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Update on Research and Treatment of Premenstrual Dysphoric Disorder

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Abstract

Many women in their reproductive years experience some mood, behavioral. or physical symptoms in the week prior to menses. Variability exists in the level of symptom burden in that some women experience mild symptoms, whereas a small minority experience severe and debilitating symptoms. For an estimated 5%–8% of premenopausal women, work or social functioning are affected by severe premenstrual syndrome. Many women in this group meet diagnostic criteria for premenstrual dysphoric disorder (PMDD). Among women who suffer from PMDD, mood and behavioral symptoms such as irritability, depressed mood, tension, and labile mood dominate. Somatic complaints, including breast tenderness and bloating, also can prove disruptive to women's overall functioning and quality of life. Recent evidence suggests that individual sensitivity to cyclical variations in levels of gonadal hormones may predispose certain women to experience these mood, behavioral, and somatic symptoms. Treatments include: antidepressants of the serotonin reuptake inhibitor class, taken intermittently or throughout the menstrual cycle; medications that suppress ovarian cyclicity; and newer oral contraceptives with novel progestins. (Harv Rev Psychiatry 2009;17:120–137.)

Keywords

mood disorders; premenstrual dysphoric disorder; premenstrual syndrome

Emotional and physical symptoms are common premenstrual complaints from women, with most experiencing one or more symptoms during the final premenstrual and the initial days of the menstrual cycle.[1–6] For the majority, such symptoms are mild. For a smaller group, however, such symptoms can be of sufficient severity to result in negative consequences for their home, social, and work lives.[7–13] Of pronounced concern to many is the effect that the illness has on their family and social relationships,[11] with some reporting feelings that life is not worth living.[14] For approximately 15% of symptomatic women, such feelings result in suicide attempts.[15–17] Given the total length of time that women experience symptoms (seven days per month on average throughout their reproductive years), as well as the illness's prevalence, the illness burden of premenstrual dysphoric disorder (PMDD) is similar to that of dysthymic disorder and other common psychiatric conditions.[18]

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Though the mix of mood, behavioral, and somatic symptoms that occur during the premenstrual phase has long been recognized, only recently have diagnostic criteria been specified and consensus guidelines formulated.[19] Previously labeled premenstrual tension and premenstrual syndrome (PMS), the condition was described as a mix of clinically significant symptoms uncharacterized by specific criteria and accompanied by an attendant lack of diagnostic clarity, targeted research, or prescribing recommendations.[19] This situation changed in 1980, when a multidisciplinary National Institute of Health consensus conference began the process of establishing clear-cut diagnostic criteria. Adopted by the Diagnostic and Statistical Manual of Mental Disorders (DSM III-R) as “late luteal phase dysphoric disorder” and subsequently termed “premenstrual dysphoric disorder” in the DSM-IV, the disorder is characterized by specific positive symptoms. The requirements for a DSM-IV diagnosis are presented in the text box.

Consistent with its focus on empirically grounded and field-test criteria, the DSM-IV required a minimum of five distinct symptoms.[20,21] While the emergence of stipulated diagnostic criteria dispelled some of the ambiguity that existed prior to the formal recognition of the disorder, some women with clinically significant symptoms still may remain untreated due to failure to meet diagnostic criteria.[22] Subthreshold rates of PMDD potentially affect an additional 18%–35% of women who experience up to four symptoms per month.[15] In an attempt to address this problem, the American College of Obstetrics and Gynecology characterized a less severe condition, that of moderate to severe PMS. This condition is defined by the occurrence of at least one psychological or physical symptom resulting in significant impairment and substantiated by prospective symptom ratings.[23] Though characterized by fewer absolute symptoms than PMDD, moderate to severe PMS may result in significant impairment due to symptom severity.

While differences in symptom burden between PMDD and moderate to severe PMS may be difficult to quantify, differences between mild PMS and moderate to severe PMS/PMDD translate into quality-of-life and economic costs. Women with moderate to severe PMS or PMDD experience greater quality-of-life detriments and work productivity losses, and incur greater health care costs, than do women with no or only mild symptoms.[7] Nonetheless, almost 90% of women suffering from PMDD may be undiagnosed.[18] Illness identification and appropriate treatment may be hindered by diagnostic inaccuracy and ambiguous research results—the product of differences in diagnostic instruments, methods, and criteria.[19]

DIAGNOSIS

Prior to the initiation of treatment for PMS/PMDD, adequate screening for conditions such as depression, dysthymic disorder, generalized anxiety disorder, and hypothyroidism is essential. Patients' social circumstances and life histories should be queried.[24] The latter queries are especially important given the association of PMS/PMDD with trauma and sexual abuse.[24–29] Given that exacerbations of dysphoria and anxiety are linked to the use of alcohol and illegal drugs, patients' use of such substances should be evaluated during the clinical interview.

