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# Selective Serotonin Reuptake Inhibitors for Premenstrual Dysphoric Disorder

## The Emerging Gold Standard?

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## Contents



## Abstract

There have been a large number of studies conducted investigating the use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of patients with premenstrual dysphoric disorder (PMDD). The 12 randomised, controlled trials with continuous dose administration of SSRIs and the eight randomised, controlled trials with luteal phase dose administration (from ovulation to menses) are reviewed.

All the treatment studies on fluoxetine, sertraline, paroxetine and citalopram have reported positive efficacy. Fluoxetine and sertraline have the largest literature, with a smaller number of studies endorsing paroxetine and citalopram. Mixed efficacy results have been reported with fluvoxamine.

In general, adverse effects from the use of SSRIs in women with PMDD are the usual mild and transient adverse effects from SSRIs including anxiety, dizziness, insomnia, sedation, nausea and headache. Sexual dysfunction and weight gain can be problematic long-term adverse effects of SSRIs, but these effects have not been systematically evaluated with long-term SSRI use in women with PMDD.

Serotonergic antidepressants have differential superiority over nonserotonergic antidepressants in the treatment of PMDD. Treatments that enhance

serotonergic action improve premenstrual irritability and dysphoria with a rapid onset of action, suggesting a different mechanism of action than in the treatment of depression. It is possible that neurosteroids, such as progesterone metabolites, are involved in the rapid action of serotonergic antidepressants in PMDD.

Future research needs to address less frequent dose administration regimens, such as 'symptom-onset' dose administration, and the recommended length of treatment.

Selective serotonin reuptake inhibitors (SSRIs) are currently recommended as the first line treatment for premenstrual dysphoric disorder (PMDD) by both recent mental health[1] and gynaecology guidelines.[2] The recommendation for SSRIs as a first line treatment is a result of the large literature endorsing their efficacy in relieving premenstrual emotional and physical symptoms, and the advantageous long-term tolerability compared with other treatment options.

In the past decade, the results of continuous (or daily) SSRI dose administration studies demonstrated that treatment response was apparent by the completion of the first menstrual cycle; thus, suggesting that the onset of action of SSRIs in treating premenstrual symptoms was more rapid than the 3 to 6 weeks often required for the treatment of major depressive disorder. Women find the administration of medication solely during the symptomatic phase of the cycle appealing, and luteal phase (or intermittent) dose administration has received much recent research interest. Luteal phase dose administration is generally initiated at ovulation, presumably to 'correct' one or more dysregulated systems at the time of periovulatory hormonal changes.

This review summarises the randomised, controlled trials and the nonblind studies that have been conducted to date with continuous and luteal phase dose administration of serotonergic medications in the treatment of PMDD.

## 1. Diagnosis

Approximately 20 to 50% of menstruating women have moderate to severe premenstrual symptoms, and epidemiologic studies using retrospective reports suggest that between 1 and 9% of women have severe premenstrual symptoms.[3] Women with severe premenstrual symptoms and impairment of functioning generally meet the diagnostic criteria for PMDD which are listed in the appendix of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[4] To meet the PMDD criteria, at least five out of 11 possible symptoms should be present in the premenstrual phase, with resolution during the first few days of menses, and at least one of the five symptoms must be depressed mood, anxiety, lability or irritability. Since the PMDD criteria is identical to the DSM-III-R criteria for late luteal phase dysphoric disorder (LLPDD),[5] except for the inclusion of one additional symptom, all individuals who met criteria for LLPDD in older treatment studies also meet the current criteria for PMDD. Both the PMDD criteria and the recently proposed diagnostic criteria for premenstrual syndrome (PMS)[2] require impaired premenstrual role functioning and prospective daily symptom charting over two menstrual cycles. The prospective daily symptom charting is necessary to confirm the timing and nature of the premenstrual symptoms, and to rule out chronic medical or psychiatric disorders, most commonly chronic depressive or anxiety disorders.

Various rating forms for daily symptom charting have been used in the treatment studies reviewed in this article. Many studies have used visual analogue scales (VAS), a 100mm line on which a participant rates her symptoms each day between anchor points of 'no symptoms' (0mm) to 'severe or extreme symptoms' (100mm).[6,7] Other studies have used Likert scale rating forms where participants rate each symptom daily on an ordinal scale. Examples of 6-point Likert scales (0 =

'none' to 6 = 'extreme') include the Daily Record of Severity of Problems (DRSP),[8] the Daily Rating Form (DRF),[9] the Daily Assessment Form (DAF),[10] and the Premenstrual Assessment Form (PAF).[11] Other Likert rating scales include the Penn Daily Symptom Report (DSR),[12] the Calendar of Premenstrual Experiences (COPE)[13] and the Prospective Record of the Impact and Severity of Menstrual Symptoms (PRISM).[14] In each treatment study, various scoring methods of the daily symptom recordings were utilised to compare the symptom scores of the symptomatic premenstrual days to the follicular days, and to exclude significant follicular symptomatology in order to confirm the PMDD diagnosis. The same scoring methods were generally used in the final treatment cycle to determine treatment outcome. Clinician ratings in several of the treatment trials reviewed have included the Clinical Global Impressions scale (CGI),[15] the Hamilton Rating Scale for Depression (HAM-D),[16] the Global Assessment Scale (GAS)[17] and the Premenstrual Tension Scale (PMTS).[18]

## 2. Aetiology

There are several recent reviews on theories for the aetiology of PMS and PMDD.[19-22] Specific abnormalities of hypothalamic-pituitary-gonadal hormones have not been identified, and it has been proposed that women with severe PMS and PMDD have a differential sensitivity to normal gonadal steroid fluctuations each cycle, particularly at ovulation.[23] The aetiology of this 'differential sensitivity' is unknown, but it likely to involve neurotransmitters and neurosteroids. Abnormal calcium,[24] noradrenergic,[19] melatonin and circadian system functioning have been reported.[25] Involvement of the γ-aminobutyric acid (GABA) system is suggested by decreased premenstrual $GABA_A$ receptor sensitivity and abnormal premenstrual allopregnanolone (an anxiolytic metabolite of progesterone that acts at the $GABA_A$ receptor) levels in women with PMDD; see reviews.[21,26]

The most consistent pathophysiological abnormality reported in women with PMDD involves the serotonin system. These abnormalities include abnormal whole blood serotonin levels, serotonin platelet uptake and tritiated imipramine binding, abnormal responses to serotonergic probes such as buspirone, fenfluramine, L-tryptophan and metachlorophenylpiperazine (m-CPP), and exacerbation of premenstrual symptoms after tryptophan depletion; see reviews.[21,22,27-29] The several studies suggesting serotonin dysregulation are further substantiated by the consistent efficacy of SSRIs in treating PMDD. The rapid decrease in premenstrual irritability and dysphoria with SSRIs suggests a unique action of SSRIs in PMDD.[30] The rapid efficacy of SSRIs in PMDD may be due in part to their ability to alter allopregnanolone levels in the brain as reported in MDD.[31,32]

## 3. Treatment Studies

A recent meta-analysis of randomised, double-blind, placebo-controlled trials of SSRIs in severe PMS and PMDD reported an odds ratio of 6.91 in favour of SSRIs over placebo.[33] This analysis included 12 studies with continuous dose administration of SSRIs and four studies with luteal phase dose administration of SSRIs. The efficacy of daily and luteal phase dose administration was equivalent. Adverse effects were significantly higher with SSRIs than with placebo.[33] Overall, treatment studies with SSRIs have reported a 60 to 70% efficacy rate compared with an approximately 30% efficacy rate with placebo. The reviewed studies in the following subsections are grouped by medication. Table I and table II list the continuous dose and luteal phase dose administration SSRI studies, respectively.

