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Guideline on the treatment of premenstrual dysphoric disorder (PMDD)

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Table of contents

Executive summary

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, and should be read in conjunction with other applicable EU and ICH guidelines (see Section 3).

1. Introduction (background)

1.1. Epidemiology and classification of PMDD

Up to 70-90 % of women of reproductive age have one or more signs of physical discomfort or emotional symptoms in the premenstrual, i.e. luteal phase of their menstrual cycle. About 20-40 % of menstruating women have premenstrual syndrome (PMS) and experience luteal phase symptoms that are bothersome. A smaller number, up to 8 %, experience more severe symptoms, which lead to substantial distress or functional impairment and are referred to as premenstrual dysphoric disorder (PMDD) (10, 11, 13, 14, 23, 38, 39, 42). Although PMDD, like PMS includes physical symptoms, it always involves a worsening of mood that interferes significantly with the woman's quality of life. The burden of illness of PMDD results from the severity of luteal phase symptoms, the chronicity of the disorder and the impairment in work, relationships and activities.

In the last decades a very broad diagnostic concept of the premenstrual disorders PMS and PMDD has been used in clinical research, which produced different diagnostic criteria and highly heterogeneous study populations.

Recent advances and research data improved the knowledge on diagnosis, frequency, pathophysiologic mechanisms, and treatment options in PMDD. This led to treatment recommendations by learned societies for PMDD.

1.2. Diagnostic criteria

In the ICD-10 the syndrome is mentioned as 'premenstrual tension syndrome' in the Gynaecology Section. At least one symptom out of a broad range of physical and emotional symptoms should be present without specification of severity. These criteria are not helpful for definition of study populations in clinical trials.

In 1987, the DSM-III included criteria for 'Late Luteal Phase Dysphoric Disorder' (LLPDD). In the DSM-IV, the name was changed from LLPDD to PMDD, with criteria that were almost identical to those of LLPDD. The DSM-IV includes PMDD as an example of a "depressive disorder not otherwise specified" (see Definitions Table 1).

The DSM-IV diagnostic criteria define the most severe subpopulation of the broader concept of PMS and were accepted by regulatory bodies outside Europe as an indication for several serotonergic antidepressants and hormonal products. Although the symptoms themselves are not unique, the restriction of the symptoms to the luteal phase of the menstrual cycle and their cyclical recurrence is considered pathognomonic of PMDD.

A criticism on these criteria has been that they are in the appendix of DSM-IV (further studies needed) and that many women with clinically significant PMS symptoms do not fulfil the full diagnostic criteria of the DSM-IV (e.g. prominent mood syndrome or minimum of five different symptoms).

The ACOG (American College of Obstetricians and Gynaecologists) recommended criteria defining moderate to severe PMS (see Definitions Table 2). The criteria include the presence of at least one psychological or physical symptom that causes significant impairment (experienced by women during the 5 days before menses and remit within 4 days of onset of menses with no recurrence at least until day 13 of the cycle, in at least three consecutive cycles) and are confirmed by means of prospective ratings.

In conclusion, for the time being, the most homogeneous study population that can be recruited is with the DSM-IV diagnostic criteria and this population should therefore be used for clinical trials in PMDD (12, 20). As research criteria these DSM-IV criteria are in the process of being updated and further validated, particularly with regard to better quantification of the different domains affected. These changes may influence the position presented in this guideline.

1.3. Pathophysiology of PMDD

The exact pathophysiology of PMDD is not well understood and clarified. The aetiology is considered multi-factorial. Research data have shown abnormalities in the hypothalamus-pituitary-ovary axis and brain serotonergic system in this patient population (16, 26).

