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LEADING ARTICLE

Luteal Phase and Symptom-Onset Dosing of SSRIs/SNRIs in the Treatment of Premenstrual Dysphoria: Clinical Evidence and Rationale

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Abstract Premenstrual dysphoria (PMD) affects 3–8 % of women in their reproductive years worldwide. This paper summarizes the studies establishing the efficacy of continuous, luteal phase, and symptom-onset dosing of selective serotonin reuptake inhibitors (SSRIs) and dual serotonin and norepinephrine reuptake inhibitors (SNRIs) in treating women with PMD. The evidence indicates that for some women, symptom-onset dosing with escitalopram, fluoxetine, and paroxetine controlled release (CR) is as effective as continuous or luteal phase dosing. The wide range of clinical efficacy of SSRIs/SNRIs suggests that they exert their therapeutic effect through multiple pathways. This paper offers a few alternative mechanisms of action to explain the rapid response to SSRIs/SNRIs in women with PMD.

1 Introduction

Premenstrual dysphoria (PMD) affects 3–8 % of women in their reproductive years worldwide [1–4]. Diagnostic criteria for PMD, as proposed for the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), include the occurrence of at least 5 symptoms in most menstrual cycles during the past year, such as affective lability, irritability, depressed mood, anxiety, loss of interest, lethargy, changes in appetite or sleep, loss of control, or bloating. These symptoms need to begin the week before and improve a few days after menses onset [5]. One of the largest and longest longitudinal prospective studies has demonstrated what was shown previously in smaller studies: selective serotonin reuptake inhibitors (SSRIs) are effective in treating PMD [6, 7]. Women with severe PMD were recruited into this Canadian multi-site trial, which consisted of a single-blind, placebo washout period lasting two menstrual cycles followed by a randomized, double-blind, placebo-controlled trial of fluoxetine at a dose of either 20 or 60 mg per day or placebo for 6 menstrual cycles. Continuous dosing of fluoxetine was significantly superior to placebo, and fluoxetine at a dose of 20 mg per day was well tolerated with maximum therapeutic efficacy [6].

A Cochrane review [8] and a subsequent update [9] have further established that all SSRIs (fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram) were highly effective in reducing premenstrual symptoms, and both continuous and luteal phase dosing were effective. Secondary analysis showed that they were also effective in treating physical, functional, and behavioural symptoms.

Continuous dosing with dual serotonin and norepinephrine reuptake inhibitors (SNRIs) has also been shown to be effective. A double-blind, placebo-controlled study with venlafaxine [10] and two preliminary studies with duloxetine [11, 12] have shown similar results to SSRIs in significantly reducing premenstrual symptoms.

More recently, a number of studies have shown that continuous dosing of the oral contraceptive levonorgestrel 90 mcg/ethinyl estradiol 20 mcg [13] as well as oral contraceptives containing drospirenone 3 mcg/ethinyl estradiol 20 mcg [14] was effective in reducing symptoms of PMD in women who are appropriate candidates for oral contraceptives as a contraceptive, the approved indication for these medications.

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2 Luteal Phase Dosing

One of the big surprises from the multitude of continuous SSRI dosing studies in PMD was that, whereas there is usually at least a 3–6 week delay between initiation of treatment and clinical response in depressed patients, the response in PMD patients was much quicker. In some studies, a rapid response was observed within 2–3 days [15, 16].

This initiated a series of studies trying to establish whether intermittent dosing (during the luteal phase only) might be effective in treating PMD, which in itself is an 'intermittent' disorder.

The first study to try this approach predates the SSRIs and used clomipramine, a tricyclic antidepressant, which is a potent, albeit non-selective, serotonin reuptake inhibitor. In a double-blind, placebo-controlled trial, women with severe PMD were treated with either clomipramine 50 ± 25 mg per day or placebo during the luteal phase only (from the day of ovulation until the onset of menstruation) for three consecutive menstrual cycles. Overall improvement in irritability and dysphoria during the three treatment cycles was greater than 70 % in the clomipramine group compared with 45 % in the placebo group [17].

