

Sertraline (Zoloft), fluoxetine (Lovan, Prozac,) for premenstrual dysphoric disorder (PMDD)

Summary

- Sertraline and fluoxetine are TGA-approved for premenstrual dysphoric disorder (PMDD). However they cannot be prescribed on the PBS for this indication.
- Premenstrual dysphoric disorder (PMDD) is a recently characterised diagnosis, provisionally listed in the appendix of DSM-IV while being better defined. It is **not** the same as premenstrual syndrome (PMS), but is a more severe manifestation.
- There is debate over the validity and usefulness of the diagnosis.
- Before considering fluoxetine or sertraline:
 - Confirm the diagnosis and assess severity with prospective monitoring
 - Consider behavioural treatment including information, coping skills training, relaxation and/or cognitive behavioural therapy.
- Dosing may be either continuous daily or intermittent in the premenstrual, luteal phase only. It is unclear whether intermittent dosing reduces common adverse effects, but it does limit drug exposure.

PBS listing

Sertraline and fluoxetine cannot be prescribed on the PBS for premenstrual dysphoric disorder (PMDD).

Reason for PBS listing

This indication is not PBS listed.

Place in therapy

Sertraline has **TGA approval** for the treatment of premenstrual dysphoric disorder (PMDD), as defined by the DSM-IV criterion in adults (18 years and above).¹ The other selective serotonin re-uptake inhibitor (SSRI) approved for this indication in Australia is fluoxetine.²

PMDD is a recently characterised diagnosis, provisionally listed in the appendix of DSM-IV while being better defined (see Figure 1).

Diagnosis: PMDD *is not* the same as PMS

PMDD is an extreme manifestation of premenstrual syndrome (PMS). While PMS is experienced by many women, the more severe disorder is experienced by relatively few.³ It is characterised by:

- severe mood changes premenstrually, which abate after menstruation
- significant functional impairment disrupting work, social activities, and/or relationships.⁴

Diagnosis requires patients to record symptoms daily for 2 months.

This diary is used to check that symptoms are cyclical as well as recurring, and to exclude an ongoing problem. Diagnosis may be complicated by the fact that some disorders (e.g. depression, anxiety) can be exacerbated premenstrually⁴, although this has not been well researched.³

Figure 1: Provisional DSM-IV criteria for diagnosis of PMDD⁴

- a. Symptoms begin 1 week before menses and resolve in the first few days after menses (over most menstrual cycles during the past 12 months).
- b. Five of the symptoms below, one of which must be a mood symptom.
- | | |
|---|--|
| <p>Mood symptoms (at least one must be present)</p> <ul style="list-style-type: none"> • Depressed mood with feelings of hopelessness • Anxiety/tension • Mood swings • Irritability/anger | <p>Other symptoms</p> <ul style="list-style-type: none"> • Decreased interest in usual activities and social withdrawal • Difficulty concentrating • Lack of energy (fatigue) • Appetite changes (overeating/undereating) • Hypersomnia/insomnia • Feeling out of control or overwhelmed • Somatic symptoms such as bloating, mastalgia or headaches |
|---|--|
- c. Symptoms must be severe enough to interfere with work, school, usual activities or interpersonal relationships.
- d. Symptoms may be superimposed on an underlying psychiatric disorder, although they should not be an exacerbation of another condition.
- e. Criteria a, b, c and d must be confirmed by prospective daily charting for a minimum of two consecutive symptomatic menstrual cycles.

Is PMDD a real disorder?

There are debates about the validity of the disorder. Supporters of the PMDD classification argue that better recognition will allow treatment of distressing and disruptive symptoms.^{5,6} Others argue that inclusion of menstruation-related mood changes in DSM-IV stigmatises women and encourages drug treatment of a normal experience.⁷

The definition of PMDD (Figure 1) was derived primarily to allow a common definition for research, and is provisionally listed in the appendix of the DSM-IV. It is not listed in the International Classification of Disease, although PMS is included under gynaecological disorders. The UK recently revoked the PMDD indication for fluoxetine, as not all European countries recognise PMDD as a disorder.⁸

These debates aside, in practice ensure that:

- women presenting with severe or disabling premenstrual symptoms are assessed
- other possible causes are excluded, including a primary diagnosis of major depression (see Table 1: Differential diagnosis)
- a clear distinction is made between PMS and the more extreme manifestation of PMDD.

There may be consumer demand for inappropriate use of these medicines in PMS.