### 3.1 Fluoxetine

The greatest number of the SSRI treatment trials has been conducted with fluoxetine and these have been reviewed extensively.[28,53] Seven randomised, double-blind, placebo-controlled trials have been conducted with continuous (daily) fluoxetine, six of these studies each involved less

**Table I.** Continuous dose administration, randomised, controlled trials of selective serotonins reuptake inhibitors in patients with premenstrual syndrome and premenstrual dysphoric disorder

| Study | Study design (no. of pts) | Measures | Key findings |
|---|---|---|---|
| Steiner et al., 1995[34] | DBPC, parallel; 2 cycles SB placebo; 6 cycles fluoxetine 20 mg/d (96), fluoxetine 60 mg/d (86) or placebo (95) | VAS | Both doses of fluoxetine superior to placebo by first and through all 6 cycles in reducing mean VAS of irritability, dysphoria, tension ($p < 0.001$). ≥50% reduction in mean VAS of irritability, dysphoria, tension by first cycle in 52% fluoxetine (both doses) *vs* 22% placebo ($p < 0.001$). Significantly more adverse effects with 60 mg/d dose than 20 mg/d or placebo ($p < 0.001$) |
| Stone et al., 1991[35] | DBPC, parallel; 1 cycle SB placebo; 2 cycles fluoxetine 20 mg/d (10) or placebo (10) | DAF, GAS | 9/10 fluoxetine *vs* 2/10 placebo had ≥50% decrease in mean luteal DAF compared with baseline ($p < 0.0003$). Higher luteal GAS in fluoxetine group *vs* placebo ($p < 0.009$) |
| Pearlstein et al., 1997[36] | DBPC, parallel; 1 cycle SB placebo; 2 cycles fluoxetine 20 mg/d (10), bupropion 300 mg/d (12) or placebo (10) | CGI, GAS | Fluoxetine superior to bupropion ($p < 0.005$) and placebo ($p < 0.001$) in number of responders (CGI of 1 or 2). Higher luteal GAS in fluoxetine group *vs* placebo ($p < 0.05$) |
| Ozeren et al., 1997 [37] | DBPC, parallel; 3 cycles fluoxetine 20 mg/d (15) or placebo (15) | COPE | 12/15 fluoxetine *vs* 4/15 placebo had endpoint luteal COPE<40 ($p < 0.009$). Endpoint luteal COPE decreased 58% with fluoxetine *vs* 23% with placebo compared with baseline ($p < 0.0001$) |
| Wood et al., 1992[38] | DBPC, crossover; 3 cycles each of fluoxetine 20 mg/d and placebo (8) | COPE | Fluoxetine superior to placebo on reducing luteal total ($p < 0.005$), behavioural ($p < 0.005$) and physical ($p < 0.05$) COPE scores compared with baseline |
| Menkes et al., 1993[39] | DBPC, crossover; 12 day washout between 3.5 cycles each of fluoxetine 20 mg/d and placebo (16) | DRF, PAF | Fluoxetine superior to placebo on reducing 8/10 DRF symptoms ($p < 0.03$). Fluoxetine decreased 16/18 PAF subscales ($p < 0.001$) compared with baseline |
| Su et al., 1997[40] | DBPC, crossover; 1 cycle washout after 3 cycles each of fluoxetine 20-60 mg/d and placebo (17) | DRF, VAS | Fluoxetine superior to placebo on 10/13 DRF symptoms ($p < 0.01$) compared with baseline. Fluoxetine superior to placebo and baseline on VAS mood and social impairment ($p < 0.01$) |
| Yonkers et al., 1997[41] | DBPC, parallel; 1 cycle SB placebo; 3 cycles sertraline 50-150mg/d (99) or placebo (101) | DRSP, CGI, HAM-D, SAS | Sertraline superior to placebo on reducing luteal total, depressive, anger/irritability and physical factor DRSP scores ($p < 0.001$). CGI of 1 or 2 in 62% sertraline *vs* 34% placebo ($p < 0.001$). Sertraline superior to placebo on luteal HAM-D ($p < 0.002$). Sertraline superior to placebo on some luteal SAS factors ($p < 0.05$) |
| Freeman et al., 1999[42] | DBPC, parallel; 3 cycles sertraline 50-150 mg/d (62), desipramine 50-150 mg/d (50) or placebo (55) | DSR, CGI, HAM-D | Sertraline superior to both desipramine and placebo on DSR total ($p < 0.001$), mood ($p < 0.001$) and pain ($p < 0.05$) scores. Desipramine not superior to placebo on DSR scores. 65% sertraline *vs* 36% desipramine and 29% placebo recipients achieved a >50% decrease in total DSR score at endpoint ($p < 0.001$) |
| Eriksson et al., 1995[43] | DBPC, parallel; 3 cycles paroxetine 10-30 mg/d (22), maprotiline 50-150 mg/d (21) or placebo (22) | VAS | Paroxetine superior to placebo for VAS irritability ($p < 0.001$) and 5 other symptoms ($p < 0.01$). Maprotiline superior to placebo on VAS depression ($p = 0.05$) and anxiety ($p = 0.01$) only. Paroxetine superior on self-rated global improvement *vs* placebo ($p = 0.0004$) and *vs* maprotiline ($p = 0.03$) |
| Veeninga et al., 1990[44] | DBPC, parallel; 2 cycles fluvoxamine 150 mg/d (10) or placebo (10) | MDQ | Methodologic flaws in subject selection. Fluvoxamine not superior to placebo |
| Wikander et al., 1998[45] | DBPC, parallel; 3 cycles citalopram 10-30 mg/d 'continuous' (17), citalopram 5mg follicular weeks/10-30 mg/d luteal weeks 'semi-intermittent' (17), citalopram 10-30 mg/d luteal weeks only 'intermittent' (18) or placebo (17) | VAS | 'Intermittent' luteal VAS irritability superior to 'continuous' ($p = 0.002$), 'semi-intermittent' ($p = 0.005$) and placebo ($p = 0.0004$). 'Continuous' ($p = 0.02$) and 'intermittent' ($p = 0.0001$) superior to placebo on self-rated global improvement |

**CGI** = Clinical Global Impressions Scale; **COPE** = Calendar of Premenstrual Experiences; **DAF** = Daily Assessment Form; **DBPC** = double-blind, placebo-controlled; **DRF** = Daily Rating Form; **DRSP** = Daily Record of Severity of Problems; **DSR** = Daily Symptom Report; **GAS** = Global Assessment Scale; **HAM-D** = Hamilton Rating Scale for Depression; **MDQ** = Menstrual Distress Questionnaire; **PAF** = Premenstrual Assessment Form; **SAS** = Social Adjustment Scale; **SB** = single-blind; **VAS** = Visual Analogue Scale.

