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Premenstrual Exacerbations of Mood Disorders

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Abstract

Premenstrual exacerbations (PMEs) of persistent mood disorders are little understood, in contrast to premenstrual dysphoric disorder (PMDD). This review's objectives are to explore the clinical and research ramifications of PME in unipolar depression and bipolar disorder, as well as diagnostic difficulties, epidemiology, underlying mechanisms, and treatment. Around 60% of women with mood disorders, according to community-based and clinical studies, report PME, and some bipolar disorder sufferers also experience symptom flare-ups around the ovulation. PME typically foresees a more serious illness course and an increased burden. The overlap of their underlying biological pathways is yet unknown, despite the fact that PME and PMDD both appear to be influenced by increased sensitivity to variations in sex hormone levels throughout the menstrual cycle. PME results for effective PMDD therapies are lessened or non-existent. Pharmacological therapies for PME in mood disorders mostly tend to benefit from customizable dosage augmentations during the luteal phase for the underlying disease. The available data, however, is scant and largely based on old, limited studies and case reports. To get accurate prevalence estimates, information on the clinical impact of PME of mood disorders, and to identify underlying processes, more systematic research using uniformly defined and prospectively assessed subgroups of PME in larger epidemiological and clinical samples is required. It is also necessary to conduct larger randomised controlled trials to find effective pharmacological and psychological therapies for affected women.

Keywords: Depression • Bipolar disorder • Mood disorders • Menstrual cycle • Premenstrual exacerbation

Introduction

Reproductive hormones affect the neurotransmitter networks and areas of the brain responsible for controlling mood and processing emotions. When it comes to a segment of women, the menstrual cycle, the per partum, and the pre menopause are all accompanied by noticeable adjustments to their emotional, cognitive, and behavioural functioning. The International Society for Premenstrual Diseases (ISPMD) makes a distinction between premenstrual exacerbations (PMEs) of continuing mental or physical disorders and core premenstrual disorders, such as premenstrual dysphonic disorder (PMDD) and severe premenstrual syndrome (PMS). There is notably few well-designed research addressing epidemiology, potential underlying mechanisms, and therapy of PME of mood disorders, even though the PMDD literature has steadily expanded alongside this difference. The purpose of this review is to examine diagnostic challenges in differentiating between PMDD and PME of bipolar and depressive disorders, to describe the information that is currently available on PME of mood disorders, and to discuss potential therapeutic and research implications.

Literature Review

An average menstrual cycle lasts 28 (21–35) days. The follicular phase, which lasts from menstruation to ovulation, is characterised by low progesterone (P4) and rising oestrogen (E2) levels that reach a high just before ovulation and then quickly fall following ovulation. E2 and P4 gradually increase throughout the luteal phase (days from ovulation to menses), peaking during the mid-follicular phase. Then, during the late luteal (premenstrual) phase, or the week before the upcoming menses, they rapidly decline [1]. The DSM-5 describes PMDD as having affective core symptoms (marked affective liability, irritability/anger/increased interpersonal conflicts, depressed mood/feelings of hopelessness, or anxiety/tension/feeling on edge) as well as additional psychological and/or physical symptoms that are limited to the premenstrual phase and disappear after the start of menses. In contrast to PMDD, premenstrual exacerbation of an on-going depressive or bipolar condition characterises PMEs of mood disorders (BD). Premenstrual breakthrough, a specific subtype of PME, is the development of symptoms of the underlying illness prior to menstruation that responds to treatment for the remainder of the cycle. The DSM-5 does not explicitly differentiate between PMDD and PME in criterion E for PMDD: "The disturbance is not merely an exacerbation of the symptoms of another disorder... although it may co-occur with any of these disorders." This is despite the ISPMD definition requiring counting each shared symptom of PME and PMDD towards PME, even if it represents a diagnostic criterion for PMDD (e.g., depressed mood). The ISPMD takes a more cautious approach in an effort to avoid overestimating the prevalence of comorbid diseases and, more crucially, to avoid treating women with the wrong dual diagnosis inadequately [2].

