Understanding and Treating Premenstrual Dysphoric Disorder: An Update for the Women's Health Practitioner

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• Premenstrual dysphoric disorder • Etiology • Treatment

From ancient times, various facets of women's personalities, capabilities, and moods have been attributed to menstruation,[1] and "instability" resulting from women's reproductive cycles has been used to justify denying women equal access to education and employment.[2]

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Over the years, varying definitions of menstrual-related mood symptomatology have been presented. The current position of the American Psychiatric Association, as articulated in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), recognizes mood disorders related to the menstrual cycle as a significant mental health issue for some women.[3] However, the label of ''disorder'' is reserved for those problems that clearly interfere with occupational or social functioning. Premenstrual dysphoric disorder (PMDD) is defined in Appendix B of the DSM-IV-Text Revision (DSM-IV-TR), under axes provided for further study, and is categorized in the text itself as a ''depressive disorder not otherwise specified.''

The negative impact of PMDD symptoms on daily function and quality of life has been documented,[4] and economic burden, specifically in terms of decreased productivity, has been established.[5] Because of this level of impairment, there is great urgency to understand the biologic and psychosocial underpinnings and treatment options for women who suffer from PMDD. Unfortunately, early medical research did not always take female-specific factors into account, and so for many years, these issues went largely unexplored from a scientific perspective. However, more recently, it has been established that the care of the female patient requires a sophisticated understanding of both reproductive and psychosocial factors across the life span. Mood changes related to the menstrual cycle lie at the interface of obstetrics and gynecology and psychiatry, presenting an important opportunity for collaboration between researchers and practitioners across disciplines.

The purpose of this article is to guide women's health practitioners in issues related to diagnosis and appropriate treatment for PMDD. It will aid non–mental health practitioners in the decision about when to refer to mental health professionals, as well as highlight how psychiatric and other women's health professionals may wish to collaborate on management plans. The review will cover the epidemiology of PMDD and issues related to diagnostic clarification. It will highlight what is known about potential biologic, psychological, and sociocultural etiologic factors, and outline treatment options.

DIAGNOSIS OF PREMENSTRUAL DYSPHORIC DISORDER

The essential features required for diagnosis of PMDD are symptoms of marked and persistent anger/irritability, depressed mood, anxiety, or affective lability, which have regularly occurred during the last week of the luteal phase in most menstrual cycles during the past year. The strict diagnostic criteria of at least 5 of 11 symptoms must be applied to differentiate PMDD from milder symptoms of premenstrual syndrome (PMS). PMDD must also be differentiated from an exacerbation of another physical or mental disorder. However, if criteria for both PMDD and another disorder are clearly met, the DSM-IV-TR states that both can be diagnosed.[3]

Differentiation from Premenstrual Syndrome

In addition to the number of required symptoms, severity of the symptoms is a key component of the diagnosis, in that symptoms must cause significant impairment in the ability to function socially or occupationally during the week before menses. The DSM-IV definition explicitly acknowledges that milder symptoms of PMS, such as mild psychological discomfort, bloating, and breast tenderness, affect up to 70% of women, and so should not be considered to be ''disordered.''

Physical Disorders as Differential Diagnoses

Physical disorders that may mimic PMDD with premenstrual exacerbations include systemic diseases such as autoimmune disorders, diabetes mellitus, anemia, and

hypothyroidism as well as gynecologic conditions such as dysmenorrhea and endometriosis.[6] These can usually be readily differentiated from PMDD by careful history, physical examination, and other relevant investigations including, but not limited to, laboratory testing, imaging, and diagnostic surgical procedures. However, clinicians must hold an index of suspicion for these differential diagnoses.

