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Ministry of Health

# Guideline on the treatment of Premenstrual Dysphoric Disorder (PMDD)

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## Introduction

There are substantial research data available to support premenstrual dysphoric disorder (PMDD) as a diagnostic entity of a severe form of premenstrual disorder, which causes clinically relevant functional impairment and requires treatment. It is considered a disorder with substantial clinical and public health impact in a [small] subpopulation of menstruating women. The aim of this guideline is to provide guidance for the evaluation of medicinal products in the treatment of PMDD. The present document should be conceived as general guidance.

Due to the chronic nature of the disorder special attention should be paid to maintenance of effect and long-term safety, and the presence and acceptance of comorbidity.

After reviewing, we have adopted the guidelines from the European Medicines Agency.

## A. Epidemiology

Premenstrual dysphoric disorder affects between 1.8% and 5.8% of menstruation women over the course of a year. Premenstrual dysphoric disorder is most accurately estimated to affect 1.8% of women who satisfy the complete criteria without functional impairment and 1.3% of women who fulfill the current criteria with functional impairment but no symptoms of another mental disease co-occurring. (DSM-5)

## B. Diagnostic criteria

Naming of the Premenstrual Dysphoric Disorder has changed over the last two decades. In the ICD-10 the syndrome is mentioned as 'premenstrual tension syndrome' in the Gynecology Section. However, Premenstrual dysphoric disorder (PMDD) has been given its own classification code and for the first time classified clearly as a gynecological, not mental, disease in the WHO's new International Classification of Diseases, ICD-11.

In DSM 4, the PMDD was classified as one of the "Conditions for further study." In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, PMDD is currently categorized as a depressive illness (DSM–5).

The diagnostic standards are mostly unaltered. Many believe that making PMDD a separate diagnostic category will give the condition more credibility and promote the expansion of evidence-based research in this field.

The new DSM-5 criteria for PMDD require a combination of symptoms that began in the final week before menses, started to improve in the days after onset of menses and were absent in the postmenstrual weeks during the past year. At least one of 5 or more required symptoms must be marked lability of affect, irritability or anger or increased interpersonal conflict, depressed mood or hopelessness or self-deprecation, or marked anxiety or tension. Decreased interest in usual activities, subjective difficulty in concentrating, lethargy or fatigue or lack of energy, marked appetite change with overeating or food cravings, insomnia or hypersomnia, feelings of being out of control and somatic symptoms such as bloating, weight gain, breast tenderness, and joint or muscle pain may also be present (American Psychiatric Association, 2013).

**TABLE 1**

## *DSM-5* criteria for premenstrual dysphoric disorder

**A**. In the majority of menstrual cycles, at least 5 symptoms must be present in the final week before menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week after menses.

**B**. One (or more) of the following symptoms must be present:

1. Marked affective lability (eg, mood swing, feeling suddenly sad or tearful, increased sensitivity to rejection)
2. Marked irritability/anger or increased interpersonal conflicts
3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts
4. Marked anxiety, tension, and/or feelings of being keyed up or on edge

**C**. One (or more) of the following symptoms must additionally be present, to reach a total of 5 symptoms when combined with symptoms from Criterion B above:

1. Decreased interest in usual activities (eg, work, school, friends, hobbies)
2. Subjective difficulty concentrating
3. Lethargy, easy fatigability, or marked lack of energy
4. Marked change in appetite, overeating, or specific food cravings
5. Hypersomnia or insomnia
6. A sense of being overwhelmed or out of control
7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of bloating, or weight gain

*Note: The symptoms in Criteria A–C must have been met for most menstrual cycles that occurred in the preceding year.*

**Adapted from**: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* 2013.[7]

**American College of Obstetricians and Gynecologists ACOG diagnostic criteria for PMS:**

Premenstrual syndrome can be diagnosed if the patient reports at least one of the following affective and somatic symptoms during the 5 days before menses in each of the three prior menstrual cycles:

- Affective:
  - Depression
  - Angry outbursts
  - Irritability
  - Anxiety
  - Confusion
  - Social withdrawal
- Somatic:
  - Breast tenderness
  - Abdominal bloating
  - Headache
  - Swelling of extremities

* These symptoms are relieved within 4 days of the onset of menses, without recurrence until at least cycle day 13. The symptoms are present in the absence of any pharmacologic therapy, hormone ingestion, or drug or alcohol use. The symptoms occur reproducibly during two cycles of prospective recording. The patients suffer from identifiable dysfunction in social or economic performance.

## C. Pathophysiology of PMDD

It is unclear exactly how PMDD works from a pathophysiological standpoint. The etiology is thought to be complex. According to research, this patient population has anomalies in the hypothalamus-pituitary-ovary axis and brain serotonergic system.