Diagnosis of PMS and PMDD requires two full monthly cycles of daily symptom charting.[9,23] While this requirement may seem to impose an unnecessary delay in initiating treatment, it allows the clinician to differentiate between mild PMS and moderate to severe PMS and PMDD, as well as to exclude menstrual cycle exacerbation of underlying psychological conditions or disorders. The Daily Record of Severity of Problems,[30,31] a 21-item measure, allows women to track 11 symptoms across the menstrual cycle. Other diagnostic measures include the Calendar of Premenstrual Experiences,[32] the Moos

Menstrual Distress Questionnaire,[33] the Premenstrual Assessment Form,[34] and the Prospective Record of the Impact and Severity of Menstruation.[35] To meet diagnostic criteria for PMDD, five luteal-phase symptoms, including at least one mood symptom, must be reported together with impairment of social, emotional, or occupational functioning. For a diagnosis of moderate to severe PMS, a woman must report at least one psychological or physical symptom that results in significant impairment.[23] Although there are no formal diagnostic criteria for a diagnosis of premenstrual exacerbation, it is to be considered in instances where a woman meets most of the diagnostic criteria for PMS or PMDD, while presenting with either a major psychiatric disorder or comorbid unstable medical condition.[20]

Definition of Search Strategy for This Review

For this review, we completed Medline and PubMed literature searches for the period of January 1950 through January 2008 using “premenstrual syndrome” and “premenstrual dypshoric disorder.” We will not discuss reviews and case reports in this article, although they were examined for background information and references. This article will discuss prevalence rates, symptom expression, and treatment recommendations. It will also consider the effect of PMDD and severe PMS in the exacerbation of mood disorders. This article tracks closely with a recently published review article by our group that was published in the *Lancet*.[36]

Prevalence Rates

Prevalence rates of premenstrual difficulties are derived primarily from retrospective reports.[2,3,6,15,37–39] While recall bias may affect such reports, the ratings are consistent with those of epidemiological studies using prospective ratings, which indicate between 2% and 8% of women in the United States and Europe experience moderate to severe symptoms.[40,41] Slightly lower estimates (1.2% for moderate to severe PMS to 5.3% for PMDD) are projected for part of Asia based upon retrospective self-reports.[42] In a European, community-based follow-up study using retrospective reports, approximately 5.8% of women were found to meet PMDD criteria, with another 18.6% reporting subthreshold symptom severity.[15] The rates were found to remain relatively stable across a 48-month period.

Clinical Presentation

While some women experience symptoms for only a few days each cycle, others are affected for up to half of each month. For symptomatic women, the six days prior to menses commonly are marked by an increase in symptom levels, with the two days prior to menses resulting in the highest symptom reports,[43] particularly involving mood symptoms of anger and irritability.[43] While symptoms can carry over into the next menstrual cycle, a diagnosis of PMDD requires that women experience no symptoms during the pre-ovulatory period.[43,44] Symptom expression tends to be consistent from month to month.[13,45]

Risk Factors and Etiology

Genetic vulnerabilities—Twin studies implicate heritable factors.[46–48] Recent association studies provide potential support for involvement of the gene coding for the serotonergic 5HT1A receptor[49] as well as for the role of allelic variants of the estrogen receptor alpha gene (ESR1).[50]

Risk factors—High body mass index,[51] stress,[2,27] and experience of traumatic events[25] may be risk factors for PMDD. Due to the experience of traumatic or stressful events,

symptomatic women may have an impaired stress response;[27,52] women with PMDD are thus more likely than controls to have histories of abuse.[53]

ETIOLOGY

Mild premenstrual symptoms are common for many reproductive-aged women. Given their prevalence, such symptoms should be seen as physiological rather than pathological, and may have evolutionary implications.[54] In lower species, sexual receptivity is enhanced and aggression reduced during the pre-ovulatory period (i.e., the period prior to ovulation), when estrogen is high.[55–60] Research conducted with female rodents suggests that cycle-dependent aggression may be related to greater sensitivity to changes in estrogen and progesterone levels.[59,61] Other studies have attempted to model hormone-related depressive behavior in rodents using the forced swim test[61,62] and by inhibiting allopregnanolone, the GABAergic neurosteroid.[63]

The Role of Steriods and Their Metabolites: Estrogen, Progesterone, Allopregnanolone

Noteworthy for the life course of presentday generations of women is the lack of the time involved in reproduction and childbearing. Historically, women experienced multiple pregnancies and lactation periods, with poor or inadequate nutrition often characterizing their diets. Extended periods of amenorrhea protected women from the long cyclic periods of fluctuating estrogen and progesterone levels linked to the appearance of premenstrual symptoms.[64]

