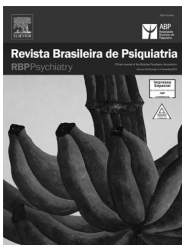
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REVIEW ARTICLE

Bipolar disorder and Premenstrual Syndrome or Premenstrual Dysphoric Disorder comorbidity: a systematic review

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DESCRIPTORS:
Bipolar Disorder;
Estrogens;
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Progesterone;
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Abstract
Objective: This article aims to review the comorbidity of premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) and bipolar disorder (BD), identify variables requiring further investigation and to remind physicians that special care is required for diagnosis and therapy. *Method*: A systematic review of articles published from 1987 to February 2012 was conducted in the Medline database with the following terms: (premenstrual syndrome OR premenstrual dysphoric disorder OR premenstrual) AND (bipolar OR mania OR manic). Seventeen articles were analyzed. *Results*: PMS and PMDD were most often comorbid among BD-II patients and vice versa. Moreover, patients with PMS or PMDD also have an increased risk of having BD-I. In addition, bipolar women susceptible to hormonal changes exhibit more severe symptoms, more frequent relapses and a worse therapeutic response. *Conclusion*: Future investigations should attempt to stabilize hormonal levels through the continuous use of contraceptives to target a reduction in symptom severity. In addition, psychiatrists should note menstrual period dates and compare symptom intensity between the luteal and follicular phases. Finally, PMS and PMDD patients should be studied separately.

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DESCRITORES:
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Progesterona;
Serotonina.

Comorbidade entre o Transtorno Bipolar e Síndrome Pré-Menstrual ou Transtorno Disfórico Pré-menstrual: uma revisão sistemática

Resumo
Objetivo: Esse artigo tem como objetivo revisar a comorbidade entre a Síndrome Pré-Menstrual (SPM) ou **Transtorno Disfórico Pré-Menstrual (TDPM)** e o Transtorno Bipolar (TB), identificar as variáveis que exigem uma investigação mais aprofundada e lembrar os médicos que as mulheres necessitam de cuidados especiais para diagnóstico e tratamento. *Método*: Foi realizada uma revisão sistemática de 1987 a fevereiro de 2012 através da base de dados Medline utilizando os seguintes descritores: (premenstrual syndrome OR premenstrual dysphoric disorder OR premenstrual) AND (bipolar OR mania OR manic). Dezessete artigos foram analisados. *Resultados*: Pacientes com SPM ou TDPM possuem comorbidade com TB-II com maior frequência e vice-versa. Mulheres com SPM ou TDPM também possuem um risco aumentado apresentar TB-I. Além disso, as mulheres bipolares suscetíveis a mudanças hormonais cursam com sintomas mais graves, recaídas mais freqüentes e pior resposta terapêutica. *Conclusão*: Futuras investigações devem estabilizar os níveis hormonais com o uso contínuo de contraceptivos na tentativa de diminuir a gravidade dos sintomas. Além disso, psiquiatras devem observar os períodos menstruais e comparar a intensidade dos sintomas entre as fases folicular e lútea. Pacientes com SPM ou TDPM devem ser estudadas separadamente.

Introduction

Premenstrual syndrome (PMS) has several definitions (Table 1), and its estimated prevalence ranges from 75% to 95%.[1,5] Premenstrual Dysphoric Disorder (PMDD) is the most severe form of PMS with more restrictive criteria and a predominance of emotional and behavioral symptoms. PMDD requires at least 5 of the 11 symptoms specified in the DSM-IV-TR Appendix B (Criteria Sets and Axes Provided for Further Study).[6] Only one of the 11 criteria is related to physical symptoms (Table 2). In contrast with PMS, PMDD affects only 3 to 9% of women.[7,8] The DSM-5 project included the PMDD criteria in the Depressive Disorders chapter.[9]

Previous studies have focused on the lifetime comorbidity of mood disorders,[10 14] anxiety disorders[15,17] and personality disorders[18] in women with PMS (PMS+) or PMDD (PMDD+).

Compared to women at other phases of their menstrual cycle, those in the premenstrual period present higher rates of hospitalization,[15] emergency treatment[17,19,21] and suicide attempts.[16,17,20,22,24] Due to these regular relapses reported during the premenstrual phase, women may have a more severe expression and evolution of psychiatric disorders.

Considering the gender differences in mood disorders, it is remarkable that BD women have a higher risk of postpartum mood episodes and pre-menopause.[25,26] Mood disorders have the same prevalence prior to puberty.[27] When the increase in sex hormones becomes evident, the female-to-male ratio of unipolar depression shifts to 2:1.[28,29] Therefore, it is possible that steroid hormones might be involved. However, in relation to Bipolar Depression, the polarity of previous episodes is a controversial issue. Some researchers found that women have more depressive episodes than men,[28,30] but others found no difference.[31,32] Researchers have been studying the relationship between neurotransmitters, female gonadal hormones and the emergence and pattern of symptoms of premenstrual dysphoria.[33,35]

Women with bipolar disorder have a higher risk of postpartum mood episodes. At the same time, women with PMDD are more likely to experience mood disorders. Estrogen and progesterone fluctuation across the menstrual cycle can modulate affective symptoms through their actions in the CNS.

It has been demonstrated that estrogen has a profound impact on mood and on the trimonoaminergic neurotransmitter system (5HT, NE, and DA),[36] GABA and glutamate, which are involved in the pathophysiology of depression.[37] Estrogen decreases MAO activity, thus increasing 5-HT availability with a resulting antidepressant effect, whereas progesterone increases MAO, which decreases 5-HT availability and depresses mood.[38]

It is currently accepted that women with premenstrual complaints differ from controls not with respect to ovarian function, but with respect to how responsive the target organs are to the influence of gonadal steroids (64). It is possible that women with PMS have an altered sensitivity to testosterone, as well as to progesterone and estrogen.