In order to distinguish PMDD from PMEs, prospective symptom ratings spanning at least two symptomatic menstrual cycles are necessary, taking into account the severity of postmenstrual symptoms. It is possible to identify the necessary pre- and postmenstrual symptom rises and declines for PMDD using the proper scales, but there is no generally accepted criteria for the corresponding rates of change to support PME of another condition. Some writers stipulate that depressive illnesses must have at least mild postmenstrual symptoms, although this definition fails to adequately account for premenstrual breakthroughs with mostly symptom-free intervals throughout the rest of the cycle. Pre- and postmenstrual evaluations should also include all symptoms of the underlying disease, not just those of PMDD, as has only sometimes been done in relevant studies, in order to distinguish PME from PMDD [3].

In BD, the issue is considerably more convoluted. The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines state that a stable state of euthymia must be attained during the remaining cycle phases, with a minimum of 2 months of prospective pre- and postmenstrual symptom charting, in order to accurately diagnose comorbid PMDD in women with BD. However, when examining comorbid PMDD, the great majority of BD research employ non-mutually exclusive categories or fail to account for continuous

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mood episodes. Due to symptom similarities, comorbidity between PMDD and PME of mood disorders may not always be easy to detect. It is a condition in which there is a premenstrual aggravation of an ongoing problem (such as depression) on a regular basis and at least five distinct PMDD symptoms (such as mood swings, rage, irritability, and physical symptoms) that are present exclusively before a period. There are no reliable estimates of the prevalence of the various comorbidities.

A mood illness known as unipolar depression carries a significant risk of relapses and chronic complications. In both community-based and therapeutic settings, there are around 2:1 more women than males. Studies examining the PME of depressive illnesses are uncommon, and more current research is sparse. However, there is widespread agreement that the majority of women seeking first therapy for PMS or PMDD are actually experiencing PME, primarily PME of unipolar depression. Although there is a paucity of actual evidence, it is likely that the majority of afflicted women will initially consult their gynaecologists. The 900 women aged 13 to 53 in the only study to date that assesses prevalence rates of PME of depression found 58 women (6.4%) to have a current depressive illness and an undetermined number to have bipolar disorder. Premenstrual symptoms were assessed prospectively over two months with extra questions for major depression (MDD) or dysthymia, and results revealed that 58% of the sample had a current depressive condition and showed PME of one or more depressed symptoms [4]. PME projected a decline in general functioning in turn. More than 40% of female antidepressant users who were not currently depressed also displayed PME. Women with MDD were questioned in two reports from the major multicenter Sequences Treatment Alternatives to Relieve Depression (STAR-D) research if they were aware of routinely recurrent premenstrual mood deterioration. Between the ages of 18 and 61, 64% of 433 normally menstruation women reported retrospectively having depression. Retrospectively reported PME was 66% prevalent in the whole STAR-D sample of 821 women with current MDD (n = 821; age range, 18–39). PME was related to older age, longer index episodes, more prior depressive episodes, a greater prevalence of familial history of BD and depressive disorders, higher levels of anxiety, more medical issues, and worse physical functioning. For women with PME, it took less time for recurrence to occur following remission during the citalopram therapy period [5]. Patients with persistent depression were randomly assigned to receive a 12-week course of sertraline or imipramine, with the option of crossover if the patient did not react. Without regard to menstrual cycle phase or medication class, premenstrual worsening of depression, anxiety, irritability, mood swings, and exhaustion at baseline predicted greater rates of depressed worsening during the follow-up evaluations. A worsening of the depressive symptoms in turn indicated treatment failure and non-response.

