# Relationship of Premenstrual Dysphoric Disorder With Bipolar Disorder:
## A Systematic Review

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**ABSTRACT**

***Objective:*** Since depression represents the most predominant mood polarity in bipolar disorder (BD), the prevalence rates of a diagnosis of premenstrual dysphoric disorder (PMDD) in women with BD and those of a diagnosis of BD in women with PMDD deserve systematic review.

***Data Sources:*** A systematic search of PubMed, EMBASE, CINAHL, PsycINFO, and Cochrane Reviews databases was carried out on November 19, 2021, using the terms [late luteal phase disorder OR premenstrual dysphoric disorder] AND comorbidity AND bipolar disorder. Articles from 1987–2021 were searched. Case studies, intervention studies, reviews, and systematic analyses were excluded.

***Study Selection:*** All studies that included a diagnosis of PMDD and BD were included.

***Data Extraction:*** The selected articles were reviewed to extract data using a data extraction form developed for this study.

***Results:*** A total of 5 studies were included in the review. Extant literature, although limited, suggests that PMDD is more common among women with BD than in the general population. Similarly, BD is more common among women with PMDD than in the general population. The proportion of people with PMDD and diagnosed with BD ranged from 10% to 45%. Conversely, the proportion of people with BD who received a diagnosis of PMDD ranged from 27% to 76%.

***Conclusions:*** Only a small number of relevant studies were available, and the findings from these were limited by the failure to employ prospective monitoring of symptoms—perhaps the most important feature necessary for confirming PMDD and differentiating it from premenstrual exacerbation of BD. Given the important clinical and heuristic implications, prospective studies are needed to clarify the relationship between the two disorders in order to improve their detection, diagnosis, and treatment.


*J Clin Psychiatry 2022;83(6):22r14416*

***To cite:*** Sharma V, Mazmanian D, Eccles H. Relationship of premenstrual dysphoric disorder with bipolar disorder: a systematic review. *J Clin Psychiatry.* 2022;83(6):22r14416.

***To share:*** https://doi.org/10.4088/JCP.22r14416



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Premenstrual dysphoric disorder (PMDD) is a cyclical mood disorder that affects approximately 2% of menstruating women in any given year.[1] A recent study from Brazil reported a much higher rate of 17.6%; however, the diagnosis was based on retrospective assessment.[2] The disorder manifests as dysphoria, mood lability, irritability, and anxiety during the premenstrual phase of the cycle and abatement or disappearance of these symptoms within a few days after onset of the menses.[3] Due to the overlapping of symptoms, daily prospective rating of at least 2 symptomatic cycles is required to differentiate PMDD from major depressive disorder, bipolar disorder (BD), and persistent dysphoric disorder. Premenstrual dysphoric disorder is associated with impairment in daily functioning and increased use of general health and mental health services, as well as increased rates of suicide attempts.[4] Although premenstrual syndrome shares symptoms with PMDD, it is not associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.[5–7] The exact etiology of PMDD is poorly understood; however, it is proposed that the disorder results from the brain's aberrant response to normal hormonal fluctuations during the menstrual cycle.[8] Risk factors include a personal history of mood or anxiety disorders, family history of premenstrual dysregulation, stress, seasonality, trauma, and sociocultural issues.[3,9]

Given the evolutionary changes in their diagnostic criteria, it is important to clarify the relationship between PMDD and BD. PMDD first appeared as a condition for further study in *DSM-IV*.[10] Prior to that, it was listed as late luteal phase dysphoric disorder in the *DSM-III-R*. In the *DSM-IV,* it was classified as a depressive disorder not otherwise specified but was accorded a separate diagnostic status in the *DSM-5*, making it the only reproductive event–related condition to have its own diagnostic label. In contrast, other psychiatric disorders (such as major depressive disorder, BD I, BD II, or brief psychotic disorder) that can begin or recur during or after pregnancy are characterized by a peripartum or postpartum onset specifier. The International Society for Premenstrual Disorders (ISPMD) recommends that premenstrual exacerbation of an underlying psychological, somatic, or medical condition should be considered a variant of PMDD.[11] According to the ISPMD, only patients with typical or core PMDD have symptom onset in the luteal phase and resolutions of these symptoms at, or shortly after, the onset of menses followed by a symptom-free week