Subsequent open label as well as randomized, placebo-controlled trials (Tables 1, 2) confirmed the effectiveness of luteal phase dosing of the SSRIs citalopram [18], escitalopram [19, 20], fluoxetine [21–23], paroxetine [24, 25], and sertraline [26–28], as well as the SNRI venlafaxine [29]. Furthermore, studies comparing continuous versus luteal phase dosing concluded that the efficacy of luteal phase only dosing does not differ from continuous dosing in treating severe PMD [30–33].

3 Symptom-Onset Dosing

In most of the above-mentioned studies, intermittent or luteal phase dosing means that the patients used the medication starting at about the time of ovulation (14–16 days prior to onset of menses) till the first or second day of menstruation. Once this regimen had been established as efficacious, the obvious next step was to determine whether symptom-onset dosing might also be effective. To date, several studies have established that for some women, symptom-onset dosing with escitalopram [19], fluoxetine [16], and paroxetine controlled release (CR) [15, 34] was as effective as continuous or luteal phase dosing.

In the first preliminary study, which compared the efficacy and tolerability of escitalopram, 27 women meeting DSM-IV criteria for PMD were randomly assigned in a double-blind manner to luteal phase or symptom-onset dosing for three consecutive menstrual cycles. Clinical improvement was reported by 11 of 13 patients in the luteal phase group and 9 of 14 in the symptom-onset group [19].

In the next study, 20 women with PMD were randomly assigned to either paroxetine CR 25 mg/day or placebo for one cycle and crossed over to the other condition for a second cycle. Subjects initiated treatment when premenstrual symptoms began and stopped within 3 days of onset of menses. Results suggested that symptom-onset treatment may be appropriate for many women with PMD, but due to the small sample size, there was limited power to establish statistical significance. Of note was the lack of noticeable withdrawal effects, probably due to the fact that paroxetine was administered during a very short period [34].

To further explore this issue, 22 women with severe premenstrual irritability, who previously responded to paroxetine, were asked to start medication in the midst of the luteal phase when irritability had been intense for 2 days. Compared with placebo, women in the paroxetine group experienced sustained reduction in irritability as early as 14 h after medication intake and the difference was significant at day 3 [15].

More recently, an in-depth study of 12 women with PMD who received 20 mg/day of fluoxetine has demonstrated the rapid response of all core PMD symptoms, not just irritability. The time course of symptom response started on the first day of treatment, with peak responsivity at 48 h and was maintained thereafter until the onset of menses [16].

Table 1 Open label trials of luteal phase and symptom-onset dosing of antidepressants in premenstrual dysphoria

Antidepressants	Daily dose (mg)	Duration (cycles)	N by treatment groups				Conclusions	References
			C	L	SO	CTRL		
Escitalopram	10–20	3		13	14		L and SO > BL	Freeman et al. [19]
Fluoxetine	20	3	24	24			L > C > BL	Steiner et al. [21]
	20	1			11	12	SO >> BL	Steinberg [16]
Venlafaxine	75–112.5	2		11			L > BL	Cohen et al. [29]

BL baseline, *C* continuous dosing, *CTRL* control, *L* luteal phase dosing, *SO* symptom-onset dosing, >> statistically significant improvement, > quality of evidence limited but positive outcome

Table 2 Randomized, placebo-controlled trials of luteal phase and symptom-onset dosing of antidepressants in premenstrual dysphoria

Antidepressants	Daily dose (mg)	Duration (cycles)	N by treatment groups				Conclusions	References
			C	L	SO	P		
Citalopram	20 ± 10	3	17	18		17	L >> C >> P	Wikander [18]
Clomipramine	25–75	3		15		14	L >> P	Sundblad et al. [17]
Escitalopram	10–20	3		101		50	L >> P	Eriksson et al. [20]
Fluoxetine	90 (weekly)	3		167		85	L >> P	Miner et al. [22]
	10 or 20	3		141		75	L >> P	Cohen et al. [23]
Paroxetine	10–20	3	51	50		51	C and L >> P	Landen et al. [33]
	10 or 20	4		48		22	L (20 mg) > P	Steiner et al. [25]
	20	2			21[a]	21[a]	SO >> P	Landen et al. [15]
Paroxetine CR	12.5 or 25	3		191		101	L >> P	Steiner et al. [24]
	25	1			20[a]	20[a]	SO > P	Yonkers et al. [34]
Sertraline	50	2		11[a]		11[a]	L > P	Young et al. [26]
	50–100	2		57[a]		57[a]	L > P	Jermain et al. [27]
	50–100	3		115		106	L >> P	Halbreich et al. [28]
	50–100	3	40	35		43	C and L >> P	Freeman et al. [30]
	25 or 50	1–2	143	157	110	79	L >> P; C (25 mg) and SO (25 mg) >> P	Kornstein et al. [32]

