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Mini-Review

Premenstrual Syndrome and Premenstrual Dysphoric Disorder

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Introduction

Premenstrual symptoms are experienced by up to 90% of women of child bearing age. A smaller subset meet criteria for premenstrual syndrome (PMS) and less than 10% are diagnosed as having premenstrual dysphoric disorder (PMDD).[1] This review will describe the epidemiology, etiology, and treatment of PMS and PMDD. When literature specifically applicable to adolescents is available, that will be noted. However, most of the research and literature has focused on adult women and this review will primarily reflect the adult literature.

Definition

PMS is used to describe an array of predictable physical, cognitive, affective, and behavioral symptoms that occur cyclically during the luteal phase of the menstrual cycle and resolve quickly at or within a few days of the onset of menstruation. To date, there is no universally accepted definition or diagnostic criteria for PMS. Over 200 premenstrual symptoms have been reported, although very few are confined to or only explained by changes in the menstrual cycle.[2] With the work of Mortola,[3,4] more specific criteria were defined in the 1980s and studies evaluating both the pathophysiology and treatment modalities were designed according to strict scientific standards. Evidence is accumulating that PMS is not a single condition but a set of interrelated symptom complexes with multiple genotypes, phenotypes, or subtypes, and several different pathophysiologic events that begin with ovulation.[2,5]

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There are no specific physical findings or laboratory tests can be utilized to make the diagnosis of PMS. The various bodies that have published definitions include the American College of Obstetricians and Gynecologists (ACOG),[6] the American Psychiatric Association,[7] and the National Institutes of Mental Health. The World Health Organization's International Classification of Diseases uses ICD-9 code 625.4 for Premenstrual Tension Syndrome and lists PMS and PMDD under this heading. There is no separate diagnostic code for PMS or PMDD.

In a Practice Bulletin published in the year 2000, ACOG[6] defined diagnostic criteria for PMS based on the work of Mortola.[3] PMS can be diagnosed if at least one of the affective and one of the somatic symptoms in Table 1 is reported five days prior to the onset of menses in the three prior menstrual cycles. The symptoms must be prospectively recorded in at least two cycles and must cease within 4 days of onset of menses and not recur until after day 12 of the cycle. These symptoms must be recorded in the absence of pharmacologic therapy, or use of hormones, drugs, or alcohol, and cause identified dysfunction in social or work related activities. According to the original article by Mortola, specific dysfunction in daily activities includes marital/relationship discord, parenting problems, social isolation, legal problems, suicidal ideation, school or work related problems such as poor performance, poor attendance, or tardiness, and seeking medical care for somatic complaints.

The ACOG Bulletin[6] emphasizes that other diagnoses which may better explain the symptoms should be excluded, including both psychiatric and nonpsychiatric disorders. Most chronic psychiatric or medical conditions will be apparent throughout the menstrual cycle. However, many conditions are also subject to menstrual magnification in which symptoms are triggered or exacerbated by the menstrual

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Table 1. ACOG Diagnostic Criteria for PMS

Affective Symptoms	Somatic Symptoms
Depression	Breast tenderness
Angry outbursts	Abdominal bloating
Irritability	Headache
Anxiety	Swelling of extremities
Confusion	
Social withdrawal	

1. Diagnosis made if there is a report of at least one of these affective and somatic symptoms in the three prior menstrual cycles during the 5 days before the onset of menses
2. The symptoms must resolve within 4 days of onset of menses and not recur until after day 12 of the cycle
3. The symptoms must be present in a least two cycles during prospective recording
4. The symptoms must adversely affect social or work related activities

Data from: American College of Obstetrics and Gynecology. ACOG Practice Bulletin, Number 15, April 2000

cycle. Examples include depressive disorders, seizures, migraine headaches, allergies, and asthma. Recognizing this phenomenon is important in distinguishing PMS/PMDD from chronic underlying conditions.[6,8] Many women with PMS/PMDD may be misdiagnosed because these underlying disorders are missed.[1,9] The differential diagnosis of PMS/PMDD is found in Table 2.