**Clinical Points**

- No systematic review has focused exclusively on the association between PMDD and BD. Understanding of this association is needed to be able to effectively diagnose and treat both disorders.
- Physicians should be aware that many patients with BD may have PMDD and vice versa, and treatments for PMDD, such as antidepressants, can negatively affect people with comorbid BD.

prior to ovulation. Interestingly, in the 11th revision of the *International Classification of Diseases and Related Health Problems* (*ICD-11*), PMDD is considered a disease of the genitourinary system rather than a psychiatric disorder.[12]

According to the *DSM-5*,[3] a major depressive episode is the most commonly reported comorbidity in women with PMDD. This is understandable given the inclusion of PMDD in the chapter "Depressive Disorders" in the *DSM-5*. Premenstrual dysphoric disorder can co-occur with BD as long as the premenstrual symptoms are not a mere exacerbation of BD and the diagnostic criteria for PMDD are met.[3] Understanding the relationship between PMDD and BD is critically important for several reasons.[13] Diagnosing PMDD in women with BD can be challenging because concurrent bipolar depression may overshadow the improvement in PMDD-related symptoms during the follicular phase of the menstrual cycle. Distinguishing between PMDD and premenstrual exacerbation—a common occurrence in women with BD—can be particularly challenging. In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), 65.2% of 293 women with BD had premenstrual exacerbation of symptoms of depression or mood swings.[14] Other studies have reported similar results.[15] Having comorbid PMDD may increase the disease burden of BD due to an earlier age of illness onset, more rapid cycling, and higher number of hypo/manic and depressive episodes, as well as suicidal thoughts or acts.[16] Optimal treatment of the comorbidity also requires a better understanding of how the disorders affect each other. Furthermore, BD and PMDD are also often comorbid with other psychiatric disorders including anxiety disorders, posttraumatic stress disorder, bulimia nervosa, substance abuse, and adult attention deficit disorder.[2,16,17] Having additional comorbid conditions has implications for the treatment of BD.[16] Antidepressants are generally considered the mainstay of drug treatment of PMDD[9,18] and other comorbidities such as obsessive-compulsive disorder or anxiety disorders, but their use in patients with BD can cause treatment-emergent hypo/mania, mixed states, or rapid cycling.[19] Understanding this relationship has heuristic implications. Both BD and PMDD are cyclical disorders, and their comorbidity may be linked to shared biological mechanisms including polygenetic risk factors, brain-derived neurotrophic factor, and catechol-*O*-methyltransferase (COMT) polymorphisms.[18,20,21]

Cirillo et al[13] conducted a systematic review to examine the comorbidity of premenstrual syndrome or PMDD in women with BD. The authors did not report the results separately for these two conditions. Recently, Slyepchenko et al[22] reviewed the literature on the phenomenology, illness burden, and neurobiology of comorbid PMDD and BD; however, this was not a systematic review. To our knowledge, no systematic review has focused exclusively on the association between PMDD and BD. The objective of this review was to examine the relationship between PMDD and BD. Specifically, we aimed to assess rates of BD in women with PMDD and, conversely, rates of PMDD in women with BD.

## METHODS

### Search Strategy and Data Sources

The search strategy focused on gathering as many studies as possible from 1987, the year in which the *DSM-III-R* that included the term *late luteal phase dysphoric disorder* (LLPDD) was published, until 2021. The term *PMDD* (same criteria as the LLPDD with the exception of 1 item) first appeared in the *DSM-IV,* which was published in 1994. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses,[23] a comprehensive literature search in PubMed, EMBASE, CINAHL, PsycINFO, and Cochrane Reviews databases was carried out on November 19, 2021, using the terms [late luteal phase disorder OR premenstrual dysphoric disorder] AND comorbidity AND bipolar disorder.