Symptom expression during specific phases of the menstrual cycle led researchers to hypothesize the involvement of gonadal steroids in the pathophysiology of PMS.[65] This hypothesis is supported by findings that symptoms are not present during nonovulatory cycles[66] and disappear entirely with ovariectomy[67–71] or the use of ovulation inhibitors.[72–76]

Exact mechanisms whereby gonadal steroid production may lead to symptom expression are not known but are theorized to involve both genomic and nongenomic effects of steroid hormones.[77] Estrogen, perhaps through its influence on the serotonin system, is linked to positive mood and well-being, whereas the decline of progesterone characteristic of the late luteal phase has led some researchers to consider a link to CNS changes in GABA and progesterone metabolites that interact with the GABA-A receptor complex.[77–82]

Since some women experience symptoms at the onset of ovulation and also during the early part of the luteal phase, an ebb in progesterone levels appears to be implicated. Arguing against this hypothesis, however, is that some women experience symptoms prior to the usual menstrual cycle–related decrease in progesterone. Treatment with a GnRH agonist (which abolishes menstrual cyclicity) followed by reexposure to progesterone can produce symptoms,[83] whereas luteal-phase administration of progesterone has not been shown to be an effective treatment.[84] In non-symptomatic women, administration of progesterone during the follicular phase has been found to enhance amygdala reactivity.[85] In addition, in postmenopausal women, sequential hormone replacement results in reports of mood changes —with progesterone, rather than estrogen, linked to the experience of dysphoric moods.[86,87]

Rather than differences in the absolute level of progesterone, alterations in allopregnanolone, a metabolite of progesterone, may be related to PMS/PMDD pathophysiology. As with progesterone, levels of this metabolite fluctuate during the menstrual cycle.[88] Some studies find that symptomatic women have lower levels than asymptomatic women,[89,90] but not all studies agree.[91] Progesterone metabolites and GABA-A receptors interact,[78–81] with symptomatic women showing less responsiveness than

controls.[92] Inhibitory responses to GABA-A receptor agonists are potentiated by allopregnanolone, possibly resulting in less sensitivity to GABA-A modulation.[93] Symptomatic women are theorized to have an inadequate allopregnanolone response to stress due to reduced functional sensitivity of the GABA-A receptor.[27] As additional support, rodent stress studies that involve social isolation find irregularities in GABA activity.[94]

Alternatively, differences in estrogen surge patterns,[95] preovulatory estrogen peaks, or postovulatory rises in progesterone are posited as symptom triggers.[83,96] Again, such theories fail to account fully for variability in timing of symptom onset. In perimenopausal women, estrogen has been found to have an antidepressant effect.[97] However, the estrogen component of hormone replacement treatments also has the potential for increasing dysphoria, tentatively by enhancing progesterone receptor expression and hence progestational activity.[98]

Other Hormonal Differences

Greater variability in thyroid indices in PMS/PMDD susceptible women has been observed.[99,100] However, PMDD should not be interpreted as masked hypothyroidism.[99–101] Circadian rhythm alterations, seen in anxiety and mood disorders, are also found.[102,103] Studies of women with PMS reveal timing aberrations of hormone secretion; advanced timing rhythmicity for melatonin,[104] cortisol, thyroid-stimulating hormone, and prolactin have thus been reported, in the absence of absolute changes in their levels.[105] Differences in levels of relaxin—a reproduction-related peptide (e.g., in pregnancy-associated changes in the cervix and pubic symphysis)—also were reported, although levels were not linked to symptom expression.[106]

Calcium metabolism differences may result in reduced luteal-phase responsiveness to vitamin D metabolism. Among symptomatic women, declines in 1,25 (OH)2D may serve as a trigger for PMDD symptoms.[107] Differences in bone and calcium metabolism and in IGF-1 levels between women with PMDD and controls may be indicative of genotypic differences.[108]

Intercellular differences of magnesium, in the presence of normal plasma levels, have been reported in women with PMS.[109–111] Such differences are not limited, however, to the luteal phase, which renders it difficult to interpret the role of magnesium in the pathophysiology of PMDD.[111]

Neurotransmitters in PMS/PMDD: Serotonin, GABA, Glutamate, and Beta Endorphins

Central neurotransmitters are clearly implicated in PMS/PMDD because of the mood and behavioral symptoms that are the hallmarks of the illness.[112] Emotions and behavior are affected by levels of sex steroids, which easily pass the blood-brain barrier. Sex steroid receptors are plentiful—for example, in the amygdala and hypothalamus, brain regions that moderate emotions and behavior.

