Diagnosis and Treatment of Premenstrual Dysphoria

Elias Eriksson, Ph.D.; Björn Andersch, M.D., Ph.D.; Hoi Por Ho, B.Sc.; Mikael Landén, M.D., Ph.D.; and Charlotta Sundblad, M.D., Ph.D.

Premenstrual dysphoria (PMD) is a severe form of premenstrual syndrome afflicting 5% to 10% of all fertile women. Cardinal symptoms—appearing regularly between ovulation and menstruation and disappearing within a few days after the onset of the bleeding—are depressed mood, tension, affect lability, and irritability. Of these symptoms, irritability is often the most prominent. Serotonin reuptake inhibitors (SRIs), but not nonserotonergic antidepressants, reduce the symptoms of PMD effectively. The onset of action of SRIs is much shorter when used for PMD than when used for depression, enabling women with PMD to restrict medication use to the luteal phase of the cycle (so-called intermittent treatment). The findings that SRIs are effective for PMD—and that sexual dysfunction is the most frequent side effect during long-term treatment—both lend support for the hypothesis that a major role for brain serotonin is to modulate sex steroid–driven behavior.

(J Clin Psychiatry 2002;63[suppl 7]:16–23)

Many women of fertile age experience changes in mood and behavior that appear around ovulation, or during the 2 weeks prior to menstruation, and disappear completely within a few days after the onset of bleeding.[1–8] Irritability is often the most prominent symptom, but depressed mood and affect lability are common complaints as well.[1–8] Many women also experience somatic symptoms in the premenstrual phase, such as breast tenderness, a sense of bloating, and headache, but these are usually of less clinical significance than the mental complaints. It is the influence of the menstrual cycle on mood and behavior that is the subject of this review.

Regardless of type and severity of symptoms, a condition that occurs regularly during the luteal phase of the cycle and disappears during the follicular phase is often referred to as *premenstrual syndrome* (PMS). This term, however, is inadequate as a medical diagnosis and indication for drug treatment, since it is poorly defined and commonly used to describe mild, clinically insignificant premenstrual symptoms that are present in a majority of women of fertile age. Moreover, most definitions of PMS are based on the assumption that the various mental and somatic symptoms women experience in the premenstrual phase are different aspects of one condition. This notion may, however, be questioned; the interrelationship between symptoms such as irritability, headache, and breast tenderness is not obvious, since these symptoms clearly are manifestations of at least partly different biological mechanisms, and since they respond differently to different forms of treatment (for references, see Eriksson et al.[6]).

The term *premenstrual dysphoric disorder* (PMDD) was first introduced in DSM-IV[9] and was recently approved by American and English authorities as an indication for pharmacologic treatment. The most important difference between PMS and PMDD is that the latter diagnosis implies that the patient suffers from mental symptoms, not only somatic complaints, and that the condition is severe enough to interfere significantly with work/school, usual social activities, or relationships with others.

Some aspects of the definition of PMDD in the DSM-IV are controversial. For example, the diagnostic relevance of all 11 symptoms listed in the manual is questionable, and the lack of emphasis on irritability as a cardinal symptom is unfortunate. In addition, whereas some researchers would argue that the DSM-IV definition of PMDD underestimates the clinical significance of somatic

From the Departments of Pharmacology (Drs. Eriksson and Sundblad and Mr. Ho), Obstetrics and Gynecology (Dr. Andersch), and Psychiatry (Dr. Landén), Göteborg University, Göteborg, Sweden.

Presented at the closed roundtable symposium "Women's Issues in Antidepressant Therapy," which was held June 12, 2000, in Los Angeles, Calif., and supported by an unrestricted educational grant from Forest Laboratories, Inc.

The authors gratefully acknowledge Margareta Lundgren for skillful assistance in the preparation of this manuscript.

The authors' research within this field has been sponsored by the Medical Research Council, Inga-Britt and Arne Lundberg's Research Foundation, Knut and Alice Wallenberg's Foundation, Thuring's Foundation, the Söderström-Königska Foundation, AstraZeneca, H. Lundbeck, Bristol-Myers Squibb, Novo Nordisk, and SmithKline-Beecham.

Corresponding author and reprints: Elias Eriksson, Ph.D., Department of Pharmacology, Institute of Physiology and Pharmacology, Göteborg University, POB 431, SE 405 30, Göteborg, Sweden.

symptoms, others would omit them completely as defining symptoms of a psychiatric condition. The requirement that one should experience at least 5 of the listed symptoms in order to fulfill the criteria for a diagnosis of PMDD is also debatable; some patients are severely distressed by a single symptom, such as irritability. Finally, according to DSM-IV, a definite diagnosis of PMDD cannot be made unless the cyclical nature of the symptomatology has been confirmed by prospective daily symptom ratings for at least 2 consecutive cycles. While this criterion should be applied in PMDD drug trials, it is unlikely that it will be adopted as standard clinical practice.

Although aspects of the DSM-IV definition of PMDD hence could be questioned, the intention to demarcate, define, and recognize a serious variant of PMS characterized by mental rather than by somatic symptoms is commendable and has inspired and facilitated research in this field. The term *premenstrual dysphoria* (PMD) is often used to describe a condition characterized by symptoms such as irritability and depressed mood and corresponding to PMDD in terms of severity, but not necessarily fulfilling exactly the criteria of PMDD that are listed in DSM-IV.[6] In this review, the term *premenstrual dysphoria* and the abbreviation "PMD" (rather than "PMDD") will be used, with this meaning, regardless of whether the study cited used PMDD criteria or not.

