# Premenstrual Dysphoria and the Serotonin System: Pathophysiology and Treatment

**Meir Steiner, M.D., Ph.D., F.R.C.P.C., and Teri Pearlstein, M.D.**

The inclusion of research diagnostic criteria for premenstrual dysphoric disorder (PMDD) in the DSM-IV recognizes the fact that some women have extremely distressing emotional and behavioral 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 and/or psychological symptoms of a concurrent psychiatric and/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 close reciprocal relationship with the gonadal hormones and has been identified as the most plausible target for interventions. Thus, beyond the conservative treatment options such as lifestyle and stress management, other nonantidepressant treatments, or the more extreme interventions that eliminate ovulation altogether, the serotonin reuptake inhibitors (SRIs) are emerging as the most effective treatment option for this population. Results from several randomized, placebo-controlled trials in women with PMDD have clearly demonstrated that the SRIs have excellent efficacy and minimal side effects. More recently, several preliminary studies indicate that intermittent (premenstrual only) treatment with selective SRIs is equally effective in these women and, thus, may offer an attractive treatment option for a disorder that is itself intermittent.

*(J Clin Psychiatry 2000;61[suppl 12]:17–21)*



The etiology of premenstrual syndrome (PMS)[1] and that of the more severe form known as premenstrual dysphoric disorder (PMDD)[2] are still uncertain. Nevertheless, clinicians and researchers are now more in agreement that PMS and PMDD are physiologic phenomena, biologically determined and only partially influenced by psychosocial events. This is underscored by recent convincing evidence of the heritability of premenstrual symptoms[3,4] and by the fact that suppression of ovulation[5] or surgical menopause[6,7] will eliminate premenstrual complaints.

There also seems to be a consensus now that PMDD is distinct from other mood disorders. The dysphoria associated with PMDD is cyclical, and the most common physical symptoms such as breast tenderness and bloating are unique, all tightly linked and entrained to the late luteal phase of the menstrual cycle with a predictable "on-off" pattern.[8–11] This regular reoccurrence of symptoms disappears during pregnancy and after menopause, and not only can it be prevented by suppression of the cyclicity of gonadal hormones, but hormone replacement therapy can provoke the reappearance of symptoms in menopausal women with a history of PMDD.[12] The genetic and environmental risk factors for PMDD are different from those for other mood disorders, and the hypothalamic-pituitary-adrenal axis function is usually normal in PMDD, unlike the overactivity of this axis in patients with major depression. Finally, the response to treatment in women with PMDD is almost immediate compared with the extended time gap usually observed in patients with other mood and anxiety disorders, and the reemergence of premenstrual symptoms is also rapid and almost predictable when treatment is stopped.[11–13]

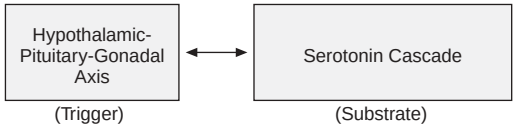
Severe PMS or PMDD affects approximately 3% to 8% of women of reproductive age worldwide, with an enormous burden of illness on themselves, their families, and society. Valid screening and diagnostic tools are now available, which should assist the clinician in identifying

*From the Department of Psychiatry and Behavioural Neurosciences, McMaster University, and the Women's Health Concerns Clinic, St. Joseph's Hospital, Hamilton, Ontario, Canada (Dr. Steiner); and the Women's Treatment Program, Butler Hospital, and the Department of Psychiatry and Human Behavior, Brown University School of Medicine, Providence, R.I. (Dr. Pearlstein).*

*Presented at the planning roundtable "New Trends in Treating Premenstrual Dysphoric Disorder," which was held September 13–14, 1999, in Naples, Fla., and supported by an unrestricted educational grant from Eli Lilly and Company.*

*Reprint requests to: Meir Steiner, M.D., Ph.D., F.R.C.P.C., Women's Health Concerns Clinic, St. Joseph's Hospital, 301 James St. S., Hamilton, Ontario L8P 3B6, Canada.*

**Figure 1. Pathophysiology of Premenstrual Dysphoric Disorder**




women with PMDD, with special emphasis on prospective daily charting (to confirm both the severity and on-offness of the symptoms).[10,14]

A long list of treatment options has been suggested over the years, including somatic and psychosocial therapies. The nonantidepressant treatment options are reviewed elsewhere in this supplement (see Pearlstein[15]). Here, after a brief review of the evidence for the involvement of the serotonergic system in the pathophysiology of PMDD, we will summarize the data that support the effectiveness and tolerability of treatments with serotonin reuptake inhibitors (SRIs) in this condition.