Serotonin

Serotonin is a brain neurotransmitter that is clearly involved in mood and behavior regulation, as evidenced by preclinical studies, by the antidepressant and anti-anxiety effects of drugs that increase serotonin availability, and by genetic[113,114] and brain-imaging studies.[115] Animal experiments aiming to shed light on the physiological role of serotonin have revealed that the most prominent behavioral effects of treatments causing serotonin depletion are enhanced aggression and sexual activity,[59,117] pointing to a significant physiological role of serotonin in the modulation of sex steroid–driven behavior.[116]

Gonadal hormones may affect behavior through their effects upon serotonergic transmission, as shown in studies with rodents[117–121] and nonhuman primates.[122,123] Given the role of serotonin in mood and aggression, as well the likely role of serotonin in sex steroid–driven behavior, this transmitter promises to be an important factor in PMS/PMDD pathophysiology. Premenstrual symptoms are diminished both by serotonin reuptake inhibitors (SRIs) and by other treatments that increase serotonin, such as releasing agents,[124,125] a precursor,[126] and a receptor agonist.[127] In contrast, tryptophan-free diets[128] and serotonin receptor antagonists[129] can evoke PMS symptoms.

Aberrations in serotonergic transmission are found in women with PMS/PMDD.[125,130–140] Symptomatic women have lower density of serotonin transporter receptors than do controls.[137,138] Luteal-phase PMDD symptoms can be provoked if levels of tryptophan, the serotonin precursor, are depleted or if a serotonin antagonist is administered.[128,129] Moreover, administration of serotonergic probes (such as L-tryptophan, buspirone, m-CPP, and fenfluramine) results in abnormal prolactin or cortisol responses in women with PMS.[125,131,133,136,139,140] Other differences include higher levels of serotonergic responsiveness in the follicular than in the luteal phase, a pattern different from that observed in controls.[130] PET studies provide preliminary evidence of an association between premenstrual symptomatology and brain serotonergic transmission.[132,141]

GABA

Imaging studies, along with an observational study, point to the possible role of another neurotransmitter, GABA.[92,142] Direct action, tolerance induction, and withdrawal effect are theorized to explain the possible influence of GABA in women with menstrual cycle phase disorders.[82] Possible aberrations in GABA-A function as the pathophysiological trigger for the disorder is not uncontested,[89–91,143] however, and progesterone withdrawal as a mechanism in PMS/PMDD pathophysiology is also disputed. From a symptom-relief standpoint, GABA-A modulation may not be practical,[144] but GABAergic and serotonergic neurons[145–147] do interact, making the role of GABA in PMS/PMDD pathophysiology theoretically consistent with the serotonin hypothesis. In addition, SRIs have been shown to affect the production of enzymes involved in progesterone metabolites that modulate GABA-A receptors.[148,149]

Glutamate

For both symptomatic and nonsymptomatic women, levels of the excitatory neurotransmitter glutamate fluctuate during the menstrual cycle. Luteal-phase levels of glutamate/creatine plus phosphocreatine in the medial prefrontal cortex are thus lower for all women. However, symptomatic women may have an increased sensitivity to such cyclical changes.[150]

Beta-Endorphins

Differences in beta-endorphin levels between the periovula-tory and premenstrual phases have been reported in women diagnosed with PMS.[151–153] The beta-endorphin withdrawal hypothesis proposed that decreased levels of endogenous opioids were linked to PMS symptom expression and pain sensitivity.[154,155] A study comparing women with PMDD (n = 27) and healthy controls (n = 27) during both the follicular and luteal phases found that during both cycle phases, women with PMDD had lower levels of cortisol and beta-endorphins, shorter pain thresholds and tolerance times, and higher blood pressure levels at rest and during pain testing.[156] These findings implicate the hypothalamicpituary-gonadal axis in PMDD pain sensitivity,[156] which is consistent with findings of potential HPG-axis dysregulation in depressive and mood disorders.[157,158]

Reactivity and Stress Responses

Women with PMS differ from controls in their acoustic startle responses, with symptomatic women exhibiting an accentuated startle response indicative of increased physiological reactivity.[159] Differences in luteal-phase reactivity are potentially indicative of increased stress responses among women with PMDD.[160] In rodent models, an increased startle response was found to result from progesterone withdrawal,[161,162] possibly indicating an upregulation of the alpha-4 unit of the GABA-A receptor complex.[161] As discussed above, neurosteroid effects on GABA-A receptor function may have behavioral implications for PMDD.[161]

Menstrual Cycle Phase-Related Cognitive Biases,Negative Affective Processing, and Impulsivity