Symptom pattern is linked to the menstrual cycle with pronounced symptoms in the period preceding menses (the luteal phase), symptom remission during the menstrual flow and a symptom-free period in the follicular phase of the cycle. Despite numerous efforts to identify endocrine disturbances in patients with PMDD, there are very few consistent endocrine findings. It seems that ovulatory cycles are a prerequisite for developing PMDD. However, the evidence suggests that ovulating women with and without PMDD do not differ with respect to levels of gonadal steroids (40). Studies on PMDD rather favour the notion that women with PMDD display higher responsiveness with respect to the influence of sex steroids on the brain than symptom-free women suggesting abnormal hypothalamic-pituitary regulation across the menstrual cycle and abnormal luteal phase cortical excitability as underlying mechanism (26). During anovulatory cycles the cyclicity of symptoms disappears and symptoms remit after menopause, during pregnancy or after bilateral ovariectomy.

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 (18, 36).

1.4. Treatment

Based on theories regarding the underlying causes of PMDD, two main treatment options have been developed: (1) targeting the hypothalamus-pituitary-ovary axis by abolishing 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) (4, 22, 31, 32). Since PMDD is an intermittent, cyclic illness periodic and continuous treatment interventions should be considered which may have different impacts on treatment compliance (see 4.3.3) and on long-term safety (see 4.5.3) (6, 15, 21, 43).

Other therapeutic approaches include pharmacological treatment of physical symptoms as well as non-pharmacological methods including psycho-behavioural approaches, lifestyle changes and dietary modifications, which are not specifically addressed in this guideline (17).

1.5. 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-IV criteria (see DSM-IV criterion C, Table 1).

Most chronic psychiatric or medical conditions will be apparent throughout the whole menstrual cycle (24). However, many conditions are also subject to menstrual magnification and are exacerbated in the late luteal or menstrual phase of the cycle leading women to believe that they may be experiencing PMDD. The underlying mechanism of this increase in symptoms is not understood.

Dysthymia, Major Depressive Disorder (MDD), Panic Disorder (PD) and Generalised Anxiety Disorder (GAD) are the most common axis I psychiatric disorders that may be concurrent or exacerbated premenstrually, with less evidence for bipolar disorders, posttraumatic stress disorder, social phobia, eating disorders and substance abuse (see Section 4.1).

Symptoms of endometriosis, polycystic ovary disease, adrenal system disorders and hyperprolactinemia may mimic symptoms of PMDD (1, 23).

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 (23).

It is therefore important that the diagnosis of PMDD is accurately documented and other conditions excluded (see 4.1).

2. Scope

The scope of the present document is to provide guidance in the identification of the target population including special populations (adolescents), study duration, efficacy and safety endpoints to establish efficacy and safety in PMDD.

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 (see sections 1.5 and 4.1).

With the most recent developments in the diagnosis and understanding of PMDD, it is considered an appropriate target for the development of pharmacological treatment. However, careful considerations on the adequate trial design of clinical studies are required. Up till now no medicinal products are approved in the EU for treatment of PMDD but data referring to the efficacy in the treatment of patients meeting PMDD diagnostic criteria according to DSM-IV are rather described in section 5.1 of the SmPC of some medicinal products, namely fluoxetine-containing medicinal products.

3. Legal basis

This guideline should be read in conjunction with Directive 2001/83 (as amended) and the following CHMP and ICH guidelines:

- Note for Guidance on Good Clinical Practice - CPMP/ICH/135/95 (ICH E6);
- Note for Guidance on General Considerations for Clinical Trials - CPMP/ICH/291/95 (ICH E8);
- Dose-Response information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4);
- Statistical Principles for Clinical Trials – CPMP/ICH/363/96 (ICH E9);
- Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10);
- Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 (ICH E11);
- Point to consider on adjustment for baseline covariates – CHMP/EWP/2863/99;
- Guideline on missing data in confirmatory clinical trials – CPMP/EWP/1776/99 ;
- Points to consider on Multiplicity issues in clinical trials - CPMP/EWP/908/99;
- Points to consider on application with 1. Meta-analysis; 2. one pivotal study - CPMP/EWP/2330/99;
- Extent of Population Exposure to Assess Clinical Safety – CPMP/ICH/375/95 (ICH E1);
- Pharmacokinetic studies in man - EudraLex vol. 3C C3A;
- Note for guidance on the investigation of drug interactions CPMP/EWP/560/95;
- Note for guidance on clinical investigation of medicinal products in the treatment of depression – CPMP/EWP/518/97;
- Guideline on clinical investigation of steroid contraceptives in women – EMEA/CPMP/EWP/519/98.