Psychiatric Disorders as Differential Diagnoses

Premenstrual exacerbations and/or magnification of psychiatric disorders, particularly depression and dysthymic disorder, can be more difficult to tease apart from PMDD[7]; however, this clarification is important because of the implications for treatment. For example, women with an underlying depressive disorder (ie, a woman who has mood symptoms throughout the month), but with increasing severity during the premenstrual period, should be treated for the underlying disorder. With successful treatment of the primary condition, premenstrual symptoms will often remit.[8]

Premenstrual exacerbations of depressive disorders are commonly reported. In the National Institute of Mental Health's Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial, the first 1500 female participants with major depression were asked whether they experienced a worsening of their depressive symptoms before menses. Of the 433 women who were not taking oral contraceptives, 64% reported worsening symptoms 5 to 10 days pre-menses.[7] In a US community sample, Hartlage and colleagues[9] found that 44% of nondepressed women taking antidepressants reported symptoms premenstrually. This supports the assertion that women who report premenstrual depressive symptoms should be screened for depressive symptoms across all phases of the cycle.

Bipolar disorder is also important to consider on the differential diagnosis of PMDD. Women with underlying bipolar disorder may experience premenstrual exacerbations of depressed mood or irritability.[10] This may be because of the bipolar disorder itself, or to fluctuations in medication levels attributable to pharmacokinetic changes in the premenstrual period. For example, lithium, a commonly used mood stabilizer in the management of bipolar disorder, is a water-soluble drug. Therefore, there is a risk for decreased lithium levels premenstrually owing to increases in the volume of distribution in the premenstrual period, although evidence has been contradictory as to whether this theoretical risk bears out in practice.[11] Once again, if a woman meets full criteria for both bipolar disorder and PMDD, both may be diagnosed. There have been several studies attempting to determine whether women with bipolar disorder are at increased risk of comorbid PMDD. Results have been contradictory and overall do not suggest that women with bipolar disorder are at increased risk for PMDD.[10]

There is also some evidence that women with personality disorders may experience increased irritability and interpersonal difficulties in the premenstrual period.[12] Again, it is important to determine whether a woman meets criteria for PMDD in addition to a personality disorder, as this has implications for treatment.

Prospective Symptom Assessment and Rating Scales

To assist clinicians in making a diagnosis of PMDD, and particularly in the context of psychiatric comorbidity, a DSM-IV-TR diagnosis of PMDD requires a minimum of 2 consecutive months of prospectively daily symptom ratings.[3] Prospective ratings are considered essential, because of debate regarding the extent to which retrospective reports of premenstrual symptoms should be considered reliable.[13] Further, some evidence suggests that owing to mood and cognitive changes, there may be

differential symptom reporting depending on the phase of the menstrual cycle in which women are queried.[14,15]

Prospective daily symptom ratings are usually made using Likert or visual analog scales. Validated tools include the Daily Record of Severity of Problems or the Penn Daily Symptom Report (as described in a recent comprehensive review by Pearlstein and Steiner[16]). However, many women, including those without PMDD, report some premenstrual symptoms during the follicular phase. A change in the symptom severity score between the luteal and follicular phases is therefore the most meaningful outcome, and a change of between 30% and 50% has been recommended as an indication of a diagnosis of PMDD.[17]

PREVALENCE AND DEMOGRAPHIC CORRELATES

Estimates of the prevalence of PMDD in community samples are difficult to obtain because of the necessity for strict diagnostic criteria. Most prevalence estimates have relied largely on retrospective data, with variable definitions of ''severe'' symptoms of PMS. In samples from North America and Europe, prevalence estimates based on DSM-IV-TR diagnostic criteria, but without the requirement for prospective symptom ratings, appear to be in the range of 5% to 6%. A German study of more than 1000 young women aged 14 to 24 yielded a 12-month baseline prevalence of PMDD of 5.8%.[18] A Canadian study of 519 women ages 18 to 55 used the Premenstrual Symptom Screening Tool (PSST) to screen for women who might benefit from treatment for PMDD. Consistent with the previous findings, the authors reported that 5.1% of the women likely suffered from PMDD.[19] Interestingly, a Japanese study of 1152 women ages 15 to 49 in a cancer screening clinic reported a prevalence of only 1.2% using retrospective symptom reporting, indicating possible cultural variability in either prevalence or symptom reporting.[20]