Late luteal phase–biased processing of information may increase symptomatic women's experience of negative mood states. Facial emotion discrimination tests administered to 28 PMDD patients and 27 controls found that women with PMDD demonstrated a luteal phase–dependent negative bias in nonverbal processing of affective content.[163] This result is consistent with fMRI research,[164] which shows increases in luteal-phase negative affect, and with phase-related negative perceptions reported by women with PMDD.[163] Such cycle-related differences in affective processing and physiological reactivity may also be observable in measures of personality. In a study of major depressive disorder (MDD) and PMDD patients, women with either MDD or PMDD had higher harm avoidance scores than did controls.[165] Women with PMDD also had higher novelty-seeking/impulsivity scores than did women with MDD, perhaps pointing to a loss of impulse control as a potential diagnostic feature of PMDD. In the cited study, impulsivity was measured by luteal-phase questionnaire report. It should be noted that such findings highlight the role of menstrual phase–specific abnormalities induced by cycle-related physiological changes, and do not suggest the existence of underlying trait differences in women with PMDD per se.

Somatic Symptom Pathophysiology

Somatic symptoms of breast tenderness, bloating, and joint and muscle pain are common among women with PMS. It is not known, however, whether such symptoms result from alterations in peripheral hormone-responsive tissues or, instead, are the effect of a lowered tolerance for physical discomfort. In women reporting symptoms of fluid retention and breast enlargement, studies have been unable to confirm tissue changes.[166,167] SRIs, however, have shown some palliative effects.[10] Prolactin-lowering agents, such as the dopamine D2 receptor agonist bromocriptine[168,169] and chasteberry (*Vitex Agnus Castus*),[170] effectively treat premenstrual mastalgia, as does luteal administration of danazol and estrogen receptor antagonists.[171,172]

Among women with PMDD, severe abdominal bloating often occurs in the absence of actual weight gain, with aldosterone, a progesterone metabolite[173] and deoxycorticosterone, an aldosterone agonist,[64,173] being the putative agents (either alone or together). Some recent evidence points to disturbed fluid-regulating mechanisms in symptomatic women during the luteal phase.[174]

Other common somatic complaints—for example, premenstrual headache, migraine, and epilepsy—may be constellations of other conditions, though women with migraines and comorbid endometriosis may be more likely to report PMDD symptoms.[175] SRIs have been used to treat migraines prophylactically, though with little evidence to support their efficacy.[176] Painful menses, dysmenorrhea, endometriosis, and menopausal symptoms often may present as PMS/PMDD.[177] These are all separate conditions, however, and require specific treatment.

COMORBIDITY AND PREMENSTRUAL EXACERBATION OF MOOD DISORDERS

Two types of comorbidity potentially characterize PMDD symptomatic women: lifetime and concurrent, with premenstrual exacerbation functioning as an alternative diagnosis for some symptomatic women. Determination of true versus apparent comorbidity is complicated by symptom overlap. Lifetime comorbidity occurs when a woman has had prior experience with a psychiatric or medical condition. Concurrent morbidity occurs when a woman's premenstrual symptoms occur independently of any current psychiatric or medical condition. Premenstrual exacerbation is present when a current psychiatric or medical ailment is worsened during the premenstrual period.[9,178]

Women with PMDD, in particular, are more likely to have a past history of mood disorders and other psychiatric disorders,[15,20,179] with lifetime estimates ranging from 30% to 70%.[180–188] PMDD may predict future MDD risk,[189,190] and life-cycle factors associated with fluctuations in gonadal steroids—such as perimenopause[191] and the postpartum period[192]—may place women with severe PMS/PMDD at greater risk for associated depressions.

Premenstrual exacerbation of PMDD symptoms generally refers to worsening of symptoms of MDD or bipolar disorder during the luteal phase[193] but can refer to exacerbation of any existing condition, such as anxiety. Premenstrual exacerbation of depression in women with mood disorders is often reported.[194–197] Increased levels of neuroactive steroid concentrations (progesterone and allopregnanolone) are shown in the luteal phase by women diagnosed with mood disorders as compared to controls.[198] In formerly stabilized patients with MDD, premenstrual breakthrough of depression is reported,[194,199] as is mania.[20,200] In a large study(n = 2,524) of women with mood disorders, 67.7% were found to have premenstrual symptoms, with women diagnosed with MDD particularly vulnerable.[201] Associations with postpartum depression and perimenopausal symptoms were also found.[201] The findings of this study on MDD and reproductive-cycle mood symptoms are consistent with those of other research.[195,196]

Women with PMS also tend to experience greater rates of anxiety disorders.[202,203] Panic disorder and PMS may be characterized by common pathophysiological mechanisms since women with PMS and those with panic disorder both show a greater tendency to panic when exposed to lactate and CO_2, as well as to other panicogenic agents.[202,203] Premenstrual exacerbation of obsessive-compulsive disorder symptoms also may be associated with a higher prevalence of PMDD.[204] In addition, women with seasonal affective disorder may be more likely to have PMDD than nondepressed women,[188] and a higher rate of seasonal affective disorder has been reported in women with PMDD.[187] Similarly, in a sample of young women, seasonal and premenstrual symptoms were found to be correlated.[102]

Other luteal-phase exacerbations of reported psychiatric illness include bulimia, substance abuse, mania, and psychosis.[20] Medical conditions reportedly exacerbated during the luteal phase include migraine headaches, asthma, allergies, seizure disorders, and genital herpes.[20] Common subjective reports of luteal-phase sleep disturbances were not substantiated, however, by polysomnographic measures and quantitative electroencephalographic analysis in a small study.[205]

TREATMENT

In discussing treatment options, we will focus on the literature concerned with severe PMS and PMDD.