The Diagnostic and Statistical Manual of Mental Health Disorders, 4th edition text revision (DSM IV TR),[7] from the American Psychiatric Association describes research criteria for PMDD (Table 3). The DSM criteria require a prospective evaluation and confirmation for at least two consecutive menstrual cycles. Symptoms must be present during the week prior to menses and remit within a few days after the onset of the follicular phase. Five out of 11 criteria must be present during the luteal phase for the majority of cycles in the previous year. One of the symptoms must be related to mood and there must be impairment in daily functioning. The symptoms cannot represent exacerbation of an existing disorder such as major depression, anxiety disorders, panic, dysthymic disorder, or personality disorder, but they may be superimposed on one of these psychiatric disorders. These criteria recognize that women may have psychiatric disorders that become exacerbated during menstruation.

Table 2. Common Conditions in the Differential Diagnosis of PMS/PMDD

Psychiatric Disorders	Medical Disorders
Depression	Anemia
Dysthymia	Autoimmune disorders
Anxiety	Chronic fatigue syndrome
Panic disorder	Diabetes
Bipolar disorder	Seizure disorders
Somatoform disorder	Hypothyroidism
Personality disorder	Endometriosis
Substance abuse	Allergies

Data from: Ling FW: Recognizing and treating premenstrual dysphoric disorder in the obstetric, gynecologic, and primary care practices. J Clin Psychiatr 2000; 61(Suppl 12):9, and Halbreich U: The diagnosis of premenstrual syndromes and premenstrual dysphoric disorder-clinical procedures and research perspectives. Gynecol Endocrinol 2004; 19:320

The National Institutes of Mental Health requires a 30% increase in the intensity of prospectively measured symptoms documented by a measurement instrument for at least two consecutive cycles. These criteria compare the 6 days before the onset of menses at the end of the cycle (luteal phase) to days 5−10 at the beginning of the menstrual cycle (follicular phase).[6,10]

In the mental health field, PMDD is categorized as a distinct clinical entity. The ACOG criteria for PMS and DSM criteria for PMDD do overlap, but PMDD focuses more on the problems with mood and involves more severe mental health symptoms, potentially leading to a higher level of dysfunction. The relationship between PMS and PMDD is not clear. Johnson[5] and Speroff and Fritz[10] both conclude that it is not useful to differentiate PMS from PMDD and agree that there is a broad spectrum of severity. Johnson suggests characterizing PMDD as severe PMS with impairment. However, Halbreich[2] argues that it is no more correct to dichotomize the physical and affective symptoms than to propose that PMS and PMDD are a continuum of the same entity. He proposes that PMDD may be a catamenial disorder and that the menstrual cycle simply serves as a trigger for the disorder without affecting the basic underlying pathophysiology of the condition. According to the ACOG[6] and APA guidelines,[7] PMS or PMDD cannot simply represent exacerbation of an existing underlying disorder and when symptoms occur outside of the premenstrual luteal phase it is relatively easy to prove the existence of an underlying problem. Halbreich[2] suggests that in some individuals there may be in essence a threshold effect. Individuals with underlying disorders such as affective or anxiety disorders may be particularly vulnerable to menstrual triggers but do not show symptomatology at other times because of factors which prevent them from being vulnerable outside of the premenstrual time frame. Halbreich raises the question about whether or not PMS, premenstrual exacerbation of an underlying disorder, and chronic major medical disorders may exist along a continuum.

Making the Diagnosis

Regardless of the definition used, there are several important findings that are usually needed to diagnosis PMS/PMDD.[1,2,5]

