Premenstrual syndrome and premenstrual dysphoric disorder: guidelines for management

Meir Steiner, MD, PhD

Departments of Psychiatry and Behavioural Neurosciences, and of Obstetrics and Gynecology, McMaster University, and Father Sean O'Sullivan Research Centre, St. Joseph's Hospital, Hamilton, Ont.

The inclusion of research diagnostic criteria for premenstrual dysphoric disorder (PMDD) in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, recognizes the fact that some women have extremely distressing emotional and behavioural symptoms premenstrually. PMDD can be differentiated from premenstrual syndrome (PMS), which presents with milder physical symptoms, headache, and more minor mood changes. In addition, PMDD can be differentiated from premenstrual magnification of physical or psychological symptoms of a concurrent psychiatric or medical disorder. As many as 75% of women with regular menstrual cycles experience some symptoms of PMS, according to epidemiologic surveys. PMDD is much less common; it affects only 3% to 8% of women in this group. The etiology of PMDD is largely unknown, but the current consensus is that normal ovarian function (rather than hormone imbalance) is the cyclical trigger for PMDD-related biochemical events within the central nervous system and other target organs. The serotonergic system is in a close reciprocal relation with the gonadal hormones and has been identified as the most plausible target for interventions. Thus, beyond conservative treatment options such as lifestyle and stress management, other non-antidepressant treatments, or the more extreme intervneitons that eliminate ovulation altogether, selective serotonin reuptake inhibitors (SSRIs) are emerging as the most effective treatment option. Results from several randomized, placebo-controlled trials in women with PMDD have clearly demonstrated that SSRIs have excellent efficacy and minimal side effects. More recently, several preliminary studies indicate that intermittent (premenstrual only) treatment with selective SSRIs is equally effective in these women and, thus, may offer an attractive treatment option for a disorder that is itself intermittent.

L'inclusion de critères diagnostics de recherche pour le trouble dysphorique prémenstruel (TDPM) dans le *Manuel diagnostique et statistique des troubles mentaux*, 4e édition, reconnaît que certaines femmes ont, avant les menstruations, des symptômes émotionnels et comportementaux qui sont cause d'une détresse extrême. Il est possible de distinguer le TDPM du syndrome prémenstruel (SPM), lequel présente des symptômes physiques plus légers, des maux de tête et des changements d'humeur moins marqués. On peut aussi distinguer le TDPM de l'amplification prémenstruelle des symptômes physiques ou psychologiques d'un trouble psychiatrique ou médical simultané. Les enquêtes épidémiologiques indiquent que jusqu'à 75 p. 100 des femmes qui ont un cycle menstruel régulier ont des symptômes de SPM. Le TDPM est beaucoup moins fréquent : il atteint seulement de 3 p. 100 à 8 p. 100 des femmes de ce groupe. L'étiologie du TDPM est en grande partie inconnue, mais on s'entend généralement pour dire que la fonction ovarienne

Correspondence to: Dr. Meir Steiner, St. Joseph's Hospital, 50 Charlton Ave. East, Hamilton ON L8N 4A8; fax 905 521-6098; mst@fhs.mcmaster.ca

Medical subject headings: clinical protocols; diagnosis, differential; premenstrual syndrome; serotonin; serotonin uptake inhibitors

J Psychiatry Neurosci 2000;25(5):459-68.

Submitted Mar. 2, 2000
Revised Aug. 15, 2000
Accepted Sept. 18, 2000

normale (plutôt qu'un déséquilibre hormonal) constitue le facteur de déclenchement cyclique d'événements biochimiques liés au TDPM dans le système nerveux central et d'autres organes cibles. Le système sérotoninergique fonctionne dans une relation de réciprocité étroite avec les hormones gonadiques et est considéré comme la cible la plus plausible d'interventions. Ainsi, outre des possibilités de traitement conservateur (modifications du style de vie et la gestion du stress, autres traitements sans antidépresseur ou interventions plus extrêmes éliminant complètement l'ovulation), les inhibiteurs spécifiques du recaptage de la sérotonine (ISRS) semblent constituer le traitement le plus efficace. Les résultats de plusieurs études randomisées et contrôlées par placebo réalisées chez des femmes atteintes de TDPM ont démontré clairement que les ISRS sont très efficaces et ont des effets secondaires minimes. Plusieurs études préliminaires récentes indiquent qu'un traitement intermittent (prémenstruel seulement) au moyen des ISRS est tout aussi efficace chez ces femmes et peut ainsi offrir une possibilité intéressante de traitement d'un trouble qui est lui-même intermittent.