### Study Selection, Eligibility Criteria, and Data Extraction

Titles and abstracts of studies retrieved in the initial search were evaluated independently by authors V.S. and D.M. to select potentially relevant studies for further review. The following inclusion criteria were applied for selecting studies: (1) original studies in English published between 1987 and 2021; (2) a diagnosis of BD as per *DSM-III-R*, *DSM-IV,* or *DSM-5*; (3) a diagnosis of LLPDD as per *DSM-III-R* or PMDD as defined in *DSM-IV* or *DSM-5*; and (4) use of validated tools to assess PMDD. Treatment studies and case reports/series were excluded. Other potentially eligible articles found upon bibliographic search were added. The selected articles were reviewed to extract the following information: first author and year of publication, study design, sample size, age, diagnostic criteria and assessment, whether or not daily prospective ratings were employed, and prevalence rate (PMDD rates with BD or, where reported, BD rates with PMDD).

## RESULTS

Results of the search and selection process are described in the PRISMA flow diagram (Figure 1). Of the 33 articles found (references listed in Supplementary Appendix 1), 16 duplicate articles were removed, and 17 were screened for relevance. Three articles were found to be relevant to the study. The rest were excluded for being reviews or case reports and not reporting prevalence rates. The references

**Figure 1. PRISMA Flowchart Illustrating Selection of Identified Articles**

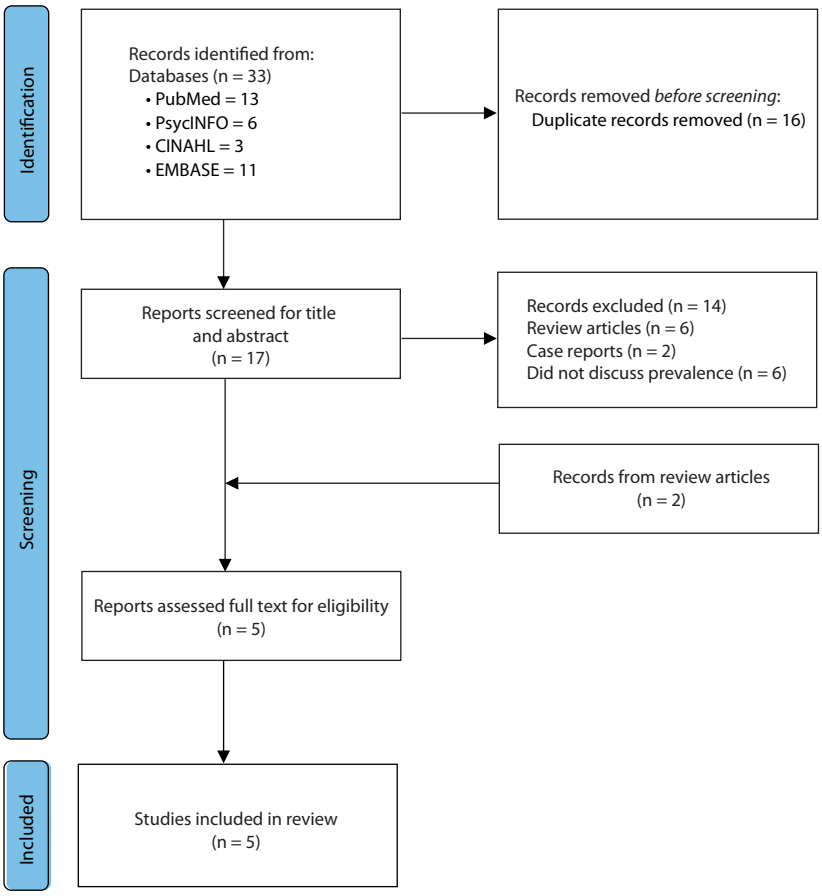


**Table 1. Summary of Included Studies**

| Authors | Title | Study design | Sample size | Age (y) | Diagnostic criteria: PMDD | Diagnostic criteria: BD |
|---|---|---|---|---|---|---|
| de Carvalho et al 2018[2] | Prevalence and Factors Associated With Premenstrual Dysphoric Disorder: A Community Sample of Young Adult Women | Cross-sectional population-based study | Total: 727 128 with PMDD | 18–24 | Mini International Neuropsychiatric Interview Version Plus | Mini International Neuropsychiatric Interview Version Plus |
| Slyepchenko et al 2017[16] | Increased Illness Burden in Women With Co-Morbid Bipolar and Premenstrual Dysphoric Disorder: Data From 1,099 Women From STEP-BD Study | Retrospective cohort | 1,099 | > 15 | Self reported reproduction questionnaire | Mini International Neuropsychiatric Interview Version Plus |
| Fornaro and Perugi 2010[17] | The Impact of Premenstrual Dysphoric Disorder Among 92 Bipolar Patients | Cross-sectional | 92 | > 18 | Structured Clinical Interview for *DSM-IV* | *DSM-IV-TR*, semistructured interview |
| Hardoy et al 2006[24] | Increased Neuroactive Steroid Concentrations in Women With Bipolar Disorder or Major Depressive Disorder | Case-controlled study | Total: 47 17 with BD | Average: 37 ± 8 | Structured Clinical Interview for *DSM-IV* | Structured Clinical Interview for *DSM-IV* |
| Wittchen et al 2002[4] | Prevalence, Incidence and Stability of Premenstrual Dysphoric Disorder in the Community | Prospective—longitudinal community survey | Total: 1,488 (74 with PMDD) | 14–24 | Munich-Composite International Diagnostic Interview | Munich-Composite International Diagnostic Interview |

Abbreviations: BD = bipolar disorder, DSM = *Diagnostic and Statistical Manual of Mental Disorders*, PMDD = premenstrual dysphoric disorder.