Few studies have estimated the prevalence of PMDD by DSM diagnostic criteria using prospective charting and the resulting prevalence rates appear to depend somewhat on the population being studied. In a study of 217 female university students, 4.6% reported a 30% or greater increase in symptom severity during the premenstrual period using prospective charting over 90 days.[21] In older premenopausal women (aged 36 to 44 years), 6.4% of the women who completed prospective ratings for one cycle met criteria for PMDD.[22] A smaller study in Indian women also reported prevalence of 6.4%,[23] and a Croatian study of young adults aged 18 to 30 reported a prevalence of 5.8% using prospectively collected daily rating scales.[24] Slightly lower rates of PMDD have been found in two prospective studies where samples were representative of the population both with respect to age and sampling frame. Sveindottir and Backstrom[25] studied 83 women sampled from the National Registry of Iceland. Although there was no psychiatric testing to rule out other psychiatric disorders, women filled out 1 month of prospective daily mood charting, revealing a prevalence of PMDD between 2% and 6%. Gehlert and colleagues[26] followed 1246 women (ages 13 to 55) sampled from four geographic regions in the United States. These women underwent psychiatric testing by trained research assistants in their homes and they also completed daily symptom checklists over two menstrual cycles. Using strict DSM-IV-TR criteria, only 1.6% of the women were diagnosed with PMDD.

Few demographic variables are predictive of PMS or PMDD. Younger age has been associated with more severe symptoms of PMDD.[27] There are also data to support a relationship between higher levels of education and reporting of premenstrual symptoms.[28] When women with PMDD and no history of major depressive disorder were compared with women with PMDD and history of depression, the PMDD patients

with no depression history were more educated.[29] However, when the total sample of older premenopausal women was considered, PMDD was associated with lower levels of education.[22]

The strict diagnostic criteria for PMDD present substantial methodological difficulties for estimating prevalence. However, the available evidence suggests that there is a small but significant proportion of women, as low as 1% but perhaps as high as 7%, who consistently experience premenstrual symptoms of sufficient severity to cause functional impairment. Younger women may experience more severe symptoms of the disorder and there may be some cross-cultural variation in symptom reporting (discussed further later in this article).

POTENTIAL ETIOLOGIC FACTORS

Over the years, there has been an increasing amount of investigation into understanding the etiology of severe premenstrual dysphoria. As with other psychiatric disorders, PMDD likely has multiple biologic, psychological, and sociocultural determinants. Unfortunately, it is very difficult to study how such factors might interact to produce the clinical picture of PMDD. In all likelihood, the causal pathway is complex, with the potential for multiple pathways to a similar clinical outcome. It is important to distinguish between factors that are associated with increased risk for PMDD and factors that may contribute to the pathophysiology of the disorder. The former factors may be regarded as correlates and are most useful for case identification and epidemiologic description, although they may also ultimately contribute clues to the etiology of the disorder. Potential causal factors may be more useful in guiding prevention and treatment of the disorder.

Biologic Factors

Heritability

One method of investigating the biologic contribution to the etiology of a disorder is to use studies of twin pairs. If twins are reared together, they are presumed to have shared early environments. Therefore, studying concordance rates for a certain disease in mono- and dizygotic twins can help determine the level of genetic contribution to the disorder (ie, the environment is controlled). Twin studies have demonstrated high heritability of premenstrual symptoms: one study of more than 1000 female twins estimated heritability of selected premenstrual symptoms at approximately 56%, with no substantial role for familial environmental factors.[30] Another study of 720 female twin pairs estimated heritability of 44%, although the prevalence of PMDD in this study was extremely high at 24%.[31]