**Table II.** Luteal phase dose administration, randomised, controlled trials of selective serotonin reuptake inhibitors in patients with premenstrual syndrome and premenstrual dysphoric disorder

| Study | Study design (no. of pts) | Measures | Key findings |
|---|---|---|---|
| Freeman et al., 1999[46] | DB, parallel; 3 cycles full cycle sertraline 50-150 mg/d (13) or luteal phase sertraline 50-150 mg/d (18) | DSR | DSR<80 in 89% luteal phase *vs* 46% full-cycle ($p < 0.02$). Luteal phase superior to full-cycle dose administration on DSR mood factor ($p < 0.05$) |
| Jermain et al., 1999[47] | DBPC, crossover; 2 cycles each of luteal phase sertraline 50-100 mg/d or placebo (50) | COPE | Sertraline superior to placebo on luteal total ($p = 0.01$), behavioural ($p < 0.01$) and physical ($p = 0.03$) COPE scores |
| Young et al., 1998[48] | DBPC, crossover; 1 washout cycle between 2 cycles each of luteal phase sertraline 50 mg/d or placebo (11) | COPE | Sertraline superior to placebo on luteal behavioural ($p = 0.005$) and physical ($p = 0.01$) COPE scores |
| Halbreich & Smoller, 1997[49] | DBPC, crossover; 1 cycle sertraline 100 mg/d; 2 cycles each of luteal phase sertraline 100 mg/d or placebo (11) | DRF, CGI, HAM-D | Sertraline superior to placebo on DRF depression ($p < 0.0001$) and impairment ($p < 0.0004$), CGI ($p < 0.0001$) and HAM-D ($p < 0.0001$) |
| Wikander et al., 1998[45] | DBPC, parallel; 3 cycles citalopram 10-30 mg/d 'continuous' (17), citalopram 5mg follicular weeks/10-30 mg/d luteal weeks 'semi-intermittent' (17), citalopram 10-30 mg/d luteal weeks only 'intermittent' (18) or placebo (17) | VAS | 'Intermittent' luteal VAS irritability superior to 'continuous' ($p = 0.002$), 'semi-intermittent' ($p = 0.005$) and placebo ($p = 0.0004$). 'Continuous' ($p = 0.02$) and 'intermittent' ($p = 0.0001$) superior to placebo on self-rated global improvement |
| Halbreich et al., in press[50] | DBPC, parallel; 1 cycle SB placebo; 3 cycles luteal phase sertraline 50-100 mg/d (142) or placebo (139) | DRSP, CGI | Sertraline superior to placebo on mean total DRSP and CGI-I (each $p < 0.001$), not on DRSP physical symptoms |
| Cohen et al., in press[51] | DBPC, parallel; 1 cycle SB placebo; 3 cycles luteal phase fluoxetine 10 mg/d (86), fluoxetine 20 mg/d (86) or placebo (88); 1 cycle SB placebo | DRSP, PMTS | Fluoxetine 20 mg/d superior to placebo on mean DRSP total, mood, physical and social functioning scores and PMTS (each $p<0.05$). Fluoxetine 10 mg/d superior to placebo on DRSP mood and social functioning scores and PMTS (each $p < 0.05$) |
| Miner et al., 2002[52] | DBPC, parallel; 1 cycle SB placebo; 3 cycles fluoxetine 90mg 14 and 7 days before menses (84), placebo 14 days before and fluoxetine 90mg 7 days before menses (83) or placebo 14 and 7 days before menses (80); 1 cycle SB placebo | DRSP, PMTS, CGI | Fluoxetine 90mg 14 and 7 days before menses superior to placebo on mean DRSP total, mood and functioning items, PMTS, and CGI-S (each $p < 0.05$), but not DRSP physical symptoms. Fluoxetine 90mg 7 days before menses not superior to placebo |

**CGI** = Clinical Global Impressions Scale; **COPE** = Calendar of Premenstrual Experiences; **DB** = double-blind; **DBPC** = double-blind, placebo-controlled; **DRF** = Daily Rating Form; **DRSP** = Daily Record of Severity of Problems; **DSR** = Daily Symptom Report; **HAM-D** = Hamilton Rating Scale for Depression; **PMTS** = Premenstrual Tension Scale; **SB** = single-blind; **VAS** = Visual Analogue Scale.

than 35 participants, while one study[34] was a large multicentre trial (see table I).

In this largest trial, women with PMDD (based on VAS scores) who remained eligible after two single-blind placebo cycles, were randomised to fluoxetine 20 mg/day, fluoxetine 60 mg/day or placebo in a parallel design for six menstrual cycles.[34] At least one treatment cycle was completed by 277 women and 180 women completed the 6-month trial. The primary treatment outcome measure was the percentage of change from baseline in the mean of the luteal VAS scores of dysphoria, irritability and tension. Both doses of fluoxetine were significantly superior to placebo by the first cycle ($p < 0.001$), and through each of the six treatment cycles ($p < 0.001$). Moderate improvement was defined as at least a 50% reduction in the mean of the three luteal VAS scores from baseline, and this was achieved in 52% of women receiving either dose of fluoxetine compared with 22% of those receiving placebo ($p < 0.001$) by the first cycle. Significantly more adverse effects were noted with fluoxetine 60 mg/day than with 20 mg/day or placebo ($p < 0.001$), including insomnia, nausea, tremor, fatigue, dizziness, anorexia and somnolence. Although the mechanism underlying the efficacy of fluoxetine for improving physical premenstrual symptoms is not clear, both

doses of fluoxetine improved premenstrual bloating and breast tenderness, but not headaches.[54] The PMTS-Self-Rated and PMTS-Observer total scores both also demonstrated superiority of fluoxetine (20 mg/day and 60 mg/day) over placebo at the end of the first cycle compared with baseline ($p < 0.001$), and these scales correlated well with VAS ratings.[55]

The results of this multisite study largely contributed to the US Food and Drug Administration (FDA) approval of fluoxetine 20 mg/day for the treatment of emotional and physical symptoms of PMDD, and fluoxetine is approved for the treatment of PMDD in other countries.