Table 3. SM-IV-TR Criteria for PMDD

I. In most menstrual cycles in the past year at least five of these symptoms (including at least one of the symptoms in category A) were present for most of the time 1 week before menses, began to remit within a few days after the onset of the follicular phase (menses), and were absent in the week after menses.
   A. Primary symptoms
      1. Markedly depressed mood, feelings of hopelessness or self-deprecating thoughts
      2. Marked anxiety, tension
      3. Marked affective lability (i.e., feeling suddenly sad or tearful)
      4. Persistent and marked anger or irritability or increased interpersonal conflicts
   B. Other symptoms
      1. Decreased interest in usual activities such as friends and hobbies
      2. Subjective sense of difficulty in concentrating
      3. Lethargy, easy fatigability, or marked lack of energy
      4. Marked change in appetite, overeating, or specific food cravings
      5. Hypersomnia or insomnia
      6. A subjective sense of being overwhelmed or out of control
      7. Other physical symptoms (e.g., breast tenderness, bloating, weight gain, headache, joint or muscle pain)
II. The symptoms markedly interfere with work, school, usual activities, or relationships with others.
III. Symptoms are not merely an exacerbation of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).
IV. Criteria I, II, and III are confirmed by prospective daily ratings for at least two consecutive symptomatic menstrual cycles.

Adapted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, (Copyright 2000). American Psychiatric Association

1. Symptoms must occur in the luteal phase and resolve within a few days after onset of menstruation.
2. The symptoms must be documented over several menstrual cycles and not be better explained by other physical or psychological conditions.
3. Symptoms must be recurrent and severe enough to disrupt normal activities.

Because approximately one half of women with retrospective complaints of PMS do not have symptoms limited to the luteal phase when they are prospectively evaluated, it is important to prospectively record the reported symptoms in relation to the menstrual cycle.[2,6,11] Because of variability between menstrual cycles, prospective recording should be done for at least 2 to 3 months to document that symptoms are occurring cyclically in the luteal phase. Assessment tools include the Self-Assessment Disk,[12] the Premenstrual Assessment Form,[13] Calendar of Premenstrual Experience (COPE),[4] the Prospective Record of the Impact and Severity of Menstrual Symptoms,[14] Premenstrual Syndrome Diary (PMSD),[15] Daily Record of Severity of Problems (DRSP),[16] Visual Analog Scales,[17] and the Penn Daily Symptom Rating (DSR).[18] Visual Analog Scales have been utilized for patients who cannot read English.[6] The DRSP and DSR may be appropriate for PMDD while the COPE and PMSD may be most appropriate for PMS symptoms rather than diagnosing PMDD.[2]

Epidemiology

Summary of Adult Studies

The exact prevalence of PMS/PMDD is unknown, but estimates are that 70−90% of menstruating women have some degree of symptoms before menses. Approximately 20−40% of women describe these symptoms as bothersome enough to impair daily functioning and are labeled as premenstrual syndrome. A further subset, representing 3−8% of women, have symptoms that are very severe, causing functional impairment that adversely affects quality of life and are classified as premenstrual dysphoric disorder.[1,6,19−21] As noted by Johnson,[5] approximately 50% of women have only a few mild symptoms for several days in the luteal phase and probably should not be diagnosed as having PMS.

Summary of Adolescent Studies

There are very few studies assessing PMS or PMDD in adolescents. All of the published studies are retrospective reports of premenstrual symptoms and as mentioned previously, retrospective reporting has been shown to be less reliable than prospective analysis in adults. Only two of the six studies indicated that a validated assessment tool for PMS was used and both used the Premenstrual Assessment Form.[22,23] One study[24] used a questionnaire based on modified PMDD criteria from the DSM IV to diagnosis PMS while a fourth used a shortened form of the Menstrual Distress Questionnaire[25] based on an article by Moos[26] in the late 1960s. Overall, more than 50% to 100% of adolescents in these studies reported at least one premenstrual symptom with 13−89% of these symptoms described as moderate or severe.[22−25,27−29]

Among the two adolescent studies using the adult validated Premenstrual Assessment Form, one enrolled 207 adolescents with a mean age of 17.6 years and found that 59% considered at least one symptom

to be severe and 43% considered at least one symptom to be extreme.[23] The second study found that 73% reported severe symptoms and 56% reported extreme symptoms.[22] It is not possible to reconcile these results with adult studies demonstrating PMDD in 3−8% of women and PMS in 20−40% because of the lack of prospective analyses.