4. Pharmacological treatment trials in PMDD

4.1. Subject characteristics and selection of subjects

PMDD can occur in menstruating women of any age (see section 4.4). Typically symptoms emerge in early adulthood and increase with age (3, 7, 28, 29). Premenstrual symptoms seem to affect women

irrespective of cultural background or socioeconomic status, although specific symptoms may vary in frequency by culture background.

Diagnosis of PMDD should be based on reliable screening methods. The diagnostic criteria for PMDD require the presence of five out of the 11 Daily Record of Severity of Problems items, at least one being one of four “essential” mood symptoms (criterion A), as well as “interference with work/school/social activity” (criterion B). Criterion A symptoms must be “present for most of the time during the last week of the luteal phase” and must be “absent in the week post menses”, while the criterion B symptom must “markedly interfere with work or school or with usual social activities and relationships with others” (see Tables 1 and 3). The method of standardizing and operationalizing DSM-IV criteria should be described in studies of PMDD (33). A minimum duration of 4 days for symptom presence in the last week of the luteal phase is required.

Prospective daily monitoring of symptoms for two consecutive menstrual cycles is an absolute requirement to meet DSM-IV criteria and until now considered to be the gold standard in PMDD clinical studies (see Table 1, DSM-IV criterion D, 7). As none of the symptoms are unique to the syndrome, patients need to keep a daily diary of symptoms for at least 2 menstrual cycles to establish the temporal relationship between the onset of symptoms and the premenstrual period and the absence of symptoms or a chronic underlying disorder during the follicular phase (12).

Several assessment instruments to establish diagnosis of PMDD are available: e.g. the DRSP (Daily Record of Severity of Problems) (30), the DSR (Penn Daily Symptom Rating), and the MDQ (Menstrual Distress Questionnaire) (10). The method of standardizing and operationalizing DSM-IV criteria should be described in studies of PMDD (33). The choice of the instrument should be justified and validated in the target population (8). Retrospective reporting is not acceptable as retrospective recall of symptoms is unreliable (27).

In any method of assessment of PMDD symptoms severity, it is important to determine baseline levels from which to quantify the actual change and cyclicity in symptom severity levels, especially symptom severity pre- and postmenstrually. Various scoring methods compare the average of symptom scores during the premenstrual days with the average of symptom scores postmenses.

Although the core element of making a diagnosis of PMDD is the daily, prospective self-report of symptoms, this diary-based information should be supplemented by a structured interview conducted by the study raters (e.g. physicians), who should be properly trained for assessment of patients with the applied rating scales. Methods should be foreseen in the study protocol to assess inter-rater reliability (see 4.2.2).

Presence and acceptance of comorbidities

PMDD may be a comorbid condition with other axis I disorders of the DSM-IV classification, particularly depression and anxiety disorders (see section 1.5). The most difficult differential diagnosis for clinicians to make is distinguishing between PMDD and MDD. Although the lifetime comorbidity between the two disorders is significant, ranging from 30 to 70%, there is consistent evidence to support the distinct nature of each diagnosis. A key feature of depressive disorders is that symptoms are almost always present every day of the cycle. However, diagnosis of PMDD in the context of another axis I disorder raises a difficult diagnostic issue and to assure the integrity of the diagnosis of PMDD concurrent axis I disorders are not recommended in the study population (19, 42).

