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Menstrual effects on mood symptoms in treated women with bipolar disorder

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Abstract

Objectives—Reports suggest women with bipolar disorder (BD) have high rates of perimenstrual mood worsening. In this prospective study, the authors compared healthy controls and depressed and euthymic BD patients on medications on mood levels, psychosocial function, and physical symptoms in the late luteal versus the early follicular phase.

Methods—At baseline, the lifetime diagnosis of bipolar I disorder or bipolar II disorder, current mood episode, and absence of premenstrual dysphoric disorder in controls were confirmed with the Structured Clinical Interview for DSM-IV Disorders. Subjects were assessed across three menstrual cycles during the late luteal and early follicular phases. Clinicians administered the Structured Interview Guide for the Hamilton Depression Rating Scale and the Mania Rating Scale to assess levels of depression and hypomania/mania, respectively. Subjects completed self-report ratings on psychosocial function and perceived stress and tracked daily mood and physical symptoms on the National Institute of Mental Health LifeChart and the Daily Rating Form. Ovulation was verified objectively with mid-cycle luteinizing hormone urine dipsticks and serum progesterone levels.

Results—The sample characteristics were similar among the three patient groups of healthy controls (10 patients), BD-euthymic (6), and BD-depressed (5). The two-way analysis of variance indicated a significant difference among the diagnostic groups on depression scores, psychosocial functioning, and levels of perceived stress. There was no significant difference for menstrual phase or the interaction of menstrual phase by diagnostic group.

Conclusions—Mood symptom level, psychosocial functioning, perceived stress, and physical discomfort were unrelated to menstrual phase in patients with BD. Appropriate maintenance treatment may prevent menstrual related mood symptoms. Use of an objective marker of ovulation is critical for research involving menstrual related outcomes.

Keywords

bipolar disorder; follicular phase; luteal phase; menstrual cycle; women

Bipolar disorder (BD) type I (BD-I) affects women and men equally (1). In contrast, variants of bipolar illness such as BD type II (BD-II), mixed states, and rapid-cycling illness are

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more common in women (2, 3). Once the mood episode has resolved, residual symptoms persist in 50% of patients (4). Women with BD are burdened with considerable family, social, and occupational dysfunction and lowered quality of life (5).

The pattern of mood variability related to menstrual cycles in women with bipolar illness has not been well-characterized. As high as 66% of women with BD-I regularly experience perimenstrual mood worsening (6). In case series and retrospective reviews, patients reported heightened perimenstrual mood symptoms and the onset of rapid-cycling that required hospitalization during the premenstrual phase (7, 8). Oral contraception (OC) has shown to alleviate mood variability in 50% patients with BD who suffer menstrual-related mood worsening (7), with monophasic pills alleviating dysphoria more effectively than phasic pills (9). However, increased aggression and irritability have been noted in patients who received androgenic progestins compared to the newer progestins (desogestrel, levonorgestrel, norgestimate, or drospirenone) (10, 11). Therefore, it is difficult to interpret data without precise descriptions of the OC agents that women received. Interpretation of earlier data are limited in other ways: (i) failure to control for the current mood episode, (ii) retrospective reporting, (iii) small samples, (iv) insufficient observational period from a single cycle or single menstrual phase; (v) no objective measure to confirm ovulation, and (vi) unclear methodology (12).

Women with premenstrual dysphoria are more likely to experience mood disorders compared to women without premenstrual symptoms (13, 14), and Premenstrual Dysphoric Disorder (PMDD) is one such discrete menstrual-related mood disorder. The defining characteristics of PMDD [a cyclic pattern of dysphoria, irritability, and mood lability (15)] suggests clinical similarities to bipolar illness; for example, a rapid-cycling illness or mixed episodes in which patients have concurrent symptoms of a depressive and hypomanic/manic episode. Despite clinical similarities between PMDD and BD in women, few studies have been undertaken to investigate associations between menstrual cycles and BD. The rate of PMDD in women who also have bipolar illness is unknown. Leibenluft (2) was unable to detect a predictable or specific pattern of menstrual-linked mood variability in women with BD and rapid cycling. Controlled, prospective research to elucidate the link between these disorders is needed (2).