## PATHOPHYSIOLOGY

The pathophysiology of severe PMS and PMDD is closely linked to an active hypothalamic-pituitary-gonadal (HPG) axis. The menstrual cyclicity of the ovarian hormones is most likely the trigger for the psychological as well as the somatic premenstrual symptoms. What has become clearer over the years is that no demonstrable hormonal imbalance exists in women with severe PMS or PMDD.[12] Normal ovarian function triggers biochemical events both in the brain and peripherally, which in turn unleash the premenstrual symptoms in vulnerable or predisposed women.

The neurotransmitter serotonin (5-HT) is in a reciprocal relationship with the HPG axis[16,17] (Figure 1), and increasing evidence suggests that 5-HT is pivotal in the pathogenesis of PMDD.[18–22]

PMDD shares many features of other mood and anxiety disorders that are also linked to 5-HT dysfunction.[23–26] Reduction in brain 5-HT neurotransmission is believed to be associated with poor impulse control, irritability, dysphoria, and increased carbohydrate craving—all symptoms known to be associated with PMDD. Several studies have in fact demonstrated that 5-HT function is altered in women with PMDD. Whole blood 5-HT levels, platelet uptake of 5-HT, and platelet $^{3}$H-imipramine binding have all been reported to be reduced in women with premenstrual syndrome.[19,27–30] Studies[31–35] using challenge tests including L-tryptophan, fenfluramine, buspirone, and *m*-chlorophenylpiperazine have also suggested abnormal 5-HT function in symptomatic women with PMS or PMDD, but differ in their findings as to whether the response to these 5-HT challenges is blunted or heightened. Acute tryptophan depletion aggravates premenstrual syndrome,[36] whereas drugs facilitating 5-HT transmission are effective in reducing premenstrual symptoms[37] (see below).

Other neurotransmitters and neuromodulators, in particular the γ-aminobutyric acid (GABA), adrenergic, and opioid systems, have also been implicated in the pathophysiology of PMS and PMDD. Reduced $GABA_A$ receptor sensitivity as well as reduced plasma GABA levels have been noted in women with PMS and PMDD, respectively, during the luteal phase.[38,39] Platelet $\alpha_2$-adrenergic receptor density correlated positively with symptom severity of PMDD,[40] possibly linking it to similar findings in other populations of anxious and dysphoric patients. The sharp drop ("withdrawal") in opiate levels during the late luteal phase has also been suggested as a factor in the etiology of premenstrual irritability, anxiety, and tension.[41,42]

The current consensus, though, is that premenstrual irritability and dysphoria are probably linked to a difference in the sensitivity of the 5-HT system in predisposed women, rendering them more vulnerable to cyclical hormonal fluctuations.[22,43–45]

## TREATMENT

Over 30 reported studies (and several more ongoing), of which at least 20 are randomized controlled trials, with a total of over 1100 female participants (study completers) discuss treatment with serotonin-enhancing drugs, and all but one (a relatively small study) confirm that these agents are both effective and mostly well tolerated in up to 70% of women with severe PMS or PMDD.[9,37,46]

The very first studies introducing the notion that SRIs might play a crucial role in helping women with severe PMS were with clomipramine, a tricyclic antidepressant that is predominantly an SRI.[47–49] Not only was the response rate very high in these studies, but the doses required were also much lower (10–50 mg/day) than those usually needed to achieve response in depression or obsessive-compulsive disorder.