4.1.1. Inclusion criteria

The following inclusion criteria should be met for phase 3 trials:

- PMDD should be diagnosed using the DSM-IV criteria. A careful diagnosis based on clearly defined, replicable severity criteria via prospective ratings for two run-in cycles is essential (see sections 4.1 and 4.2 (14)).
- A regular menstrual cycle: the length varies among individuals and varies slightly within an individual. Therefore cycles within the lower limit of 24 days and an upper limit of 35 days are considered to be within a normal range.

The determination of ovulatory cycles is required for pharmacodynamic trials where ovulation-related underlying mechanisms are studied (14).

4.1.2. Exclusion criteria

- Not menstruating, including pregnant

- Any axis I disorder (e.g. Dysthymia, MDD, PD, GAD, anxiety disorders), alcoholism or substance abuse during the last 2 years prior to the trial.
- Any medication for PMS or PMDD including, but not limited to hormones, bromocriptine, GnRH agonists, vitamin B6 (>100mg), calcium supplements (>1500 mg/day), sterols and plant-derived products, anxiolytics, and antidepressants during the 3-month period prior to screening and during the study. In case hormonal contraceptives are used before the start of the trial as baseline therapy for contraception (depending on the medication studied), stratified analysis for add-on medication should be pre-specified.
- Contraindication to study medication depending on the medication studied (see section 1.4).

4.2. Methods to assess efficacy and assessment tools

4.2.1 Definition of the primary endpoints

The primary outcome should be prospective self-recording of overall premenstrual symptomatology. Improvement should be documented as the mean difference between the average luteal phase 2 prospectively assessed qualification scores as baseline score and luteal phase ratings of the end-of-treatment cycle for each patient after 6 months of treatment (see section 4.3.3). The primary endpoint should assess the difference in improvement between treatment groups. The scores of improvement per cycle should also be compared, in addition to the end scores in symptomatology (see 4.3.2 Data analyses). Several valid and reliable daily rating forms are available for the prospective recording of PMDD symptoms (10, 13). Results should be discussed in terms of both clinical relevance and statistical significance.

In order to allow an estimate of clinical relevance, improvement should also be expressed as the proportion of responders. Definition of responders should be based on clinical consideration and done prospectively. It has been suggested in PMDD treatment trials to regard as responders those patients showing a 50 % reduction in symptom ratings between baseline and end of treatment (2). When evaluating response it should be considered that not all scales end at zero. (2).

There is no data-based evidence of superiority of one type of rating scale over another in determining the outcome. However rating scales that combine measurement of affective symptoms, physical and functional impairment on a daily basis should be preferred. The choice of the rating scales should be justified from the test quality criteria (reliability, validity). The use of electronic diaries is recommended. Most psychometric evidence is available for the 'Daily Record of Severity of Problems' (DRSP) that was developed for diagnosing and evaluating PMDD (see Definitions Table 3; 6, 8, 41). The 24-item DRSP uses a 6-point rating scale to evaluate 11 symptom domains of the psychological and physical symptoms of PMDD and 3 items that measure functional impairment. Since impairment or dysfunction is the essential component of PMDD, its improvement should be an essential part of the primary outcome measure (see also section 4.2.2).

The Calendar of Premenstrual Experience (COPE) and the Premenstrual Symptom Diary (PMSD) may be used to assess PMS symptoms, but should not be used in PMDD studies (10, 13, 34, 35, 37).

4.2.2 Definition of secondary endpoints

Secondary outcome measures include change from baseline in components of the PMDD criteria, which include physical, affective and functional symptoms.

<u>Important secondary endpoints:</u>

- Change from baseline in psychological and physical impairment.
- Change from baseline in functional impairment:

  - Reduction of productivity or inefficiency at work, home or school,
  - Interference with hobbies or social activities,
  - Interference with relationships.

All assessment tools used should be justified based on psychometric properties (4, 23). Multiplicity adjustments if necessary should be undertaken according to the Points to consider on Multiplicity issues in clinical trials (CPMP/EWP/908/99).