Physical problems related to the menstrual cycle affect a subset of women with BD. Among 80 patients with BD, 65% had menstrual irregularities and 38% developed new menstrual abnormalities after starting medications (16). Although the antimanic agent valproate disrupts ovarian function and is associated with polycystic ovarian syndrome in 10% of women receiving this agent (16, 17), women who tolerate maintenance valproate therapy benefited from improved mood stability and resolution of troubling premenstrual symptoms, even compared to healthy controls (18).

The induction of anovulation is beneficial for reducing symptoms of PMDD. Treatments for PMDD include the suppression of ovulation with OC treatment or gonadotropin releasing hormone (GnRH) agonists, and the adding back of estradiol and progesterone results in the re-emergence of mild to severe menstrual symptoms (19). However, some patients may be susceptible to the mood-impairing effects of anovulation. Stress-induced functional hypothalamic amenorrhea has been described in women with severe depression and interpersonal sensitivity when compared to healthy controls (20) indicating that the data on anovulation and mood symptoms is not entirely consistent. Anovulation from peripheral hormone therapy is associated with menstrual related dysphoria, whereas anovulation from central stress factors could exacerbate mood symptoms. From these reports, the connection between menstrual cycles and bipolar mood exacerbations remains unclear.

In this prospective observational study, the authors characterized mood symptoms, psychosocial functioning, and perceived stress throughout the menstrual cycle. We hypothesized that depressed or euthymic women with BD would have (i) increased levels of depression and hypomanic/manic symptoms, (ii) decreased psychosocial functioning, (iii) elevated levels of perceived stress, and (iii) physical discomfort in the late luteal (LL) phase compared to the early follicular (EF) phase when compared to healthy controls.

Patients and methods

The study protocol was approved by the University of Pittsburgh Institutional Review Board, Pittsburgh, PA, USA. All subjects provided written informed consent. At baseline, the lifetime diagnosis of BD-I or BD-II, current mood episode, and absence of PMDD in controls were confirmed with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (21). Age, race, number of past BD episodes, hospitalizations, medical history, medications, and alcohol use were recorded. Enrolled women were 18-45 years of age with regular menstrual cycles (length: 25-31 days with at least six cycles/year, i.e., not anovulatory). Women with current alcohol or substance abuse or dependence, pregnancy or known anovulation (from use of OC or GnRH therapy, polycystic ovarian syndrome), menopause (< 1 menses/year), or uncontrolled thyroid disease were not enrolled. We focused on the comparison of women with BD and healthy women to explore for differences in premenstrual mood and physical symptoms across menstrual phases noting that the presence of increased premenstrual symptoms could uncover a primary disorder such as unipolar depression. Following evaluation with the SCID-I, women with PMDD, functionally impairing premenstrual syndrome, unipolar depressive disorder, or a primary psychotic disorder were excluded from the study. Based on the SCID-I diagnosis, BD-I or BD-II patients without current major depression, hypomanic, manic, or mixed episode (i.e., currently euthymia) were defined as *BD-euthymic*. Patients with BD-I or BD-II and a current episode of major depression were defined as *BD-depressed*. We excluded patients with SCID-I criteria for a current hypomanic, manic, or mixed episode, and clinically significant hypomanic/manic symptom levels [Mania Rating Scale (MRS) ≥ 5]. The final study sample included 10 healthy female controls and 11 women with BD (6 euthymic and 5 depressed).