The association of PMS with axis I comorbidity and its mechanism was extensively studied in the latter part of the twentieth century, and there has been a resurgence of publications on this topic since 2007. Many researchers have studied the influence of menstrual cycle phases on mood in BD patients, however the results vary.[39,41] Among other subjects, Kim et al. reports the occurrence of PMS/PMDD and BD in two review articles.[42,43] In the present review, PMS/PMDD and BD comorbidity is the central topic because the most accepted hypothesis is that this subgroup of women may be predisposed to negative mood effects due to hormonal fluctuation.[44]

The aim of this article is to evaluate the comorbidity of PMS or PMDD with Bipolar Disorder (BD), to identify variables requiring further investigation and to remind physicians that special care is required for diagnosis and therapy. Therefore, this is the first systematic review of the association between BD and PMS/PMDD.

Table 1 Diagnostic Criteria for PMS (ACOG)[10]

A. Symptoms must occur during the 5 days before menses for at least 3 menstrual cycles in a row. At least one affective and one somatic symptom must be present.	
Affective Symptoms	**Somatic Symptoms**
Depression	Breast tenderness
Angry-outbursts	Abdominal bloating
Irritability	Headache
Anxiety	Swelling of extremities
Confusion	
Social withdrawal	
B. Symptoms are relieved within 4 days without recurrence until cycle day 13	
C. Symptoms are present in the absence of medicine, hormone ingestion or alcohol use	
D. Symptoms occur during 2 cycles prospectively	
E. Patient suffer social or economic dysfunction	

ACOG: American College of Obstetricians and Gynecologists

Table 2 Research criteria for PMDD (DSM-IV-TR)*[6]

A. Symptoms must occur during the week before menses, improve several days after the onset of menses and remit for up to 7 days.
Five or more of the following symptoms must be present, and at least one must be (1), (2), (3), or (4):
1. Depressed mood or hopelessness
2. Anxiety or tension
3. Affective lability
4. Irritability or anger
5. Decreased interest in usual activities
6. Concentration difficulties
7. Marked lack of energy
8. Marked change in appetite, overeating, or food cravings
9. Hypersomnia or insomnia
10. Feeling overwhelmed or out of control
11. Other physical symptoms i.e., breast tenderness, bloating
B. Symptoms must interfere with work, school, usual social activities or relationships.
C. Symptoms are not merely an exacerbation of another disorder.
D. Criteria A, B, and C must be confirmed by prospective daily ratings for at least two consecutive symptomatic cycles.

*Summarized.

Methods

Search strategy and eligibility criteria

The search strategy aimed to gather as many studies as possible on the issue. Epidemiological, clinical and therapeutic data were all collected. To achieve this goal, we used the following search terms in the Medline database: (premenstrual syndrome OR premenstrual dysphoric disorder OR premenstrual) AND (bipolar OR mania OR manic). The search was limited to studies from 1987, the year that the DSM-III-R included the criteria for late luteal phase dysphoric disorder (LLPDD), to February 2012. The name was changed to PMDD in the DSM-IV, although the disorder was described as having almost identical criteria to those of LLPDD (only 1 item was added). Articles were included based on the following criteria: (1) type of study (original article or case report) and (2) language (English, Spanish or Portuguese). If more than one article referred to the same study, the article with the shorter follow-up was excluded. We further examined the reference lists of the included articles in an effort to find studies that were missed in the database search. We excluded articles that did not separately evaluated bipolar subjects. Two researchers verified whether they met the eligibility criteria. In case of disagreement, the final decision was made by consensus.

Results

Forty-nine references on BD and PMS/PMDD were identified. We did not find any additional research through additional searches. We excluded 14 articles because they were reviews, 12 were published before the DSM-III-R (1987), one was in French and five were letters. Seventeen abstracts were potentially relevant according to our criteria.

Studies characteristics

Nine studies evaluated the comorbidity of BD and PMS, 4 studies assessed the comorbidity of BD and PMDD (one used the LLPDD criteria and was included in the PMDD group), and one evaluated both.[45]

Prevalence

Eight studies determined the PMS/PMDD prevalence in BD patients, four of which investigated PMDD and BD, including one that evaluated PMS and PMDD.

In relation to PMDD, Choi et al.[45] examined its prevalence in 183 age-matched women (30 BD-I vs. 31 BD-II vs. 122 healthy controls), and PMDD was present in 6.7% of patients with BD-I, 22.6% of those with BD-II, and in 1.6% of controls.[45] This study found that patients with BD-II disorder had statistically significant differences compared to the control group ($p < 0.0001$, 95% CI-NI).[45] Choi et al.[45] also evaluated the prevalence of "moderate to severe PMS," and a trend of distinction was found between the BD-I and BD-II groups ($p = 0.069$) as well as a difference between BD-II patients and controls ($p = 0.003$).[45] These results should be interpreted with caution because the analysis did not consider the pharmacological treatment status. As we know, BP-I patients may be more likely to receive treatment than BP-II patients, which might suppress the PMDD symptoms. Therefore, the pharmacological treatment status is a potential confounder.

Wittchen et al.[46] evaluated mental disorder co-morbidity and PMDD in a community sample (N = 1,251) of women between 14-24 years old in a 12-months follow-up.[46] Regarding PMDD and bipolar disorder, they found that among subthreshold PMDD patients (n = 201), 3.8% were BDI (OR: 5.3, $p < 0.05$, 95% CI-NI) and 0.3% BDII (OR: 0.5) (46). Among the PMDD patients (n = 74), 5.7% were BDI (OR: 7.9, $p < 0.01$, 95% CI-NI) and 4.9% were BDII (OR: 8.1, $p < 0.01$, 95% CI-NI), while in the PMDD - group (n = 828), 0.8% were BDI and 0.6% were BDII.[46] Wittchen et al.[46] found substantial co-morbidity between PMDD+ and BD-I and BD-II patients (approximately 10%), particularly because the study was conducted with a large community sample.