The menstrual cycle is associated with the pattern of symptoms, which include significant symptoms in the time before menses (the luteal phase), symptom remission during menstrual flow, and a symptom-free period in the follicular phase. There have been various attempts to uncover endocrine abnormalities in people with PMDD, but very few findings have been consistent. It appears that ovulatory cycles are necessary for the onset of PMDD. However, the research suggests that gonadal steroid levels in ovulating women with and without PMDD are similar. Studies on PMDD tend to support the idea that women with PMDD are more sensitive to the effects of sex steroids on the brain than are women without the disorder, with abnormal hypothalamic-pituitary regulation throughout the menstrual cycle and abnormal luteal phase cortical excitability being suggested as the underlying mechanisms. The cyclicity of symptoms diminishes during anovulatory cycles, and symptoms abate during menopause, pregnancy, or bilateral ovariectomies.

It is likely that there is a genetic component to the existence and severity of premenstrual symptoms, as women whose mothers reported premenstrual symptoms are more likely to develop PMS compared to women whose mothers have not been affected. In addition, higher concordance rates are observed in monozygotic twins compared with dizygotic twins

There are risk factors associated with the development of PMDD including:

- A previous history of mood disorder.
- Genetic susceptibility,
- Premenstrual mood changes and depression.
- Past or current history of traumatic events such as sexual abuse or domestic violence
- Cigarette smoking
- Obesity

Major theories developed to explain the pathophysiology of PMDD include the followings:

- Ovarian hormone dysregulation:
    - PMDD is caused by an imbalance in the estrogen-to-progesterone ratio, with a relative progesterone deficiency
    - Chronic exposure to progesterone and Allopregnanolone (progesterone metabolite) and rapid withdrawal from ovarian hormones may play a role in the etiology of PMDD. ALLO is a potent positive modulator of GABAA receptors and has sedative, anesthetic, and anxiolytic properties.

- Serotonin and other neurotransmitters dysregulation
- PMDD shares many of the phenomenological features of depression and anxiety states that have been linked to serotonergic dysregulation
- This theory is the most popular at present. Although genetic predisposition and societal expectations may play a role, the strongest scientific data implicate serotonin as the primary neurotransmitter whose levels are affected by ovarian steroid levels.
- Other neurotransmitter systems that have been implicated include the opioid, adrenergic, and gamma-aminobutyric acid (GABA) systems
- Psychosocial hypothesis
  - The psychosocial theory postulates that PMDD is a conscious demonstration of a woman's conflict with her femininity and motherhood
- Cognitive and social learning theory
  - This theory suggests that the onset of menstrual bleeding is an adverse psychological outcome for some women and PMDD is a display of maladaptive coping strategies in other to reduce immediate stress
- Sociocultural theory
  - This theory postulates that PMDD is a manifestation of a conflict between the societal expectation of the dual role of a woman as both a productive part of the workforce and a mother.

## D. Differential diagnosis

The diagnosis of PMDD requires interdisciplinary expertise. PMDD should be separated from differential diagnostic categories including both psychiatric and nonpsychiatric disorders and physicians should be trained in handling the DSM-V criteria (see the table)

Most chronic psychiatric or medical conditions are visible throughout the menstrual cycle. However, many conditions are magnified by menstruation and are exacerbated in the late luteal or menstrual phase of the cycle, leading women to believe they have PMDD. The underlying cause of this increase in symptoms is unknown.

The most common psychiatric disorders that may be concurrent or exacerbated premenstrually are dysthymia, major depressive disorder (MDD), panic disorder (PD), and generalized anxiety disorder (GAD), with less evidence for bipolar disorders, posttraumatic stress disorder, social phobia, eating disorders, and substance abuse.

Symptoms of endometriosis, polycystic ovary disease, adrenal system disorders and hyperprolactinemia may mimic symptoms of PMDD.

Other medical disorders that may demonstrate a premenstrual increase in symptoms include migraines, asthma, seizure disorders, irritable bowel syndrome, diabetes, chronic fatigue symptom, allergies and autoimmune disorders. Differentiating these conditions from PMDD is usually straightforward because the key symptoms are not part of the typical PMDD set of symptoms and emotional symptoms are not prominent

## E. Treatment

Two primary treatment options have been developed based on theories about the underlying causes of PMDD: (1) targeting the hypothalamus-pituitary-ovary axis by eliminating fluctuations in gonadal hormone levels (e.g., GnRH analogues, oestradiol, combined oral contraceptives (COCs)) and (2) targeting brain serotonergic synapses by increasing central serotonergic transmission (e.g., SSRI, NSRI Because PMDD is a cyclic, intermittent illness, both periodic and continuous treatment interventions should be considered, as they may have different effects on treatment compliance and long-term safety.

Other therapeutic approaches include pharmacological treatment of physical symptoms as well as non-pharmacological methods such as psycho-behavioral approaches, lifestyle changes, and dietary modifications, which are not addressed in this guideline.