At baseline and at 1-, 2-, and 3-month visits, subjects underwent clinician-rated evaluations for depression levels with the Structured Interview Guide for the Hamilton Depression Rating Scale with the Atypical Depression Supplement (SIGH-ADS) (22). Atypical symptoms such as hypersomnia, lethargy, and increased appetite are important to assess since they are common in women with mood disorders and are reported frequently by patients with bipolar depression. Additionally, the symptoms contribute to considerable problems in functioning. We assessed mania/hypomania levels at every visit with the clinician-rated MRS (23). The SIGH-ADS and MRS ratings were used to confirm the clinical status of participants assigned to the BD-euthymic (SIGH-ADS ≤ 9 and MRS ≤ 4) and BD-depressed (SIGH-ADS ≥ 10 and MRS ≤ 4) groups. We obtained self-report ratings of psychosocial function on the Short-Form Health Survey (SF-12) (24) and perceived stress, during the LL and EF phases. The clinical rater (DS) was blinded to the subjects' menstrual phase. We counterbalanced for order and equal number of assessments in each menstrual phase. New episodes, medication exposure, and alcohol use were recorded.

Menstrual chart

The menstrual cycle was divided into four epochs: *Epoch1* (EF) = day 3 (third day after menses) to day 8; *Epoch2* (late follicular phase): days 9 to 14 after menstruation [final day Epoch2 = day of luteinizing hormone (LH) surge]; *Epoch3* (early luteal phase): days -14 to -7 before menstruation (day -7 = 7 days post-LH surge); *Epoch4* (LL): days -6 to -1 before menstruation. Ovulation was verified with the LH surge urine dipstick 8-14 days after the

first day of menses (25) and serum progesterone levels at 7-days post-LH surge performed at the University of Pittsburgh, Magee Womens Hospital General Clinic Research Center, Research Laboratory (NIH/NCRR grant# MO1-RR000056).

Subjects charted their menstrual mood and physical symptoms daily on the modified Daily Rating Form (DRF) (26), the onset and days of menses, and their urine dipsticks for the LH surge. The DRF is a self-rating scale with confirmed validity for assessing PMDD-type symptoms of mood, labile mood, anxiety, irritability, vegetative symptoms, and interpersonal function.

Mood chart

The National Institute of Mental Health (NIMH)-prospective life chart is a self-report instrument with high construct validity for depression (27). Daily mood level is ranked as follows: 0 = severe depression (incapacitated or requiring hospitalization); 1 = moderate depression with difficulty in functioning; 2 = moderate depression but able to function; 3 = mild depression; and 4 = euthymic mood. Similarly, manic or hypomanic symptom severity is ranked as: 5 = mild; 6 = moderate but able to function; 7 = moderate with difficulty in functioning; and 8 = severe (incapacitated/requires hospitalization). Daily levels of irritability and generalized anxiety were ranked as follows: 0 = none, 1 = mild, 2 = moderate, 3 = severe; with subjects also recording the number of hours slept each day. Suicidality was tracked daily as follows: 0 = none; 1 = feelings of life not worth living; 2 = wishes to be dead; 3 = suicidal ideation without attempt or self-injury; 4 = actual suicide attempt. Each subject was informed that if she scored 3 or more on the suicidality item that she must immediately contact the study physician (DS) and her own treatment team, comprised of her psychiatrist, therapist and other supports, including the emergency room. The self-report charts were reviewed at every study visit by the principal investigator to monitor subject safety.

Outcome measures

The outcome measures were the SIGH-ADS, MRS, SF-12, and perceived stress scores and the mean NIMH-life chart and DRF scores for corresponding days of each menstrual Epoch. Since menstruation could affect mood and physical symptoms in the first three days of the EF phase, the mean daily rating scores for Epoch1 were assessed with and without the first three days. As the mean ratings were not significantly different, we report the scores with the first three days of Epoch1.

Statistical analysis

We assessed the sample characteristics of all the subjects which included age, age of menarche, number of ovulatory cycles, cycle length, number of EF phases, number of early luteal phases, and number of LL phases (Table 1). For the subjects with BD, we also assessed the age of onset, number of years of illness, number of antimanic drug treatments, and antidepressant therapy (Table 1). To investigate possible differences among the diagnostic groups of healthy control, BD-euthymic, and BD-depressed subjects, we used the analysis of variance (ANOVA), Pearson's chi-square test, and Fisher's Exact test (count data). To examine differences among the diagnostic groups, menstrual phases, and the interaction of diagnosis, and menstrual phase on the continuous measures of mood levels, psychosocial function, and perceived stress, we used the two-way ANOVA (Table 2). For the exploration of the mood and physical symptoms obtained from the NIMH-life chart and the DRF forms, we used linear mixed-effects and logistic-regression models.