A common misconception is that PMS/PMD is a modern invention and a typical manifestation of life in contemporary Western societies.[10] This notion is challenged by the fact that premenstrual complaints were described by Hippocrates (600 B.C.), Trotula from Salerno (11th century), and a large number of authors during the Renaissance.[6,10] In addition, several epidemiologic studies have demonstrated that premenstrual complaints are common in non-Western societies.[6]

A large number of studies have explored the prevalence of premenstrual complaints in Europe and in the United States, with fairly congruent results. These investigations found that a majority of fertile women experience mild premenstrual symptoms, whereas 5% to 10% are afflicted by a serious variant corresponding to PMD/PMDD.[6] Recent epidemiologic studies have supported the assumption that irritability is the single most disturbing symptom.[11]

An influence of the premenstrual phase on mood should not be regarded as pathologic per se, since estrus cycle–related irritability may also be observed in nonhuman species (in the sexually nonreceptive phase) (see below)[6] and mild cycle-related complaints are present in a majority of women of fertile age. How severe premenstrual complaints should be in order to be regarded as the manifestation of a disorder, and candidates for treatment, could be a matter of debate. The fact that the percentage of women of fertile age reporting that they suffer from a severe variant of this condition is relatively constant in many different epidemiologic studies, however, suggests that the difference between nonsignificant premenstrual complaints and PMD is fairly obvious to the afflicted patient.[6] It should be noted that there are many other psychiatric disorders–social phobia, generalized anxiety disorder, dysthymia, eating disorders, attention deficit disorder–for which the borderline between what may be regarded as "normal" complaints and a psychiatric diagnosis is not razor-sharp; still, it is important that those with serious symptoms are offered a diagnosis and treatment. As with these debilitating disorders, it is important that patients with serious premenstrual psychiatric symptoms be diagnosed and treated.

The high prevalence of mild premenstrual complaints among the general female population has led to a trivialization of the serious form of this condition. Therefore, it is important to emphasize that PMD undermines quality of life, has significant social consequences, may be associated with an increased risk of suicide, and may be associated with a predisposition to major depressive disorder.[6,12]

There also may be a relationship between PMD and somatic illness. In line with this notion, we recently found that women with PMD have a higher waist-hip ratio (M.L.; E.E.; F. Baghei, M.D., et al., unpublished data, January 2001)—an index of abdominal obesity—and lower heart-rate variability (M.L.; E.E.; B. Wennerblom, M.D., Ph.D., et al., unpublished data, January 2001) than symptom-free controls. As far as we know, no studies investigating the possible relationship between PMD and cardiovascular disease have been undertaken; however, since both high waist-hip ratio and low heart-rate variability appear to be important risk factors in this context, such a study is warranted. Notably, 2 other serotonin-related psychiatric disorders, depression and panic disorder, are associated with a significantly increased risk for cardiovascular disease.[13,14]

Several studies have revealed that PMD is hereditary to a great extent,[15] but nothing is known regarding the specific genes involved. Obvious candidate genes are those that code for proteins important in the formation and effects of sex steroids, as well as proteins involved in brain serotonergic neurotransmission.

THE IMPORTANCE OF SEX STEROIDS IN PMD

Since symptoms of PMD appear only during a specific phase of the menstrual cycle, it is tempting to suggest that they are associated with fluctuations in the secretion of ovarian sex steroids. This idea is supported by the fact that symptoms are absent during anovulatory cycles[16] and that they can be effectively relieved by means of ovariectomy or by treatment with an ovulation-inhibiting gonadotropin-releasing hormone analogue.[17–22]

A large number of studies have addressed whether serum estrogen and progesterone levels throughout the

menstrual cycle differ between women with PMD and women without premenstrual complaints.[6] Although the results of these investigations have not been unanimous, a general impression from the literature is that no such differences exist.[6]

The degree to which a woman experiences premenstrual complaints is hence probably not dependent on the amount of estrogen and progesterone produced by the ovaries, but rather on how sensitive the brain is to the influence of these hormones. This hypothesis is supported by the observation that treatment with estrogen- and gestagen-containing oral contraceptives, which leads to a replacement of the endogenous sex steroids by exogenous hormones, usually does not lead to a reduction in symptoms.[23] Of importance in this context is also a recent study showing that administration of female sex steroids may cause a relapse in symptomatology in women with PMD who have become symptom-free by means of treatment with an ovulation inhibitor; in women with no history of premenstrual complaints, the same treatment regimen did not provoke PMD-like symptoms.[21] The idea that some women are more sensitive to the dysphoria-inducing effects of sex steroids than others also gains support from studies showing that menopausal women medicating with sequential hormonal replacement therapy often experience PMD-like symptoms during the days they are taking the gestagen,[24] and that women with a history of PMD are particularly susceptible to this side effect.[25]

It has previously been suggested that premenstrual complaints are triggered by a decline in progesterone levels during the late luteal phase; PMD thus has been regarded as a manifestation of progesterone withdrawal. Studies of gestagen-induced dysphoria, however, suggest that the symptoms are triggered by high levels of progesterone around ovulation (sometimes with a delay of a few days), rather than by the declining levels premenstrually.[21,24] In support of this theory, administration of gestagens (or estrogen) during the later part of the luteal phase does not reduce symptoms of PMD.[6]