Epidemiologic surveys have estimated that as many as 75% of women of reproductive age experience some symptoms attributed to the premenstrual phase of the menstrual cycle.[1] More than 100 physical and psychological symptoms have been reported to occur premenstrually.[2] Most women are able to manage these symptoms through lifestyle changes and conservative therapies.

Premenstrual symptoms are often classified under the generic term "premenstrual syndrome" (PMS), which is listed in the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision (ICD-10) under disorders of the genitourinary system. The symptoms included are menstrual migraine, menstrual molimen and premenstrual tension not otherwise specified.[3] Approximately 3% to 8% of women of reproductive age report much more severe premenstrual symptoms of irritability, tension, dysphoria and lability of mood, which seriously interfere with their lifestyle and relationships.[1,4–8] Without relief from these symptoms, a woman's functioning in the home, in social situations and at work can be substantially impaired each month, often over a span of many years.[5,9,10] This cluster of primarily emotional and behavioural symptoms is so disruptive that a series of research diagnostic criteria for what is now called "premenstrual dysphoric disorder" (PMDD) have been developed and published in the 3rd revised and 4th editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R and DSM-IV).[11,12] Women who meet the diagnostic criteria for PMDD do not usually respond to conservative and conventional interventions and often seek the expertise of a health professional.

Etiology

The etiology of severe PMS and PMDD is largely unknown, but the current consensus seems to be that normal ovarian function (rather than hormone imbalance) is the cyclical trigger for premenstrual-related biochemical events within the central nervous system and other target organs.[13,14] That PMS and PMDD are biological (rather than psychological or psychosocial) phenomena is primarily underscored by recent, convincing evidence of the heritability of premenstrual symptoms[15] and the elimination of premenstrual complaints with suppression of ovarian cyclicity[16] or surgical menopause.[17,18] This viewpoint encourages investigation of the neuroendocrine-modulated central neurotransmitters and the role of the hypothalamic–pituitary–gonadal (HPG) axis in PMDD.

Increasing evidence suggests that, of all the neurotransmitters studied to date, serotonin (5-HT) may be important in the pathogenesis of PMDD.[19–21] PMDD also shares many of the features of other mood and anxiety disorders that have been linked to serotonergic dysfunction.[22–24] In addition, reduction in brain 5-HT neurotransmission is thought to lead to poor impulse control, depressed mood, irritability and increased carbohydrate craving — all mood and behavioural symptoms associated with PMDD.[25] Animal studies have established reciprocity between fluctuations in ovarian steroid levels and serotonergic function, showing that estrogen and progesterone influence central serotonergic neuronal activity. In the hypothalamus, estrogen induces a diurnal fluctuation in 5-HT,[26] whereas progesterone increases the turnover rate of 5-HT.[27] Several challenge tests have also suggested abnormal 5-HT function in women with premenstrual dysphoria. A blunted growth hormone and cortisol response to tryptophan[28] as well as a blunted or delayed prolactin response to fenfluramine and buspirone challenges have been reported by most[29–31] but not all[32] investigators. These studies imply, at least in part, a recurrent, cyclic 5-HT dysfunction in women with premenstrual mood changes.

Taken together, most research indicates that women with PMDD may be behaviourally or biochemically sub- or supersensitive to biological challenges of the serotonergic system. It is not yet clear whether these women present with a trait or state marker of PMDD.