Hormones

Female sex hormones The cyclical nature of PMDD lends itself to the hypothesis that dysfunction in hormonal changes related to the menstrual cycle is a primary biologic determinant of the disorder. However, despite the temporal relationship between symptoms of PMDD and phases of the menstrual cycle, the relationship between female sex hormones and PMDD does not appear to be a simple linear one. The most likely explanation is that women with PMDD are in some way vulnerable to the normal physiologic changes associated with the menstrual cycle. This hypothesis has now been supported in two studies, where women with PMDD showed differential response to women with no premenstrual complaints in response to challenge with physiologic levels of estrogen and progesterone.[32,33] In the first study, women with PMDD had more depressed mood than controls and in the second study, they responded to hormonal challenge with altered gonadotropin levels. Huo and

colleagues[34] recently identified allelic variation in ESR1, the estrogen-alpha receptor gene in women with PMDD, providing preliminary evidence of a possible underlying mechanism for these differential responses.

Providing further support to the hypothesis that some women may be susceptible to the changes associated with the menstrual cycle, there is some evidence that women with PMDD may also be more susceptible to mood disorders in the perinatal period and at perimenopause. This has led researchers to hypothesize that there may be a ''reproductive'' subtype of depression to which some women are prone.[35] Other hormones besides estrogen and progesterone have also been examined in PMDD patients. Several groups have investigated a potential role for the centrally active progesterone metabolite allopregnanolone. There appears to be a relationship between serum concentrations of allopregnanolone and the severity of symptoms in women with PMDD/PMS.[36,37] It has been hypothesized that differences between women with PMDD and controls are related to differences in sensitivity to allopregnanolone, and not to absolute levels of the neurosteroid.[38] This has been supported in various studies involving the GABA-A receptor, where allopregnanolone acts in the central nervous system. Imaging studies have shown that women with PMDD have differential GABA-A receptor sensitivity,[39] and women with PMDD show differential sensitivity to other compounds with GABA-A activity. PMDD patients are also reported to be more sensitive than control subjects to the anxiogenic effects of the benzodiazepine antagonist flumazenil[40] and less sensitive than controls to a number of benzodiazepines,[41,42] In addition, the severity of symptoms in women with PMDD appears to be related to their sensitivity to GABA steroids.[43] This sensitivity normalizes during treatment with serotonin reuptake inhibitors, possibly because of the drug's modulating effect on allopregnanolone levels, via GABA-A receptors.[44]

Androgens Androgens have also come under investigation in PMDD, in large part because of the prominence of irritability in the PMDD symptom profile. Eriksson and colleagues[45] have observed elevated testosterone levels in women with severe premenstrual irritability. A positive correlation between free testosterone concentrations and irritability has also been observed by our group, but only in patients who reported severe symptoms.[46] One study revealed significantly lower total and free plasma testosterone levels in PMS patients as compared with healthy controls.[47] Some success has been reported in treating PMDD with androgen antagonists.[45]

Other endocrine factors

Other endocrine factors, including cortisol, thyroid hormone, prolactin, melatonin, aldosterone, and endorphins, have also been postulated as contributors to PMS/PMDD. As yet, however, there is little consistent evidence for their involvement.[16,48]

Serotonin

Research investigations using a number of experimental models have also consistently demonstrated an important role for serotonin in the pathophysiology of PMDD. Relationships between serotonin function and secretion of ovarian hormones have also been established, making a complex interaction between hormone secretion and serotonin fluctuation plausible.[49] PMDD patients have lower whole blood serotonin levels[50] and lower platelet serotonin uptake[51] during the premenstrual phase. Melke and colleagues[52] found that women with premenstrual dysphoria had fewer platelet paroxetine binding sites (ie, fewer serotonin transporters) than controls. Differences in brain serotonergic function across the menstrual cycle between women with PMDD and controls have also been identified using positron emission technology

(PET).[53] Challenges with serotonergic agents, such as L-tryptophan, fenfluramine, and buspirone, have similarly provided evidence of serotonin dysfunction in women with PMDD,[54–58]

Several studies have attempted to delineate the genetic basis for differences in serotonin function and metabolism in women with PMDD. Research into AP-2, 5HT transporter, tryptophan hydroxylase, and monoamine oxidase genotypes has mostly been inconclusive.[52,59,60] However, Praschak-Rieder and colleagues[61] found an association between PMDD and 5HTLLPR heterozygosity in women with seasonal affective disorder, and Steiner and colleagues[46] identified a relationship between polymorphism in the serotonin transporter gene and severity of PMDD symptoms.