It is well established that androgens may provoke irritability, the cardinal symptom of PMD. We have suggested that a modest hyperandrogenicity may increase one's predisposition to PMD.[26] This theory is supported by 2 studies reporting slightly elevated serum levels of testosterone in women with PMD as compared with controls, but there are other investigations that have not replicated this finding (for references, see Eriksson et al.[26]). The notion that androgens may be involved in the pathophysiology of PMD is, however, supported by the preliminary observation that treatment with an androgen antagonist seems to reduce symptoms.[26] The observation that women with PMD often display an abdominal distribution of fat tissue (see above) also agrees with the hypothesis that PMD is associated with testosterone, since waist-hip ratio is strongly correlated with the degree of androgenicity.[27]

BRAIN NEUROTRANSMISSION IN PMD

During the past decade, many papers have suggested that the neurotransmitter serotonin may be involved in the pathophysiology of PMD. Although there are as yet no robust findings suggesting that patients with PMD differ from controls with respect to brain serotonergic activity, the indirect evidence supporting an involvement of serotonin is compelling.

First, animal experiments have established that brain serotonergic neurons predominantly modulate aspects of behavior that are also regulated by sex steroids, such as aggression/irritability and sexual behavior.[28] It hence appears as if one of the most important physiologic roles of serotonin is to modulate sex steroid–driven behavior, of which PMD may be regarded as a typical example. Of special importance in this context is the fact that serotonin, as judged by animal experiments, may counteract the cardinal symptom of PMD, irritability. In addition, other symptoms often reported by women with PMD, including depressed mood and carbohydrate craving, also have long been assumed to be under serotonergic control.[28]

Second, it is well known that estrogen, progesterone, and testosterone influence brain serotonergic activity.[29–31] However, it should be emphasized that the influence of sex steroids on brain neurotransmission is not restricted to the serotonergic neurons; many other transmitters are also reported to be modulated by male and female sex hormones.

Third, women with PMD differ from controls with respect to a number of biological markers believed to indirectly reflect brain serotonergic transmission, including platelet monoamine oxidase activity,[32] density of serotonin transporters in platelets,[33] the ratio between the dopamine metabolite homovanillic acid and the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid,[34] and serotonin-mediated release of prolactin.[6] Although it is difficult to interpret the results of these kinds of studies, the large number of reports hinting at a relationship between PMD and putatively serotonin-related parameters suggest that these findings may not be merely accidental.

The fourth and most persuasive argument for the putative involvement of serotonergic neurons in the pathophysiology of PMD is the observation that pharmacologic agents facilitating brain serotonergic neurotransmission effectively relieve PMD symptoms in most patients.[35] As is discussed below, the serotonin reuptake inhibitors (SRIs), which inhibit the transport protein that removes serotonin from the synaptic cleft, are the most extensively studied (and probably the most effective) compounds in this respect. However, the serotonin-releasing compounds fenfluramine and *m*-chlorophenylpiperazine (*m*-CPP),[36,37] the serotonin precursor tryptophan,[38] and a serotonergic receptor (5-HT_{1A}) agonist, buspirone,[39,40] have also been shown to be superior to placebo in reducing the symptoms of PMD (Table 1). Conversely, inhibition of serotonergic activity,

Table 1. Effects of Manipulation of Brain Serotonergic Activity on the Symptoms of Premenstrual Dysphoria[a]

Treatment	Effect on Serotonergic Neurotransmission	Effect in PMD
Serotonin reuptake inhibitors Citalopram Clomipramine Fluoxetine Paroxetine Sertraline	Blockade of the reuptake inhibition = facilitated transmission	Marked symptom relief
Serotonin releasing compounds Fenfluramine *m*-Chlorophenylpiperazine	Enhanced release = facilitated transmission	Symptom relief
Buspirone	Activation of 5-HT_{1A} receptors = facilitated 5-HT_{1A}–mediated transmission	Symptom relief
Tryptophan	Enhanced synthesis = facilitated transmission	Symptom relief
Vitamin B_6 (pyridoxine)	Enhanced synthesis = facilitated transmission	Symptom relief
Tryptophan-free diet	Reduced synthesis = impaired transmission	Aggravated symptomatology

[a]Based on references 36–41.

achieved by administering a tryptophan-free diet, aggravates irritability in women with PMD.[41] Pyridoxine (vitamin B_6) has been attributed some symptom-reducing effect in PMD (for references, see Eriksson et al.[6]); tentatively, this effect could be due to the fact that this vitamin is a cofactor for tryptophan hydroxylase, an enzyme of importance for the synthesis of serotonin.[28]

Although the evidence that serotonin plays an important role in the pathophysiology of PMD is strong, the involvement of other neurotransmitters should not be ignored. According to a recent hypothesis, premenstrual complaints are associated with the well-established effects of allopregnanolone, a progesterone derivative, on receptors for γ-aminobutyric acid (GABA) of the GABA-A subtype.[42–47] Recent studies[48,49] suggesting that women with PMD differ from symptom-free women with respect to GABA-A receptor responsiveness support this theory. However, the extent to which this hypothesis will lead to new, effective treatment strategies for PMD is uncertain. The most well-established pharmacologic way to facilitate GABA-A activity—administration of benzodiazepines—is apparently only modestly effective in PMD[4] and should usually be avoided, given the risk for drug dependence.