To verify data completeness, we assessed the number of ovulatory cycles for which we had clinician-rated and self-report data for the subjects. We confirmed that all subjects provided

data across a mean of 3.0 ± 1.7 ovulatory cycles; the patients in the healthy control, BD-euthymic and BD-depressed groups provided data for 2.4, 2.3, and 3.2 cycles respectively (Table 1). We then calculated the number of daily observations in the EF and LL phases which we would expect from a complete data set (i.e., from 21 subjects with three months of self-report data). A typical patient would have 6 ± 2 days of EF and 6 ± 2 days of LL phases (see Methods). A complete self-report data set would include 756 ± 252 days of observations. We obtained a mean of 615 observations (range: 543-713, median = 651, mode = 695) from the subjects (19 subjects provided complete data and 16-21 subjects provided partial or complete data). For the clinician-rated forms completed at office visits: we verified that 21 subjects completed 55 office visits, 19 subjects completed all visits, and 19-21 attended some or all visits (Table 2). This exploration provides assurance that we obtained sufficient observations for the clinician- and self-report items to warrant statistical analyses.

We (HS and DS) managed the extensive self-report data with procedures to reduce the data using clinically informed algorithms that we implemented in the *R*-computer language (www.r-project.org) (28). These procedures allowed us to analyze the extensive data with standard statistical methods. The algorithms involved (i) checks to ensure that the dates of the participants' self-report data mapped onto the dates of the biologically confirmed ovulatory cycles (from the urine LH surge tests and serum progesterone levels); (ii) isolation of data obtained from ovulatory cycles only and data from one or more contiguous cycles for use in the analyses; and (iii) further isolation of data from the defined menstrual cycle Epochs to allow for analyses of data representing the EF and LL menstrual phases.

Results

The mean age of participants was 32 years; the mean age of menarche was 11.7 years. There were no significant differences among the diagnostic groups on age or menarchal age (Table 1). We included 7 patients with BD-I and 4 patients with BD-II; the BD-euthymic group included 5 BD-I and 1 BD-II patients; the BD-depressed group included 2 BD-I and 3 BD-II patients. Among the patients with BD, most patients ($n = 7$) received the combination of mood-stabilizing and antidepressant drug therapy, 3 received only mood-stabilizing drug monotherapy, and 1 received fluoxetine only (at baseline, she added lithium by the third visit). The mood-stabilizing agents included: lamotrigine ($n = 4$), aripiprazole ($n = 3$), carbamazepine ($n = 5$), valproate ($n = 2$), lithium ($n = 2$), and risperidone ($n = 1$); the antidepressants included: bupropion sustained release ($n = 3$), sertraline ($n = 2$), citalopram ($n = 1$), and fluoxetine ($n = 1$).

In the BD-euthymic group, we confirmed that the six patients had no hypomanic or manic symptoms at baseline and follow-up visits (MRS = 0, consistently). In the BD-depressed group, 3 patients had depressive symptoms with no or minimal hypomanic symptoms (MRS = 0-6) at baseline and follow-up; 2 received mood-stabilizing and antidepressant therapy; and 1 received only mood-stabilizing drug therapy. Two BD-depressed patients developed mild mixed symptoms at one or more follow-up visits (MRS = 8-13); one received mood-stabilizing drug therapy only; and one received fluoxetine only (these two patients required medication adjustment to alleviate their symptoms: one switched from depakote to carbamazepine and the other added lithium therapy).