- **General Principles of Treatment**

When managing women with PMDD, there are certain principles which should be adhered to. Even though not evidence-based, there is little doubt that reduction of stress, for instance, is a great help in ameliorating symptoms. Also, dietary measures such as avoidance of carbohydrate binges and limitation of alcohol and caffeine in- take is often of benefit. There are data from non- randomised trials that exercise improves PMDD symptoms. However, in cases of moderate to severe PMDD, it is important that medical therapy is instituted sooner rather than later to avoid unnecessary suffering. Women with marked underlying psychopathology as well as PMDD should be referred to a psychiatrist. Symptom charts/diaries should be used to assess the effect of treatment.

- **Service Delivery**

Ideally, women with severe PMDD should be treated by a multidisciplinary team which might comprise a hospital or community gynecologist, psychiatrist or psychologist, dietitian and counsellor. Referral to a gynecologist should be for women who have been fully evaluated as having severe PMDD and when simpler forms of therapy have been explored.

- **Medical Treatment of PMDD**

The two chief evidence-based medical treatments of moderate to severe PMS are categorized by ovulation suppression and selective serotonin reuptake inhibitors:

- **Serotonin Reuptake Inhibitors**

  SSRIs have been proven to be effective in the treatment of severe mood and somatic symptoms of PMDD. The ones that have been particularly linked with the relief of symptoms are Clomipramine (a tricyclic antidepressant), Selective serotonin reuptake inhibitors like escitalopram, fluoxetine, and noradrenaline reuptake inhibitor venlafaxine. Antidepressants that predominantly affect noradrenergic transmission are not as effective for PMDD as SSRIs which means that the effect of SSRIs in PMDD is not just an antidepressant effect. This is supported by the fact that the beneficial effect of SRIs begins rapidly in PMDD whereas antidepressant effect takes several weeks. Thus, clinicians can use SRIs intermittently from mid-cycle to menses to treat symptoms of PMDD as opposed to continuous treatment.

  Side-effects of SSRIs are usually mild. Nausea is the most common adverse effect, but it usually wears off in a couple of days after starting the therapy and doesn't reappear even if

the therapy is intermittent. Reduced libido and anorgasmia are other common adverse effects, but they are absent in drug-free intervals

- **Cognitive Behavioral Therapy**

  When treating women with severe PMS, cognitive behavioral therapy should be considered routinely as a treatment option.

  A recent study examined the relative effectiveness of fluoxetine (20 mg daily) and cognitive behavioral therapy (CBT) (ten sessions), and combined therapy (fluoxetine plus CBT) in women with Premenstrual Dysphoric Disorder (PMDD). This was a randomized treatment trial lasting 6 months; follow-up was undertaken 1 year post-treatment. Significant improvement occurred in all three treatment groups after 6 months of treatment. Fluoxetine was associated with a more rapid improvement but at follow-up, CBT was associated with better maintenance of treatment effects compared with fluoxetine. There appeared to be no additional benefit of combining the treatments and no difference in efficacy between the treatment groups. A clinical psychology service should be available for women with PMDD.

- **Ovarian suppression**

  Although the underlying cause of severe PMS remains unknown, cyclical ovarian activity appears to be an important factor. A logical treatment for severe PMS, therefore, is to suppress ovulation and thus suppress the cyclical endocrine/biochemical changes which cause the distressing symptoms. A number of drugs are capable of performing this function, but they are not without their own side-effects which may influence the efficacy of the treatment or the duration for which they may be given.

- **Combined oral contraceptive pill**

  Although widely used in clinical practice, their efficacy in treating PMDD has not been strongly supported by evidence. Women on OCP experience more hormone-related symptoms on hormone-free days and hence OCP treatment with fewer hormone-free days might be beneficial. When treating women with PMDD, newer contraceptive pill types may represent effective treatment for PMDD and should be considered as one of the first-line pharmaceutical interventions of these women.

- **Transdermal estradiol**

  Placebo-controlled trials have demonstrated that implanted and transdermal (patch) 17β estradiol combined with cyclical progestogen is effective for the management of physical and psychological symptoms of severe PMDD. Implants are less commonly used for PMDD since patches have become available due to their long lasting effects. A recently concluded study from the author's unit has shown benefits of 100mcg patches over placebo with benefits lasting up to 14 months. Additional barrier or intrauterine methods of contraception should be used when estradiol (patches and implant) are used in PMS as ovulation suppression cannot be guaranteed. There are insufficient data to confirm long-term endometrial and breast safety because long-term randomized prospective safety studies are lacking. However, logic dictates that the hormonal environment is not significantly different from how it would otherwise be in this premenopausal population and observation has not shown any problems over 20 years of usage.