Hardoy et al.[47] compared the prevalence of PMDD in three diagnostic groups to 13 patients out of 17 (76.5%) with BD, 9 patients out of 14 (64.3%) with MDD, and 6 patients out of 16 (37.5%) controls.[47] The proportion of women with PMDD

Table 3 Bipolar disorder (BD) and premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) comorbidity articles results

Author	Year	Sample/N	Symptoms/Criteria	Results
Dias et al.[55]	2011	191 with PME of BD and 102 without	Number of premenstrual symptoms Number of mood episodes overall Number of depressive episodes Number of manic or hippomanic episodes Median time to relapse Prevalence of rapid cycling	Greater in women with PME Greater in women with PMS Greater in women with PMS No difference Lower in PMS group No difference
Choi et al.[45]	2010	30 BDI,31 BDII and 61 healthy controls	Prevalence of PMDD Prevalence of moderate to severe PMS PMS effect on the GSS scale Association of seasonality and PMS (BDI/BDII)	Higher in BDII Higher in BDII No interaction Stronger in BD group
Fornaro et al.[48]	2010	92 female outpatients and Inpatients BDI and BDII	Prevalence of PMDD Educational level Marital status Mean age at onset of mood disorder Rates of BDII and cyclothymia Rates of BDI Prevalence of post-partum depression Mean age at the moment of the evaluation Rapid cycling Seasonal pattern Psychotic features Melancholia Past hospitalization Past suicidality Carbohydrate craving Scale score (CGI, YMRS) Axis I comorbidity Total mean number of comorbid conditions	Early in BD with PMS Women with PMS were younger No difference No difference No difference No difference No difference No difference No difference
Payne et al.[50]	2009	665 BD I, 1746 MDD	Mean age at onset of mood disorder Age at interview Married prevalence Depression at the time of interview Number of past depressive or manic episodes History of pregnancy Longest MDE (weeks) Years educated Family analyses for premenstrual mood symptoms	Early in BD with PMS Women with PMS were younger No difference No difference No difference No difference No difference No difference No difference
Payne et al.[49]	2007	665 BDI disorder, 112 BDII	Prevalence of PMS Associations between premenstrual and postpartum mood symptoms in women with a previous pregnancy Association of depressed stated at the time of the interview with reproductive cycle-associated mood symptoms	No difference No associations More premenstrual and perimenopausal symptoms in BDI women depressed at the time of the interview
Hsiao et al.[83]	2007	6 case reports, 2 with BD and PMS	24-year-old woman with manic episodes 2-3 days before menstruation 34-year-old woman with delusions and hallucinations one week before menstruation	Premenstrual doses of an antipsychotic Mood stabilizer and antipsychotic doses were increased during the luteal phase
Hardoy et al.[47]	2006	4 BD I, 13 BDII, 14 MDD and 16 controls	Prevalence of PMDD in the three groups Prevalence of PMDD in mood vs. controls Plasma concentration of steroids Correlation between PD, OCD or ED comorbidity and steroids concentrations	No difference Borderline significant Progesterone and 3α,5α-THPROG: higher in PMDD+ No association

Table 3 Bipolar disorder (BD) and premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) comorbidity articles results *(cont.)*

Author	Year	Sample/N	Symptoms/Criteria	Results
Becker et al.[78]	2004	Case report	43 years-old woman with 30 years history of treatment-resistant rapid cycling bipolar II disorder with follicular phase depressive and luteal phase mood elevation symptoms Complain about the premenstrual symptom PAF scores Number of subjects with significant premenstrual symptom change of DRSP	Lamotrigine 300 mg/day, divalproex sodium 500 mg/day and levothyroxine 175 lg/day More in controls Controls had higher scores in some items BD with treatment-responsive had less fluctuation
Wittchen et al.[46]	2002	201 subthreshold PMDD 74 PMDD+ 828 PMDD	BD-I and II prevalence BD-I and II prevalence	Higher prevalence only for BD-I Higher prevalence for both
Angst et al.[52]	2001	141 peri-MS+ and 106 controls	BD prevalence	Higher in peri-MS+
Gregory et al.[53]	2000	Eight of the 72 subjects with MDE were BD	Mood at four different reproductive cycle events (premenstrual, use of oral contraceptives, postpartum and perimenopausal) Family history of BD	Women with severe depression in two or more of them were more likely to have BD No difference
Blehar et al.[51]	1998	186 BDI	Prevalence of regular mood changes in premenstrual or menstrual phase Primary symptoms as increased irritability, anger outbursts and mood lability versus depression	High prevalence Most patients felt irritability, anger and mood lability
Parry et al.[57]	1996	15 LLPDD+ women and 15 controls	Prevalence of hypomania Years of education	Higher in LLPDD+ No difference
Jacobsen[77]	1993	16 rapid cycling BDII outpatients, 11 of them with PMS	Response to low-dose valproate treatment Sustained response to valproate	Most PMS+ patients needed high doses BDII women with primary PMS are less responsive
D'Mello et al.[87]	1993	2 case reports	29 years-old woman with premenstrual mania 5 days before menses and euthymic during intermenstrual period 41-year-old with premenstrual mixed mania and stable mood between menses	lithium and thiothixene and maintained only with lithium (1,800 mg/day - serum D'Mello et level = 0.9 mEq/L) lithium 900 mg/day with serum levels in the 0.6 to 0.8 mEq/L range
McMillan et al.[58]	1989	16 euthymic patients with affective disorder, only 4 BD	Influence of PMS in attention Scale score (DRS, MAACL, HRS)	No difference None of the BD patients confirmed premenstrual depression with the scales

