and past-year depressive episodes, but not in total lifetime and past-year number of episodes. Finally, the cohort of women in STEP-BD mostly consisted of Caucasian women (88.7%), which limits our ability to generalize these results cross-culturally.

In summary, our results support converging evidence suggesting that some women with BD might be particularly vulnerable to mood instability during periods of intense hormonal fluctuation. The closer gap between age of menarche and the onset of BD in women with co-morbid PMDD is intriguing and should stimulate future research to identify the women at higher risk.

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Significant Outcomes

- Women with co-morbid BD and PMDD had increased illness burden marked by earlier age of illness onset, higher rates of rapid cycling and more number of depressive and hypo/manic episodes.
- BD with co-morbid PMDD was associated with more comorbidities including anxiety disorders, post-traumatic stress disorder, bulimia nervosa, substance abuse, and adult attention deficit disorder.
- Findings of a shortened gap between menarche and BD onset in women with PMDD set a precedent for research on hormones in BD onset.

Limitations

- This study was a post-hoc analysis, not originally designed to investigate the impact of co-morbid PMDD in women with BD.
- Our study design did not enable us to confirm the presence of premenstrual symptoms through prospective symptom charting.
- The cohort of women in STEP-BD mostly consisted of Caucasian women, which limits our ability to generalize these results cross-culturally.

Figure 1.

Kaplan-Meier survival plots and log-rank test results of a) age of onset of bipolar disorder in women with and without premenstrual dysphoric disorder; b) gap between age menarche and onset of bipolar disorder in women with and without premenstrual dysphoric disorder. Abbreviations: PMDD = Premenstrual Dysphoric Disorder

Figure 2.
 Psychiatric comorbidities in women with and without premenstrual dysphoric disorder
 comorbid with bipolar disorder
 *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$. Abbreviations: PMDD = Premenstrual Dysphoric
 Disorder.

Table 1

Demographic Characteristics of Women with Bipolar Disorder Part of STEP-BD

	PMDD			No PMDD			T Statistic (df)	Sig.
	Mean	SD		Mean	SD			
Age, mean (SD)	34.07	9.06		34.43	9.76		-0.62 (1,097)	0.536
Race	n	%		n	%		Chi Sq.	Sig.
White or Caucasian	447	90.1		541	89.9		7.216	0.205
Black or African American	33	6.7		30	5.0			
Native American, Eskimo, or Aleut	4	0.8		2	0.3			
Asian or Pacific Islander	5	1.0		16	2.7			
No Primary Race	2	0.4		3	0.5			
Other	5	1.0		10	1.7			
Marital Status								
Single/Divorced/Widowed/Separated	305	61.7		390	65.5		1.693	0.193
Married/Common Law	189	38.3		205	34.5			
Education								
Less than 7th Grade	1	0.2		0	0.0		15.281	0.033
7th – 9th Grade	4	0.8		3	0.5			
Partial High School	17	3.4		14	2.4			
High School Diploma/GED	71	14.4		61	10.3			
Some college	148	30.0		171	28.7			
Technical School or Associate Degree	58	11.8		59	9.9			
College Diploma (Bachelor's Degree)	139	28.2		184	30.9			
Graduate or Professional Degree	55	11.2		103	17.3			
Current Employment Status								
Full-time	146	29.8		177	29.9		11.771	0.108
Part-time for pay	81	16.5		99	16.8			
Homemaker	44	9.0		40	6.8			
Disabled	70	14.3		85	14.4			

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	PMDD			No PMDD			T Statistic (df)	Sig.
	Mean	SD	n	Mean	SD	n		
<i>Age, mean (SD)</i>	34.07	9.06		34.43	9.76		-0.62 (1,097)	0.536
Leave of Absence	6	1.2	15					
Unemployed	136	27.8	150					
Retired	2	0.4	8					
Other	5	1.0	17					

Abbreviations: Chi Sq = Chi Square Statistic; GED = General Education Diploma; PMDD = Premenstrual Dysphoric Disorder; SD = Standard Deviation; Sig. = Significance; STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

Table 2
Mood and Female-Specific Mood Characteristics of Women with and without Premenstrual Dysphoric Disorder