Impact on Quality of Life

The impact of PMS/PMDD on the quality of life is an important part of the definition of these disorders. One study included a sample of 18−45-yr-old women from a large medical group in Southern California. All women who were continuously enrolled as patients for the previous 18 months and did not decline contact were interviewed by phone to determine eligibility for the study. Inclusion criteria were a self-reported 26−32 day cycle length and willingness to keep a daily diary for 64 days. The diary included an assessment of PMS symptoms and utilized the DRSP. Subjects who met criteria for the diagnosis of PMS showed significantly higher work absenteeism and impairment in work productivity. Women with PMS also had significantly more days per month of impairment in relationships with others, as well as impairment in work, school, and household activities.[30] Analysis of economic impact on this group of women revealed that a diagnosis of PMS was associated with a statistically significant increase of $59 per year in direct medical costs such as outpatient visits, laboratory tests, and radiology services and an increase of $4333 in indirect costs such as decreased work productivity and missed hours at work.[31]

Risk Factors

Risk factors for PMS include advancing age (beyond 30 years) and genetic factors. However, as indicated above, PMS symptoms are identified in adolescents and can begin around age 14, or 2 years post-menarche, and persist until menopause.[1] Some studies suggest that women whose mothers report PMS are more likely to develop PMS (70%, versus 37% of daughters of unaffected mothers).[32,33] In addition, concordance rates for PMS are significantly higher in monozygotic twins (93%) compared with dizygotic twins (44%).[32] There are no significant differences in personality profile or level of stress in women with PMS compared with asymptomatic women. However, women with PMS may not handle stress as well.[6] One recent article, prospectively evaluating a community cohort of 1488 women aged 14−24 over a 42-month period, found that traumatic events such as a physical threat, childhood sexual abuse, and severe accidents increased the odds of developing PMDD.[34]

Pathophysiology

The exact etiology of PMS is currently unknown but it is probably a result of an interaction between sex steroids and central neurotransmitters.[35] Alterations in neurotransmitters including endorphins, γ-aminobutyric (GABA), and serotonin have all been implicated, and women with PMS/PMDD are felt to be more sensitive to normal cyclical hormonal fluctuations.[36]

There is inconsistent evidence for differences (e.g., a drop) in circulating endorphins in symptomatic patients. Women with PMS and PMDD may have an alternation in the GABA receptor complex response. Various studies have demonstrated both reduced GABA receptor sensitivity and reduced plasma GABA in the luteal phase. Serotonergic dysregulation with reduced serotonergic function in the luteal phase is the most plausible theory. However, not all women respond to selective serotonin reuptake inhibitors (SSRI), implying that other factors must be involved.[2,5,37]

The levels of sex steroids, estrogen, progesterone, and testosterone are normal, but women with PMS may be more vulnerable to normal fluctuations. This vulnerability may be in part related to serotonin.[36] Further evidence for the lack of abnormal hormonal changes in the luteal phase comes from several studies. One study utilizing the progesterone antagonist mifepristone to induce menses found no relationship between the induction of menses and the timing or severity of PMS symptoms.[38] In another placebo-controlled study, women with PMS who had ovarian suppression with a gonadotropin-releasing hormone (GnRH) agonist were found to have recurrence of PMS symptoms when given estrogen and progesterone while there was a lack of mood change in the placebo group.[39] This study strongly suggested an abnormal response to normal hormonal changes.

There is no proof of a relationship between PMS and prolactin, growth hormone, thyroid hormone, adrenal activity, luteinizing hormone, follicle-stimulating hormone, antidiuretic hormone, insulin, aldosterone, renin-angiotensin, and cortisol. Furthermore, vitamin deficiencies including zinc, vitamin A, vitamin E, thiamine, magnesium, and pyridoxine (vitamin B_6) have been implicated but not documented and, to date, the data show inconsistent scientific evidence.[10]

Clinical Manifestations

More than 200 symptoms of PMS/PMDD have been described in literature, ranging from mild symptoms to those severe enough to interfere with normal

activities.[2] Common affective symptoms are irritability, anxiety/tension, mood lability, crying easily, depression, expressed anger, confusion, forgetfulness, hypersomnia/insomnia, and social isolation/withdrawal. Common physical symptoms include fatigue, abdominal bloating, breast tenderness, headache, swelling of extremities, joint or muscle pain, acne, and food cravings/increased appetite.[3,4,7]

Therapy

No single treatment is universally acceptable as effective. Studies have yielded conflicting results with most therapies, and many trials have not been well controlled. The various treatment modalities include the following:

Lifestyle Changes

Many techniques considered lifestyle changes still need to be definitively proven in controlled studies. However, establishing good exercise and stress management practices can improve overall feelings of well being.