Comparing the depressed and euthymic patients with BD, we detected no significant differences on age of onset, number of years of illness, mood-stabilizing agents, concomitant antidepressant therapy, or exposure to valproate (Table 1). Among the diagnostic groups, the two-way ANOVA indicated a significant difference on depression levels (SIGH-ADS: $df = 2$, F -statistic = 38.14, $p < 0.001$), the mental component of psychosocial functioning (SF-12:

df = 2, F -statistic = 76.21, $p < 0.001$), and perceived stress (df = 2, F -statistic = 11.94, $p < 0.001$); and a possible significant difference on hypomanic symptoms (MRS: df = 2, F -statistic = 3.82, $p = 0.03$) (Table 2). The physical component of psychosocial functioning (SF-12) was not significant for diagnosis. Depression scores, mania ratings, psychosocial functioning, and perceived stress were not significant for menstrual phase or the interaction of menstrual phase with diagnostic group (Table 2).

On the daily self-report NIMH-life chart and DRF forms, we obtained daily observations of individual symptom items across the menstrual cycle for three months. The symptom-item data from the EF and LL phases were used in the statistical analyses. Analyses with linear mixed-effects and logistic-regression models indicated significant associations ($p < 0.01$) between diagnostic group and the life-chart symptoms of generalized anxiety (df = 14, t -value = 3.14), irritability (df = 14, t -value = 3.40), suicidal ideation (df = 18, t -value = 3.54), and rapid mood shift [z -value = 3.06, $\text{Pr}(z\text{-value}) = 0.002$]; and the DRF symptoms of physical discomfort (df = 18, t -value = 2.68) and social withdrawal (df = 18, t -value = 3.19). There were possible significant associations ($p = 0.01\text{--}0.03$) between diagnostic group and life-chart symptoms of mania (df = 13, t -value = 2.58) and feelings of wellbeing (df = 16, t -value = 2.36); and the DRF symptoms of fatigue (df = 18, t -value = 2.64) and increased appetite (df = 18, t -value = 2.68). The self-report symptoms were not significantly associated with menstrual phase or the interaction of menstrual phase with diagnostic group.

Discussion

These data suggest that susceptibility to increased symptoms and problems with functioning may be unrelated to menstrual phase in treated women with BD with euthymia or depressive episodes. This report extends the published findings on the lack of relationship between menstrual phase and changes in depression (29), and the lack of correlation between premenstrual symptoms and BD (30). Study strengths include: (i) the collection of repeated-measures of prospective mood and menstrual data from daily self-report ratings and monthly clinical assessments; (ii) the data represented groups of women with BD and an appropriate comparison group of healthy individuals; (iii) the findings apply to patients without mixed or manic symptoms who continued their maintenance treatments for BD; and (iv) there is no reported literature on menstrual-related symptoms in untreated patients. Although we cannot generalize the findings to women with mixed or hypomanic/manic episodes, colleagues have not discovered any relationship between hypomanic/manic symptoms and menstrual phase (29). We reduced potential bias by obtaining prospective clinical ratings from an expert rater (DS) who was blind to the subjects' phase during the ovulatory cycle. The rigorous protocol involved confirmation of ovulatory status with two methods: the mid-cycle LH surge urine test and the mid-cycle serum progesterone measurement. This is an important design feature because anovulation may prevail in women with BD as a consequence of the antimanic therapy (31).

We received nearly complete data from 19 subjects and partial data from 2 subjects. Still, a possible limitation is the missing data. We made reasonable assumptions that the data were missing at random and we used statistical analyses which do not produce biased results for the missing at random data. The loss of power (which can be present in a larger sample) to detect associations cannot be corrected through the statistical analyses. With inadequate power, associations that are clinically significant are not detected to be statistically significant, e.g., analyses of the discrete mood and physical symptoms.

Endogenous menstrual cycles (as well as puberty or pregnancy) result in physiologic states of prolonged exposure and cyclic declines in neurosteroid levels. Neurosteroids are steroid compounds that are synthesized in the brain. Allopregnanolone (ALLO), or its active 5β

isomer, 3 α 5 β -THP [a neurosteroid synthesized from progesterone) (32)], modulates GABA activity at GABA-A receptors (33) (34). GABA-A receptors in the brain mediate inhibitory processes, regulate anxiety, and alter limbic activity to affect behavioral response (35). Animal models suggest that selective serotonin reuptake inhibitors (SSRI) can increase brain levels of ALLO, up-regulate GABA-A activity, and abolish aggressive behavior (36, 37).