Finally, the finding that serotonergic drugs, and particularly the selective serotonin reuptake inhibitors (SSRIs) treat PMDD rapidly (see further discussion later in this article), strongly supports the hypothesis that serotonin is involved in the etiology of PMDD. However, it is notable that only 60% of PMDD patients respond to treatment with SSRIs,[62] suggesting that serotonin may not be the only etiologic variable in all PMDD patients.

Psychosocial Factors

Sociocultural factors

As noted previously, a limited number of studies have examined symptoms of PMS and PMDD in non-Western societies. This research has often been plagued by a number of important methodological concerns and, in particular, questionable validity of instruments that have been translated for use in populations other than those in which they were developed. There may be variations in how women respond to questions based on phrasing, expectations, or cultural issues.[63]

As a result of observed cross-cultural differences, the concept of "menstrual socialization" has been proposed as a determinant of premenstrual complaints, suggesting that PMS is a culture-bound syndrome, specific to Western cultures in which most women have been socialized to have negative expectations about menstruation.[64] More specifically, it is argued that North American culture and media perpetuate the idea that the premenstrual period will be associated with negative affect and mood instability,[2] causing women to interpret normal physiologic changes that are essentially neutral in nature to have negative connotations.[65] A role for expectations about menstruation in premenstrual symptom reporting was illustrated in a study where women who viewed a videotape describing the negative consequences of PMS later reported more severe premenstrual symptoms than did women in a control group who watched a neutral video.[66] Similarly, women who were led to believe that they were premenstrual reported significantly more severe physical symptoms than did women who were led to believe that they were not premenstrual.[67] These findings are of particular note in the context of a study that demonstrated that a group intervention designed to positively reframe the experience of menstruation can significantly reduce premenstrual impairment in women with PMDD.[68]

Life stress

Several studies have demonstrated an association between PMS/PMDD and stressful life events,[69–71] and particularly day-to-day stress.[72] Women with premenstrual symptoms also tend to rely more than other women on less effective strategies for coping with stress, such as avoidance or wishful thinking, than on strategies such as problem-focused coping or direct action,[2,73] High levels of state and trait anxiety have been observed in PMS patients.[74,75]

The consistent relationship between life stressors and PMS/PMDD has prompted the suggestion that symptoms may develop as "a learned, legitimate, feminine way of expressing frustration"[65] and, in particular, expressing frustration with the conflict between women's productive and reproductive social roles.[64] This is supported by data from one study that examined personality characteristics of women seeking treatment for premenstrual complaints and found unusually high mean scores on the subscale of the Minnesota Multiphasic Personality Inventory that assesses identification with a traditional feminine social role. This is despite the fact that their sample was highly educated and largely working outside of the home. Further, premenstrual complaints were associated with strong tendencies to overcontrol or repress angry feelings.[76] Further research is needed to elucidate the relationship between traditional gender role socialization and, particularly, silencing one's anger in premenstrual symptoms.

Sexual abuse

Past sexual abuse is reported by a significant proportion of women seeking treatment for PMS: a prevalence of 40% was reported in a population of women seeking treatment at a PMS clinic[77] and 32% among psychiatric inpatients with PMS.[78] This can be compared with a rate of 12.4% in the general population of women.[79] Sexual abuse, and childhood sexual abuse particularly, has lasting effects on both psychological and physiologic responses to stress.[80] Through effects on HPA axis function, past abuse could predispose women to psychiatric disorders, including PMDD. Preliminary evidence suggests that the high prevalence of sexual abuse among women seeking treatment for premenstrual symptoms may account for findings of dysregulated cardiovascular and neuroendocrine responses to laboratory stress in PMDD patients.[81] In fact, Bunevicius and colleagues[82] found that women with PMDD with and without histories of sexual abuse had differential autonomic nervous system response to a challenge with the a-receptor agonist clonidine. In one recent study, more than 80% of women with sexual abuse history seeking treatment for PMS had not previously disclosed the abuse to any health care provider,[83] suggesting that abuse history should be routinely assessed in women with suspected PMDD.