Education

Adolescents should be educated regarding menstrual physiology and the relationship of changing hormones to symptoms. A small study of college students with PMS demonstrated a decrease in perimenstrual symptoms with a health promotion intervention in a peer group setting that positively reframed menstrual cycle perceptions.[40]

Stress Management

The teen can also be taught or referred for techniques to manage stress such as biofeedback, self-hypnosis, relaxation exercises, massage, reflexology, guided imagery, light therapy, and yoga.[41–50] Some of these techniques have shown promise in randomized and controlled trials. Additional information about these techniques and a summary of the studies can be found in Girman et al[41] and Pearlstein and Steiner.[42]

Cognitive Behavioral Therapy

If symptoms of stress are more significant, psychological counseling including cognitive-behavioral therapy or group therapy may be helpful.[5,41,42] Several studies including controlled and randomized trials have demonstrated improvement in PMS symptoms with cognitive behavior therapy.[51–54]

Exercise

Regular exercise, compared with being sedentary, improves PMS symptoms in some women.[41,42,55–57] Although more evidence is needed comparing the efficacy of different types of exercise,[42] one study indicated that aerobic exercise may be most beneficial.[57] The efficacy of exercise may be related to release of endorphins, counteracting possible declines in endorphin levels in the luteal phase.[42,58]

Minerals, Vitamins, Herbal Preparations, and Dietary Manipulation

There have been some positive outcomes for therapies involving the use of minerals, vitamins, herbal preparations, and dietary manipulation. However, although some of these modalities show definite promise, more research needs to be done to definitively recommend any of these therapies.[5,6,41,42,59]

Minerals

Calcium (1,200 mg/day) in the form of calcium carbonate was reported to reduce physical and emotional symptoms in a well-designed, multicenter study.[5,6,41,60] Further evidence for a role for calcium was found in a recent case-control study, nested in the Nurses' Health Study II, which prospectively evaluated women initially free from PMS and followed them three times between 1991 and 1999. The results showed that high intake of calcium and vitamin D were associated with a reduced risk of developing PMS.[61]

Magnesium (200 to 400 mg/day) has been noted to reduce negative mood and to reduce water retention and appears to be more effective than placebo in some studies. The mechanism of action is not fully understood and the usage is not well studied.[6,41,62,63] Futhermore, a recently published double blinded placebo controlled study of intravenous magnesium infusion in adult women with PMDD found no statistically significant differences in mood symptoms. There was also no evidence of magnesium deficiency in the women with PMDD compared to a control group.[64]

Vitamins

Pyridoxine (vitamin B_6) has been used extensively in the past, particularly in treating the emotional symptomatology of PMS. However, review of the literature has shown conflicting results, and it is considered to be of limited benefit. The other concern is that peripheral neuropathy can develop with doses higher than 100 mg/day.[5,6,41,58,65]

Vitamin E (400 IU/day) was found to improve somatic and affective symptoms. However, there is limited evidence for its effectiveness.[6,59,66]

Herbal Preparations

Vitex agnus-castus (Chasteberry, 20 mg/day) has been found to be superior to placebo in reducing PMS symptoms in some studies. Long-term randomized trials are needed but this modality is promising. Chasteberry extracts can potentially affect gonadotropins

as well as estrogen, progesterone, and prolactin. It also may have agonistic effects at dopamine receptors. It should be avoided in pregnancy and breastfeeding.[5,41,59,67–69]