Screening and diagnosis

There are no objective diagnostic tests for PMS and PMDD; therefore, a complete medical and psychiatric history must be elicited. Screening should also include a complete review of physical systems and medical disorders, and a detailed review of heritable disorders, including psychiatric disorders, in the patient's family. Since the symptoms of anemia and thyroid disease often mimic those of PMS or PMDD, the patient should undergo laboratory investigations if she is considered at risk for these conditions. Before making a diagnosis of PMS or PMDD, concurrent major mental disorders, personality disorders and medical conditions must be excluded.

Prospective daily rating of symptoms is essential in making a diagnosis. The patient should chart her symptoms for at least 2 consecutive symptomatic menstrual cycles. To date, there is no consensus among investigators as to the best instruments for prospectively confirming the diagnosis of PMDD, although there are now several scales and calendars to facilitate this.[33–36] A patient in whom PMDD is suspected should be assessed at least once during each cycle phase to ensure that she subjectively endorses phase-appropriate mood symptoms, corroborating her daily charting (none or minimal during the follicular phase; lifestyle-impairing during the luteal phase).

The psychiatric, medical and psychosocial screens, together with verification of the timing of symptoms, enable the clinician to make a diagnosis. Possible diagnoses after screening include: 1) PMS or PMDD; 2) another psychiatric or medical illness only; 3) PMS or PMDD coexisting with another illness; 4) premenstrual exacerbation / magnification of an underlying psychiatric or medical illness; or, 5) no diagnosis (situational, psychosocial stressors).[37]

To meet the criteria for PMDD, women must not only show symptoms by charting daily for a minimum of 2 consecutive, symptomatic menstrual cycles, but their chief complaints must also include 1 of the 4 core symptoms (irritability, tension, dysphoria, lability of mood) and at least 5 of the 11 total symptoms (Table 1). The symptoms must have occurred within most menstrual cycles during the last year and must have interfered with social or occupational roles. It has been suggested that there should be at least a 30% change (worsening) in symptoms between the follicular and the luteal phase to make a diagnosis of PMDD, regardless of the daily rating scale that is being used.[36,38,39] The charting must demonstrate clear worsening of symptoms premenstrually, and remission within a few days after menstruation begins, commonly referred to as "on-offness" of symptoms. This is in stark contrast with the ICD-10 criteria, which require only 1 symptom for a diagnosis of PMS. Unlike the criteria for PMDD, the presence of an emotional symptom is not required for the diagnosis of PMS, nor is there a requirement for prospective confirmation or for functional impairment.[3]

A woman may have a psychiatric or medical disorder as well as PMS or PMDD. In such cases, the premenstrual symptoms are distinct from the other disorder, and arise during the luteal phase and remit during the follicular phase. Patients can also demonstrate premenstrual exacerbation or magnification of an underlying psychiatric or medical illness. Dysphoria and fatigue, in particular, are symptoms that PMS and PMDD share with various medical and psychiatric disorders. Other symptoms shared by PMS and PMDD and psychiatric illnesses are panic, anxiety, bulimia and substance abuse. In premenstrual exacerbation or magnification of a medical or psychiatric illness, the symptoms persist

Table 1: Criteria for premenstrual dysphoric disorder (PMDD, modified from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition[12])

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 at least one must be (1), (2), (3), or (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 2 consecutive symptomatic menstrual cycles

throughout the menstrual cycle but worsen premenstrually. Some women have continuous symptoms (as in dysthymia) or cyclical symptoms that do not match the phases of their menstrual cycle (as in cyclothymia). Women who do not meet the criteria for any diagnosis may subjectively sense disruptive symptoms as a result of psychosocial stressors and likely still benefit from charting and conservative interventions.