Table 1: Differential diagnoses for women with symptoms of PMS or PMDD³

Psychiatric	Physical
Major depression	Endometriosis
Dysthymia	Thyroid disorders
Bipolar disorder	Seizure disorders
Generalised anxiety	Autoimmune disorders
Panic disorder	Dysmenorrhoea
Perimenopausal mood symptoms	Allergy

Behavioural measures appear beneficial and may have sustained benefit

Behavioural changes such as limiting salt, caffeine and alcohol in the diet are often suggested for PMS and PMDD, but these have not been evaluated.⁹

Regular moderate exercise may help relieve physical symptoms.⁹

Consider psychological therapies such as cognitive behavioural therapy (CBT). CBT and coping skills training have shown promise in the treatment of PMDD and unlike drug therapy, changes may be sustained when treatment stops.¹⁰⁻¹³ A three-armed trial comparing fluoxetine, CBT and fluoxetine+CBT found similar improvements in all groups. Fluoxetine users improved more rapidly, but the ultimate outcome was similar for all treatment types.¹⁰

Psychological therapies in trials have included

- information about PMDD
- an emphasis on coping skills
- behavioural strategies to manage stress in the premenstrual phase
- relaxation training
- assertiveness training.

There may be therapeutic value in recognising that the symptoms are distressing and affect women's lives. The fact that trials provide ongoing follow-up and discussion of symptoms may account for high placebo effects in both drug and non-drug trials.

Evidence base for SSRIs in PMDD

From the 30–40 trials available, it seems likely that sertraline and fluoxetine reduce the mood symptoms of PMDD. Both intermittent (luteal phase, between ovulation and menses)^{5,14–16} and continuous daily dosing^{5,17–19} regimens have shown similar effects. (See *Dosing issues*)

However questions remain about:

- to what extent function is improved (clinical impact)
- whether effects are sustained with prolonged use (most trials of three months duration)
- the safety and suitability of these drugs for long-term use.

Questions about the evidence

There have been large placebo effects in PMDD trials of SSRIs. In most trials, patients on placebo also improved over time—but to a lesser extent than drug treatment groups.^{14,15,20} For example, PMDD symptom scores after active treatment were reduced by 30–40%, while placebo scores were reduced by about 20%.^{14,20}

Although a recent study (n=167) found differences in average symptom scores, placebo-treated and sertraline-treated patients were not significantly different by the third month.²⁰

Further, the validity of a Cochrane review¹⁹ which described SSRIs as 'highly effective in treating premenstrual symptoms' has been questioned, and should be treated with caution as the methodology may have overestimated the treatment effect.^{21,22}

Compared to existing therapy

Other treatments focusing on ovulation suppression (e.g. danazol, gonadotrophin-releasing hormone agonists) have had significant adverse effects. Use of oral contraceptives to suppress ovulation has been proposed but not well investigated.⁹

Safety issues

If SSRIs are chosen as the primary treatment for PMDD, this is potentially long-term treatment for women in their reproductive years. The safety of such prolonged use is unknown.

While SSRIs do not appear to be teratogenic²³, they have been associated with withdrawal effects in neonates (e.g. jitteriness, agitation).^{24,25} An increased risk of preterm birth and other adverse effects in neonates has been associated with use of SSRIs in the third trimester.²⁴

Discuss these risks and contraception needs with the woman when prescribing. However PMDD symptoms are likely to resolve in pregnancy.⁹

Adverse drug reactions

- PMDD trials report the common known adverse effects of SSRIs (insomnia, gastrointestinal disturbances, fatigue and decreased libido).
- Adverse effects are dose-related.
- Intermittent dosing appears to be effective and limits drug exposure. However it is not clear how intermittent dosing influences the severity and frequency of adverse effects—including possible withdrawal symptoms with sertraline. While one study found adverse effects (nausea, headache, insomnia) reduced over three months of intermittent use¹⁴, another found that adverse effects persisted with intermittent dosing compared to continuous use.²⁰ Clinical drug interactions might be more difficult to manage with intermittent dosing.

Dosing issues

Fluoxetine:

- Continuous dosing: 20 mg per day
 Intermittent dosing: 20 mg per day for 14 days prior, until first day of menses.

A trial of a higher (60 mg) dose showed significant increase in adverse effects with no additional benefit.¹⁷

Sertraline:

- Continuous dosing: 50–150 mg per day (depending on response)
 Intermittent dosing: 50–100 mg for 14 days prior, until first day of menses. (If 100 mg, start at 50 mg for 3 days each month)

In sertraline trials, average doses after 3 months have been between 70–100 mg.^{5,14,18,27} Prescribers and consumers need to judge whether adverse effects of higher doses are justified by treatment benefits. (See *Adverse drug reactions*)

Some consumers may find intermittent dosing schedules more difficult to manage, however they may be worth using initially to limit drug exposure.

Information for patients

Talking about the impact of premenstrual symptoms on women's lives and supportive and/or problem-solving therapy may have a therapeutic effect. If symptoms are related to menstruation, women may be able to plan to limit stressors at the time when they are less able to cope. The symptom diary may be helpful in unravelling timing of symptoms, stressors and management strategies.

Patients should receive the Consumer Medicine Information (CMI) for the drug prescribed from either their doctor or pharmacist.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.