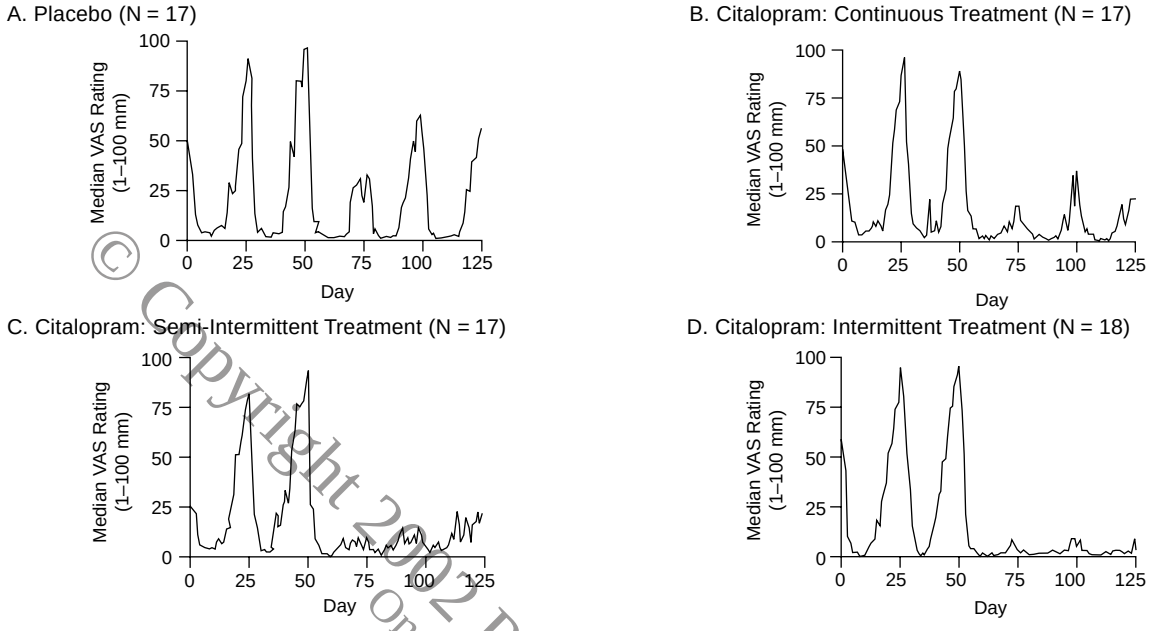
It has recently been suggested that the effect of SRIs in PMD may be due to a direct interaction between these compounds and an enzyme involved in the formation of allopregnanolone.[50] According to this theory, the effect of SRIs on PMD would hence be completely independent of serotonin. Given the fact that premenstrual symptoms can be influenced not only by SRIs, but also by a variety of other compounds modulating brain serotonergic neurotransmission in different ways, this theory, however, seems somewhat farfetched.

TREATMENT WITH SRIs

In a small open trial published in 1990,[51] clomipramine, a strong yet nonselective SRI, dramatically reduced premenstrual irritability and depressed mood. The efficacy of clomipramine in PMD has been subsequently confirmed in 2 placebo-controlled studies; moreover, 4 of the more selective SRIs—citalopram, fluoxetine, paroxetine, and sertraline—have been shown to be superior to placebo for this indication (for references, see Eriksson[35]). There are by now approximately 20 placebo-controlled trials supporting the efficacy of SRIs in PMD, and at least 2 of these comprised very large patient populations (1 with fluoxetine,[52] 1 with sertraline[53]). In a re[55]cent meta-analysis, it was concluded that SRIs are indeed an effective treatment for PMD and should be regarded as first-line treatments[54] (see also comments in Steiner[55]). Fluoxetine is the SRI with the most extensive documentation and is now officially approved for PMDD in several countries (including the United States and the United Kingdom).

In all other established indications for SRIs, such as depression, panic disorder, and obsessive-compulsive disorder, there is a latency period of 2 to 3 weeks between onset of medication and substantial improvement in symptoms.[28] We were therefore surprised to find that the symptom-reducing effect of clomipramine on PMD was apparent within 1 to 2 days after onset of treatment.[56] This short onset of SRI action in PMD is of clinical significance, since it enables women with PMD to restrict drug intake to the luteal phase of the cycle (intermittent treatment). It is also of pharmacologic importance since it demonstrates that SRIs do not always display a slow onset of action. The lag phase associated with SRI use in other indications has been taken as support for the hypothesis that this class of drugs does not elicit acute elevation of transmitter levels in serotonergic synapses in brain, possibly due to receptor-mediated feedback mechanisms. The discovery that the beneficial effect of SRIs in PMD is characterized by a short onset of action, however, challenges this theory, as does the fact that certain serotonin-related side effects of SRIs (nausea, sexual dysfunction) are also evident shortly after the start of medication. The observation that the forceful serotonin releaser fenfluramine exerts a prompt symptom reduction in PMD,[36] but not in depression, also supports the notion that the lag phase of SRIs in the treatment of depression is not due to

Figure 1. Daily Self-Rated Irritability in Women With Premenstrual Dysphoria During 2 Reference Cycles and 3 Treatment Cycles[a]



[a]Adapted with permission from Wikander et al.[57] The treatment given was (A) placebo, (B) continuous treatment with the serotonin reuptake inhibitor citalopram (20 ± 10 mg/day) each day of the cycle, (C) semi-intermittent treatment with citalopram (5 mg/day during the follicular phase, 20 ± 10 mg/day during the luteal phase), or (D) intermittent treatment with citalopram (placebo during the follicular phase, 20 ± 10 mg/day during the luteal phase). Intermittent treatment with citalopram led to a more impressive symptom reduction (during the third treatment cycle) as compared with placebo (p = .0004) but also as compared with continuous treatment with citalopram (p = .002). Abbreviation: VAS = visual analogue scale.

an inability of these drugs to elicit an acute increase in the synaptic levels of serotonin, but to other factors.