BD: bipolar disorder; BDI: bipolar disorder I; BDII: bipolar disorder II; BDD: Body Dysmorphic Disorder; CGI: Clinical Global Impression Scale; DRS: Daily Rating Scale; DRSP: Daily Record of Severity of Problems-Short Form; ED: eating disorder; GSS: Global Seasonality Score; HRS: Hamilton Rating Scale; MAACL: Multiple Affect Adjective Checklist; MDE: major depressive episode; OCD: Obsessive-compulsive Disorder; PAF: Premenstrual Assessment Form; PD: panic disorder; peri-MS+: with perimenstrual symptoms; PMDD: premenstrual dysphoric disorder; PMDD+: with premenstrual dysphoric disorder; PMDD-: without premenstrual dysphoric disorder; PME: premenstrual exacerbation; PMS: premenstrual syndrome; PMS+: with premenstrual syndrome; PMS-: without premenstrual syndrome; THPROG: allopregnanolone; YMRS: Young Mania Rating Scale.

did not differ significantly among these groups ($Chi^2 = 5.3$, $p = 0.068$).[47] However, if all patients with mood disorders were grouped together, the difference compared with controls was borderline significant ($\chi^2 = 3.7$, $p = 0.05$), most likely due to the small sample size.[47] The sample size increases when the two mood disorders groups are joined, and consequently, the power of the analysis reaches statistical significance. Fornaro and Perugi studied 92 BD-I and II patients and detected 25 (27.2%) patients with a lifetime history of PMDD according to the DSM-IV criteria.[48] Three of these patients (12.0%) had BD-I, while 22 (88.0%) had BD-II.[48] In addition, PMDD+ was associated with higher rates of cyclothymia and BD-II than PMDD- (72% versus 36% and 88% versus 60%, respectively). On the other hand, BDI

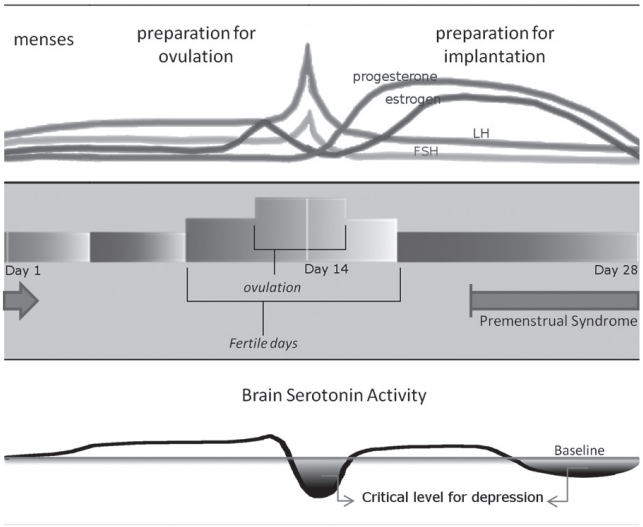


Figure 1 Relationship between hormonal fluctuation and brain serotonin activity in predisposed women.

was more frequent among PMDD- patients compared to PMDD + patients (40% versus 12%). It should be highlighted that PMDD is more frequent among patients with BD-II or cyclothymia than BD-I. The authors also found that the total mean number of comorbid conditions was greater in BD patients with PMDD+.[48] Nevertheless, Fornaro and Perugi did not a rigorously distinguish among PMDD cases within different menstrual phases.

Regarding the studies that evaluated PMS, in 2007 Payne et al.[49] examined the prevalences of premenstrual mood symptoms in BD-I and BD-II patients, which were 65.1% (433 of 665) and 70.5% (79 of 112), respectively.[49] Two years later, Payne et al. evaluated 435 BD-I patients, the majority of whom had PMS (64.1%).[50] Blehar assessed only BD-I women, and 66.1% (119/180) of them reported regular mood changes during the menstrual or premenstrual phase.[51] Angst et al.[52] assessed seven psychological symptoms for the perimenstrual period in a community cohort study and found comorbidity with psychiatric syndromes.[52] They found that the prevalence of BD was 9% among the 106 controls, 17% among the 88 depressed peri-MS and 15% among non-depressed peri-MS women (p all = 0.27).[52]

In summary, eight studies assessed the prevalence of PMS/PMDD in BD patients. Two of them found a greater prevalence of PMS/PMDD in BD-II.[45,48] Payne et al.[50] and Blehar et al.[51] only evaluated BD-I, but they found a high prevalence of PMS.[50,51] Hardoy did not separate BD-I from BD-II and found no difference in the prevalence of PMDD in BD patients when compared to MDD patients or controls. However, we should emphasize the small sample size.[47] Wittchen et al. compared the prevalences of BD-I and BD-II in subthreshold PMDD+, PMDD+ and PMDD- samples and found significant differences in the first two groups however in the subthreshold PMDD+ group only with BD-I.[46]

Reproductive cycle-related mood symptoms

One article described associations between post-partum depression and PMDD+ BD-I and BD-II patients (PMDD+: 36.0% vs. PMDD-: 14.9%, p = 0.026).[48] Another study examined whether premenstrual mood symptoms could predict postpartum mood symptoms in 517 women with BD-I with a previous pregnancy and found that the result was not statistically significant (p = 0.206).[49] The diffeårence between the two results may reflect the difference in the population because Payne evaluated only BD-I patients and PMS while Fornaro and Perugi described PMDD in BD-I and BD-II.[48,49]