Treatment

A wide range of therapeutic interventions have been tested in the treatment of premenstrual symptoms. For women who do not meet criteria for PMDD or other physical and psychological disorders, conservative treatments are appropriate, and nonpharmacologic management should be encouraged. Unfortunately, there have been few randomized controlled trials to determine the efficacy of these more conservative interventions (Table 2); however, there is some evidence that these patients may best respond to individual or group cognitive–behavioural psychotherapy in combination with lifestyle changes. Recommended dietary changes (especially during the luteal phase) should include reducing or limiting intake of tobacco, chocolate, caffeine and alcohol. Some women report improvement as a result of eating small, frequent meals high in complex carbohydrates, as well as taking vitamins and minerals in moderation. A recent study identified the efficacy of a specially formulated carbohydrate-rich beverage compared with placebo.[40] Patients should be encouraged to decrease excess sodium in the diet when edema or fluid retention occurs and, if possible, to reduce their body mass index to less than 25 kg/m^2.[41] Regular exercise is important[42,43] and particularly effective when combined with the regular practice of stress management techniques. Patients should also be taught to review their own monthly diaries and identify triggers that exacerbate symptoms.

Table 2: Conservative interventions to treat PMS or PMDD

Charting	Daily charting of symptoms
Diet	Reduction or elimination, especially in the luteal phase, of salt, chocolate, caffeine and alcohol; small, frequent meals high in complex carbohydrate; vitamins and minerals in moderation
Exercise	Moderate, regular, aerobic exercise
Stress reduction	Stress management courses or counselling, if necessary, or both
Relaxation	Relaxation courses or audiotapes
Relationship	Assertiveness course or marital counselling, if necessary, or both
Self-help groups	If available
Education	Self-help books

Most nonpharmacologic interventions that have been proven efficacious require a series of interventions. Cognitive–behavioural therapy in the form of 12 weekly individual sessions significantly improved symptoms and functional impairment in women with PMS randomly assigned to immediate treatment, compared with those in the waiting-list control group.[44] Ear, hand and foot reflexology administered once weekly for 8 weeks by a trained reflexologist significantly decreased premenstrual symptoms in women who received treatment compared with those who received "sham" reflexology.[45]

Of the low-risk pharmacologic interventions that have been studied under controlled conditions (Table 3), calcium carbonate (1000 to 1200 mg daily) significantly improved affect and alleviated water retention, food cravings and pain after 3 treatment cycles.[46,47] Magnesium supplementation (200 mg or 360 mg daily during the luteal phase) significantly reduced premenstrual fluid retention after 2 cycles of treatment.[48,49] There have been enough studies of vitamin B6 to allow for a systematic review, which concluded that doses of up to 100 mg daily are likely to be of moderate benefit in treating premenstrual symptoms and depression.[50] Additional treatments that have demonstrated efficacy include nutritional supplements[51,52] and daily administration of vitamin E.[53] A systematic review of evening primrose oil concluded that this intervention was ineffective for this disorder.[54] Mefenamic acid given premenstrually alleviated fatigue, headache, aches and pains, and improved mood,[55] whereas premenstrual administration of naproxen reduced pain in one study,[56] and daily naproxen administration improved menstrual migraine in another.[57] Daily or luteal-phase administration of spironolactone appears efficacious for somatic and physical symptoms, including weight gain and bloatedness.[58–60] For mastalgia, bromocriptine (1.25 to 7.5

Table 3: Low-risk pharmacological interventions supported by the evidence

Supplement	Dosage
Vitamin B6	100 mg daily
Calcium	1000 to 1200 mg daily
Magnesium ion	200 mg daily or 360 mg daily (14 days before menses)
Vitamin E	400 IU daily

mg daily during the luteal phase) was helpful in 10 of 14 randomized trials.[61]

The pharmacological approaches to PMDD and severe PMS include psychotrophic medications and hormonal interventions. The newer antidepressants in particular, including many of the selective serotonin reuptake inhibitors (SSRIs)[9,62–77] as well as clomipramine[78,79] and L-tryptophan,[80] have demonstrated excellent efficacy and minimal side effects in women with severe PMS and PMDD in whom conservative treatment has failed (Table 4). There is increasing evidence that intermittent low-dose SSRI treatment significantly improves both psychological and physical premenstrual symptoms within the first few cycles of treatment.[72–77,79] Intermittent treatment typically consists of starting medications 14 days before menstruation starts and continuing daily treatment until menstruation or shortly thereafter. In spite of considerable differences in chemical structure, all SSRIs appear to be effective for PMDD and PMS. SSRI treatment is not contraindicated for women taking oral contraceptives.