C continuous dosing, *CR* controlled release, *L* luteal phase dosing, *P* placebo control, *SO* symptom-onset dosing, >> statistically significant improvement, > quality of evidence limited but positive outcome

[a] Total N, cross-over design

Since many women complain of PMD symptoms for only 3–5 days premenstrually, and patients on a luteal phase dosing regimen may forget to start their medications until they become symptomatic, symptom-onset dosing may be a more practical treatment regimen. Furthermore, a shorter treatment interval reduces medication exposure, potential side effects, and cost.

4 Mechanism of Action

As is true in many other psychiatric disorders, clinicians first establish the therapeutic efficacy of a medication, and working backwards, clinical scientists try to elucidate the mechanism of action of the medication and deduce the underlying pathophysiology of the condition. PMD is no different, and it is proving to be a highly complex disorder.

The initial rationale for treating premenstrual symptoms with SSRIs was the notion that PMD is a mini-episode of depression, time-limited to the late luteal phase of the menstrual cycle. This notion has by now been refuted [35].

4.1 Premenstrual Dysphoria as a Distinct Disorder

Several lines of evidence suggest that PMD is NOT a mini-episode of depression, further supporting the notion that late-luteal phase or symptom-onset dosing may be warranted. These include:

1. Most women with severe PMD present with a symptom profile different from that observed in women with depressive or anxiety disorders [36].
2. The hallmark of PMD is irritability, usually associated with physical symptoms such as feeling 'bloated', breast tenderness, and weight gain [37].
3. Symptoms are limited to the late luteal phase of the menstrual cycle and remit within 1–2 days after onset of menses [5], also referred to as the 'on–offness' of symptoms [38].
4. Symptoms of PMD (including psychological, physical, functional, and behavioural) respond to serotonin-related compounds but do not respond to non-serotonergic antidepressants [39].
5. Women with PMD respond differently to SSRIs/SNRIs than do women with depression: the former responds within a few days of administration while the latter needs a few weeks; the former has been shown to respond to luteal phase as well as symptom-onset dosing, while the latter requires continuous dosing; and women with PMD will typically experience a recurrence of symptoms with discontinuation of treatment (within two cycles), whereas the patients with a single episode of depression can be slowly weaned off the

medication after a successful course of treatment without experiencing an immediate relapse.

4.2 Serotonin and the Hypothalamic–Pituitary–Gonadal Axis

Although absolute levels of female gonadal hormones do not seem to differ between women with severe PMD and the rest of the female population with regular menstrual cycles, women with severe PMD are more sensitive to the normal gonadal hormonal fluctuations [40]. The behavioural and mood fluctuations that women with severe PMD experience are believed to be a biological central nervous system response to these normal hormonal fluctuations [41–43].

There is reciprocity between the hypothalamic–pituitary–gonadal (HPG) axis and the serotonergic system, and increasing evidence suggests that serotonin (5-HT) is a major contributor to the pathogenesis of PMD [44–47].

The mechanism of action of SSRIs in PMD may be different from the mechanism underlying their therapeutic effect in depressive and anxiety disorders. Their wide range of clinical efficacy indicates that SSRIs exert their therapeutic effect through multiple pathways. The most well established is their ability to increase 5-HT synaptic availability. However, SSRIs may have an effect on allopregnanolone (ALLO) biosynthesis (the progesterone-derived neurosteriod in the brain) that is unrelated to 5-HT reuptake inhibition [48, 49]. ALLO is a positive allosteric modulator of gamma-aminobutyric acid type A ($GABA_A$) receptors with potential benzodiazepine-like therapeutic effects such as alleviating irritability and dysphoria. SSRIs are believed to have an enhancing effect on the rate-limiting enzyme involved in the synthesis of ALLO from its precursor progesterone, thus increasing the availability of ALLO. It is this increase that may account for the therapeutic action of SSRIs in PMD [50–52]. In support of this alternative therapeutic pathway, women with depression have been demonstrated to exhibit increased brain ALLO levels when treated with fluoxetine [49], and women with PMD have been shown to exhibit lower ALLO levels in the late luteal phase than controls [53–56], different sensitivity to neuroactive steroids, and decreased sensitivity to $GABA_A$ receptors [57], as well as increased sensitivity to pregnenolone in a preliminary open label trial of citalopram [58].