Payne et al. also used a sample of 197 women with BD-I who had undergone both pregnancy and menopause and searched for associations between premenstrual symptoms and postpartum or perimenopausal and either postpartum or perimenopausal mood symptoms (or both).[49] However, no differences were found (Premenstrual-postpartum: p = 0.317; Premenstrual-perimenopausal: p = 0.227; Premenstrual – either postpartum or perimenopausal mood symptoms: p = 0.847; Premenstrual – both: p = 0.288).[49]

Payne et al. observed an association between a depressive state at the time of the interview and a report of premenstrual symptoms in a sample of 665 BD-I patients (BD-I depressed at interview: 34.8%, BD-I not depressed at interview: 26.4%, p = 0.04).[49] However, in another study conducted two years later, they did not find a difference in the rate of depression between PMS+ and PMS- patients and concluded that being depressed can affect PMS reporting (p = 0.56).[50] The history of pregnancy among BD-I patients with and without PMS was the same [BDI PMS+ (n = 231) = 82.8% vs. BDI PMS- (n = 119) = 76.28%, p = 0.1292].[50]

In addition, Gregory et al. analyzed patients' moods at four different reproductive cycle events (i.e., premenstrual, taking oral contraceptives, postpartum and perimenopausal) and concluded that women with severe depression at two or more of these time points were more likely to have BD (p = 0.02).[53] The higher prevalence of bipolar depression during different phases of the reproductive cycle reinforces the hypothesis of a hormonal influence on disease progression.[54] Therefore, whenever a patient has depression related to the menstrual cycle, BD should be a differential diagnosis.

Illness Course

Choi et al. combined BD-I and BD-II patients into one patient group and searched for an association between seasonality and "moderate to severe PMS".[45] They found that the association of both was stronger in the patient group compared to the control group (healthy females without psychiatric illness) (p = 0.029) and suggested that a common biological mechanism of these two cyclic conditions may be involved in the development of BD cyclicity.[45] However, Fornaro and Perugi found similar seasonal patterns in a sample with BD-I and BD-II with regard to PMDD (PMDD+ 36.0% vs. PMDD-: 39.4%, p = ns).[48] Both studies present methodological problems because they have small samples and did not include a calendar method or hormone estimation. The measurements were based on self-reporting and retrospective evaluation, which is prone to bias. This may explain the disparate results. These methodological limitations reduce the validity of the studies.

Dias et al. compared the frequency of mood episodes between 191 women with premenstrual exacerbation (PME) of BD and 102 women without, all at a premenopausal age.[55] The first group had more premenstrual mood episodes overall ($p = 0.02$) compared to the other group, but they experienced mainly depressive symptoms ($p < 0.001$, 95% CI-NI).[55] Moreover, among 66 women with premenstrual exacerbation and 63 without exacerbation who were in a recovery state at baseline, they observed a greater risk for relapse in the PME group ($p = 0.04$).[55] PME may be a marker for a more recurrent and symptomatic course of illness among premenopausal women with BD.[55]

Complaints about premenstrual symptoms were researched by Karadag et al., who found that control subjects with no history of medical/mental disorder complained significantly more about premenstrual symptom changes than the euthymic BD women ($p < 0.05$, 95% CI-NI).[56] Control subjects experienced more menstrual-related mood and behavioral changes compared to women with treatment-responsive BD in both retrospective and prospective assessments.[56] However, no significant differences between the groups were observed with respect to vegetative symptoms (e.g., somatic complaints, change in appetite and sleep disturbances).[56] Karadag et al. concluded that, in euthymic BD women, mood-stabilizer treatment might have a prophylactic effect against premenstrual symptoms.[56]

Concerning premenstrual symptoms, Blehar et al. noted that 75% (76/101) of women with BD-I described them primarily as increased irritability, anger outbursts and mood lability, whereas 25% (24/101) reported their chief symptom to be depression.[51]

The prevalence of rapid cycling did not show any differences between the two groups retrospectively studied by Fornaro and Perugi (PMDD+: 24.0% vs. PMDD-: 26.9%, p = ns) and prospectively studied by Dias et al. (PME+: 2.0% vs. PME-: 2.1%).[48,55] However, retrospectively, the group with PMS was more likely to report rapid cycling (PME+: 28.8% vs. PME-: 10.5%, $p = 0.05$) (55). Fornaro and Perugi also did not find a difference in the rates of psychotic features (PMDD+: 8.0% vs. PMDD-: 20.9%, p = ns).[48]

Differences in personality and transient clinical syndromes (such as hypomania) during the menstrual phases were evaluated in 15 LLPDD+ (a disorder very similar to PMDD) women and 15 controls.[57] The LLPDD+ subjects scored higher on measures of hypomania at all menstrual cycle phases ($p < 0.03$, 95% CI-NI).[57] The high-scoring subjects in these items are evidence of periods of elevated, unstable moods, overactivity and destructibility, impulsiveness, and irritability. The findings also lend support to the underlying vulnerabilities of LLPDD patients for affective clinical syndromes.[57]

Most of these studies found differences between BD patients with PMS/PMDD and controls on evaluated criteria. However, the samples are small and each criterion was evaluated by only a few studies. Further studies with larger samples and rigorous methodologies are required.

Family morbidity

We conducted a family analysis for premenstrual mood symptoms in 196 families of BD-I patients.[50] The overall rate of symptoms was only marginally higher in those with a positive family history of premenstrual symptoms compared to those with a negative BD history (65.0% vs. 62.1%).[50] This difference did not reach statistical significance (OR = 1.13; $p = 0.563$).[50]

Sociodemographic characteristics

Sociodemographic characteristics did not show any difference among BD women with or without PMS/PMDD.