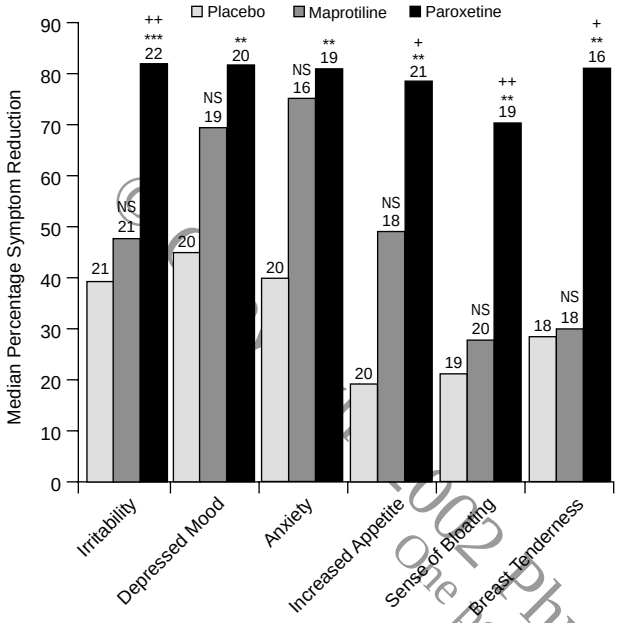
A large number of controlled trials have now confirmed that the SRIs may be administered intermittently, during luteal phases only, for the treatment of PMS.[35] In a recent placebo-controlled trial with the SRI citalopram, we found that intermittent treatment is in fact *more* effective than continuous treatment (Figure 1).[57] This unexpected finding was subsequently confirmed in a trial using sertraline.[58] The most likely explanation for these observations is that continuous administration of some of the SRIs in PMD is associated with a certain development of tolerance, which may be avoided by intermittent drug administration.

In the treatment of depression, drugs facilitating noradrenergic neurotransmission seem neither less nor more effective than those that preferentially or selectively influence serotonin. The same does not hold true in the treatment of PMD. We hence have shown that maprotiline, a selective norepinephrine reuptake inhibitor, is clearly less effective than the SRI paroxetine in reducing premenstrual irritability (as well as other symptoms) (Figure 2).[59] The superiority of serotonergic antidepressants over antidepressants acting via other neurotransmitters for the treatment of PMD has subsequently been confirmed in 2 controlled studies.[60,61] Notably, serotonergic antidepressants previously have been shown to be superior to noradrenergic drugs in the treatment of obsessive-compulsive disorder[62] and panic disorder.[63]

In summary, premenstrual irritability and depressed mood can be very effectively treated with the SRIs, including citalopram, clomipramine, fluoxetine, paroxetine, and sertraline. The response rate among patients taking these drugs for PMD is high (60%–100%), and many become symptom free.[35] Somatic complaints such as breast tenderness and sense of bloating also improve with SRI treatment.[35] Whether this reduction in self-rated somatic symptoms is secondary to an improvement in mood or due to a primary effect on somatic symptoms remains to be explored. The doses of SRIs used to treat PMD should be the same as those used for depression, or lower; with respect to clomipramine, the dose for PMD can be much lower (150 mg/day for depression vs. 10–50 mg/day for PMD). The treatment should usually be given intermittently rather than continuously; patients experiencing initial side effects each time they start medication, however, may find continuous medication preferable. Withdrawal symptoms are usually not a problem during intermittent treatment with an SRI for PMD, probably due to the fact that treatment periods are no longer than 2 weeks. The most common side effect during long-term treatment is sexual dysfunction (anorgasmia, reduced libido), but with intermittent drug use, side effects are restricted to 2 weeks of the cycle, usually making them bearable.

The alternative pharmacologic strategies suggested for PMD appear to be ineffective (evening primrose

Figure 2. Percentage Reduction in Premenstrual Irritability, Depressed Mood, Anxiety, Increased Appetite, Sense of Bloating, and Breast Tenderness in Patients Treated With Placebo, Maprotiline, or Paroxetine[a]



[a]Adapted with permission from Eriksson et al.[59] Abbreviation: NS = not significant vs. placebo. The number above each bar indicates the number of subjects displaying the symptom in question before treatment and hence included in the calculation.
**p < .01 vs. placebo.
***p < .001 vs. placebo.
+p < .05 vs. maprotiline.
++p < .01 vs. maprotiline.

oil, progesterone), less effective than SRIs (pyridoxine, oral contraceptives, spironolactone, alprazolam, tryptophan, buspirone), limited by severe side effects (ovulation inhibitors), or insufficiently studied (calcium, St. John's wort, *m*-CPP).[4,6]

Why Are SRIs Effective for PMD?

The fact that antidepressants are efficacious for treating PMD may lead to the conclusion that PMD is equivalent to depression. Several observations, however, challenge this notion: (1) the dose required for PMD is lower than the dose required for depression (particularly with respect to clomipramine), (2) the onset of therapeutic effect is much shorter in PMD than in depression, and (3) noradrenergic antidepressants are not effective for PMD. Therefore, the beneficial effect of SRIs in PMD is most likely *not* a manifestation of their antidepressant properties.[35]

A more likely explanation to the very beneficial effects of SRIs in PMD is to be found in the fact that serotonergic neurons exert a pronounced, inhibitory influence on aggression and irritability, as shown in numerous animal experiments (for references, see Eriksson and Humble[28]). Recent studies in our laboratory show that the irritability/aggression displayed by female Wistar rats (1) is dependent on the phase of the estrus cycle, (2) disappears after ovariectomy and can be revived by administration of estrogen plus progesterone, and (3) can be substantially reduced by treatment with SRIs.[64] An influence of SRIs on hormone-related irritability may thus be observed also in nonhuman species.