The anxiolytics alprazolam[81–83] and buspirone[84] have also demonstrated efficacy in most trials; however, the magnitude of the therapeutic effect is less than that of SRIs, while the side effect profile and potential for dependence are cause for caution.

The second line of pharmacological treatment includes hormonal agents. In particular, gonadotropin-releasing hormone (GnRH) agonists can temporarily suppress the menstrual cycle (often called "medical ovariectomy" or "medical menopause"). In clinical trials, GnRH agonists have proven very successful in relieving physical symptoms (Table 4). Unfortunately, the long-term use of GnRH agonists is limited by the occurrence of side effects that mimic menopause and the potential for hypo-estrogenism and osteoporosis. Preliminary evidence suggests that "add-back" therapy with low-dose estrogen and progesterone replacement therapy may prevent some of these side effects.[85] Intranasal buserelin[86,87] or intramuscular leuprolide[88,89] are the most appropriate GnRH treatments for clinical use. In clinical trials, danazol has also been effective ,[90–94] most recently in the treatment of premenstrual mastalgia.[95] The final line of treatment is ovariectomy. Two open studies have demonstrated the effectiveness of ovariectomy in the complete relief of severe premenstrual symptoms.[17,18]

Oral contraceptives suppress ovulation while maintaining menstruation due to periodic withdrawal. The one clinical trial testing oral contraceptives for the treatment of PMS was a negative study,[96] which supported the conclusions of other less rigorous research. Until additional research has been done, oral contraceptives are not recommended for the treatment of PMS or PMDD.

Women who manifest severe physical symptoms or a psychiatric disorder with premenstrual magnification should be treated for their primary condition. Premenstrual symptoms usually remit considerably with successful treatment of the primary condition, and residual symptoms can be treated as indicated.

SSRIs and reproduction

Side effects attributable to SSRIs are usually mild and transient.[97] We have recently reported that the length of the menstrual cycle may be shortened in women receiving fluoxetine (60 mg daily) compared with women receiving fluoxetine (20 mg daily) or placebo; however, the significance of this finding is as yet unknown.[98] Perhaps the most troublesome SSRI side effect for women is sexual dysfunction, defined as "normal libido and arousal with delayed or absent orgasm." This side

Table 4: Pharmacological interventions to treat PMS and PMDD that are supported by evidence

Drug class	Drug	Dosage
Antidepressants	Fluoxetine	20 mg/d, every day or during luteal phase only
	Sertraline	50–150 mg/d, every day or during luteal phase only
	Paroxetine	10–30 mg/d, every day or during luteal phase only
	Citalopram	5–20 mg/d, every day or during luteal phase only
	Clomipramine	25–75 mg/d, every day or during luteal phase only
Anxiolytics	Alprazolam	0.25–1.0 mg/tid, 6–14 days before menses
	Buspirone	25 mg/d, 12 days before menses
Ovulation suppressants (GnRH agonists)	Buserelin	400–900 mg/day (intranasal)
	Leuprolide	3.75–7.5 mg/mo (intramuscular injection)
	Danazol	200–400 mg/d, intermittent

effect can be reduced by reducing the dose, taking "drug holidays," substituting another agent or augmenting treatment with various agents.[99] Unfortunately, few clinical trials have included a systematic assessment of sexual function; therefore, the prevalence of anorgasmia as an SSRI side effect in women with PMDD is currently unknown. Clinicians should ask patients about sexual side effects.