Therefore, overall there is convincing evidence for important roles for biologic and sociocultural variables in the development and interpretation of premenstrual symptoms. A weakness of much of the existing literature is that many of the sociocultural risk factors have largely been investigated in the context of their association with premenstrual symptoms rather than the syndrome of PMDD, and it is not known whether these findings can be generalized. Also, there is very little existing literature investigating how biologic and sociocultural variables may interact in the development of severe PMS and PMDD. For example, childhood sexual abuse has lasting effects on multiple biologic and psychological variables, including endocrine responses to stress and coping styles, which ultimately contribute to a woman's risk for adulthood depression.[84] Further interdisciplinary research into risk factors for PMDD will provide a more complete understanding of the roots of this disorder.

TREATMENT OF PREMENSTRUAL DYSPHORIC DISORDER

Insofar as PMDD has multiple biologic and sociocultural etiologic determinants, its treatment should involve an integrated approach, tailored to each patient's particular set of circumstances. A stepwise approach is recommended, with treatment appropriately reflecting the severity and functional impairment associated with the symptoms. In all cases, treatment should also be provided to address any comorbid psychiatric or

medical disorders and issues related to any persistent life stressors or any past or current physical or sexual abuse.

Healthy Lifestyle

For women with mild symptoms, education about the condition, supportive counseling, and general healthy lifestyle measures, such as regular exercise and healthy diet, may be sufficient to result in symptom improvement. Expert opinion is that lifestyle modifications should be the first approach taken in all women presenting with premenstrual complaints, and can be conveniently given a 2-month trial while the patient completes the prospective daily ratings necessary to confirm the diagnosis of PMDD.[85]

Dietary changes can have a noticeable impact on symptom severity: women should be encouraged to reduce or eliminate intake of salty foods, sugar, caffeine (especially coffee), red meat, and alcohol. Increased consumption of fruits, vegetables, legumes, whole grains, and water is also recommended. Finally, eating smaller, more frequent meals that are high in carbohydrates may specifically improve symptoms of tension and depression.[85]

Although evidence for an effect of exercise on PMDD symptoms is largely anecdotal, regular exercise can be advised as part of a healthy lifestyle regimen. Aerobic exercise for 20 to 30 minutes, three to four times per week has been recommended.[86] Reduction of body weight to within 20% of ideal, where possible, is an appropriate goal.[8]

For many women, PMDD is associated with sleep irregularities.[48] To alleviate the associated distress and discomfort, adoption of a regular sleep-wake pattern may be helpful. Women should be encouraged to adhere to consistent bedtimes and waking times during the premenstrual period, and ideally across the menstrual cycle.

Encouraging women to avoid planning stressful activities for the premenstrual period whenever possible can be helpful. This can be facilitated by having women complete symptom assessment forms before, during, and after treatment. Women should be encouraged to review their own daily diaries and identify triggers for symptom exacerbation.

Dietary Supplements

Several dietary supplements are recommended in the lay press for treatment of PMS/PMDD symptoms. Unfortunately, with few exceptions, little scientific evidence is available to support these recommendations.[87] However, so long as they are used at doses that are within the range of recommended daily intake, use of certain dietary supplements need not be discouraged.