While a number of treatment options have been put forward to alleviate PMS symptoms, few are backed by clinical evidence. Importantly, even effective treatments do not reduce all symptoms equally. In addition, study results often are reported in terms of “responder” versus “nonresponder” status, and the use of summary symptom-change scales obscures the effect of treatment upon specific symptoms.[206] Nonetheless, treatment should be targeted to meet individual symptom profiles.[206]

Serotonin Reuptake Inhibitors

SRIs have a demonstrated treatment efficacy for the management of PMS/PMDD symptoms,[207] with response rates of 60%–90% reported for active treatment, as opposed to 30%–40% for placebo.[208] Both mood and physical symptoms remitted with SRI use.[10,209–214] The serotonergic tricyclic antidepressant clomipramine,[215,216] the selective SRIs (e.g., citalopram,[217,218] escitalopram,[219] fluoxetine,[210–212,220–224] sertraline,[225,226] and paroxetine),[209,227–230] and the serotonin and noradrenaline reuptake inhibitor venlafaxine[231,232] all lessen both mood and somatic symptoms, while improving quality of life and social functioning.[12,221,227,233] For PMS patients with severe mood symptoms, SRIs offer a strong first-treatment option.[234,235]

The beneficial effect of SRIs in PMS seems not to result from their antidepressant effect: antidepressants that primarily effect noradrenergic transmission thus prove less effective on PMS/PMDD symptoms,[209,220,236] and SRIs' effects upon PMS/PMDD symptoms are rapid in comparison with their slower efficacy in MDD. The rapid action of SRIs in PMS/PMDD makes intermittent luteal-phase dosing—that is, dosing during the last 14 days of the cycle—an appealing alternative to continuous therapy.[215,217,224,230,237–240] Sertraline,[237–239,241,242] fluoxetine,[214,224] citalopram,[217] paroxetine,[228,230] and clomipramine[215] have all shown good efficacy in intermittent dosing during the luteal phase. Even briefer periods of active SRI treatment have been shown to be superior to placebo.[229] Symptom-onset dosing—a newer dosing strategy that involves women taking medication when their symptoms begin (usually around 7 days prior to menses) and stopping at the onset of menses or within 3 days thereafter—has shown early promising results.[229,243,244]

In a recent randomized, controlled trial of continuous versus intermittent dosing of an SRI (paroxetine) in PMDD, continuous dosing was found to act quickly and to have a high response rate (85%–90%). Irritability symptoms, affect lability, and mood swings showed the greatest improvement, and fatigue the least.[230] Intermittent dosing was equally effective as continuous treatment for irritability and mood swings, whereas depressed mood, tension, fatigue, and somatic issues were less remitted. For social functioning, continuous treatment was more effective than placebo. These findings are consistent with other studies, which found somatic symptoms less amenable to intermittent treatment than were mood symptoms.[224] For somatic symptoms, continuous treatment may be warranted.[230] Of the women on continuous therapy, 80% said they wanted to continue, versus 66% on intermittent treatment and 36% on placebo.[230] Clinical experience suggests, however, that many, but not all, women with PMS may prefer half-cycle, intermittent dosing rather than continuous treatment.

Side effects of SRIs are usually tolerable. Nausea is common but typically abates after the first few days of treatment and does not return, even with intermittent treatment.[230] Sexual side effects (reduced libido and anorgasmia) persist for the duration of treatment but do not carry over during the drug-free periods of intermittent treatment.[245]

Discontinuation symptoms may appear when medication is stopped abruptly,[246–248] although SRIs are not addictive. With intermittent treatment, discontinuation symptoms are not problematic, indicating that two weeks may not be sufficient time to provoke withdrawal

symptoms.[217,229] In summary, treatment efficacy of SRIs for PMDD is compelling.[10,112,212,214,242]

Other CNS-Acting Drugs

Lithium[249] and nonserotonergic antidepressants[209,220,250] have failed to show efficacy in dealing with PMS/PMDD symptoms. Buspirone,[127,251] a serotonergic agonist, appears to have a weak beneficial effect. While alprazolam, the high-affinity benzodiazepine, presents conflicting reports of efficacy,[144,252–254] it may have merit as an adjunct for women with symptoms of premenstrual insomnia or extreme anxiety. Careful monitoring is necessary due to the risk of dependence and is especially warranted in cases of prior reported substance abuse.