The fact that all psychotropic medications diffuse readily across the placenta may raise concern regarding the use of these agents during pregnancy. Because knowledge about the risk of in utero exposure to psychotropic medications is incomplete, women should be counselled on the use of contraception while taking these medications. SSRIs have been shown to be relatively safe in first-trimester or late prenatal exposure.[100–103] The largest amount of data regarding SSRI use in pregnancy involves fluoxetine and indicates that this drug is safe in pregnancy. A review of all published literature, which included outcomes of more than 1000 pregnancies in which the mother was taking fluoxetine, has concluded that in utero exposure to fluoxetine did not affect global IQ, language development or behavioural development in preschool-aged children.[104]

Prognosis and outcome

To date, no single intervention has proven to be equally effective in treating *all* women with severe PMS or PMDD, although SSRIs have demonstrated tolerability and efficacy in more than 60% of patients studied.[105–107]

Patients should be assessed every 2 weeks (i.e., during both the follicular and luteal phases) within the first month of commencing therapy and instructed to continue to chart their symptoms daily. Dosage strategies vary; however, most recent investigations have demonstrated the efficacy of most therapeutic drugs at low dosages. If efficacy has not been attained after several increases in dosage, other treatment options should be considered. There is also evidence that response will be relatively immediate in women with PMS or PMDD; thus, if there is no change in symptoms within 2 to 3 menstrual cycles, an alternative therapy should be considered. Continued symptom charting helps to track efficacy, symptom response to changes in dosage, symptoms upon termination of therapy, and real versus perceived side effects. For example, women who report headaches or nausea as side effects are often surprised to see that they rated these symptoms as just as severe before commencing therapy.

Investigators have yet to reach a consensus on how to define efficacy. Clinically, the easiest way to define efficacy is by the reduction of luteal symptoms (that is, the luteal symptoms remit significantly or the difference between the follicular and luteal phases is less than 30%). It has become obvious that intervention alone

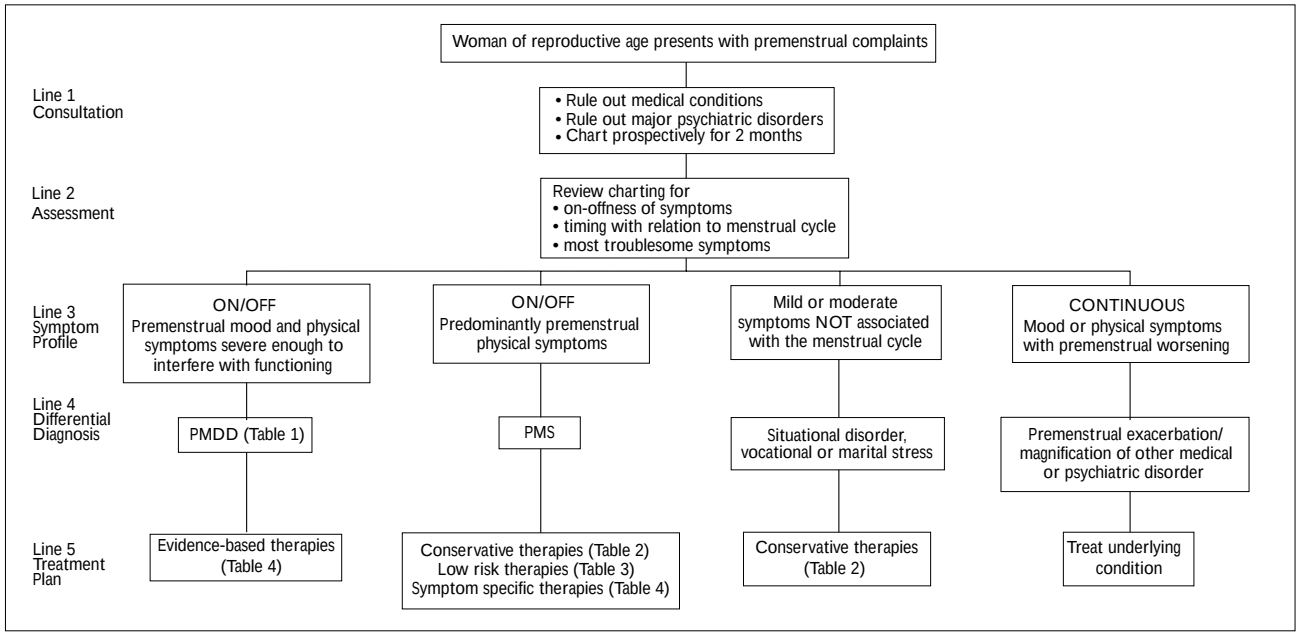

Fig. 1: Algorithm for diagnosing and treating premenstrual syndrome and premenstrual dysphoric disorder

cannot predict efficacy, and more consideration is now being given to psychiatric history as well as to family psychiatric history, especially to mood disorders in the families of women with PMDD.