Age at onset / age at interview

In one study with 665 BD-I women, the difference in the age at onset was statistically significant between women with (mean age = 18.3) and without (mean age = 21.3) PMS (50). The same study also found differences in age at the time of the interview between both groups (mean age: PMS+ = 41 vs. PMS- = 45, $p = 0.0002$).[50]

However, another study compared 92 female outpatients and inpatients with BD-I and BD-II and did not find significant variation in the mean age at onset of mood disorders in PMDD+ versus PMDD- women (24.2 years vs. 23.9 years, p = ns).[48] Additionally, they did not report difference in the mean age at the time of evaluation between these groups (mean age: PMDD+= 49.6 years vs. PMDD-= 49.1 years, p = ns).[48]

The difference in the results most likely occurred because the first study evaluated a large population of BD-I with PMS, while the second evaluated a smaller sample with BD-I and BD-II with PMDD.

Marital status

Payne et al. reported no difference in marriage prevalence between BD-I patients with or without PMS (50.90% vs. 41.03%, respectively, p=0.06) (50). Consistent with this finding, Fornaro and Perugi found no difference in marital status between patients with BD-I and BD-II who were either inpatients or outpatients, with or without PMDD.[48] The rates for these patients were as follows: ''never married'' PMDD+: 12% vs. PMDD-: 27.7%, ''married'' PMDD+: 52% vs. PMDD-: 35.4% and ''widowed or divorced'' PMDD+: 36% vs. PMDD-: 37% (p = ns).[48]

Presence of Depression at interview

Payne et al. investigated depression at the time of the interview and found that this rate did not differ between women with and without premenstrual mood symptoms.[50] The number of major depressive episodes in BD-I patients with PMS (mean = 20.67) showed no significant difference compared to BD-I patients without PMS (mean = 20.17, $p = 0.90$) regarding the number of manias (mean = 25.55 vs. 15.61, respectively, $p = 0.1374$).[50] Payne also found no difference when comparing the duration of the longest major depressive episode in BD-I patients with (mean = 50.52 weeks) and without (mean = 54.11 weeks, $p = 0.64$) PMS.[50]

Educational status

Regarding the years of education, neither Payne et al., Parry et al., nor Fornaro and Perugi found any differences between the two groups.[48,50,57] Payne evaluated BD-I patients with (mean years of education = 14.45) or without (mean years of education = 14.39, $p = 0.83$) PMS.[50] In addition, Fornaro and Perugi reported that 52.0% of PMDD+ versus 37.3% of PMDD- had 8 years or less of education; 40.0% versus 40.3% reported high school-level education, respectively, and 8.0% versus 22.3% reported a university-level education (p = ns).[48]

Parry et al. also found no difference in the number of years of education (x = 15 ± 0.4, range 12-18 years) between the 15 people of the control group and the 15 patients with LLPDD. Both were free of psychoactive medication and hormonal contraceptives.[57]

Scale evaluation

McMillan et al. evaluated mood in 16 euthymic patients with mood disorders, of which only four were bipolar.[58] None of the BD patients were confirmed to be premenstrually depressed according to the Daily Rating Scale (DRS),[59] the Multiple Affect Adjective Checklist (MAACL) and the Hamilton Rating Scale (HRS).[60] They also found no influence of PMS on attention and suggested that premenstrual dysphoric mood fluctuations are a different phenomenon from clinical depression.[58]

Choi et al. sought to determine whether PMS affected the Global Seasonality Score (GSS) of patients with BD-I, BD-II and controls, but they found no interaction using the 3 groups (p = 0.112).[45] Analyzing the association between seasonality and PMS, the mean GSS was significantly higher in subjects with "moderate to severe PMS" compared to those without this condition (p < 0.0001, 95% CI-NI).[45]

Karadag et al. compared the Premenstrual Assessment Form (PAF) scores of women with treatment-responsive BD and control subjects.[56] Interestingly, controls experienced more premenstrual symptom changes for the sub-groups of the PAF corresponding to low mood/loss of pleasure, affective lability, atypical depressive features, "hysteroid" features, hostility/anger, anxiety, impulsivity, organic mental features, sign of water retention, and impaired social functioning compared to the BD group.[56] They found no difference in the scores of other PAF items.[56]

Karadag et al. applied the Daily Record of Severity of Problems-Short Form (DRSP) in 34 euthymic treatment-responsive BD females and 35 controls with no medical/mental disorder to evaluate premenstrual and postmenstrual symptoms.[56] BD women experienced less fluctuation of mood and behavior during two consecutive menstrual cycles than control subjects.[56] No differences in the vegetative symptoms were observed between the two groups.[56] It is worth remembering that this is a small sample. The hypotheses that lithium and/or valproate could be a protective factor for PMS in BD patients are controversial.[56] One explanation would be that BD women could not recognize the more subtle variations related to the menstrual cycle because they experience dramatic mood fluctuations as part of their illness.[56] In addition to these findings, the authors observed significant group and cycle-by-group interaction effects for the following DRSP items: depressed mood, anxiety (during the second month), mood swings, anhedonia (during the second month), difficulty in concentrating, and "out of control" feelings.[56] No significant differences were observed in the following DRSP items between the BD and control groups: anger/irritability, lack of energy, changes in appetite, and sleep disturbances.[56]

Hormonal Rates

Progesterone is metabolized in the ovaries and the brain to form the potent neuroactive steroids allopregnanolone and pregnenolone, which are positive allosteric modulators of the type A GABA neurotransmitter system in the brain.[61] Imaging studies have reported altered GABAergic function in women with PMDD when compared with healthy control subjects.[62,63] Some studies reported luteal phase deficits in allopregnanolone in women with PMDD,[64,65] although other studies showed no relation.[66,67] Failure to demonstrate a significant effect of diagnosis on plasma neuroactive steroids does not necessarily detract from the importance of these steroids in the pathogenesis of PMDD because a dissociation between peripheral and brain levels of allopregnanolone has been demonstrated in rodents.[68] Women with PMS demonstrate decreased pregnenolone responsiveness possibly due to altered sensitivity of GABA-A receptors.[69]