Hormonal Interventions: Estrogens, Anti-estrogens, Androgens, and Gonadotrophin-Releasing Hormone Agonists

Since sex steroids prompt the symptoms of PMS/PMDD, direct action upon these substances would seem the most direct treatment approach. Progesterone deficiency as the cause of symptoms, however, has little research support,[255] and reports of luteal-phase treatment with either progesterone[84] or estrogen[256] are unpromising.

The goal of hormonal treatment of PMS/PMDD hence is to suppress the hypothalamus-gonadal cyclicity that triggers the symptoms. Long-acting GnRH agonists[72–76] interrupt this cycle and have strong evidence of efficacy. Since medical menopause results, however—with attendant problems of flushing and increased risk of osteoporosis—add-back therapy with estrogen and a gestagen (a hormone with progestational activity) is generally recommended; the gestagen component reduces the risk of endometrial hyperplasia caused by estrogen. A meta-analysis[76] supports the feasibility of add-back therapy, although some patients report a recurrence of symptoms with add-back gestagen therapy.[257] As an alternative, combining a GnRH agonist with continuous treatment with tibolone may prove efficacious.[76,258]

Danazol, a synthetic partial androgen antagonist/agonist and gonadotropin inhibitor, also prevents PMS symptoms when dosed to inhibit ovulation.[259–264] Its side effects of hirsutism and possible teratogenicity, however, argue against its use as an initial treatment. Low-dose administration during the luteal phase is not effective for PMS generally but does help with mastalgia.[171] Reduction in mastalgia can also be accomplished by luteal administration of an estrogen receptor antagonist.[172]

A permanent, but more invasive, method is surgical bilateral oophorectomy, which effectively abolishes symptoms.[67,68,71] It should be considered, however, only as a last resort when other, more conservative treatments have failed. Add-back therapy is required, as in the case with long-acting GnRH agonists. If a hysterectomy is performed, estrogen alone is required. Surgical approaches are too invasive for most patients, however, unless a concomitant gynecological condition necessitates hysterectomy. For younger patients, ovarian preservation is recommended unless the PMS/PMDD is severe and debilitating, in which case the patient may request a bilateral oophorectomy. Prior treatment of two to three months duration with a GnRH agonist is an effective way to simulate the effect of ovarian removal and may help identify whether oophorectomy is likely to be helpful.

Inhibition of ovulation through administration of estrogen at requisite doses[265–267] is a relatively straightforward and effective therapy. Transdermal patches[267,268] or sub-cutaneous implants[265] are recommended over oral therapy. Dosages range from 100 mg to 200 mg, which are higher than for hormone replacement therapy but less than for oral contraceptives. Again, a progestogen is necessary unless the patient has had a hysterectomy.

In such instances, a levonorgestrel intra-uterine system can be used. While overall evidence for this treatment is limited, there is straightforward evidence that estrogen inhibits ovulation (and thus symptoms)[267] and that the IUS protects against hyperplasia.[269]

Combined Oral Contraceptives

Oral contraceptive (OC) management of PMS/PMDD, while widespread in clinical practice, is not supported by strong evidence. Placebo-controlled trials have been limited, and the results primarily negative.[270,271] OC treatment with fewer hormone-free days might be beneficial since women on OC report more hormone-related symptoms on the seven hormone-free days,[272] while reducing the number of hormone-free days results in fewer symptom complaints.[273] Use of a novel OC (drospirenone plus ethinyl estradiol) has shown promise.[274–276] Efficacy was found in reducing PMDD symptoms, including loss of productivity and impairment of social relationships, at least over a short time frame.[275] Efficacy studies done with drospirenone and with only four hormone-free days also support this approach.[277,278] The therapeutic benefit of these two options may be attributable to the antialdosterone and antiandrogenic effects of drospirenone, a gestagen.[279] Androgenic hormones have thus been linked to increased symptoms of irritability in women with PMDD.[280] In cases of premenstrual breakthrough of depression in women being treated with antidepressants, adding ethinyl estradiol and drospirenone has shown benefit.[194]

Other Treatments

Circadian rhythm abnormalities have been reported in women with PMS/PMDD.[102,103,105] Trials using bright light-treatments provide support for this therapy.[281–283] However, no data exist on the duration of therapeutic efficacy. For the somatic symptoms of PMS—notably, bloating and breast pain—spironolactone, an aldosterone antagonist, has proved superior to placebo.[173,284–286]