Calcium supplementation shows some promise for treatment of PMS/PMDD. One large trial found that 1200 mg of calcium daily reduced symptoms of PMS, including depression, by the second or third treatment cycle.[88] This study has some methodological limitations, in particular the lack of exclusion on the basis of follicular phase symptoms, and thus requires replication. However, increased calcium intake has benefits beyond those associated with reduction of PMS symptoms, particularly with respect to prevention of osteoporosis, and is not associated with any adverse effects so long as doses do not exceed 1500 mg daily.[86]

There is also evidence for efficacy of vitamin B6 (pyridoxine) in treating premenopausal women with depression.[89] This has led to investigation into pyridoxine as a treatment for premenstrual mood symptomatology, although no trials have been done in women with strictly diagnosed PMDD. A recent double-blind placebo-controlled trial of 94 women with premenstrual mood and somatic symptoms revealed

a greater decrease in psychiatric symptoms with 80 mg of vitamin B6 compared with placebo.[90] It should be noted that vitamin B6 supplementation is not without risk and higher doses have been associated with peripheral neuropathy.[91]

Although early research suggested that magnesium supplementation was effective for fluid retention in women with PMS, follow-up research has not supported its efficacy for psychiatric symptoms.[92] The effects of complex carbohydrate supplementation have been studied with the rationale that increased tryptophan availability might increase serotonin synthesis. To date, there are two reports of positive effects of a carbohydrate-rich beverage on affective symptoms in women with PMS.[93,94] Soy supplementation also reduced physical but not affective symptoms in a small sample of women with PMS.[95]

Herbal, Complementary, and Other Treatments

Herbal, complementary, and other treatment options have also been addressed in recent reviews, and the strongest evidence appears to be for *Vitex agnus castus* (Chasteberry), which may act as a dopamine agonist to reduce follicle-stimulating hormone (FSH) or prolactin levels, although it may be more beneficial for physical rather than psychological symptoms of PMDD.[16] There are small randomized controlled trials (RCTs) to support saffron and Qi therapy.[96,97]

There have been reports of initial positive RCTs of massage, reflexology, chiropractic manipulation, and biofeedback. Open trials also suggest support for yoga, guided imagery, photic stimulation, and acupuncture.[16] Bright light therapy has been studied as a treatment for PMDD with the rationale that it may induce rapid increase in serotonin (without the side effects of psychotropic medication). Although there has been little evidence to date, a systematic review of four trials suggests that bright light therapy may be an effective option for women with PMDD.[98]

Psychoeducation and Behavioral Treatment

Group psychoeducation can be effective in managing PMS and PMDD. A controlled trial of a psychoeducational group intervention with a focus on positive reframing of women's perceptions of their menstrual cycles found that women with PMDD who received the intervention had reduced premenstrual symptoms and premenstrual impairment, although there were no differences in post-treatment depression or anxiety scores.[68] Several other studies have also noted efficacy of group support in managing symptoms of PMS.[99–101] Relaxation therapy, which is also effective in treating PMS, may be particularly appropriate for women who report a high degree of daily stress.[102,103]

Psychotherapy

Lustyk and colleagues[104] performed a systematic review of the literature to assess the efficacy of cognitive behaviour therapy (CBT) for PMS and PMDD. They identified seven published peer-reviewed studies, of which only five had control groups and only three could be regarded as RCTs. They concluded that on the basis of the existing literature, psychotherapy may provide some benefit; however, effect sizes did not approach those of pharmacotherapy or even behavioral treatments such as relaxation.

Pharmacotherapy for Premenstrual Dysphoric Disorder: Serotonergic Drugs

For women who do not respond to conservative therapies or who have severe symptoms in need of immediate treatment, serotonergic medications, the SSRIs specifically, are the first line of treatment. Over the past several years, the efficacy and safety of using SSRIs in the treatment of PMDD have been well established. As

this topic has been comprehensively reviewed in several recent publications[17,105,106] only the relevant conclusions will be summarized here.