**Table 2. Rates of Comorbidity of Bipolar Disorder and Premenstrual Dysphoric Disorder**

| Authors | BD I + PMDD[a] | BD II + PMDD[b] | BD + PMDD[c] | PMDD + BD[d] |
|---|---|---|---|---|
| de Carvalho et al 2018[2] | … | … | … | 19/128 (14.8%) |
| Slyepchenko et al 2017[16] | 322/732 (43.9%) | 175/367 (47.7%) | … | 497/1,099 (45.2%) |
| Fornaro and Perugi 2010[17] | 3/29 (10.3%) | 22/60 (36.7%) | 25/92 (27.1%) | … |
| Hardoy et al 2006[24] | … | … | 13/17 (76.4%) | … |
| Wittchen et al 2002[4] | … | … | … | 8/74[e] (10.5%) |

[a]The proportion of people with BD I who were diagnosed with PMDD.
[b]The proportion of people with BD II who were diagnosed with PMDD.
[c]The proportion of people with BD who were diagnosed with PMDD.
[d]The proportion of people with PMDD who were diagnosed with BD.
[e]PMDD was a weighted 12-month prevalence.
Abbreviations: BD = bipolar disorder, BD I = bipolar disorder type I, BD II = bipolar disorder type II, PMDD = premenstrual dysphoric disorder.
Symbol: … = not reported.

of the review articles were explored, and 2 more relevant publications were found. In total, 5 articles (all observational studies) were included in the systematic review.

### Description of Selected Studies

The details of studies included are summarized in Table 1. Of the 5 studies included, 2 were conducted in Italy and the rest in Brazil, the US, or Germany. Only 1 study had a prospective design, 2 studies were cross-sectional, and the others were a retrospective cohort study and a case-control study. The diagnosis of BD was established using the Structured Clinical Interview for *DSM-IV*,[7,16,24] Mini International Neuropsychiatric Interview Version Plus (MINI),[2] and the Munich-Composite International Diagnostic Interview (M-MINI).[25] The M-MINI incorporates the *DSM-IV* and *ICD-10* criteria. PMDD was diagnosed following a *DSM-IV*–based semistructured interview,[16,24] the MINI,[2,16] and M-MINI.[25] None of the studies used the diary data to confirm a diagnosis of PMDD.

Fornaro and Perugi[17] studied the impact of PMDD in 92 outpatients or inpatients with a *DSM-IV* diagnosis of BD I or II. The participants met the *DSM-IV* criteria for PMDD including the requirement that the "disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders)."[17] There was excellent interrater reliability ($\kappa = 0.89$) for this diagnosis.[17] Using the *DSM-IV* criteria, a total of 25 (27.1%) reported a lifetime history of PMDD. In regard to subtypes of BD, women with comorbid PMDD had higher rates of BD II and cyclothymia (88% and 72%, respectively) vs those without PMDD (60% and 36%). Only 12% of patients with PMDD had BD I compared to a rate of 38.8% in women without PMDD.[17] Women with PMDD had a significantly higher mean number of comorbid disorders ($2.4 \pm 1.8$ vs $1.6 \pm 1.4$).[17] Comorbid disorders that were more common in women with PMDD vs without PMDD included postpartum depression (36% vs 15%), obsessive-compulsive disorder (24% vs 8%), and body dysmorphic disorders (24% vs 6%).[17] The presence of PMDD was not significantly associated with demographic and clinical features of BD such as age, level of education, marital status, age at onset, rapid cycling, seasonality, psychotic features, melancholic features, suicidality, and past hospitalization.[17]