Methodological limitations, such as the lack of prospective ratings, have hampered studies assessing the impact of vitamin B-6 (pyridoxine) in PMS/PMDD treatment. Efficacy judgments cannot be conclusively made, but a quantitative review found vitamin B-6 superior to placebo.[287] High doses of this vitamin, however, may result in neurotoxicity.[287,288] While calcium supplements may be helpful,[107,289–291] results for magnesium treatments have been mixed, with some studies showing positive benefit[292] and others not.[293] In addition, supplemental magnesium may cause side effects, such as diarrhea or an upset stomach. Chasteberry, perhaps through its anti-prolactin effects, may show some benefit.[170,294–297] While the use of alternative treatments, such as oil of primrose, is popular, available evidence suggests they are ineffective, except possibly in the management of breast symptoms.[298]

No large-scale, randomized, control trials using St. John's Wort for PMDD or menstrual disorders have been completed,[299] though a small pilot study did show efficacy in PMS.[300] St. John's Wort has known interaction effects with SRIs and other medications, however, and may interfere with the effectiveness of oral contraceptives. In addition, while caffeine, sugar, and alcohol intake have been associated with increased PMS symptoms,[301] dietary interventions—such as reducing the consumption of sugar and eating small, frequent meals—have little scientific evidence to support their efficacy. In contrast, increasing the intake of complex carbohydrates may be helpful, perhaps due to raising the levels of tryptophan, the dietary precursor of serotonin and other neurotransmitters.[302,303] Aerobic exercise[304] and cognitive-behavioral therapy[305–308] likewise may be helpful. Treatments that lack consistent, evidence-based support include nonsteroidal anti-inflammatories (NSAIDs), mefenamic acid,[309] naproxen,[310] and the opioid receptor blocker naltrexone.[311] However,

NSAIDs may prove useful in alleviating some physical symptoms, such as cramps, aches, and pain.

Future Research: Characterization of PMDD Subtypes

While SRIs offer a strong firstline treatment option, some women may be nonresponsive to current PMDD treatments.[206] Re-analysis of existing data sets is warranted to define subgroups, to characterize treatment efficacy rates in order to further improve response rates, and to achieve greater understanding of the pathophysiology of PMDD.[206]

SUMMARY

There is strong empirical support for the reality of a severe premenstrual condition that involves mood, behavioral, and somatic symptoms and impairments. Recent research in genetics, neuroendocrine challenge studies, and functional imaging add credence to the validity of PMDD as a diagnostic category.

PMDD affects an estimated 5% of women of child-bearing age.[15] Key to effective management is clear diagnosis. PMS/PMDD must be distinguished from other diagnoses, notably depression, anxiety disorders, premenstrual exacerbation of another condition, or mild physiological symptoms. Prospective daily rating of symptoms over two menstrual cycles is warranted. Patients may chart their most severe symptoms or use a validated instrument, such as the Daily Record of Severity of Problems. To meet diagnostic criteria, five luteal-phase symptoms, including at least one mood symptom, must be present together with a reported impairment of social, emotional, or occupational functioning, albeit with the attendant disadvantage of excluding women who have a smaller number of severe symptoms. Key to diagnosis is the absence of symptoms within a few days following the onset of menstruation. In symptomatic women, premenstrual symptoms appear to be triggered by sensitivity to normal cyclical fluctuations in sex steroids following ovulation. Research thus suggests that the CNS responsiveness to sex steroids is enhanced, indicating that transmitters such as serotonin, GABA, and glutamate are of importance in this context.[158,312] Inhibiting ovulation—through the use of GnRH analogues, estrogen, and new oral contraceptives—effectively eliminates symptoms. SRIs likewise reduce symptoms and are recommended for initial PMDD treatment. Treatments show different symptom efficacy. Whereas the suppression of ovulaton benefits both behavioral and physical symptoms, SRIs primarily alleviate irritability, depressed mood and anxiety, the lability of affect, and, with continuous use, some physical symptoms. GABAergic agents may be used to treat anxiety and anxious-depressive symptoms, whereas mastalgia is most effectively eased with dopamine agonists, such as bromocriptine.[206]

Requirements for Diagnosis of Premenstrual Dysphoric Disorder

A. Symptoms must occur during the week before menses and remit a few days after onset of menses. Five of the following symptoms must be present and include at least one of 1–4.

1. Depressed mood or dysphoria
2. Anxiety or tension
3. Affective lability
4. Irritability
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
11. Other physical symptoms (e.g., breast tenderness, bloating)

B. Symptoms must interfere with work, school, usual activities or relationships.

C. Symptoms must not merely be an exacerbation of another disorder

D. Criteria A, B, and C must be confirmed by prospective daily ratings for at least two consecutive menstrual cycles.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, 4th ed.[9]

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