Among the selective SRIs (SSRIs), both fluoxetine and sertraline have large databases that unequivocally demonstrate that these drugs are effective and well tolerated in women with PMDD. Several open-label studies with fluoxetine[13,50–53] and with sertraline,[54,55] as well as randomized controlled trials with these drugs,[56–69] all support the efficacy of these drugs in women with severe PMS or PMDD. Two open-label studies[70,71] and one double-blind, placebo-controlled trial[72] also confirm the effectiveness of paroxetine. Similarly, a randomized controlled trial[73] has proved the efficacy of citalopram. The only relatively small double-blind, placebo-controlled trial[74] with fluvoxamine has shown the active medication to be no better than placebo. A later open-label study, though, confirmed the efficacy of fluvoxamine for PMDD as well.[75]

In most of the drug trials with SRIs, the dose needed to achieve response was relatively low, although only one dose-response study,[59] using fluoxetine, was able to establish that there is no advantage in increasing the dose beyond 20 mg/day and that patients taking 60 mg/day had a significantly higher incidence of side effects.

The onset of action/response with SRIs in PMDD is very rapid, sometimes as short as 1 to 2 days, which has prompted several investigators to consider intermittent (luteal phase only) rather than continuous dosing of the medication. To date, the effectiveness and tolerability of the intermittent dosing regimen have been confirmed for sertraline,[65–67] fluoxetine,[76] and citalopram,[73] with several additional randomized placebo-controlled trials currently under way. Of note is the recent trial with citalopram[73] which showed that not only was the drug more effective than placebo, but intermittent dosing was more effective than continuous dosing.

In most of these studies, the treatment period was usually for 3 menstrual cycles; only one randomized placebo-controlled trial[59] with fluoxetine had a treatment period of 6 cycles. Three open-label trials[13,52,53] with fluoxetine of longer duration (between 12–18 months) and one with paroxetine[77] suggest that the effect does not decline with time, but to further clarify the issue of tolerance, more longer studies are required.

Given that in most women with severe PMS and PMDD, the cardinal symptoms are irritability and dysphoria, it is perhaps not surprising that the SRIs are so effective in this condition. What is surprising, though, is the observation that these agents are also extremely effective in alleviating the somatic complaints, in particular breast tenderness and bloating.[48,72,78] Whether this is a primary, direct effect on the somatic symptoms per se or just a perceived secondary benefit (due to the reduction in irritability/dysphoria that renders the somatic symptoms less bothersome) has yet to be determined.

The DSM-IV criteria[2] for PMDD require the establishment and documentation of premenstrual impairment in psychosocial functioning, but few of the large-scale treatment studies have actually monitored prospectively the impairment in social or role functioning and the effects treatment has on this aspect of the disorder. Three studies have reported improvement in social impairment with fluoxetine using a visual analogue measure for work efficiency and social activity[79] and a subtotal score of social impairment derived from the Premenstrual Tension Syndrome Scale,[80] respectively. Only one study[64] has systematically monitored functioning and quality of life in a large number of women treated with sertraline for PMDD. Psychosocial functioning was measured using the Daily Record of Severity of Problems, the Social Adjustment Scale, and the short form of the Quality of Life Enjoyment and Satisfaction Scale (all self-rating scales). The results clearly indicate that sertraline was superior to placebo in improving interpersonal and role functioning and quality of life in women with PMDD.[81]

## CONCLUSION

Overwhelming evidence now supports the effectiveness and tolerability of SRIs in the treatment of severe PMS and PMDD using continuous dosing, and some initial evidence suggests that intermittent (premenstrual only) dosing might be at least as effective if not better than continuous dosing.