Ginkgo biloba (Ginkgo leaf extract) has been shown to improve breast tenderness, fluid retention, and mood in a placebo-controlled study published by Tamborini in a French journal and referenced in multiple reviews. The dose is 80 mg twice a day from day 16 of the menstrual cycle through day 5 of menses. Ginkgo does have significant side affects that must be considered. It inhibits platelet activating factor and may increase bleeding risks. It also interacts with the CYP 450 enzymes and may not be appropriate for individuals on certain medications. Finally there is concern about increasing the risk of seizures.[5,41,59]

Hypericum perforatum (St. John's Wort) has SSRI-like effects and reduced PMS scores compared to baseline in a small, open, uncontrolled trial.[70] However, there are drug interactions with this herb because it affects the cytochrome P450 system.[5,41]

Primrose oil does not appear to be effective in the small studies conducted to date.[59]

Dietary Manipulation

Mood and carbohydrate food craving improved in randomized trials evaluating the intake of simple and complex carbohydrates. Carbohydrates may increase tryptophan, which is a precursor to serotonin.[5,59,71]

Other dietary recommendations have been made based on observation and theoretical rationale leading to suggestions to eliminate high sodium foods and caffeine as well as consume a low-fat, high-fiber diet and eliminate refined carbohydrates. Elimination of sodium, caffeine and refined carbohydrates has been based on observation that women with more severe PMS symptoms consume more of these types of food. The dietary fat and fiber recommendation comes from the theory that lower fat and high fiber diets will reduce estrogen levels which may improve PMS symptoms in some women. However, these dietary changes have not been adequately studied to date to assess efficacy for PMS.[41]

Suppression of Ovulation

Because PMS/PMDD appears to be a cyclic disorder of menses occurring in the luteal phase, suppression of ovulation has been used as a therapy. Some authorities consider combined oral contraceptive pills (OCP) to be first-line medications. However, data on their effectiveness is mixed and symptoms in some individuals worsen with use of oral contraceptives. OCPs also appear to primarily improve physical rather than mood-related symptoms.[5,6,58,72]

A newer OCP containing the progestin drosperionone, a derivative of spironolactone, has recently been studied because it has both antimineralicorticoid and antiandrogenic properties.[58] Several open label studies have shown decreased somatic symptoms including abdominal bloating and breast tenderness.[58,73] One double blind placebo controlled study of a standard 21/7 formulation OCP containing drospirenone and 30 micrograms of ethinyl estradiol was conducted for PMDD.[74] Statistically significant improvement with this OCP was limited to appetite, acne, and food cravings. However, a more recent multicentered, double-blind, randomized study utilizing a 24/4 formulation OCP containing drosperinone and 20 micrograms of ethinyl estradiol demonstrated improvement in both mood and physical symptom scores measured on the Daily Record of Severity of Problems in subjects with PMDD.[75] Although most authors recommend that oral contraceptive pills should be considered if the symptoms are primarily physical and not mood related,[6] this newer 24/4 drosperinone pill appears be effective for both types of symptoms. Possible reasons for efficacy of this newer formulation include the lower estrogen dose as well as improved follicular suppression with a more stable hormonal environment due to the longer length of hormonal dosing, e.g. 24 hormonal tablets rather than 21.[75]

Continuous hormonal therapy with combined hormonal contraceptives can also be considered to suppress cyclic changes and endogenous sex hormone variability.[5,10,76] One observational cohort study that extended use of the 30 μg ethinyl estradiol/drosperinone OCP for 42–126 days showed greater reduction in edema, breast tenderness, and bloating in extended regimen users compared to the standard 28-day regimen.[77] Medroxyprogesterone acetate (Depo-Provera) is an alternative contraceptive to suppress ovulation. However, studies of natural progesterone and synthetic progestins have failed to show any benefit when delivered by vaginal suppository or orally.[5,6,10]

Last resort treatments include GnRH and bilateral salpingo-oophorectromy.[10] Most studies have shown benefit from the use of GnRH, but the hypoestrogenic effects with loss of bone density is concerning, especially for adolescents, and would limit use. GnRH with add-back therapy with estrogen and progesterone can be considered when other modalities have failed.[5,6,76,78] However, add-back regimens may cause a recurrence in PMS/PMDD symptoms. Some authors have used progestin-only add-back with norethindrone.[5] Bilateral salpingo-oophorectomy would not be considered in adolescents.