Whereas acute, short-term allopregnanolone exposure decreases anxiety, chronic exposure to elevated allopregnanolone can produce decreased expression and binding to the GABA-A receptor as well as uncoupling of the receptor from several anxiolytic modulators, leading to increased anxiety.[70,71] Progesterone metabolite effects on mood and behavior also appear to be biphasic in nature.[64] In high concentrations, pregnanolone and allopregnanolone produce anxiolytic, sedative, antiepileptic, and anesthetic effects.[28,72,73] At lower blood levels, similar to those observed during the luteal phase, allopregnanolone can cause anxiety, aggression, impulsive behavior, and negative mood in predisposed individuals.[29,38] While higher doses, similar to those observed in late pregnancy, are noted to improve mood.[74]

3α,5α-THDOC is synthesized in the brain from peripheral deoxycorticosterone,[75] which also increases in the brain in response to stress via the blood brain barrier.[76] It is a barbiturate-like ligand of the GABA-A receptor with a common mechanism of action with allopregnanolone. Steroid hormones may modulate the excitability of hypothalamic neurons by genomic and non-genomic mechanisms, which in turn might be involved in controlling the activity of the HPA axis.[76]

Hardoy et al. evaluated 17 women with BD (4 BD-I and 13 BD-II), 14 women with MDD and 16 healthy control subjects).[47] All patients were euthymic for three months. This study examined plasma concentrations of the steroids cortisol, progesterone, 3α,5α-THPROG (allopregnanolone) and 3α,5α –THDOC.[47]

Hardoy et al. found that the concentrations of progesterone and allopregnanolone differed significantly between the 3 groups of subjects (progesterone: BD = 11.0 ± 2.6, MDD = 4.0 ± 3.6, controls = 1.0 ± 1.1, p < 0.0001, 95% CI-NI; allopregnanolone: BD = 9.6 ± 2.3, MDD = 5.1 ± 1.2, controls = 2.1 ± 0.8, p < 0.0001, 95% CI-NI).[47] Furthermore, the concentrations of these steroids were even greater in women with BD than in those affected by MDD.47 No differences in the levels of cortisol or 3α,5α -THDOC were observed in these comparisons.[47]

The same study found higher concentrations of progesterone and 3α,5α -THPROG, a potent positive allosteric modulator of GABA, in euthymic BD patients with and without PMDD.[47] However, these patients were euthymic for at least 3 months, so these results cannot be compared to previous studies. Women with a lifetime diagnosis of mood disorder (BD or MDD) but who are currently in a condition of clinical well-being exhibited higher plasma concentrations of progesterone and 3α,5α -THPROG during the luteal phase of the menstrual cycle than healthy controls.[47]

It is unclear why those women lost the inhibition of progesterone release. Thus, high levels of progesterone and its metabolite in the luteal phase is a possible biological marker for mood disorders in women.

A bias due to medication or comorbidity was evaluated.[47] Drug-free patients with BD or MDD showed similar differences in steroid concentrations relative to controls as drug-treated patients.[47] However, only 8 patients were drug-free, corresponding to 2 BD (11.8%) and 6 MDD (42.8%) patients.[47] Patients affected by mood disorders (BD or MDD) but without comorbidity for Panic Disorder (PD), Obsessive-compulsive Disorder (OCD), or Eating Disorder (ED) had higher plasma levels of progesterone and allopregnanolone compared to controls, which was similar to patients with comorbidity for either of these conditions.[47] Therefore, the differences in neuroactive steroid concentrations were not attributable to comorbidity with PD, OCD, or ED. Comparing the concentrations of progesterone and allopregnanolone between subjects with PMDD and those without it yielded a significant difference.[47]

Treatment Response

Jacobsen compared "anticycling" mood stabilizer responses to valproate between rapidly cycling women with (N = 11) and without (N = 5) PMS.[77] These study tested low-dose valproate as a treatment for cyclothymia, rapid cycling BD-II and PMS.[77] However, he found that patients with primary PMS had less sustained responses[78] to valproate than cyclothymic or BD-II patients with secondary PMS. Only three of eight (38%) women with PMS reported a good response to low-dose valproate treatments. The remaining five rapid cycling BD-II patients needed high-dose valproate treatments.[77] It is worth noting that these results may be due to the small sample size.

Valproate most likely enhances the GABA concentration, which would increase 5HT activity, so it is possible that some women with PMS might improve. Reports from human and animal studies indicate that eventually all GABA-A receptor agonists can induce symptoms similar to depressed mood, anxiety, irritability, aggression, and other typical symptoms of PMS/PMDD.[77] GABA-A receptor agonists at high doses are anxiolytic, anti-aggressive, sedative/anesthetic, and anti-epileptic.[79] However, in low concentrations or doses, there are severe adverse emotional reactions in a subset of individuals (2-3%) and moderate reactions are seen in up to 20% of patients.[80]

It is also important to note that valproate can induce polycystic ovary syndrome and could interfere with normal menstrual functioning, making it difficult to establish whether menstrual dysfunction is secondary to psychotropic medication use or related to BD.[81,82] Nevertheless BD females that improve with valproate take advantage not only from improved mood stability but also can enhance premenstrual symptoms.[56]

Case reports and Case series

Hsiao and Liu wrote two case reports about BD and PMS comorbidity.[83] They made a prospective evaluation with a series of laboratory tests (which involved testing for the levels of hemoglobin, thyroid-stimulating hormone, fasting glucose, estradiol, progesterone, prolactin, and follicle-stimulating hormone) and scales.