The mechanism of action of SRIs in PMDD is believed to be different from the one that underlies their therapeutic effect in major depression or obsessive-compulsive disorder. Thus, the ability of SRIs to enhance 5-HT activity is not the only mechanism responsible for their wide range of clinical efficacy. In the case of PMDD, it has been suggested that the effect of SSRIs on allopregnenolone biosynthesis is independent from 5-HT reuptake inhibition and may be due to a specific action on the enzymes that synthesize allopregnenolone from its precursor progesterone. It is hypothesized that the increase in allopregnenolone synthesized during the action of SSRIs acts on $GABA_A$ receptors, which might explain the rapid alleviation of irritability and dysphoria associated with PMDD.[82,83]

This hypothesis is further supported by recent animal data suggesting that the changes in expression of $GABA_A$ receptor subunits result from progesterone withdrawal.[84] Women with PMS have lower levels of allopregnenolone than controls[85] and have different sensitivity to neuroactive steroids and a decreased $GABA_A$ receptor sensitivity.[38] In a preliminary open-label trial,[86] citalopram has been shown to increase pregnenolone sensitivity.

The uniqueness of the SRIs is further underscored by the observation that most other antidepressants do not seem to be effective in treating PMDD. In a recent study,[68] sertraline was found again to be effective in treating women with severe PMS, but desipramine was not better than placebo. This finding is in keeping with those of 2 previous studies[61,72] showing that paroxetine and fluoxetine were effective, whereas the comparison antidepressants, maprotiline and bupropion, respectively, were not.

Finally, all the studies that have demonstrated the effectiveness of SRIs in PMDD have excluded women taking oral contraceptives and those under the age of 18 years. It is noteworthy that many women who are prescribed SSRIs for other approved indications are taking oral contraceptives, and no untoward effects whatsoever have been reported. Similarly, there is a growing acceptance of the appropriateness of the use of SSRIs in children and adolescents, and again, the effectiveness and tolerability profile in younger age groups is not much different from that observed in adults. Nevertheless, it would be prudent to await further studies before prescribing SRIs for PMDD in younger girls.

*Drug names:* bupropion (Wellbutrin), buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Sarafem), fenfluramine (Pondimin), fluvoxamine (Luvox), maprotiline (Ludiomil), paroxetine (Paxil), sertraline (Zoloft).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, the following agents mentioned in this article are not approved by the U.S. Food and Drug Administration for the treatment of PMDD: bupropion, buspirone, citalopram, clomipramine, desipramine, fenfluramine, fluvoxamine, maprotiline, paroxetine, and sertraline.