The short time to onset of action of SRIs in PMD also supports the hypothesis that their efficacy is due to the anti-irritability effect of serotonin, rather than to antidepressant activity. Recent preliminary studies thus suggest that the beneficial effects of SRIs on symptoms such as irritability and affect lability in patients with stroke or dementia also are observed very shortly after the onset of treatment.[35]

It is not known which regions of the brain are involved in the beneficial effects of SRIs in PMD; likewise, we do not yet know where the effects of these drugs in conditions such as depression, panic disorder, and obsessive-compulsive disorder are being exerted. Brain regions of possible importance for the beneficial effects of SRIs in PMD are the amygdala and certain parts of the hypothalamus, since these are structures characterized by a high density of sex steroid receptors and serotonergic nerve terminals and assumed to be involved in the regulation of aggression. In accord with the theory that both hyperandrogenicity and serotonergic dysfunction may play important roles in PMD, we have found that androgenization of female rats leads to a reduction in serotonin release in the amygdala.[65]

In conclusion, the impressive efficacy of SRIs in PMD is probably not equivalent to the antidepressant effect of these compounds, but tentatively related to the well-established anti-irritability effect of serotonin. In conjunction with the notion that sexual dysfunction is the most common side effect during long-term treatment with SRIs,[66] the efficacy of SRIs in PMD supports the theory that a major role for serotonin—in man as well as in experimental animals—is to modulate sex steroid–related behavior. Future studies should further explore whether the SRIs are also effective for other sex steroid–related conditions and to what extent sex steroids are involved in other serotonin-related disorders (such as depression, eating disorders, and obsessive-compulsive disorder), as has recently been suggested.[67–76]

Drug names: alprazolam (Xanax and others), citalopram (Celexa), fluoxetine (Sarafem), paroxetine (Paxil), sertraline (Zoloft).

REFERENCES

1. Frank RT. Hormonal causes of premenstrual tension. Arch Neurol Psychiatry 1931;26:1053–1057
2. Backstrom T, Hammarback S. Premenstrual syndrome: psychiatric or gynecological disorder? Ann Med 1991;23:625–633
3. Endicott J, Amsterdam J, Eriksson E, et al. Is premenstrual dysphoric disorder a distinct clinical entity? J Womens Health Gend Based Med 1999;8:663–679