	PMDD			No PMDD			OR (95% CI)	Chi Sq.	Sig
	n	%	n	%	n	%			
Lifetime Diagnosis									
Bipolar I	322	64.8	410	68.1		0.86 (0.67, 1.11)	1.347		0.246
Bipolar II	175	35.2	192	31.9					
First Episode Polarity									
Manic Onset	81	18.1	100	18.5		0.97 (0.70, 1.35)	0.027		0.870
Depressive Onset	367	81.9	441	81.5					
Antidepressant Mania									
Yes	203	44.9	215	38.3		1.14 (0.87, 1.50)			n.s.
No	249	55.1	346	61.7					
Rapid Cycling									
Yes	207	64.9	204	48.8		1.43 (1.01, 2.01)			0.039
No	112	35.1	214	51.2					
Severe Mood Symptoms During Pregnancy									
Yes	179	57.0	112	35.8		2.38 (1.73, 3.28)	29.389		<0.001
No	135	43.0	201	64.2					
Severe Mood Symptoms During Postpartum									
Yes	174	65.2	126	49.4		1.92 (1.35, 2.72)	13.249		<0.001
No	93	34.8	129	50.6					
Severe Mood Symptoms while taking Oral Contraceptive Pills									
Yes	207	50.7	134	28.4		2.60 (1.97, 3.43)	46.038		<0.001
No	201	49.3	338	71.6					
Total Number of Episodes – Lifetime									
0	4	0.8	4	0.7		1.00 (Ref)			
1	4	0.8	9	1.5		0.85 (0.11, 6.55)			n.s.
2 to 12	91	18.3	182	30.2		0.86 (0.18, 4.18)			n.s.
13 or more	203	40.8	203	33.7		1.29 (0.27, 6.18)			n.s.
Missing	195	39.2	204	33.9		1.32 (0.28, 6.30)			n.s.

PMDD vs No PMDD									
	PMDD			No PMDD					
	n	%	n	%	OR (95% CI)	Chi Sq.	Sig		
Number of Hypo/Manic Episodes – Lifetime									
0	4	0.8	6	1.0	1.00 (Ref)				
1	25	5.0	47	7.8	1.17 (0.16, 8.71)				n.s.
2 to 9	142	28.6	253	42.0	1.02 (0.15, 7.17)				n.s.
10 or more	265	53.3	238	39.5	1.76 (0.25, 12.34)				n.s.
Missing	61	12.3	58	9.6	1.71 (0.24, 12.43)				n.s.
Number of Depressive Episodes – Lifetime									
0	4	0.8	20	3.3	1.00 (Ref)				
1	12	2.4	30	5.0	6.96 (0.80, 60.43)				n.s.
2 to 9	141	28.4	217	36.0	8.66 (1.11, 67.71)				0.040
10 or more	285	57.3	273	45.3	11.20 (1.44, 87.40)				0.021
Missing	55	11.1	62	10.3	9.27 (1.15, 74.57)				0.036
Total Number of Episodes – Past Year									
0	41	8.2	77	12.8	1.00 (Ref)				
1	68	13.7	113	18.8	1.03 (0.61, 1.72)				n.s.
2 to 12	231	46.5	257	42.7	1.35 (0.86, 2.11)				n.s.
13 or more	42	8.5	26	4.3	1.88 (0.96, 3.69)				n.s.
Missing	115	23.1	129	21.4	1.29 (0.79, 2.13)				n.s.
Number of Hypo/Manic Episodes – Past Year									
0	87	17.5	153	25.4	1.00 (Ref)				
1	122	24.5	178	29.6	1.25 (0.86, 1.82)				n.s.
2 to 9	182	36.6	164	27.2	1.59 (1.10, 2.29)				0.013
10 or more	62	12.5	39	6.5	2.19 (1.31, 3.65)				0.003
Missing	44	8.9	68	11.3	0.93 (0.55, 1.57)				n.s.
Number of Depressive Episodes – Past Year									
0	44	8.9	113	18.8	1.00 (Ref)				
1	139	28.0	179	29.7	1.95 (1.25, 3.06)				0.003
2 to 9	209	42.1	209	34.7	1.96 (1.27, 3.04)				0.003
10 or more	28	5.6	20	3.3	2.72 (1.33, 5.56)				0.006
Missing	77	15.5	81	13.5	1.87 (1.11, 3.15)				0.020

	PMDD			No PMDD			OR (95% CI)	Chi Sq.	Sig
	n	%	n	%	n	%			
Age at First Episode	14.62	6.37	16.75	7.52			169,134.000 (5.013)		<0.001
Age at First Episode – Hypo/Mania	18.97	7.79	21.13	8.47			160,031.500 (4.706)		<0.001
Age at First Episode - Depression	15.24	6.70	17.31	7.75			149,018.000 (4.570)		<0.001
Duration of Illness	19.43	9.79	17.68	10.39			2.823 (1.076)		0.005
Age at Menarche	12.39	1.66	12.68	1.61			131,965.500 (2.979)		0.003
Menarche/Bipolar Onset	1.51	6.45	3.05	7.67			166,107.000 (3.162)		0.002

Abbreviations: Chi Sq = Chi Square Statistic; CI = Confidence Interval; OR = Odds Ratio; PMDD = Premenstrual Dysphoric Disorder; SD = Standard Deviation; Sig. = Significance.