## REFERENCES


1. World Health Organization. Mental, behavioral and developmental disorders. In: Tenth Revision of the International Classification of Diseases (ICD-10). Geneva, Switzerland: World Health Organization; 1996
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994:717–718
3. Condon JT. The premenstrual syndrome: a twin study. Br J Psychiatry 1993;162:481–486
4. 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
5. 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
6. Casson P, Hahn PM, Van Vugt DA, et al. Lasting response to ovariectomy in severe intractable premenstrual syndrome. Am J Obstet Gynecol 1990; 162:99–105
7. Casper RF, Hearn MT. The effect of hysterectomy and bilateral oophorectomy in women with severe premenstrual syndrome. Am J Obstet Gynecol 1990;162:105–109
8. Endicott J, Amsterdam J, Eriksson E, et al. Is premenstrual dysphoric disorder a distinct clinical entity? J Womens Ment Health 1999;8:663–679
9. Eriksson E. Serotonin reuptake inhibitors for the treatment of premenstrual dysphoria. Int Clin Psychopharmacol 1999;14(suppl 2):S27–S33
10. Steiner M, Streiner DL, Steinberg S, et al. The measurement of premenstrual mood symptoms. J Affect Disord 1999;53:269–273
11. Endicott J. History, evolution, and diagnosis of premenstrual dysphoric disorder. J Clin Psychiatry 2000;61(suppl 12):5–8
12. Roca CA, Schmidt PJ, Bloch M, et al. Implications of endocrine studies of premenstrual syndrome. Psychiatr Ann 1996;26:576–580
13. Pearlstein TB, Stone AB. Long-term fluoxetine treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1994;55:332–335
14. Steiner M, Wilkins A. Diagnosis and assessment of premenstrual dysphoria. Psychiatr Ann 1996;26:571–575
15. Pearlstein T, Steiner M. Non-antidepressant treatment of premenstrual syndrome. J Clin Psychiatry 2000;61(suppl 12):22–27
16. 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 PMS. Neuropsychopharmacology 1994;11:201–213
17. Tuiten A, Panhuysen G, Koppeschaar H, et al. Stress, serotonergic function, and mood in users of oral contraceptives. Psychoneuroendocrinology 1995;20:323–334
18. Rojansky N, Halbreich U, Zander K, et al. Imipramine receptor binding and serotonin uptake in platelets of women with premenstrual changes. Gynecol Obstet Invest 1991;31:146–152
19. Rapkin AJ. The role of serotonin in premenstrual syndrome. Clin Obstet Gynecol 1992;35:629–636
20. Steiner M. Female-specific mood disorders. Clin Obstet Gynecol 1992;35: 599–611
21. Yatham LN. Is 5-$HT_{1A}$ receptor subsensitivity a trait marker for late luteal phase dysphoric disorder? a pilot study. Can J Psychiatry 1993;38: 662–664
22. Steiner M, LePage P, Dunn E. Serotonin and gender specific psychiatric disorders. Int J Psychiatry Clin Pract 1997;1:3–13
23. Pearlstein TB, Frank E, Rivera-Tovar A, et al. Prevalence of axis I and axis II disorders in women with late luteal phase dysphoric disorder. J Affect Disord 1990;20:129–134
24. Endicott J. The menstrual cycle and mood disorders. J Affect Disord 1993; 29:193–200
25. Wurtman JJ. Depression and weight gain: the serotonin connection. J Affect Disord 1993;29:183–192
26. Mann JJ. Role of the serotonergic system in the pathogenesis of major depression and suicidal behaviour. Neuropsychopharmacology 1999;21 (suppl 2):99S–105S
27. Taylor DL, Mathew RJ, Ho BT, et al. Serotonin levels and platelet uptake during premenstrual tension. Neuropsychobiology 1984;12:16–18