Medications to Suppress Somatic Symptoms

Prostaglandin inhibitors in the form of non-steroidal anti-inflammatory drugs (NSAID) have been used to

treat PMS particularly for the physical symptoms. These regimens have included taking naproxen sodium, naproxen, or mefenamic acid during the luteal phase and stopping therapy after menses begin. Spironolactone, 100 mg/day on days 15 through 28, has been shown to have some positive effects on somatic and affective symptoms, but the results are not conclusive. Spironolactone may be helpful in patients with breast tenderness, bloating, or weight gain from fluid retention. However, other diuretics are not effective.[5,6,21,76,79]

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRI) are the drugs of choice and first line therapy for severe PMS/PMDD.[80] Placebo-controlled studies have shown that they are effective for severe PMS and PMDD and improve both physical symptoms and mood.[81] Fluoxetine, sertraline, paroxetine, and citalopram, escitalopram are all effective.[37,82–84] Velafaxine inhibits both serotonin and norepinephrine uptake and has been successful in patients with PMDD.[5,37,85,86] Using these drugs intermittently only during the luteal phase (i.e. 14 days prior to onset of menses) rather than continuously is equivalent for reducing symptoms. Unlike treatment for depression, symptoms improve within 24–48 hours of initiating therapy and there are no reports of discontinuation symptoms when SSRIs are used intermittently for PMDD. Low doses are usually effective and the most common adverse effects include insomnia, gastrointestinal disturbances, and fatigue. Other side effects include dizziness, sweating, and sexual function disturbances, but these medications are usually well tolerated.[81]

In the Fall of 2004, the FDA issued a public health advisory warning about an increase in suicidal thinking and behavior in children and adolescents treated with antidepressants. Fluoxetine is the only SSRI approved for treatment of depression in the adolescent population When using these medications, it is crucial to discuss the FDA warning with patients and their families as well as to ensure close monitoring during therapy. There is one paper describing three case reports of teenagers with PMDD who were successfully treated with fluoxetine after failing other treatment modalities.[87] However, randomized controlled trials of adolescents with PMS/PMDD are lacking. There is a need to demonstrate that SSRIs have similar beneficial effects in adolescents. The dose of fluoxetine for treatment of PMS/PMDD is 20 mg per day for both the continuous or intermittent regimen.[21]

Anxiolytics and Other Antidepressants

Studies have shown some positive effects on somatic and/or affective symptoms from anxiolytics and other antidepressants. Suggested therapies have included benzodiazepines, specifically alprazolam, which affects the GABA receptor complex; the tricyclic antidepressant clomipramine which is a nonselective serotonin reuptake inhibitor, and buspirone which is a partial serotonin receptor agonist. These medications can be given in the luteal phase rather than continuously.[21,88–91] None of these therapies would be recommended for routine use in adolescents, but they could be considered for selected adolescents with severe symptoms unresponsive to other treatment modalities. Clomipramine is on the FDA warning list for antidepressants and suicidality in adolescents and alprazolam carries a risk of tolerance and dependence.

Summary: Steps in the Treatment of PMS/PMDD

The following steps for treating PMS/PMDD are based on recommendations outlined in an ACOG Practice Bulletin[6] and in a recent review by Johnson[5]:

Step 1: A. If mild/moderate symptoms: Recommend supportive therapy with good nutrition, complex carbohydrates, aerobic exercise, calcium supplements, and possibly magnesium or chasteberry fruit
B. If physical symptoms predominate: Try spironolactone or NSAIDs, or hormonal suppression with OCPs or medroxyprogesterone acetate.

Step 2: When mood symptoms predominate and are significantly impairing function: Initiate SSRI therapy. An anxiolytic can be used for specific symptoms not relieved by the SSRI medication.

Step 3: If not responsive to steps 1 or 2: Try GnRH agonists. This would not be done in an adolescent without consultation with a gynecologist.

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