4. Freeman EW. Premenstrual syndrome: current perspectives on treatment and etiology. Curr Opin Obstet Gynecol 1997;9:147–153
5. Korzekwa MI, Steiner M. Premenstrual syndromes. Clin Obstet Gynecol 1997;40:564–576
6. Eriksson E, Sundblad C, Yonkers KA, et al. Premenstrual dysphoria and related conditions: symptoms, pathophysiology and treatment. In: Steiner M, Yonkers KA, Eriksson E, eds. Mood Disorders in Women. London, England: Martin Dunitz; 2000:269–294
7. Pearlstein T, Stone AB. Premenstrual syndrome. Psychiatr Clin North Am 1998;21:577–590
8. Halbreich U. Premenstrual syndromes: closing the 20th century chapters. Curr Opin Obstet Gynecol 1999;11:265–270
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press; 1994
10. Stohlman M. The monthly malady: a history of premenstrual suffering. Med Hist 2000;44:301–322
11. Angst J, Sellaro R, Merikangas KR, et al. The epidemiology of premenstrual symptoms. Acta Psychiatr Scand 2001;104:110–116
12. Yonkers KA. The association between premenstrual dysphoric disorder and other mood disorders. J Clin Psychiatry 1997;58(suppl 15):19–25
13. Ford DE, Mead LA, Chang PP, et al. Depression is a risk factor for coronary artery disease in men: the precursors study. Arch Intern Med 1998; 158:1422–1426
14. Kawachi I, Sparrow D, Vokonas PS, et al. Symptoms of anxiety and risk of coronary heart disease: The Normative Aging Study. Circulation 1994;90: 2225–2229
15. Kendler KS, Karkowski LM, Corey LA, et al. Longitudinal population-based twin study of retrospectively reported premenstrual symptoms and lifetime major depression. Am J Psychiatry 1998;155:1234–1240
16. Hammarback S, Ekholm UB, Backstrom T. Spontaneous anovulation causing disappearance of cyclical symptoms in women with the premenstrual syndrome. Acta Endocrinol (Copenh) 1991;125:132–137
17. Muse KN, Cetel NS, Futterman LA, et al. The premenstrual syndrome: effects of "medical ovariectomy." N Engl J Med 1984;311:1345–1349
18. Bancroft J, Boyle H, Warner P, et al. The use of an LHRH agonist, buserelin, in the long-term management of premenstrual syndromes. Clin Endocrinol (Oxf) 1987;27:171–182
19. Hammarback S, Backstrom T. Induced anovulation as treatment of premenstrual tension syndrome: a double-blind cross-over study with GnRH-agonist versus placebo. Acta Obstet Gynecol Scand 1988;67:159–166
20. Mezrow G, Shoupe D, Spicer D, et al. Depot leuprolide acetate with estrogen and progestin add-back for long-term treatment of premenstrual syndrome. Fertil Steril 1994;62:932–937
21. Schmidt PJ, Nieman LK, Danaceau MA, et al. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. N Engl J Med 1998;338:209–216
22. Leather AT, Studd JW, Watson NR, et al. The treatment of severe premenstrual syndrome with goserelin with and without "add-back" estrogen therapy: a placebo-controlled study. Gynecol Endocrinol 1999;13:48–55
23. Bancroft J, Rennie D. The impact of oral contraceptives on the experience of perimenstrual mood, clumsiness, food craving and other symptoms. J Psychosom Res 1993;37:195–202
24. Hammarback S, Backstrom T, Holst J, et al. Cyclical mood changes as in the premenstrual tension syndrome during sequential estrogen-progestagen postmenopausal replacement therapy. Acta Obstet Gynecol Scand 1985; 64:393–397
25. Bjorn I, Bixo M, Nojd-Strandberg K, et al. Negative mood induction by progestagen is related to a history of premenstrual syndrome. Acta Physiol Scand 1999;167:A7–A8
26. Eriksson E, Sundblad C, Landen M, et al. Behavioural effects of androgens in women. In: Steiner M, Yonkers KA, Eriksson E, eds. Mood Disorders in Women. London, England: Martin Dunitz; 2000:233–246
27. Bjorntorp P. The android woman: a risky condition. J Intern Med 1996;239: 105–110
28. Eriksson E, Humble M. Serotonin in psychiatric pathophysiology, a review of data from experimental and clinical research. In: Pohl R, Gershon S. The Biological Basis of Psychiatric Treatment. Basel, Switzerland: Karger; 1990:66–119
29. Bethea CL, Pecins-Thompson M, Schutzer WE, et al. Ovarian steroids and serotonin neural function. Mol Neurobiol 1998;18:87–123
30. Fink G, Sumner B, Rosie R, et al. Androgen actions on central serotonin neurotransmission: relevance for mood, mental state and memory. Behav Brain Res 1999;105:53–68
31. Rubinow DR, Schmidt PJ, Roca CA. Estrogen-serotonin interactions: implications for affective regulation. Biol Psychiatry 1998;44:839–850
32. Hallman J, Oreland L, Edman G, et al. Thrombocyte monoamine oxidase activity and personality traits in women with severe premenstrual syndrome. Acta Psychiatr Scand 1987;76:225–234
33. Rapkin AJ. The role of serotonin in premenstrual syndrome. Clin Obstet Gynecol 1992;35:629–636
34. Eriksson E, Alling C, Andersch B, et al. Cerebrospinal fluid levels of monoamine metabolites: a preliminary study of their relation to menstrual cycle phase, sex steroids, and pituitary hormones in healthy women and in women with premenstrual syndrome. Neuropsychopharmacology 1994; 11:201–213
35. Eriksson E. Serotonin reuptake inhibitors for the treatment of premenstrual dysphoria. Int Clin Psychopharmacol 1999;14(suppl 2):S27–S33
36. Brzezinski AA, Wurtman JJ, Wurtman RJ, et al. *d*-Fenfluramine suppresses the increased calorie and carbohydrate intakes and improves the mood of women with premenstrual depression. Obstet Gynecol 1990;76:296–301
37. Su TP, Schmidt PJ, Danaceau M, et al. Effect of menstrual cycle phase on neuroendocrine and behavioral responses to the serotonin agonist *m*-chlorophenylpiperazine in women with premenstrual syndrome and controls. J Clin Endocrinol Metab 1997;82:1220–1228
38. Steinberg S, Annable L, Young SN, et al. A placebo-controlled study of the effects of L-tryptophan in patients with premenstrual dysphoria. Adv Exp Med Biol 1999;467:85–88
39. Rickels K, Freeman E, Sondheimer S. Buspirone in treatment of premenstrual syndrome [letter]. Lancet 1989;1:777
40. Landen M, Eriksson O, Sundblad C, et al. Compounds with affinity for serotonergic receptors in the treatment of premenstrual dysphoria: a comparison of buspirone, nefazodone, and placebo. Psychopharmacology 2001;155:292–298
41. Menkes DB, Coates DC, Fawcett JP. Acute tryptophan depletion aggravates premenstrual syndrome. J Affect Disord 1994;32:37–44
42. Wang M, Seippel L, Purdy RH, et al. Relationship between symptom severity and steroid variation in women with premenstrual syndrome: study on serum pregnenolone, pregnenolone sulfate, 5 alpha-pregnane-3,20-dione and 3 alpha-hydroxy-5 alpha-pregnan-20-one. J Clin Endocrinol Metab 1996;81:1076–1082
43. Rapkin AJ, Morgan M, Goldman L, et al. Progesterone metabolite allopregnanolone in women with premenstrual syndrome. Obstet Gynecol 1997;90:709–714
44. Smith SS, Gong QH, Hsu FC, et al. GABA(A) receptor alpha4 subunit suppression prevents withdrawal properties of an endogenous steroid. Nature 1998;392:926–930
45. Bicikova M, Dibbelt L, Hill M, et al. Allopregnanolone in women with premenstrual syndrome. Horm Metab Res 1998;30:227–230
46. Sundstrom I, Backstrom T, Wang M, et al. Premenstrual syndrome, neuroactive steroids and the brain. Gynecol Endocrinol 1999;13:206–220
47. Le Melledo JM, Van Driel M, Coupland NJ, et al. Response to flumazenil in women with premenstrual dysphoric disorder. Am J Psychiatry 2000; 157:821–823
48. Sundstrom I, Andersson A, Nyberg S, et al. Patients with premenstrual syndrome have a different sensitivity to a neuroactive steroid during the menstrual cycle compared to control subjects. Neuroendocrinology 1998;67: 126–138
49. Sundstrom I, Nyberg S, Backstrom T. Patients with premenstrual syndrome have reduced sensitivity to midazolam compared to control subjects. Neuropsychopharmacology 1997;17:370–381
50. Griffin LD, Mellon SH. Selective serotonin reuptake inhibitors directly alter activity of neurosteroidogenic enzymes. Proc Natl Acad Sci U S A 1999; 96:13512–13517
51. Eriksson E, Lisjo P, Sundblad C, et al. Effect of clomipramine on premenstrual syndrome. Acta Psychiatr Scand 1990;81:87–88
52. Steiner M, Steinberg S, Stewart D, et al. Fluoxetine in the treatment of premenstrual dysphoria. Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group. N Engl J Med 1995;332:1529–1534
53. Yonkers KA, Halbreich U, Freeman E, et al. Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment: a randomized controlled trial. Sertraline Premenstrual Dysphoric Collaborative Study Group. JAMA 1997;278:983–988
54. Dimmock PW, Wyatt KM, Jones PW, et al. Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review. Lancet 2000;356:1131–1136