The first randomised, double-blind, placebo-controlled trial of fluoxetine for the treatment of PMDD involved 20 women with LLPDD.[35] The diagnosis of LLPDD was assessed with the DAF. Nonresponders to an initial single-blind placebo cycle were randomised to fluoxetine 20 mg/day or placebo in a parallel design for two treatment cycles. With treatment response defined as a 50% or greater decrease in the mean luteal symptom DAF score compared to baseline, nine of ten participants who had received fluoxetine were responders, while two of ten who had received placebo were responders ($p < 0.0003$). Significant superiority of fluoxetine over placebo was noted on luteal GAS scores compared to baseline ($p < 0.009$) and on each daily rating LLPDD item ($p < 0.02$).

The same research group subsequently conducted a study comparing fluoxetine with bupropion, a nonserotonergic antidepressant, and placebo.[36] Study design was similar to the earlier study except that 34 women with LLPDD who continued to meet entrance criteria after an initial single-blind placebo cycle were randomised to fluoxetine 20 mg/day, bupropion 100mg three times daily or placebo in a parallel design for two treatment cycles. Defining responders as having a CGI-Improvement scale score of 1 or 2 ('much' or 'very much improved'), fluoxetine was superior to placebo ($p < 0.001$) and bupropion ($p < 0.005$), and bupropion was not superior to placebo. Fluoxetine was also significantly superior to placebo based on endpoint luteal GAS ($p < 0.05$) and on modified HAM-D ratings ($p < 0.05$) compared with luteal baseline ratings. This study added to the results from an earlier study[43] that SSRIs were selectively effective for PMS and PMDD compared with nonserotonergic antidepressants.

Another fluoxetine study used the COPE to diagnose PMDD and monitor response, with response defined as a COPE score of <40.[37] Individuals who met the entrance criteria were randomised to fluoxetine 20 mg/day or placebo in a parallel design for three treatment cycles. Twelve of 15 participants who received fluoxetine were considered responders compared with four of 15 who received placebo ($p < 0.009$). Compared with the baseline luteal total COPE scores, the endpoint luteal total COPE scores decreased 58% in the fluoxetine group and 23% in the placebo group ($p < 0.0001$). The most common adverse effects with fluoxetine were gastrointestinal irritability, insomnia and sexual dysfunction.

The COPE was also used as an assessment and treatment outcome measure in a small study.[38] Eight women who met LLPDD criteria were randomised in a double-blind, crossover study to fluoxetine 20 mg/day or placebo, with three treatment cycles on each treatment. Seven out of the eight participants improved on fluoxetine, with a decrease in the mean luteal total COPE score of 62%. The mean luteal total ($p < 0.005$), behavioural ($p < 0.005$) and physical ($p < 0.05$) COPE scores were significantly more improved with fluoxetine than with placebo and compared with luteal baseline scores.

A crossover trial utilised the PAF and the DRF to diagnose LLPDD and monitor treatment outcome.[39] Sixteen women with LLPDD were randomly assigned to receive fluoxetine 20 mg/day or placebo for three and a half cycles, followed by a 12-day washout, then by crossover to the other treatment for an additional three and a half cycles. Fluoxetine was significantly more effective than placebo on eight out of ten DRF symptom scores ($p < 0.03$). Fluoxetine significantly improved 17/18 PAF subscale scores (16 subscales $p < 0.005$, one

subscale $p < 0.03$) while placebo improved 5/18 subscale scores (two subscales $p < 0.005$, three subscales $p < 0.03$) compared with baseline. Nausea, insomnia, sweating and menstrual disturbances were significantly more associated with fluoxetine than placebo.

Another crossover study utilised a flexible dose of fluoxetine versus placebo.[40] Seventeen women had a diagnosis of PMDD determined by DRF ratings and VAS ratings of depression, irritability and anxiety for three baseline cycles. Eligible individuals were then randomised to fluoxetine 20 to 60 mg/day or placebo for three treatment cycles, followed by a one cycle washout, followed by three cycles of the other treatment. The mean dose of fluoxetine was $30 \pm 11$ mg/day. Fluoxetine significantly improved most PMDD symptoms (depression, anxiety, irritability, mood lability, work inefficiency, social isolation, impulsiveness, food cravings, breast pain and bloating) compared with placebo ($p < 0.01$) and compared with baseline ($p < 0.01$) based on daily symptom ratings. Fluoxetine was also superior to placebo and to baseline based on composite VAS mood ratings ($p < 0.01$) and VAS social impairment ratings ($p < 0.01$).

Two large multisite trial of luteal phase dose administration with fluoxetine have been recently reported (see table II). One study compared luteal phase fluoxetine 10 mg/day and 20 mg/day to placebo.[51] After a single-blind placebo cycle, 260 women with PMDD assessed by the DRSP were randomly assigned to receive fluoxetine 10 mg/day, fluoxetine 20 mg/day or placebo from ovulation to menses for three cycles, followed by one cycle of single blind placebo. Fluoxetine 20 mg/day was superior to placebo in reducing the mean luteal DRSP total, and the mood, physical symptoms and social functioning subscale (each $p < 0.05$) scores compared with baseline. Fluoxetine 10 mg/day was superior to placebo in reducing the mean luteal DRSP mood and social functioning subscale (each $p < 0.05$) scores compared with baseline. The lower dose of luteal phase fluoxetine did not significantly improve premenstrual physical symptoms. The increase in mean premenstrual DRSP ratings during the single-blind, placebo cycle that followed fluoxetine treatment resulted in a loss of the significant difference between fluoxetine and placebo. A comparison of the change from the follicular phase baseline to endpoint of Arizona Sexual Experience Scale scores[56] did not suggest a significant difference between either dose of fluoxetine and placebo on sexual function. However, in terms of spontaneously reported adverse effects, decreased libido was significantly more common with fluoxetine, and accidental injury was significantly more common with placebo.

The other recent large luteal phase fluoxetine study examined the efficacy of the fluoxetine 90mg weekly dose.[52] The diagnosis of PMDD was determined with DRSP ratings, and 247 women who continued to meet criteria for PMDD after one cycle of single-blind placebo were randomised to three cycles of fluoxetine 90mg administered 14 and 7 days before menses to placebo 14 days before and fluoxetine 90mg 7 days before menses or to placebo 14 and 7 days before menses. Fluoxetine 90mg administered 14 and 7 days before menses was significantly superior to placebo on the mean luteal DRSP total, mood symptoms and functioning scores, the PMTS score, the CGI-S score, and the work, family life and social life scores of the Sheehan Disability Scale[57] (each $p < 0.05$). Fluoxetine 90mg administered 7 days before menses was not significantly superior to placebo on any of these measures. Neither dose administration regimen of weekly fluoxetine was superior to placebo on improving premenstrual physical symptoms. Adverse effects spontaneously reported by 10% or more of women taking either dosage regimen of fluoxetine included nausea, headache and insomnia.