28. Rapkin AJ, Edelmuth E, Chang LC, et al. Whole blood serotonin in premenstrual syndrome. Obstet Gynecol 1987;70:533–537
29. Ashby CR Jr, Carr LA, Cook CL, et al. Alteration of platelet serotonergic mechanisms and monoamine oxidase activity in premenstrual syndrome. Biol Psychiatry 1988;24:225–233
30. Steege JF, Stout AL, Knight DL, et al. Reduced platelet tritium-labeled imipramine binding sites in women with premenstrual syndrome. Am J Obstet Gynecol 1992;167:168–172
31. Bancroft J, Cook A, Davidson D, et al. Blunting of neuroendocrine responses to infusion of L-tryptophan in women with perimenstrual mood change. Psychol Med 1991;21:305–312
32. Bancroft J, Cook A. The neuroendocrine response to *d*-fenfluramine in women with premenstrual depression. J Affect Disord 1995;36:57–64
33. Fitzgerald M, Malone KM, Li S, et al. Blunted serotonin response to fenfluramine challenge in premenstrual dysphoric disorder. Am J Psychiatry 1997;154:556–558
34. 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
35. Steiner M, Yatham LN, Coote M, et al. Serotonergic dysfunction in women with pure premenstrual dysphoric disorder: is the fenfluramine challenge test still relevant? Psychiatry Res 1999;87:107–115
36. Menkes DB, Coates DC, Fawcett JP. Acute tryptophan depletion aggravates premenstrual syndrome. J Affect Disord 1994;32:37–44
37. Steiner M, Judge R, Kumar R. Serotonin re-uptake inhibitors in the treatment of premenstrual dysphoria: current state of knowledge. Int J Psychiatry Clin Pract 1997;1:241–247
38. 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
39. Halbreich U, Petty F, Yonkers K, et al. Low plasma gamma-aminobutyric acid levels during the late luteal phase of women with premenstrual dysphoric disorder. Am J Psychiatry 1996;153:718–720
40. Gurguis GN, Yonkers KA, Phan SP, et al. Adrenergic receptors in premenstrual dysphoric disorder, I: platelet $\alpha_2$ receptors: $G_i$ protein coupling, phase of menstrual cycle, and prediction of luteal phase symptom severity. Biol Psychiatry 1998;44:600–609
41. Rapkin AJ, Shoupe D, Reading A, et al. Decreased central opioid activity in premenstrual syndrome: luteinizing hormone response to naloxone. J Soc Gynecol Investig 1996;3:93–98
42. Chuong CJ, Coulam CB, Bergstralh EJ, et al. Clinical trial of naltrexone in premenstrual syndrome. Obstet Gynecol 1988;72:332–336
43. Halbreich U, Tworek H. Altered serotonergic activity in women with dysphoric premenstrual syndromes. Int J Psychiatry Med 1993;23:1–27
44. Leibenluft E, Fiero PL, Rubinow DR. Effects of the menstrual cycle on dependent variables in mood disorder research. Arch Gen Psychiatry 1994; 51:761–781
45. Kouri EM, Halbreich U. State and trait serotonergic abnormalities in women with dysphoric premenstrual syndromes. Psychopharmacol Bull 1997;33:767–770
46. Steiner M, Born L. Advances in the diagnosis and treatment of premenstrual dysphoria. CNS Drugs 2000;13:287–304
47. Eriksson E, Lisjo P, Sundblad C, et al. Effect of clomipramine on premenstrual syndrome. Acta Psychiatr Scand 1990;81:87–88
48. Sundblad C, Modigh K, Andersch B, et al. Clomipramine effectively reduces premenstrual irritability and dysphoria: a placebo controlled trial. Acta Psychiatr Scand 1992;85:39–47
49. 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
50. Rickels K, Freeman EW, Sondheimer S, et al. Fluoxetine in the treatment of premenstrual syndrome. Curr Ther Res 1990;48:161–166