There are 3 major concerns regarding the prognosis in severe PMS or PMDD: 1) the average age of onset is around 26 years, 2) there is evidence that symptoms gradually worsen over time, and 3) there is evidence that symptoms recur when treatment is halted.[105,106] For these reasons, therapeutic goals must be set to ensure maximal safety and efficacy for the patient.

Diagnosis and treatment algorithm (Fig. 1)

The first step in assessing a patient who presents with PMS is to rule out other medical conditions or major psychiatric disorders and chart symptoms prospectively for at least 2 consecutive symptomatic cycles (Line 1, Consultation). The next step is to review the prospective charting for on-offness of symptoms, most troublesome symptoms, and the timing of symptoms with relation to the menstrual cycle (Line 2, Assessment). With this data in hand, the clinician can define the clustering of symptoms (Line 3, Symptom Profile) and work toward a differential diagnosis (Line 4). Once a differential diagnosis has been made, the clinician can begin to create a Treatment Plan (Line 5). The plan will vary, but should start with conservative therapies and move up the spectrum of evidence-based therapies as required. Women with a diagnosis of PMDD or PMS may be at risk of severe symptoms throughout their reproductive lifecycle. Therapeutic goals should be the cessation of symptoms, or their reduction to tolerable levels; if pharmacologic interventions are required, the emphasis should be on minimizing the dosage and side effects.

Conclusion

Most women of reproductive age experience premenstrual symptoms that can be physical or affective in nature. Approximately 5% of these women experience severe premenstrual symptoms that markedly influence work, social activities or relationships. Prospective charting of premenstrual symptoms for at least 2 menstrual cycles is required to facilitate an accurate diagnosis of this condition. While many women meet criteria for PMS or PMDD, others have premenstrual worsening of a pre-existing condition, or a continuous or intermittent condition not related to the menstrual cycle.

Treatment of women with PMS or PMDD should begin with conservative and low-risk interventions, followed by prescribed pharmacological interventions. Low-dose SSRIs have demonstrated excellent efficacy with minimal side effects, and there is increasing evidence that intermittent treatment is as efficacious as continuous daily treatment. Second-line therapy consists of modification of the menstrual cycle and should be considered only after all other treatment options have failed.

Acknowledgement

The author wishes to acknowledge the assistance of Janice Rogers in the preparation of this manuscript.

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CANADIAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

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This Award was established to honour individuals for a meritorious career in, and outstanding contribution to, neuropsychopharmacology in Canada as evidenced by their activities in education, administration and / or patient care. Achievement in research is not a necessary criterion for this Award.

The Award, which does not have to be awarded each year, consists of a bronze medal engraved with the name of the recipient.

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The names of nominees should be received by Dr. Andrew Greenshaw by November 30th, 2000. Supporting documentation must be received by December 31st, 2000. For each award, this documentation shall consist of:

1. Six copies of a two-page summary prepared by the sponsor describing the nominee's work and its importance in furthering the field of neuropsychopharmacology.
2. Six copies of the nominee's curriculum vitae and list of publications.
3. Six copies of a brief biographical sketch of the candidate prepared by the sponsor.

Formal presentation of the Award will be made to the recipient during the Annual Meeting of the College.

Please send the name of the nominee and a short supportng letter to:

Dr. Andrew J. Greenshaw
President - CCNP
Universityof Alberta, Department of Psychiatry
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8440-112 St.
Edmonton AB T6G 2B7

Deadline for receipt of initial nomination and short supporting letter is November 30, 2000.