The first case is a 24-year-old woman with recurrent manic episodes from 2–3 days before menstruation until the second day after menstruation began for the previous two years. She was treated with premenstrual doses of an antipsychotic medication.[83]

The other case is a 34-year-old woman with a single manic episode at postpartum onset. The patient developed psychotic symptoms one week before almost every menstrual period, with full remission observed 3-4 days after the onset of menstruation.[83] The mood stabilizer and the antipsychotic doses were increased during the luteal phase. After three months, the severity of psychotic symptoms decreased, and the PRISM severity score (PSS) decreased from 88% to 17%. One year later, her premenstrual psychotic symptoms remained, but they did not disturb the quality of her life.[83]

Becker et al. reported a case about a 43-year-old woman with a 30-year history of treatment-resistant menstrually related rapid cycling bipolar disorder.[78] This patient had failed to respond to or tolerate all previous medication. Lamotrigine was increased gradually, and the mood cycle amplitude attenuated. There was a notable decrease in the severity and duration of her depressive symptoms, specifically during the follicular phase of the menstrual cycle.

In the six months prior to initiating LTG, the patient recorded mood and physiological premenstrual symptoms on the Endicott Premenstrual Assessment Form.[84] In the luteal phase compared with the follicular phase, the mean depressive symptoms were 67% (range: 39-96) lower, the mean joy and efficiency ratings were 129% (range: 96-200) higher, and the mean work impairment score dropped by 63% (range: 26-108) (i.e., she experienced improved work function). Her medications at the time of the evaluation included divalproex sodium 500 mg/day (serum VPA 21 lg/mL), venlafaxine 225 mg/day and levothyroxine 175 lg/day (serum TSH 1.9 lIU/mL) for the hypothyroidism. Venlafaxine was tapered gradually as LTG increased until a dose of 300 mg was attained and maintained with good adherence.

Lamotrigine might be able to treat pathological entrainment of mood with the menstrual cycle. The efficacy in this patient with LTG could be related to its robust actions against the depressive aspects of bipolar disorders and its lack of a tendency to cause sedation.[85] The hypothesis that certain antiglutamatergic agents, such as LTG, may offer more robust antidepressant actions and less sedation while certain GABAergic agents, such as valproate, may provide more robust antimanic actions and more sedation86 warrants systematic investigation. This patient not only achieved euthymia without the use of antidepressants, but she also exhibited a clear attenuation of a longstanding relationship between mood and the menstrual cycle.

D'Mello et al. reported two cases of premenstrual mania.[87] The first case describes a 29-year-old woman with premenstrual mania. She was treated with lithium and thiothixene and maintained only with lithium (1,800 mg/day - serum level = 0.9 mEq/L). The second case describes a 41-year-old woman who had a major depressive episode 4 years before and since then had experienced premenstrual mixed mania according to the DSM-III with a stable mood between menses. She was treated with lithium 900 mg/day with serum levels in the 0.6 to 0.8 mEq/L range. She remained stabilized after 2 years of follow-up. No significant differences in the serum

levels were observed during the menstrual phases in both cases. In both cases, lithium therapy interrupted the recurrent premenstrual mood symptoms.

D'Mello et al. reports the importance of investigating the interface between LLPDD and BD.[87] Case reports have little value in the hierarchy of evidence, but clinicians may understand the importance of diagnosing and treating this comorbidity.

Discussion

To the best of our knowledge, no systematic reviews have examined the comorbidity of BD and PMS/PMDD. The present work aimed at reviewing the comorbidity of PMS or PMDD and BD, identifying the variables that require further investigation and reminding physicians that special care is required for diagnosis and therapy.

Clearly women need specific attention regarding psychiatric and psychological aspects because their clinical features may be influenced by all reproductive cycle events, the use of pills, thyroid diseases or any event that may influence gonadal hormones and neurotransmitters sensibility.

The studies analyzed suggest increased risks among women either the PMS or PMDD for BD-I or BD-II and a greater risk of women with BD-II of having PMS or PMDD. Furthermore, women with BD and PMS report increased mood lability, anger, irritability, severe symptoms and frequent relapses of their BD illness and a worse therapeutic response. Insomnia is common in PMS,[88] and sleep deprivation may induce or perpetuate mania in BD patients.[89] These symptoms might be one of the factors that explain the higher intensity of manic episodes and longer subsyndromal episodes in bipolar women with PMS.[55]

Future research should attempt to stabilize hormonal levels with continuous use of contraceptives or naturally, as in gestation and menopause, to see if this causes a reduction in the severity of illness. In addition, psychiatrists should note menstrual period dates and compare symptom intensity between the luteal and follicular phases. Further characterization of the role of neuroactive steroids in mood disorders may lead to the development of new therapeutic approaches.

Several human studies have suggested an estrogen-serotonin hypothesis.[90] Estrogen decrease might increase MAO and reduce 5HT receptor sensitivity, which may lead to depression in susceptible women.[90]

This review demonstrates the importance of diagnosing PMS/PMDD comorbidity, the worse course of disease, the higher number of coexisting psychiatric diseases and the need for a consensus about the PMS/PMDD criteria and the evaluation tools. Still, BD and PMS/PMDD should be further investigated because a lack of research exists. Furthermore, there were also some methodological limitations in this review: the studies used different criteria to diagnose PMS. Retrospective diagnoses of PMDD and generalizations from the data were not allowed because of the small samples.

Conclusion

This overview points to an established correlation between BD and PMS/PMDD. Nevertheless, this is still an under-studied topic. On the other hand, **some reports** have demonstrated the absence of a relationship between BD and the menstrual cycle phases, which **emphasizes** that research should be conducted with PMS/PMDD patients separately.

Disclosures

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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*

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