51. Brandenburg S, Tuynman-Qua H, Verheij R, et al. Treatment of premenstrual syndrome with fluoxetine: an open study. Int Clin Psychopharmacol 1993;8:315–317
52. Elks ML. Open trial of fluoxetine therapy for premenstrual syndrome. South Med J 1993;86:503–507
53. de la Gandara Martin JJ. Premenstrual dysphoric disorder: long-term treatment with fluoxetine and discontinuation. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1997;25:235–242
54. Freeman EW, Rickels K, Sondheimer SJ, et al. Sertraline versus desipramine in the treatment of premenstrual syndrome: an open-label trial. J Clin Psychiatry 1996;57:7–11
55. Castro RR, Montalban SR, Bisen JRD, et al. Sertraline efficacy in the treatment of premenstrual dysphoric disorder (PMDD). Eur Neuropsychopharmacol 1998;8(suppl 2):S309
56. Stone AB, Pearlstein TB, Brown WA. Fluoxetine in the treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1991;52:290–293
57. Wood SH, Mortola JF, Chan YF, et al. Treatment of premenstrual syndrome with fluoxetine: a double-blind, placebo-controlled, crossover study. Obstet Gynecol 1992;80:339–344
58. Menkes DB, Taghavi E, Mason PA. et al. Fluoxetine treatment of severe premenstrual syndrome. BMJ 1992;305:346–347
59. 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
60. Ozeren S, Corakci A, Yucesoy I, et al. Fluoxetine in the treatment of premenstrual syndrome. Eur J Obstet Gynecol Reprod Biol 1997;73:167–170
61. Pearlstein TB, Stone AB, Lund SA. Comparison of fluoxetine, bupropion, and placebo in the treatment of premenstrual dysphoric disorder. J Clin Psychopharmacol 1997;17:261–266
62. Su T-P, Schmidt P, Danaceau MA, et al. Fluoxetine in the treatment of premenstrual dysphoria. Neuropsychopharmacology 1997;16:346–356
63. Diegoli MS, da Fonseca AM, Diegoli CA, et al. A double-blind trial of four medications to treat severe premenstrual syndrome. Int J Gynaecol Obstet 1998;62:63–67
64. Yonkers KA, Halbreich U, Freeman E, et al. Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment: a randomized controlled trial. JAMA 1997;278:983–988
65. Halbreich U, Smoller JW. Intermittent luteal phase sertraline treatment of dysphoric premenstrual syndrome. J Clin Psychiatry 1997;58:399–402
66. Young SA, Hurt PH, Benedek DM, et al. Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: a randomized, double-blind, placebo-controlled crossover trial. J Clin Psychiatry 1998; 59:76–80
67. 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
68. 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
69. Jermain DM, Preece CK, Sykes RL, et al. Luteal phase sertraline treatment for premenstrual dysphoric disorder: results of a double-blind, placebo-controlled, crossover study. Arch Fam Med 1999;8:328–332
70. Yonkers KA, Gullion C, Williams A, et al. Paroxetine as a treatment for premenstrual dysphoric disorder. J Clin Psychopharmacol 1996;16:3–8
71. Sundblad C, Wikander I, Andersch B, et al. A naturalistic study of paroxetine in premenstrual syndrome: efficacy and side-effects during 10 cycles of treatment. Eur Neuropsychopharmacol 1997;7:201–206
72. 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
73. Wikander I, Sundblad C, Andersch B, et al. Citalopram in premenstrual dysphoria: is intermittent treatment during luted phases more effective than continuous medication throughout the menstrual cycle? J Clin Psychopharmacol 1998;18:390–398
74. Veeninga AT, Westenberg HG, Weusten JT. Fluvoxamine in the treatment of menstrually related mood disorders. Psychopharmacology 1990;102: 414–416
75. Freeman EW, Rickels K, Sondheimer S. Fluvoxamine for premensturual dysphoric disorder: a pilot study. J Clin Psychiatry 1996;57(suppl 8):56–59
76. Steiner M, Korzekwa M, Lamont J, et al. Intermittent fluoxetine dosing in the treatment of women with premenstrual dysphoria. Psychopharmacol Bull 1997;33:771–774
77. Sundblad C, Wikander I, Andersch B, et al. A naturalistic study of paroxetine in premenstrual syndrome: efficacy and side-effects during 10 cycles of treatment. Eur Neuropsychopharmacol 1997;7:201–206
78. Steiner M, Romano S, Babcock S. Fluoxetine's efficacy in improving physical symptoms associated with PMDD. Eur Neuropsychopharmacol 1999;9(suppl 5):S208
79. Brown E, Romano SJ, Pearlstein T, et al. Comparing fluoxetine's efficacy in improving mood, physical and social impairment symptoms associated with PMDD across three randomized, placebo-controlled clinical trials. Presented at the 39th annual meeting of the New Clinical Drug Evaluation Unit; June 1–4, 1999; Boca Raton, Fla. Poster 54
80. Steiner M, Romano SJ, Dillon J. Efficacy of fluoxetine in improving mood symptoms, physical symptoms and social impairment in patients with PMDD. J Womens Health 1999;8:713
81. Pearlstein TB, Halbreich U, Batzar ED, et al. Psychosocial functioning in women with premenstrual dysphoric disorder before and after treatment with sertraline or placebo. J Clin Psychiatry 2000;61:101–109
82. 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
83. Guidotti A, Costa E. Can the antidysphoric and anxiolytic profiles of selective serotonin reuptake inhibitors be related to their ability to increase brain 3α, 5α-tetrahydroprogesterone (allopregnenolone) availability? Biol Psychiatry 1998;44:865–873
84. Smith SS, Gong QH, Hsu FC, et al. $GABA_A$ receptor $alpha_4$ subunit suppression prevents withdrawal properties of an endogenous steroid. Nature 1998;392:926–930
85. Bicikova M, Dibbelt L, Hill M, et al. Allopregnenolone in women with premenstrual syndrome. Horm Metab Res 1998;30:227–230
86. Sundstrom I, Backstrom T. Citalopram increases pregnenolone sensitivity in patients with premenstrual syndrome: an open trial. Psychoneuroendocrinology 1998;23:73–88