De Carvalho et al[2] assessed the prevalence of PMDD retrospectively in a community sample of 727 women aged 18–24 years. Participants were diagnosed using the MINI. A total of 17.6% of women had PMDD, and the disorder was significantly more prevalent among older women and women of lower socioeconomic status.[2] A diagnosis of PMDD was significantly associated with BD (Poisson regression = 2.31, CI = 1.60–3.33, $P < .001$).[2] The comorbidities significantly associated with PMDD included current major depressive disorder, agoraphobia, BD, current suicide risk, generalized anxiety disorder, social phobia, and specific phobia. Women with PMDD were also at significantly higher risk of suicide.[2]

Hardoy et al[24] determined the plasma levels of neuroactive steroids during the luteal phase of the menstrual cycle in women with BD or major depressive disorder. The sample included 17 patients with BD (4 type I and 13 type II), 14 patients with major depressive disorder, and 16 participants with no personal history of psychiatric illness and no family history of anxiety or mood disorders (control group).[24] All patients had not had any relapses for at least 3 months.[24] The majority of patients were taking psychotropic drugs including antipsychotics, mood stabilizers, and antidepressants.[24] Premenstrual dysphoric disorder was present in 13 (76.5%) of 17 patients with BD and in 9 (64.3%) of 14 patients with major depressive disorder.[24] Of the 16 participants in the control group, 6 (37.5%) had PMDD.[24] Although there were no significant differences in the proportion of women with PMDD between the groups ($\chi^2_2 = 5.3$, $P = .068$), the observed rates of PMDD in bipolar patients were more than twice that observed for the controls.[24] The lack of statistical significance could be attributable to the relatively small sample sizes in this study.[24] Another important point is that the observed rate for the control subjects (37.5%) is more than 6 times higher than the general population rates reported elsewhere.[24] Compared with the control group, women with mood disorders had higher plasma concentrations of neuroactive steroids during the luteal phase of the menstrual cycle.[24] The concentrations of the steroids were greater in women with BD than in those with major depressive disorder.[24] The higher concentrations of neuroactive steroids in women with mood disorders were not attributable to the effect of drug treatment or comorbidity with panic disorder, obsessive-compulsive disorder, or eating disorder.[24]

Wittchen et al[4] studied the prevalence, incidence, and comorbidity of PMDD in a community sample of 1,488 females aged 14–24 years who were followed for 48 months. The Munich-Composite International Diagnostic

Interview[26] based on the World Health Organization's CIDI version 1.2[27] was used to assess PMDD.[4] At baseline, 5.8% of the sample had PMDD. An additional 18.6% of females were considered as "near-threshold" cases due the failure to meet the required impairment criterion.[4] Approximately 10% of women with PMDD had BD (type I, 5.7% and type II, 4.9%; OR 7.9 and 8.1, respectively [$P < .01$]). Similarly, there was a significant association with anxiety disorders (47% ± 4% PMDD vs 24% ± 9% among non-PMDD cases).[4]