Several nonblind trials with fluoxetine have also suggested efficacy. Three earlier nonblind studies with prospectively-confirmed PMS samples, each with ten individuals, had suggested that fluoxetine 20 mg/day was helpful for alleviating premenstrual symptoms.[58-60] A controlled study with fluoxetine 10 mg/day reported efficacy, but the method of diagnosis of PMS was not specified

and daily ratings were not obtained.[61] One study compared continuous fluoxetine 20 mg/day to luteal phase dose administration 20 mg/day in 48 women with PMDD.[62] The PRISM calendar was used as both an assessment and treatment outcome measure. Women were assigned to either fluoxetine treatments depending on previous psychiatric diagnoses. Seventy-five percent of the women receiving luteal phase dose administration and 67% of the women receiving continuous dose administration were rated as responders. The results of this study suggested that continuous and luteal phase dose administration were equally effective.

The long-term efficacy of fluoxetine in PMDD needs systematic study but the maintenance of efficacy has been suggested by two nonblind trials. One study monitored 60 women with LLPDD over a mean of 18.6 months and all maintained their response as determined by CGI.[63] In this study, 20 of 21 participants who discontinued fluoxetine after at least 1 year of treatment had a recurrence of premenstrual symptoms within three cycles, particularly irritability and anxiety. Another study conducted a 1-year follow-up of women who had remained on fluoxetine 20 mg/day after 6 months of treatment and women who discontinued fluoxetine after 6 months.[64] On the basis on CGI ratings, women who had continued on fluoxetine had maintained greater symptom relief than those who had discontinued it.

### 3.2 Sertraline

The second largest published continuous dose administration SSRI trial involved the administration of sertraline or placebo to 234 women with PMDD[41] (see table I). The diagnosis of PMDD and primary treatment outcome was determined by the DRSP. Nonresponders to one cycle of single-blind placebo were randomised to flexible dose sertraline (50 to 150 mg/day) or placebo in a parallel design. The trial was completed by 200 women and the average dose of sertraline achieved in the third treatment cycle was 106 ± 35 mg/day. At endpoint, total premenstrual DRSP scores had decreased by 32% in the sertraline group versus 11% in the placebo group ($p < 0.001$). The total DRSP score and the depressive, anger/irritability and physical symptoms factor scores had each significantly improved with sertraline compared with placebo ($p < 0.001$) at endpoint. Observer-rated CGI ratings indicated that 62% of sertraline-treated individuals were much or very much improved compared with 34% of the placebo group ($p < 0.001$), and HAM-D ratings at endpoint also demonstrated significant efficacy for sertraline compared with placebo ($p < 0.002$). Adverse effects that were significantly more common with sertraline than placebo were nausea, diarrhoea and decreased libido. Women with PMDD had pretreatment functional impairment and decreased quality of life similar to populations with dysthymia and major depression, and sertraline improved premenstrual functioning and quality of life significantly more than placebo.[41,65]

In another large continuous dose administration study (see table I), sertraline was compared to desipramine and placebo in 167 women.[42] Diagnosis was determined by the DSR, 74% of the sample met criteria for PMDD, the rest of the sample having prospectively-confirmed PMS. After screening, participants were randomly assigned to flexible dose sertraline (50 to 150 mg/day), flexible dose desipramine (50 to 150 mg/day) or placebo in a parallel design for three treatment cycles. The average dose of sertraline in the third treatment cycle was 105 ± 37 mg/day and the average dose of desipramine was 115 ± 40 mg/day. A 50% or greater improvement in total premenstrual DSR score at endpoint compared with baseline was achieved by 65% of the sertraline group, 36% of the desipramine group and 29% of the placebo group ($p < 0.001$). At endpoint, sertraline was significantly more effective than desipramine or placebo by total DSR ($p < 0.001$), and mood ($p < 0.001$) and pain ($p < 0.05$) factor scores, and desipramine was not significantly better than placebo on total DSR or factor scores. Superiority of sertraline over both desipramine and placebo was noted on endpoint versus baseline premenstrual HAM-D ($p < 0.001$) and CGI-Severity ($p = 0.02$).

Nausea occurred significantly more with sertraline than placebo, and adverse effects that occurred significantly more with desipramine group than placebo included dry mouth, dizziness and constipation.

This is the largest study[42] in the literature comparing a SSRI to a nonserotonergic antidepressant and demonstrating the selective superiority of a SSRI in PMDD. A further analysis of the women in the sertraline group from this study identified that pretreatment follicular phase fatigue, anxiety, irritability and mood swings predicted higher total premenstrual DSR score at endpoint (less response).[66] The explanation for why certain follicular phase or trait baseline characteristics might influence sertraline efficacy is unclear. An earlier preliminary nonblind study by the same research group comparing sertraline and desipramine in 32 women with prospectively-confirmed PMS by DSR ratings had reported that sertraline decreased total premenstrual DSR scores more than desipramine, but the difference was not statistically significant.[67]

The largest number of luteal phase dose administration studies have been conducted with sertraline (see table II), and the results of these studies in addition to the results of the previous two daily dose administration studies led to the US FDA approval of both continuous and intermittent dose administration of sertraline for PMDD. A large multicentre study compared luteal phase sertraline 50 to 100 mg/day to placebo.[50] 281 women with PMDD assessed by the DRSP were randomly assigned after a single-blind placebo cycle to three cycles of sertraline 50 to 100 mg/day or placebo from ovulation to menses only. The mean luteal phase sertraline dose at endpoint was 74 ± 22 mg/day. Luteal phase sertraline was significantly superior to placebo at endpoint based on mean total DRSP scores ($p < 0.001$), CGI-I ratings ($p < 0.001$), and several functioning and quality of life measures. Luteal phase sertraline was not superior to placebo in improving premenstrual physical symptoms. Spontaneously reported adverse effects that were significantly more common with sertraline than placebo included nausea and dry mouth.

Two placebo-controlled, crossover studies of luteal phase sertraline used the COPE to determine the diagnosis of PMDD and as a treatment outcome measure. In one study 50 women with PMDD were randomised to luteal phase sertraline 50 mg/day or placebo for two cycles, switching to the other treatment for the final two cycles.[47] Participants who did not respond in the first cycle were raised to sertraline 100 mg/day (or two tablets of placebo) in the second cycle. The primary treatment outcome measure was the mean change from baseline to endpoint in luteal COPE total score. A significant treatment effect was reported for sertraline compared with placebo at the second cycle for the COPE total ($p = 0.01$), behavioural factor ($p < 0.01$) and physical factor ($p = 0.03$) scores. The 100 mg/day dosage of luteal phase sertraline was more beneficial than 50 mg/day in 25% of women. The only adverse effect spontaneously reported with sertraline in 10% or more of participants was insomnia. In the other crossover study, 11 women with PMDD completed two cycles of luteal phase sertraline 50 mg/day or placebo, followed by a single cycle washout, followed by crossover to the other treatment for the final two cycles.[48] Sertraline was significantly superior to placebo in reducing luteal phase COPE behavioural ($p = 0.005$) and physical ($p = 0.014$) scores compared to baseline luteal phase scores.