55. Steiner M. Recognition of premenstrual dysphoric disorder and its treatment. Lancet 2000;356:1126–1127
56. Sundblad C, Hedberg MA, Eriksson E. Clomipramine administered during the luteal phase reduces the symptoms of premenstrual syndrome: a placebo-controlled trial. Neuropsychopharmacology 1993;9:133–145
57. Wikander I, Sundblad C, Andersch B, et al. Citalopram in premenstrual dysphoria: is intermittent treatment during luteal phases more effective than continuous medication throughout the menstrual cycle? J Clin Psychopharmacol 1998;18:390–398
58. Freeman EW, Rickels K, Arredondo F, et al. Full- or half-cycle treatment of severe premenstrual syndrome with a serotonergic antidepressant. J Clin Psychopharmacol 1999;19:3–8
59. Eriksson E, Hedberg MA, Andersch B, et al. The serotonin reuptake inhibitor paroxetine is superior to the noradrenaline reuptake inhibitor maprotiline in the treatment of premenstrual syndrome. Neuropsychopharmacology 1995;12:167–176
60. Pearlstein TB, Stone AB, Lund SA, et al. Comparison of fluoxetine, bupropion, and placebo in the treatment of premenstrual dysphoric disorder. J Clin Psychopharmacol 1997;17:261–266
61. Freeman EW, Rickels K, Sondheimer SJ, et al. Differential response to antidepressants in women with premenstrual syndrome/premenstrual dysphoric disorder: a randomized controlled trial. Arch Gen Psychiatry 1999;56: 932–939
62. Thoren P, Asberg M, Cronholm B, et al. Clomipramine treatment of obsessive-compulsive disorder, 1: a controlled clinical trial. Arch Gen Psychiatry 1980;37:1281–1285
63. Modigh K, Westberg P, Eriksson E. Superiority of clomipramine over imipramine in the treatment of panic disorder: a placebo-controlled trial. J Clin Psychopharmacol 1992;12:251–261
64. Ho HP, Olsson M, Westberg L, et al. The serotonin reuptake inhibitor fluoxetine reduces sex steroid-related aggression in female rats: an animal model of premenstrual irritability? Neuropsychopharmacology 2001;24:502–510
65. Sundblad C, Eriksson E. Reduced extracellular levels of serotonin in the amygdala of androgenized female rats. Eur Neuropsychopharmacol 1997;7:253–259
66. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol 1999;19:67–85
67. Cyranowski JM, Frank E, Young E, et al. Adolescent onset of the gender difference in lifetime rates of major depression: a theoretical model. Arch Gen Psychiatry 2000;57:21–27
68. Gregoire AJ, Kumar R, Everitt B, et al. Transdermal oestrogen for treatment of severe postnatal depression. Lancet 1996;347:930–933
69. Appleby L, Warner R, Whitton A, et al. A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. BMJ 1997;314:932–936
70. Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. Am J Obstet Gynecol 2000;183:414–420
71. Amsterdam J, Garcia-Espana F, Fawcett J, et al. Fluoxetine efficacy in menopausal women with and without estrogen replacement. J Affect Disord 1999;55:11–17
72. Casas M, Alvarez E, Duro P, et al. Antiandrogenic treatment of obsessive-compulsive neurosis. Acta Psychiatr Scand 1986;73:221–222
73. Eriksson T. Antiandrogenic treatment for obsessive-compulsive disorder [letter]. Am J Psychiatry 2000;157:483
74. Bergman L, Eriksson E. Marked symptom reduction in two women with bulimia nervosa treated with the testosterone receptor antagonist flutamide. Acta Psychiatr Scand 1996;94:137–139
75. Peterson BS, Zhang H, Anderson GM, et al. A double-blind, placebo-controlled, crossover trial of an antiandrogen in the treatment of Tourette's syndrome. J Clin Psychopharmacol 1998;18:324–331
76. Rosler A, Witztum E. Treatment of men with paraphilia with a long-acting analogue of gonadotropin-releasing hormone [see comments]. N Engl J Med 1998;338:416–422