Slyepchenko et al[16] used STEP-BD data to study the effect of PMDD on the course of BD. A total of 1,099 females aged ≥ 15 years who had a diagnosis of BD I (n = 732) or II (n = 367) were studied. The *DSM-5* criteria were applied to diagnose BD and PMDD; however, it is unclear whether women met the criterion involving improvement in symptoms in the follicular phase.[16] A self-report reproductive questionnaire was used to gather information about mood symptoms associated with reproductive events including premenstrual symptoms (depression, anhedonia, mood swings, irritability/anger, tension/anxiety, crying easily, feeling overwhelmed or out of control, insomnia or hypersomnia, food craving, low energy, concentration difficulties, bloating, breast tenderness, and abdominal pain) and symptoms experienced from taking oral contraceptives.[16] Among women with BD I, 322 (44%) had PMDD, and of those with BD II, 175 (47.7%) had PMDD. Of women with PMDD, 64.8% had BD I and 35.2% had BD II.[16] Women with comorbid PMDD had an earlier onset of BD and a smaller interval between onset of BD and age of menarche.[16] As well, women had more mood episodes as well as higher rates of rapid cycling.[16] Comorbidity with PMDD was also associated with higher prevalence of other psychiatric disorders including panic disorder, generalized anxiety disorder, posttraumatic stress disorder, alcohol and drug abuse, bulimia, and adult ADHD.[16] Women with comorbid PMDD reported earlier age of menarche and having had a shorter interval between the age of menarche and the onset of BD.[16] Comorbidity with PMDD was also associated with more mood instability with the use of hormonal contraceptives and greater mood instability during after pregnancy.[16]

### Relationship Between PMDD and BD

A description of the relationship is detailed in Table 2. The extant literature suggests that PMDD is a common diagnosis in women with BD.[16,17,24] Similarly, a large number of women with PMDD suffer from BD.[2,4] A large study[4] of adolescents and young adults from Germany found that 10% of women with PMDD had a diagnosis of BD I or II, and women with PMDD were 8 times more likely to have a diagnosis of BD compared to those without PMDD. Fornaro and Perugi[17] found that 27.1% of women with BD I or II had a lifetime diagnosis of PMDD. Women with PMDD had higher rates of cyclothymia and BD II (72% and 88%, respectively). In the STEP-BD study, 45.2% of women with PMDD had BD.[16] In regard to diagnostic subtypes, BD I was more common than a diagnosis of BD II (64.5% vs 35.2%). A diagnosis of PMDD was present in 43.9% of women with BD I and 47.7% of women with BD II. In contrast, Fornaro and Perugi[17] found a higher prevalence of BD II compared to BD I among women with PMDD. Reasons for the discrepant findings are unclear; however, differences in the study samples and participants' age could have contributed to the disparate findings. Women in the STEP-BD study[16] were approximately 15 years older than women in the Fornaro and Perugi[17] study (49.6 [13.7] years vs 34.07 [9.04] years). Also, participants in the STEP-BD study[16] were outpatients, while both outpatients and inpatients were recruited in the other study.[17] Hardoy et al[24] found that PMDD was more common in women with BD (76.4%) compared to those with major depressive disorder (64.3%), this being the only controlled study to report comparative rates.

There is inconsistency of findings in regard to the effect of PMDD on the course of BD[2,16,17] including age at onset and cycle frequency. Similarly, there are mixed findings on the risk of rapid cycling.[16,17] Having PMDD might indicate greater vulnerability to mood instability during and after pregnancy. A recent systematic review found a positive relationship between PMDD and postpartum depression.[27]

## DISCUSSION

This review highlights the paucity of studies on the prevalence of PMDD in women with BD and vice versa. Only 2 studies have been published since 2012, when the last and only systematic review on the topic was published. None of the studies we reviewed here confirmed the diagnosis of PMDD using prospective daily ratings of symptoms in the final week of menses, over at least 2 symptomatic cycles. Due to the unreliability of retrospectively obtained information, a prospective record of symptoms over at least 2 symptomatic cycles is recommended for diagnostic confirmation.[3] Nonetheless, the limited evidence suggests that PMDD is more common among women with BD than in the general population. Similarly, BD is more common among women with PMDD than in the general population. These results suggest that women with PMDD should be assessed for BD as well as comorbid psychiatric disorders. Similarly, a diagnosis of BD should necessitate assessment for PMDD. Distinguishing between symptoms of PMDD and BD can be challenging. Both conditions are cyclic and typically begin during adolescence. A correct diagnosis of BD may be delayed by as long as 8 years,[28] and for PMDD the average delay is 20 years.[29] Clinicians using the *ICD-11* to diagnose PMDD may not sufficiently inquire about the psychiatric comorbidity, further delaying the appropriate diagnosis and optimal treatment.