4.3 Serotonin and Estrogen

It has been suggested that severe PMD is linked to a genetic variant in the estrogen receptor α gene (ESR1) [59]. Positron emission tomography (PET) studies have shown different serotonergic responses, as measured by the $5\text{-}HT_{1A}$ receptors binding potential and 5-HT precursor trapping, between women with severe PMD and controls [60, 61].

The interplay between estrogen and 5-HT leads to an overall increase in 5-HT synthesis and availability and a decrease in 5-HT breakdown in brain regions associated with mood regulation [62, 63].

The rapid action of antidepressants in PMD may be partially accounted for by a membrane-initiated estrogen response using nongenomic secondary messengers instead of the slower pathway of transcription regulation. However, given that PMD is associated with a late luteal decrease in estrogen levels, any effect on the serotonin system may be occurring before the late luteal phase, in which estrogen levels are higher, priming the system for SSRI/SNRI treatment.

4.4 Other Mechanisms of Action

The fact that SSRIs/SNRIs have multiple therapeutic effects and that, in the case of PMD, hormonal interventions can have similar beneficial effects to the serotonergic compounds, suggests that the synaptic-dominated model of brain function may not represent the only mechanism of action [64]. Several other mechanisms, such as neuromodulation as well as nonsynaptic diffusion neurotransmission (which includes both the diffusion of neurotransmitters and other neuroactive substances through the extracellular fluid to reach extrasynaptic receptors and the diffusion of substances such as nitric oxide through both the extracellular fluid and cellular membranes to act within the cell) may play a major role in the rapid onset of response to SSRIs/SNRIs in women with PMD [65, 66].

5 Conclusion

Research has shown that continuous dosing with SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) and SNRIs (venlafaxine and duloxetine) is highly effective in reducing premenstrual symptoms. Numerous studies have confirmed the effectiveness of luteal phase dosing of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and venlafaxine, and concluded that the efficacy of luteal phase dosing does not differ from that of continuous dosing in treating severe PMD.

Given the rapid onset of response to SSRIs in women with PMD, studies have tried and succeeded in establishing that for some women, symptom-onset dosing with escitalopram, fluoxetine, and paroxetine CR is as effective as continuous or luteal phase dosing.

Treatment algorithms for women with 'pure' PMD, women with comorbid subsyndromal mood and/or anxiety disorders, and women with established mood and/or anxiety disorders who experience premenstrual exacerbation of symptoms despite treatment with SSRIs/SNRIs have previously been published [67]. Although these algorithms predate the publications on symptom-onset dosing, they are still pertinent. Women with prospectively documented 'pure' PMD who respond to luteal phase dosing can be given the option of symptom-onset dosing. Women with subsyndromal mood and/or anxiety disorders may benefit from continuous dosing and women already treated with SSRIs/SNRIs for mood and/or anxiety disorders but who experience premenstrual exacerbation of symptoms may benefit from an increased dose during the luteal phase.

The wide range of clinical efficacy of SSRIs/SNRIs indicates that they exert their therapeutic effect through multiple pathways. The literature suggests a few alternative mechanisms of action that may explain the rapid response to SSRIs/SNRIs in women with PMD. One is the effect of SSRIs on ALLO biosynthesis independent of 5-HT reuptake inhibition. The increase in ALLO availability may be the mechanism underlying the ability of SSRIs to alleviate irritability and dysphoria in women with PMD. Other suggested mechanisms include neuromodulation and nonsynaptic diffusion neurotransmission, though neither has been studied in this context. These mechanisms, which to date have mostly been studied in animal models, should be studied in humans to further elucidate the therapeutic mechanism of action of SSRIs/SNRIs in PMD as well as the underlying pathophysiology of PMD, in order to streamline the pharmacotherapy in women with PMD.

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