Percutaneous estradiol, either as an implant or as a patch, combined with cyclical progestogen, has been shown to be effective for the management of physical and psychological symptoms of severe PMDD.

- **Progestogen intolerance**

  Use of continuous estradiol normally necessitates the addition of cyclical progestogen (10 - 12 days) to avoid endometrial build-up in women who have a uterus. The progestogen releasing system (Mirena) can maximise efficacy by minimising PMS-like adverse effects. Even the low systemic levels of levonorgestrel released by the Mirena, can initially produce PMS-type adverse effects in the progestogen intolerant woman. Despite this, it might still be of advantage to use a Mirena or vaginal progesterone (Cyclogest pessaries or Crinone gel 8% – not licensed for this indication) in the progestogen intolerant woman. Treatment with the lowest possible dose of progestogen is recommended to minimise adverse effects.

- **Danazol**

  Cycle suppression may be achieved using Danazol, an androgenic steroid. Studies have demonstrated benefit for several symptoms, but due to masculinizing side-effects, especially at higher, cycle-suppressing doses, it is not commonly used.

- **Gonadotrophin releasing hormone (GnRH) analoguesHS**

  GnRH analogues have been very successfully employed for many years to suppress ovarian steroid production. Early resort to GnRH therapy for PMS is not recommended due to the potential side-effects and cost. Prolonged use should be retained for women with the most severe symptoms. A recent meta-analysis of GnRH analogues has confirmed their efficacy compared with placebo. Data show that symptoms due to the hypoestrogenic state can be virtually eliminated and bone mineral density can be maintained by the use of HRT. Continuous combined therapy is preferable to sequential combined therapy in order to minimise the risks of symptom re-appearance of PMS-like progestogenic effects.

  When treating women with PMDD, with GnRHa therapy, treatment should only be continued for 6 months when used alone. Treatment should be combined with HRT to reduce bone density loss. Women on long- term treatment should have annual measurement of bone mineral density (ideally by dual energy X-ray absorptiometry). Treatment should be stopped if bone density declines significantly in scans performed one year apart. General advice about how exercise, diet and smoking affect bone mineral density should be given.

- **Surgical Treatment of PMDD**
  - **Hysterectomy**

    Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the ultimate form of ovulation suppression and the only true cure for PMDD as this removes the ovarian cycle completely. The procedure is only rarely performed for this indication, as a lesser alternative can usually be found. When treating women with PMDD, surgery should not be contemplated without preoperative use of GnRH analogues as a test of cure and to ensure that HRT is tolerated. Such therapy should be reserved for sufferers of extremely severe PMS in whom other treatment has failed. When appropriately targeted, this intervention can have life altering benefits. It is essential that adequate hormone therapy is given (including consideration of testoster- one replacement) to prevent simply replacing one set

of symptoms with another. Women who have had a hysterectomy with ovarian conservation will often continue to have cyclical symptoms in the absence of menstruation.

- **COMPLEMENTARY THERAPIES (CAMs)**

When treating women with PMS, complementary medicines may be of benefit, but clinicians need to consider that data from clinical studies are limited and underpowered. Interactions with conventional medicines should also be considered. It is difficult to assess the true value of most of these therapeutic interventions because they are freely available without prescription or physician recommendation, and with little regulation of efficacy or safety. Most are not licensed or registered for the treatment of PMS.

Alternative interventions which have been used to treat PMS. Treatments have been selected where reasonable efficacy data exist (randomised controlled data if possible).

- **Magnesium**

  Preliminary small studies suggest that magnesium may also be helpful in PMS. There is some evidence that regular use of magnesium supplements is of benefit in managing premenstrual syndrome. However, more data would be desirable.

- **Calcium / Vitamin D**

  Studies suggest that blood calcium and Vitamin D levels are lower in women with PMDD and that calcium supplementation may reduce symptom severity, but it is unknown whether this may prevent the initial development of PMS. In a recent case control study, after adjustment for risk factors

  Women in the highest quintile of total Vitamin D intake (median, 706 IU/d) had a relative risk of 0.59 (95% confidence interval, 0.40-0.86) com- pared with those in the lowest quintile (median, 112 IU/d) (P = .01 for trend). The intake of skimmed or low-fat milk was also associated with a lower risk (P<.001). A high intake of calcium and Vitamin D may therefore reduce the risk of PMS but large-scale clinical trials addressing this issue are required. At present, the only interventional data are from small trials. Given that calcium and Vitamin D may also reduce the risk of osteoporosis and some cancers, clinicians may consider recommending these nutrients even for women with PMS but more data are required to deter- mine efficacy and to optimise regimens.

- **Agnus Castus**

  The fruits of Vitex agnus castes (The chaste tree) contain a mixture of iridoids and flavonoids. The mechanism of action may be related to modulation of of stress induced prolactin secretion via dopamine without directly affecting lutenising or follicle stimulating hormones.

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