Assessing the prevalence of PMDD as per the *DSM-5* diagnostic criteria is challenging for several reasons. First, the overlap of symptoms of BD and PMDD makes it difficult to distinguish between symptoms of these disorders. Of a total of 11 symptoms of PMDD (criteria B and C), 6 are symptoms of a major depressive episode (sad mood,

anhedonia, poor concentration, lack of energy, change in appetite, and insomnia or hypersomnia), and 2 symptoms are shared with the anxious distress specifier (feelings of being keyed up and a sense of being out of control). Irritability can be a symptom of hypo/mania; thus, mood lability and physical symptoms (breast tenderness, joint or muscle pain, and bloating) are the only symptoms that are not shared with common comorbidities. Feinstein,[30] who coined the term *comorbidity*, defined it as the presence of "a distinct additional clinical entity." Given that the majority of PMDD symptoms overlap with symptoms of BD, it is difficult to argue that the two disorders are distinct clinical entities. Second, the *DSM-5* position on the comorbidity of PMDD is ambiguous.[3] While it emphasizes the requirement of a symptom-free postmenstrual period for a diagnosis of PMDD; the manual also recommends that the diagnosis "can be considered in individuals in addition to the diagnosis of another mental or physical disorder if the individual experiences symptoms and changes in level of functioning that are characteristic of premenstrual dysphoric disorder and markedly different from the symptoms experienced as part of the ongoing disorder."[3] The ISPMD[31] makes a distinction between core/variant PMDD and an independent comorbid disorder, arguing that suppression of the menstrual cycle (eg, with a gonadotropin-releasing hormone agonist) should not change the independent comorbidity. Unlike some other disorders included in the chapter Depressive Disorders, such as major depressive disorder or persistent depressive disorder, a diagnosis of PMDD does not require exclusion of an episode of hypo/mania. Nonetheless, there are reports of hypomanic symptoms in women with PMDD. Aalouane et al[32] described successful treatment of a woman with PMDD and hypomania in the absence of a major depressive episode. Parry et al[33] used the Millon Clinical Multiaxial Inventory[34] to study personality traits among women with LLPDD. Compared to normal controls, women with LLPDD had less compulsive but more passive/aggressive and borderline/cycloid traits. Women in the latter group also had more depression and hypomania.[33] Third, prospective daily rating for confirmation of diagnosis is not always feasible because the long-term course of BD I and II is marked by the presence of mood symptoms 47.3% and 53.9% of the time, respectively.[35,36] Moreover, prospective monitoring of mood symptoms is necessary to establish euthymia while the prospective daily ratings are being carried out. In the Harvard Study of Moods and Cycles, less than 50% of women completed the prospective charting necessary for a formal diagnosis.[37] Finally, failure to rule out premenstrual exacerbation may lead to underdiagnosis or misdiagnosis of PMDD because juxtaposition of bipolar mood symptoms may overshadow the symptom free interval after the menses. Moreover, in some cases, it may be difficult to ascertain the extent to which the psychotropic drugs for BD may be affecting the symptom profile of PMDD.

Premenstrual dysphoric disorder is the only menstrual-related disorder listed in the *DSM-5*. Despite the overlapping of symptoms with BD and its association with BD, PMDD is classified as a depressive disorder in the *DSM-5*.[38] This means that there is no other option available (eg, a pre- or perimenstrual specifier) to highlight the impact of the menstrual period on the course of BD. A systematic review found that, depending on the type of the study (eg, retrospective or prospective), 44%–68% of women with BD have menstrual cycle–related mood changes.[39] The effect of the menstrual cycle is not restricted to depression but involves the full spectrum of mood episodes including symptoms of hypo/mania and mixed states.[39] In the STEP-BD study, of 293 women followed prospectively for 1 year, 191 women (65.2%) had premenstrual exacerbation.[16] Compared to women without, those with premenstrual exacerbation had more mood episodes (mainly depressive), a shorter time to relapse, and more severe symptoms.[16] Thus, similar to PMDD, the premenstrual exacerbation may signal a BD phenotype characterized by more frequent and severe episodes.