Eleven women with PMDD who responded to single-blind sertraline 100 mg/day for 1 month were randomised to luteal phase sertraline 100 mg/day or placebo, each for two cycles, in a double-blind crossover study.[49] The diagnosis of PMDD was obtained from the DRF, and the DRF, HAM-D and CGI were treatment outcome measures. Luteal phase sertraline was significantly superior to placebo in reducing premenstrual symptoms as measured by daily depression ratings ($p < 0.0001$), daily impairment ratings ($p < 0.0004$), HAM-D ($p < 0.0001$) and CGI ($p < 0.0001$). Individuals who had responded to full-cycle sertraline continued to respond to luteal phase sertraline.

Another study randomised 31 women with PMS to full-cycle sertraline or luteal phase sertraline for three treatment cycles in a double-blind, parallel design.[46] The diagnosis of PMS was determined by the DSR and 20 of the 31 participants had PMDD. Sixteen of the women were already 'improved' (luteal mean DSR <50) after participation in a previous study. Sertraline was titrated up to 150 mg/day by the third treatment cycle, depending on clinical response, and was tapered over menses in the luteal phase group. The average dosage in the third treatment cycle was 100 ± 41 mg/day in the full cycle group and 80 ± 37 mg/day in the luteal phase group. When response was defined as a total luteal DSR score <80, 89% of participants improved with luteal phase dose administration compared with 46% on full-cycle dose administration ($p < 0.02$). The DSR mood factor (mood swings, nervous tension, feeling out of control and confusion) was significantly lower (more improved) with luteal phase dose administration than full-cycle dose administration ($p < 0.05$). There were no significant differences in adverse effects reported between the full-cycle and luteal phase dose administration regimens.

One of the potential advantages of luteal phase dose administration is fewer adverse effects. However, a recent study reported that continuous dose administration of sertraline was better tolerated than luteal phase dose administration in women with PMS, but the method of diagnosis of PMDD was unclear.[68]

### 3.3 Paroxetine

The one published controlled trial with paroxetine assigned 65 women with prospectively-confirmed PMS (based on VAS scores of irritability and dysphoria) to three cycles of flexible-dose paroxetine (10 to 30 mg/day), flexible-dose maprotiline (50 to 150 mg/day), or placebo (see table I).[43] Participants rated irritability, depressed mood, tension/anxiety, increased appetite/carbohydrate craving, bloating and breast tenderness daily on VAS through the treatment cycles. At the end of the third treatment cycle, paroxetine, but not maprotiline, was significantly superior to placebo in terms of percentage reduction versus baseline for luteal irritability ($p < 0.001$) and each of the other five symptoms ($p < 0.01$) assessed daily by VAS. Maprotiline did significantly reduce premenstrual depression ($p = 0.05$) and anxiety ($p = 0.01$) compared with placebo in terms of absolute luteal VAS score at the end of the third treatment cycle, but maprotiline did not significantly decrease premenstrual irritability, increased appetite, bloating or breast tenderness. Self-rated global improvement demonstrated significant superiority of paroxetine over maprotiline ($p = 0.03$) and placebo ($p = 0.0004$). Frequent adverse effects with paroxetine were nausea, dry mouth, sedation, yawning and sexual dysfunction, and with maprotiline were dry mouth, constipation and sedation. This study was the first to identify the differential efficacy of an SSRI versus a nonserotonergic antidepressant for PMS.

These researchers offered participants in the above trial the opportunity to openly receive flexible dose paroxetine.[69] Women continued to rate the same six VAS symptoms throughout ten open treatment cycles and two cycles following discontinuation of the paroxetine. Eighteen women completed the trial achieving an average dose of 17 ± 1 mg/day during the luteal phase. Women had chosen to take paroxetine continuously, during the luteal weeks only, or 'semi-intermittently', with a lower dose in the follicular phase and a higher dose in the luteal phase. After ten cycles of unblinded treatment with paroxetine, it had significantly reduced luteal VAS scores of irritability ($p = 0.0002$), depressed mood ($p = 0.0003$), anxiety/tension ($p = 0.01$), increased appetite/carbohydrate craving ($p = 0.0005$), and bloating ($p = 0.002$) compared with pretreatment luteal VAS scores. Of note, the VAS ratings in the two post-treatment cycles demonstrated a significant increase in premenstrual irritability ($p = 0.04$) and depressed mood ($p = 0.01$) compared with the scores from the tenth treatment cycle.

A previous nonblind study with paroxetine had also reported efficacy.[70] Fourteen women diag-

nosed with PMDD based on DRSP ratings were assessed by continued DRSP ratings, and luteal HAM-D and CGI scores. Nonresponders to one cycle of single-blind placebo cycle received nonblind flexible-dose paroxetine for three cycles. The average dose was 22 ± 10 mg/day by the end of treatment. Significant improvement was noted at the end of the third treatment cycle compared with the placebo baseline cycle on the DRSP scores for irritability/anger, behavioural dyscontrol, trouble sleeping (each $p < 0.05$), for anxiety, bloating, headache (each $p < 0.01$) and breast tenderness ($p < 0.0001$). End of treatment HAM-D and CGI scores also showed significant improvement versus the baseline placebo cycle.

Results from a study of the controlled release form of paroxetine recently presented at a national meeting suggested that both continuous and intermittent dose administration were superior to placebo in 186 women with PMDD on the basis of VAS irritability and mood items, CGI and the Sheehan Disability Scale.[71,72]

### 3.4 Citalopram

The one published randomised, controlled trial with citalopram assigned 69 women with prospectively-confirmed PMS (based on VAS scores of irritability and dysphoria) to one of four groups in a parallel design: citalopram 10 to 30 mg/day ('continuous'), citalopram 5 mg/day for the follicular weeks and 10 to 30 mg/day for the luteal weeks ('semi-intermittent'), placebo for the follicular weeks and citalopram 10 to 30 mg/day for the luteal weeks ('intermittent'), or placebo (see table I and table II).[45] According to self-rated global improvement, both continuous ($p = 0.02$) and intermittent ($p = 0.0001$) citalopram treatments were significantly superior to placebo. On the basis of premenstrual VAS irritability ratings during the third treatment cycle, intermittent citalopram was superior to placebo ($p = 0.0004$), continuous citalopram ($p = 0.002$) and the 'semi-intermittent' citalopram regimen ($p = 0.005$). These authors postulated that the superiority of the intermittent dosage regimen in this study compared with continuous dose administration might be a result of tolerance to the SSRI not developing.[30,45] A preliminary report suggested that nonblind citalopram 20 to 40 mg/day, administered daily or during the luteal phase, improved premenstrual symptoms in women unresponsive to other SSRIs.[73]

### 3.5 Fluvoxamine

The one published randomised, controlled study with fluvoxamine is the only study with a SSRI that has not reported superiority of the SSRI versus placebo (see table I).[44] In this study 20 women with premenstrual symptoms were randomised to receive fluvoxamine 150 mg/day or placebo for two menstrual cycles in a parallel design. Participants rated their symptoms four times a month during the two baseline screening cycles and the two treatment cycles. Both fluvoxamine and placebo reduced premenstrual emotional and physical symptoms with no significant differences demonstrated between the treatments. The lack of prospective daily ratings, and the lack of specified subject selection criteria (such as the exclusion of concurrent psychiatric disorders), makes the results of this study difficult to draw useful conclusions from.