The effect of antimanic agents on neurosteroid activity is not fully understood. In women with BD, valproate may reduce progesterone levels during the luteal phase (38). The effect of valproate on the concentrations of GABA (measured with glutamate and glutamine) in white or gray matter was not significantly different between patients with BD and control subjects (39). Lithium does not change GABA levels in the brains of healthy people who were imaged with magnetic resonance spectroscopy (40). However, their findings cannot be generalized to bipolar illness since brain responses to lithium may differ vastly in patients with BD.

Ovulatory cycles may cause changes in levels of neurosteroids. However, we have limited information of the impact of ovulation on the pharmacokinetics of antimanic drugs. One study of lamotrigine (drug levels obtained every 1-3 days) indicated no cyclic variation in steady-state levels across the luteal and follicular phases (41).

SSRI agents such as fluoxetine (42) or sertraline (43) are used effectively to treat and prevent severe premenstrual syndrome or PMDD. In a comparison of women with and without premenstrual syndrome, investigators confirmed that normal ovarian function results in symptoms only in women with susceptibility for premenstrual symptoms (19). In this study, five of eight antidepressant-treated patients received an SSRI. Additional research is needed to explore the potential effects of antimanic agents on neurosteroid activity and the impact on mood regulation in women with BD.

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Table 1

Sample characteristics

Characteristics	All subjects (n = 21)	Healthy controls (n = 10)	BD-euthymic (n = 6)	BD-depressed (n = 5)
All subjects				
Age, mean (SD)	32.0 (8.8)	30.5 (9.9)	32.0 (9.6)	36.8 (4.1)
Age of menarche, mean (SD)	11.7 (4.3)	12.4 (2.0)	12.8 (1.5)	8.8 (8.2)
Length of cycles, days, mean (SD)	29.0 (3.5)	29.0 (2.6)	30.0 (3.3)	28.0 (5.5)
No. ovulatory cycles in the study	3.0	2.4	2.3	3.2
No. early follicular phases	26	8	7	11
No. late luteal phases	29	15	5	9
Patients with bipolar disorder				
Age of onset, mean (SD)	–	–	16.8 (6.1)	16.6 (6.2)
Years of illness, mean (SD)	–	–	15.2 (9.1)	20.2 (3.4)
≥ 2 antimanic drugs, n (%)	7 (33)	0	5 (83)	2 (40)
1 antimanic drug, n (%)	3 (14)	0	1 (17)	2 (40)
No antimanic drugs, n (%)	1 (5)	–	0 (0)	1 (20)
Antidepressant therapy, n (%)	8 (38)	0	3 (50)	5 (100)
Valproate therapy, n (%)	4 (17)	0	3 (50)	1 (20)

BD = bipolar disorder.

Table 2

Outcome measures of depression severity, functioning, and perceived stress

Outcomes	Diagnosis			Menstrual Phase	
	Healthy controls (n = 10)	BD-euthymic (n = 6)	BD-depressed (n = 5)	Early follicular (n = 26)	Late luteal (n = 29)
SIGH-ADS (29 item)	3.2 (0.5)	5.7 (1.8)	14.7 (1.1)	8.7 (1.3)	7.2 (1.3)
Percent atypical balance	12.2 (6.2)	22.0 (9.5)	28.1 (2.3)	24.2 (3.7)	21.1 (5.3)
Mania Rating Scale	–	1.0 (0.7)	2.0 (0.7)	1.3 (0.5)	0.5 (0.3)
SF-12 mental	54 (0.7)	49 (2.9)	31 (1.4)	44 (2.4)	46 (2.4)
SF-12 physical	54 (1.3)	50 (2.9)	49 (2.0)	51 (1.7)	52 (1.5)
Perceived stress	18.1 (0.3)	20.6 (1.3)	22.2 (0.5)	20.4 (0.6)	19.8 (0.6)

Values are presented as mean (standard error).

BD = bipolar disorder; SIGH-ADS = Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement; SF-12 = Short-Form Health Survey.