Limitations of the review should be acknowledged. The largest and the only prospective study was a post hoc analysis and was not originally intended to investigate the association of PMDD and BD.[16] The details of psychotropic drug use were not available in some studies. This is important because the use of these drugs may have affected the prevalence of PMDD as well as the course of BD. Use of antidepressants may attenuate symptoms of PMDD but increase the risk of rapid cycling, hypo/mania, and suicidality in patients with a bipolar diathesis. Use of mood stabilizers is associated with a reduction in the premenstrual mood exacerbations.[40,41] Similarly, use of oral contraceptives impacts symptoms of both BD and PMDD. A major limitation of the extant literature is the lack of studies with prospective monitoring of symptoms—perhaps the most important feature necessary for confirming PMDD, and its differentiation from premenstrual exacerbation of BD.

This review highlights the need for studies to clarify the relationship between PMDD and BD including its subtypes. It is important to determine whether women with BD who are currently symptomatic could reliably be diagnosed with PMDD using the *DSM-5* criteria. Studies are also needed to assess the prevalence of BD among women in community as well as clinical settings considering the effect of medications on the course of both disorders. Researchers should be aware that women with BD who meet the *DSM-5* diagnostic criteria for PMDD might have a more favorable illness course and responsiveness to treatment compared to those who are unable to have symptom free intervals in the follicular phase of the cycle due to the concomitant symptoms of BD. More work is required to clarify the distinctions between PMDD, premenstrual syndrome, premenstrual exacerbation, and relapse of BD. A recent systematic review found a positive relationship between PMDD and postpartum depression.[27] Given the scarcity of similar data in women with BD, it is important to clarify the effect of PMDD on the course of BD during and after pregnancy and investigate the possibility of a shared endophenotype between PMDD, BD, and

postpartum depression. Studies are also needed to clarify the comparative effect of premenstrual exacerbation vs PMDD on the course, comorbidity, and responsiveness to treatment in women with BD. Karadag et al[40] found that successful treatment of BD with lithium or valproate resulted in fewer prospectively assessed premenstrual exacerbations than in healthy controls. Currently, there are no studies on the use of mood stabilizers, oral contraceptives, or allopregnanolone in women with PMDD and BD.[18] Antidepressants are commonly recommended and are effective for PMDD; however, these drugs may not be appropriate for patients with BD.

## CONCLUSION

Findings of this review are consistent with the results of an earlier systematic review in highlighting the association of BD with PMDD; however, diagnosing PMDD in women with BD especially in clinical settings can be challenging. Given the important clinical and heuristic implications, prospective studies are needed to clarify the relationship between the two disorders in order to improve their detection, diagnosis, and treatment. Additional studies to systematically assess the current menstrual phase and general medical and medication profile are also needed.

***Submitted:*** February 14, 2022; accepted May 23, 2022.

***Published online:*** October 26, 2022.

***Relevant financial relationships:*** **Dr Sharma** reports personal fees from the Neuroscience Education Institute and grants from Assurex, Genome Canada, Sage Therapeutics, Stanley Medical Research Institute, and Sunovion Pharmaceuticals and participation in the advisory boards for Sunovion Pharmaceuticals and Otsuka, outside the submitted work. **Dr Mazmanian** has received grant support from Social Sciences and Humanities Research Council of Canada and Gambling Research Exchange Ontario, outside the scope of the submitted work. **Ms Eccles** has no conflicts to report.

***Funding/support:*** None.

***Acknowledgment:*** The authors thank Elizabeth Russell, Librarian at Parkwood Institute, London, Ontario, Canada, for her assistance with the literature search.

***Supplementary material:*** Available at Psychiatrist.com.

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*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

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# Supplementary Material

**Article Title:** Relationship of Premenstrual Dysphoric Disorder With Bipolar Disorder: A Systematic Review

**Authors:** Verinder Sharma, MBBS; Dwight Mazmanian, PhD, CPsych; and Heidi Eccles

**DOI Number:** 10.4088/JCP.22r14416

## List of Supplementary Material for the article

1. **Appendix 1** Studies Found Through Literature Search by Database

## Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix:

Appendix 1: Studies found through literature search by database

Pub Med


1. Cirillo PC, Passos RB, Bevilaqua MC, López JR, Nardi AE. Bipolar disorder and Premenstrual Syndrome or Premenstrual Dysphoric Disorder comorbidity: a systematic review. Braz J Psychiatry. 2012 Dec;34(4):467-79. doi: 10.1016/j.rbp.2012.04.010.

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