A nonblind trial of fluvoxamine 100 mg/day in ten women with PMDD reported significant improvement of most premenstrual symptoms versus baseline as measured by the DSR after two cycles.[74] Sixty percent of the ten women had at least a 50% decrease in total luteal DSR scores, and the symptoms that improved the most were irritability ($p = 0.001$), anxiety ($p = 0.002$), feeling out of control ($p = 0.002$) and decreased interest in usual activities ($p = 0.0008$). Significant improvement was also noted on the HAM-D and CGI compared with pretreatment baseline scores. Problematic adverse effects included insomnia, fatigue, dry mouth, nausea and decreased libido.

## 4. Other Serotonergic Treatments

As reviewed in section 3, three studies have demonstrated that SSRIs were differentially effective, demonstrating superiority to both non-

serotonergic antidepressants and placebo in treating PMDD.[36,42,43] Antidepressants that are not considered SSRIs, but which are largely serotonergic in action, have also been used as treatments for PMS and PMDD (see table III). In addition to inhibiting the serotonin transporter, both venlafaxine and clomipramine and their major metabolites also inhibit norepinephrine uptake. Nefazodone and its major metabolite influence serotonin synapses through antagonist activity on postsynaptic serotonin 5-$HT_{2A}$ receptors as well as by inhibiting the serotonin transporter.

Venlafaxine was recently reported to be superior to placebo in reducing mood and physical symptoms in 143 women with PMDD diagnosed with the DSR, which also served as a primary treatment outcome measure.[75] Single-blind placebo was administered during the second screening cycle and nonresponders to placebo were randomised to flexible-dose venlafaxine (50 to 200 mg/day) or placebo for four treatment cycles in a parallel design followed by a 2-week taper. The average dose of immediate release venlafaxine at endpoint was 130 ± 52 mg/day. At endpoint, luteal total DSR scores improved 50% or more versus baseline in 60% of the venlafaxine group compared with 35% of the placebo group ($p = 0.003$). The four primary DSR factors each improved significantly with venlafaxine compared with placebo: emotion ($p < 0.001$), function ($p = 0.01$), pain ($p = 0.02$) and physical symptoms ($p = 0.003$). Significant improvement was also noted at endpoint with venlafaxine compared with placebo on total HAM-D ($p = 0.002$) and CGI ($p < 0.001$). Nausea, insomnia, dizziness and decreased libido were significantly more associated with venlafaxine than placebo.

Clomipramine was initially reported to be effective for PMS in a nonblind trial,[80] and has subsequently been reported to be more effective than placebo with both daily[79] and luteal phase[78] dose administration. In the first study, clomipramine 25 to 75 mg/day was administered to 40 women with prospectively-confirmed PMS based on daily VAS ratings of irritability and dysphoria.[79] Participants were treated for three cycles in a parallel design. Compared with pretreatment VAS scores, both premenstrual irritability and dysphoria improved significantly by more than 80% with clomipramine versus approximately 40% with placebo ($p < 0.001$). Both premenstrual irritability and dyspho-

**Table III.** Controlled trials of other serotonergic agents in patients with premenstrual syndrome and premenstrual dysphoric disorder

| Study | Study design (no. of pts) | Measures | Key findings |
|---|---|---|---|
| Freeman et al., 2001[75] | DBPC, parallel; 1 cycle SB placebo; 4 cycles venlafaxine 50-200 mg/d (68) or placebo (75) | DSR, CGI, HAM-D | ≥50% decrease in total luteal DSR in 60% venlafaxine *vs* 35% placebo ($p < 0.003$). Venlafaxine superior to placebo on DSR factors emotion ($p < 0.001$), function ($p = 0.011$), pain ($p = 0.016$) and physical symptoms ($p = 0.003$). Venlafaxine superior to placebo on HAM-D ($p = 0.002$) and CGI ($p < 0.001$) |
| Landen et al., 2001[76] | DBPC, parallel; 2 cycles of nefazodone 100-300 mg/d (22), buspirone 10-30 mg/d (19) or placebo (22) luteal phase only, followed by 2 cycles of continuous dose administration | VAS, CGI | Buspirone ($p < 0.001$) superior to placebo, nefazodone not superior to placebo on self-rated global improvement. Continuous buspirone improved irritability only ($p = 0.03$). Intermittent nefazodone improved affective lability only ($p = 0.05$) |
| Steinberg et al., 1999[77] | DBPC, parallel; 3 cycles of tryptophan 6 g/d or placebo, luteal phase only | VAS | Tryptophan superior to placebo in decreasing VAS mood score ($p = 0.004$) |
| Sundblad et al., 1993[78] | DBPC, parallel; 3 cycles of clomipramine 25-75 mg/d (15) or placebo (14) luteal phase only | VAS | Luteal phase clomipramine superior to placebo in reducing luteal VAS irritability ($p = 0.02$), dysphoria ($p = 0.01$) and tension ($p = 0.04$) scores |
| Sundblad et al., 1992[79] | DBPC, parallel; 3 cycles of clomipramine 25-75 mg/d (20) or placebo (20) | VAS | Clomipramine superior to placebo in reducing luteal VAS irritability, dysphoria ($p < 0.001$). Clomipramine reduced luteal VAS scores compared with baseline 80% *vs* placebo 40% ($p < 0.001$) |

**CGI** = Clinical Global Impressions Scale; **DBPC** = double-blind, placebo-controlled; **DSR** = Daily Symptom Report; **HAM-D** = Hamilton Rating Scale for Depression;. **SB** = single-blind; **VAS** = Visual Analogue Scale.

ria VAS scores were significantly lower in the clomipramine group compared with the placebo group at the end of the third treatment cycle ($p < 0.001$).

These same researchers subsequently treated 29 women with prospectively-confirmed PMS with flexible dose clomipramine (25 to 75 mg/day) or placebo for three treatment cycles in a parallel design, the clomipramine being administered from ovulation to a taper over the first 3 days of menses.[78] Clomipramine was superior to placebo in reducing premenstrual irritability and dysphoria VAS scores compared with baseline, 70% versus 45%, respectively. Mean premenstrual VAS scores from the three treatment cycles were significantly lower in the clomipramine group compared with the placebo group for irritability ($p = 0.02$), dysphoria ($p = 0.01$) and tension ($p = 0.04$). VAS ratings obtained from the post-treatment cycle demonstrated significant return of premenstrual irritability, depressed mood and tension immediately following cessation of medication in the clomipramine and placebo groups. In both of these studies, several adverse effects were more common with clomipramine than placebo, such as nausea, vertigo, fatigue, dry mouth, constipation and sweating.