Fluoxetine, sertraline, and paroxetine have received Food and Drug Administration (FDA) indications for PMDD, although a Cochrane Database meta-analysis also reveals good evidence of effectiveness for fluvoxamine, citalopram, and the serotonergic tricyclic antidepressant clomipramine as well.[106] There has been an RCT supporting the efficacy of the selective serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine XR dosed continually across the menstrual cycle and a recent single-blind trial revealing preliminary evidence of effectiveness for the SNRI duloxetine.[107,108] For reasons still poorly understood, although SSRIs generally require 2 to 4 weeks for therapeutic effectiveness in depression, they are reported to be effective for PMDD when used either continuously or only in the premenstrual (luteal) phase of the menstrual cycle. Perhaps because of the lack of continued administration, there is no discontinuation syndrome when they are used in this manner. Evidence does indicate that symptoms can recur rapidly when treatment is discontinued, particularly in the women with the most severe symptoms at baseline.[109]

Manipulation of Menstruation

The next line of treatment for severe PMDD involves manipulating the usual hormonal fluctuations associated with the menstrual cycle with the goal of suppressing ovulation. Although many hormonal regimes have been suggested for this purpose, few have demonstrated efficacy. Oral contraceptives provide a reasonably safe means of inhibiting ovulation; however, the efficacy of most oral contraceptives in the treatment of PMDD is not well established. The FDA has recently approved a combination of ethinyl estradiol and drospirenone for the treatment of PMDD and a recent Cochrane Database systematic review supports its efficacy.[110] It is thought that the anti-androgen and anti-mineralocorticoid properties of drospirenone account for the efficacy of this product (as compared with traditional oral contraceptive pills). Likely because the potential for adverse effects with oral contraceptives (eg, deep vein thrombosis, pulmonary embolism) exceeds that of the SSRIs, the FDA indication for this treatment has been limited to women who also wish to use the medication for contraceptive purposes.

The best studied class of drugs for this purpose is the gonadotropin-releasing hormone (GnRH) agonists, such as leuprolide acetate, which have been clearly demonstrated to alleviate symptoms of PMS/PMDD.[62,111] However, GnRH agonists appear to be less effective in treating affective symptoms of PMDD than physical symptoms,[112] and long-term use of GnRH agonists has been associated with a number of unfavorable side effects, including risk for hypoestrogenism and osteoporosis,[9] particularly when the therapy is used for longer than 6 months.[62] Add-back estrogen-progesterone supplementation may prevent some of the undesired side effects of GnRH therapy, but effects of add-back therapy on treatment efficacy may be undesirable.[62] The adverse effects of add-back therapy are purported to be attributable to the use of progesterone; however, estrogen-only add-back therapy is not realistic in premenopausal women owing to the increased risk of reproductive cancer. Segebladh and colleagues[113] attempted to discern the optimal hormonal add-back strategy in 27 women with PMDD. The results of their RCT concluded that low-dose estrogen (0.5 mg estrodiol) plus progesterone was superior to high-dose estrogen (1.5 mg estrodiol) plus progesterone in terms of preventing PMDD symptom recurrence.

The synthetic steroid danazol appears to reduce affective and physical symptoms of PMS/PMDD[114]; however, its practical use is limited by the need for concurrent administration of a reliable contraception method. At low doses (200 mg/d), ovulation

and thus conception are still possible, and danazol can cause virilization of the fetus. Doses sufficient to inhibit ovulation (600–800 mg/d) have been associated with undesirable side effects, including weight gain, mood changes, and acne.[62]

The final treatment option for women with severe PMDD symptoms and no response to other therapies is permanent suppression of ovulation through oophorectomy. Bilateral oophorectomy with hysterectomy has been reported to be highly effective in permanently eliminating symptoms of PMS.[115] However, because of the extreme nature of this treatment method, it is not recommended even for severe cases. It is possible that the sudden change in hormonal milieu associated with surgical menopause could also be a trigger for mood problems in vulnerable women.

SUMMARY

Existing evidence indicates that there is a small but significant population of women in whom premenstrual symptoms, and particularly affective symptoms, severely impair functioning. Although PMDD is predominantly regarded as a biologically based illness, there is also evidence that variables such as life stress, history of sexual abuse, and cultural socialization are important determinants of premenstrual symptoms. In diagnosing and treating PMDD patients, attention to biologic and sociocultural variables is recommended.

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