Discussion

A thorough analysis revealed that 44–65% of women with BD experienced menstrual cycle-related mood alterations in retrospective studies (66–68%) and prospective studies (44–65%). In the premenstrual period, around ovulation, and throughout the menstrual phase, depressive, hypomanic, manic, or mixed symptoms are primarily entrained (i.e., likely to have their beginning in) or made worse. Indicating that there may be a range of symptom trajectories during the menstrual cycle in women with BD, a subset of patients demonstrates PME of depressed symptoms while others experience premenstrual or periovulatory worsening of hypomanic or manic symptoms. A total of 293 women with bipolar disorder (BD) between the ages of 18 and 40 who participated in the longitudinal Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) reported PME of depressive or mood swing symptoms 65.2% of the time. Regardless of cycle phase, self-reported PME of symptoms over a 1-year follow-up period was associated with higher symptom intensity, more depressive episodes, mood elevation, and a shorter time to relapse into syndromal or subsyndromal episodes. The STEP-BD initiative itself, however, does not, in turn, distinguish PME from comorbid PMDD. A concomitant PMDD diagnosis was evaluated using a questionnaire that included the DSM-5 PMDD criteria in a more recent STEP-BD study on 1099 BD women. In BD women with PMDD, there was an earlier onset of BD, a smaller gap between the age of onset and menarche, more comorbid Axis I disorders, more hypomanic/manic and depressive episodes, and higher rates of rapid cycling, all of which are indicative of worse clinical outcomes and a greater burden of illness. Since this study ignored any potential overlap between PMDD symptoms and PME of BD, a sizable fraction of PMDD patients may have met the ISPMD definition of PME. The increased proportion of retrospectively recognised fast cycling in the group of people with concomitant PMDD may possibly be explained by disregard for PME. Prospective studies have not shown a connection between PME and fast cycling in BD. Many prospective small-scale investigations or case reports failed to discover consistent correlations between BD and the menstrual cycle, indicating that not all BD sufferers experience PME or that effective therapy may reduce related symptoms.

Sex hormones and their cyclical changes have an impact on physiological systems involved in drug processing and are thought to be a major contributor to drug pharmacokinetic and pharmacodynamic variability. This holds true for antidepressant therapies as well, showing less consistent effectiveness and negative consequences in women and causing conflicting data on potential sex differences in response to antidepressant therapy. Menstrual cycle-related variations in medication blood levels may be especially dangerous for women with PME or mental disorders, necessitating special drug monitoring and adaptation. A recent small-scale study revealed a connection between PME in (hypo-) manic and psychotic symptoms and a drop in lithium serum levels during the luteal phase in women with BD, despite the absence of systematic research on this issue for PME of depression. A larger dose of lithium during the premenstrual phase in one case report seems to compensate for the premenstrual drop in blood levels and to avoid PME symptoms [6,7].

Conclusion

In conclusion, the scant empirical data reveals that PME symptoms are present in about 60% of women with depressive disorders and a comparable percentage of women with BD. In both illnesses, PME predicted decreased functioning, a more chronic or repeated course of illness, and nonresponse to therapy. The majority of research, however, struggle with objective validation of ovulation, lack of control over the use of hormonal contraceptives and psychiatric medications, and retroactive evaluations of PME. Larger community-based and clinical studies are therefore required, along with a thorough analysis of PME risk factors, prospective ratings covering the full spectrum of depressive or BD symptoms and PMDD symptoms, and the development of understandable algorithms for the definition of pre- to postmenstrual change scores to specify PME. There are specific methodological problems with studies on menstrual cycle-related alterations in women with BD. The vast majority of studies do not differentiate between PME of BD and BD comorbid with PMDD. Although several distinct operationalization of the various subtypes of menstrual cycle effects in BD, such as entrainment, exacerbation, comorbidity of BD with PMS/PMDD, and magnification, defined as BD with PME and concomitant PMDD/PMS, have been proposed. Additionally, there hasn't been enough research done on other important cycle periods in BD, especially the preovulatory phase. The frequency and significance of precisely characterised subtypes of menstrual cycle-related events in BD must be evaluated in this situation through more extensive, systematic study. The effectiveness of psychological therapies for PME of mood disorders has not yet been studied, despite strong evidence that they enhance treatment adherence, symptoms, and psychosocial functioning in mood disorders, including unipolar depression and bipolar disorder. It might be used and evaluated on women with PME of depression and BD, potentially more precisely and individually. Future intervention research may also include other strategies, such as the acceptance of symptoms, mindfulness techniques, instruction in cycle awareness and self-monitoring, and the use of individually customised coping mechanisms. In conclusion, surprisingly little study has been done on the prevalence, underlying causes, and available treatments for PME of mood disorders. There is a definite need for further systematic study on all of these topics, as well as a thorough examination of menstrual cycle-related occurrences in mood disorders, given the enormous burden on afflicted women. The function of PME should be incorporated into the training curriculum of psychiatrists, gynaecologists, and psychologists for an optimal

clinical care management, as has already been suggested for PMDD.

Acknowledgement

None.

Conflict of Interest

None.

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