Nefazodone was recently reported to not be superior to placebo or buspirone in 63 women with prospectively-confirmed PMS assessed by VAS ratings of seven symptoms.[76] Participants were randomised to two cycles of luteal phase dose administration followed by two cycles of continuous dose administration of nefazodone (mean luteal phase dose 228 ± 54 mg/day, mean continuous dose 304 ± 95 mg/day), buspirone (mean luteal phase dose 21 ± 6 mg/day, mean continuous dose 27 ± 10 mg/day) or placebo. Self-rated CGI ratings indicated that buspirone was superior to placebo ($p = 0.001$) but nefazodone was not superior to placebo. VAS ratings indicated that continuous buspirone was superior to placebo on irritability only ($p = 0.03$) and luteal phase nefazodone was superior to placebo on affective lability only ($p = 0.05$).

The results of this study contradict the results of nonblind trials with nefazodone. One study of 23 women with PMDD treated openly with flexible dose nefazodone (average dose 319 mg/day, range 100 to 600 mg/day) for two menstrual cycles reported significant improvement on several DSR symptoms compared with baseline.[81] A 50% or greater decrease in premenstrual DSR score compared with baseline was achieved in 41% of the 23 women. The DSR symptoms that improved significantly included nervous tension, anxiety, confusion, swelling, insomnia, poor coordination, food craving and cramps. The most frequent adverse effects were nausea, headache, fatigue, flushing, dry mouth, insomnia and gastrointestinal symptoms. Recently, three women were reported to have improvement of emotional and somatic premenstrual symptoms with nefazodone 50mg twice daily during the luteal weeks only.[82] This case series did not define how the diagnosis of PMDD or treatment response was determined. A small crossover study in three women with premenstrual exacerbation of MDD reported that increasing nefazodone during the luteal phase by 50mg twice daily was superior to placebo in reducing premenstrual symptoms.[83]

A few studies exist of other treatments that enhance serotonergic action. Tryptophan, a serotonin precursor, was reported to decrease PMDD symptoms in 69 women.[77] Women with PMDD (by VAS ratings) were randomised to tryptophan 6 g/day or placebo for three cycles from ovulation to menses only. Tryptophan was superior to placebo in reducing the mean luteal VAS-mood score compared with baseline ($p = 0.004$). Another study reported that dexfenfluramine (which releases serotonin presynaptically as well as inhibiting serotonin reuptake) was reported to improve premenstrual dysphoria, increased appetite and carbohydrate cravings, but the diagnosis of PMS was not confirmed by prospective daily ratings.[84] Mood improved 2 hours after challenge with the serotonin agonist m-CPP during the luteal phase in women with PMDD compared with controls ($p < 0.05$).[40] As mentioned earlier in this section,

some premenstrual symptoms have improved with buspirone, a partial 5-$HT_{1A}$ receptor agonist.[76,85] Ingestion of carbohydrates has been reported to improve premenstrual dysphoria in women with[86] and without[87] prospectively-confirmed PMS. Carbohydrates may increase the availability of tryptophan in the brain, leading to enhanced serotonin synthesis.[86] As reviewed, some of these serotonergic agents are not effective for major depression, suggesting an unknown, yet unique and rapid, serotonergic action for premenstrual irritability and dysphoria.[30]

## 5. Conclusion

There is a need for prospective long-term treatment studies to provide guidelines for the recommended length of treatment and for the prediction of relapse rates following antidepressant discontinuation. Many women with severe PMS and PMDD take SSRIs indefinitely, and there is a paucity of literature studying this issue. With the exception of one fluoxetine study, all controlled antidepressant trials have been of less than 6 months in duration. A naturalistic study with paroxetine for 10 months and two longer-term nonblind studies with fluoxetine suggest long-term SSRI efficacy, but these are uncontrolled studies. A few studies have reported the return of premenstrual symptoms following SSRI discontinuation, but the acute treatment before discontinuation has been shorter in these studies than the usual length of treatment in the community for PMS or PMDD. Another area deserving research inquiry is to examine if SSRI dose administration regimens should change at perimenopause, or with hormone replacement strategies administered during perimenopause, in women with PMDD.

Luteal phase dose administration with dosages up to fluoxetine 20 mg/day, sertraline 100 mg/day and citalopram 30 mg/day have not led to reports of discontinuation symptoms following the abrupt cessation of the SSRI at menses. Thus, there does not seem to be differential advantages of short half-life and long half-life SSRIs in luteal phase regimens. Luteal phase dose administration is preferred by many women who do not want to take medication during the asymptomatic follicular phase, and luteal phase dose administration has the potential advantages of financial savings, decreased adverse effects and decreased fetal exposure if pregnancy occurs.

However, a systematic comparison of adverse effects with continuous and luteal phase SSRI dosage regimens has not been conducted, nor has a systematic comparison of adverse effects from different SSRIs been conducted. A study of 101 women using SSRIs for PMS and PMDD from several months to greater than 2 years identified the following adverse effects by written questionnaire: reduced libido (45%), delayed orgasm (28%), nausea (22%), sweating (19%), weight gain (20%), headache (16%), vertigo (14%) and insomnia (12%).[88] Sexual dysfunction was the major reason for noncompliance with SSRIs. In this study, there was no significant difference between continuous and intermittent dose administration in terms of adherence to SSRI treatment. There is a need for prospective systematic assessment of long-term adverse effects, including sexual dysfunction and weight gain, in women receiving SSRIs for PMDD.

In conclusion, SSRIs, other antidepressants with substantial serotonergic activity and other treatments that enhance serotonergic transmission, have a role in the treatment of PMS and PMDD. The evidence is substantial for the efficacy of both continuous and luteal phase dose administration of SSRIs for PMDD, and the current studies indicate that both dosage strategies have similar efficacy rates (60 to 70%). Other treatments, such as anxiolytics, calcium, gonadotropin releasing hormone agonists and other hormonal treatments have lower efficacy rates and/or problematic long-term adverse effects.[89] An early case report suggested relief of premenstrual symptoms in a woman with a single dose of fluoxetine 20mg taken 7 days before the expected day of menses,[90] but fluoxetine 90mg administered 7 days prior to menses was reported to not be superior to placebo for PMDD.[52] One SSRI dose is unlikely to be beneficial for

women with severe PMS or PMDD, but the administration of SSRIs only on symptomatic days ('symptom-onset' dose administration) needs further systematic study, particularly if future studies demonstrate fewer adverse effects with intermittent dose administration regimens compared with continuous dose administration.

*In summary*, given the current clear and impressive efficacy literature for SSRIs, and their recommendation as the first line treatment by both psychiatric and medical experts, SSRIs can legitimately be considered the 'gold standard' treatment for PMDD.

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