Although the assessment of efficacy should be based on prospective self-rating, this should be supplemented by observer-ratings based on structured patient interviews undertaken by the clinician

and global assessment of symptom severity, improvement and adverse events. Physicians must be trained for using the different rating scales (see 4.1).

4.3. Strategy and design of clinical trials

4.3.1 Pharmacokinetics/ Pharmacodynamics, dose finding and interaction

For guidance on dose finding, pharmacokinetics and interactions reference is made to other relevant guidelines. Investigation of drug plasma levels might be supportive for dose-selection. Special dose regimen (i.e. continuous versus intermittent or luteal phase only dosing regimen) should be predefined and justified.

Pharmacodynamic data should be obtained depending on the mode of action of the examined substance.

4.3.2 Therapeutic confirmatory studies

Confirmatory studies should be randomised, double-blind, parallel group and placebo controlled. There is a list of minimal requirements clearly stated in the Points to consider on application with 1. Meta-analysis; 2. one pivotal study (CPMP/EWP/2330/99) that have to be fulfilled for one pivotal study-application. In PMDD, the subjective nature of the primary endpoint is considered an additional argument to request replication.

In case of inclusion of an active control arm, the choice and dose of the comparator should be justified on the basis of placebo-controlled evidence of efficacy of the comparator.

Generally a placebo wash-out period to exclude placebo responders is not useful and may impair generalisation of the results. Exclusion of placebo-responders should be justified.

In addition, information of patients screened but not included in the study should be documented.

Prior and concomitant medication should be documented in detail. Relevant medication has to be washed out.

In controlled settings such as clinical trials, some women become anovulatory due to stress. Therefore, especially in treatments not aiming at suppressing ovulation, corpus luteum formation should be monitored before and under therapy, e.g. by measuring progesterone, to ensure that symptom loss or mitigation is attributable to a therapeutic effect.

Blinding

Special attention should be paid to blinding even though this might be difficult in studies investigating medicinal products which may influence the menstrual bleeding pattern (e.g. COCs). The applicant should indicate a priori how this will be handled.

Data analyses

Given the chronicity and cyclicity of the symptoms, the maintenance of therapeutic efficacy should be demonstrated over at least 6 cycles.

For details on the statistical analysis refer to the statistical guideline (ICH E9) as well as the Guideline on missing data in confirmatory clinical trials – CPMP/EWP/1776/99.

4.3.3 Study duration

Since PMDD is a chronic condition, clinical studies should be long enough to provide information about effectiveness, tolerability and patient compliance. In order to establish efficacy, placebo-controlled data are needed over at least 6 cycles (2 run-in cycles + 6 treatment cycles), especially since a large placebo effect is expected (9). Intermittent, luteal phase treatment strategies may enhance treatment compliance (see 1.4) (15).

4.4. Studies in special populations

4.4.1. Adolescents

There are very few studies assessing PMDD in adolescents. Premenstrual symptoms are identified in adolescents and can begin around the age of 14, or 2 years post-menarche, and persist until menopause (5, 28, 29). Though the diagnosis is not frequently made, the literature suggests that a similar proportion of teenagers in comparison with adults would also meet criteria for PMDD. There is a need to demonstrate that specific therapeutic strategies have similar beneficial effects in adolescents and it is requested to include adolescents in the development program according to the prevalence in the general population (3).

Special ethical considerations and safety concerns in adolescents have to be taken into account. Depending on the substance studied, relevant guidelines with specific safety topics and identified risks should be taken into account. Depending on the class of the investigated medicinal product, special attention should be paid to attempted and completed suicides by using a suitable suicide rating scale or review of relevant AE data. Suicidality should be prospectively assessed by using proper instruments, e.g. the C-CASA method20, or the C-SSRS, which is an existing documentation system that allows documenting according to the C-CASA categories (25). However, alternative approaches that may be less cumbersome can be used as well.

4.5. Clinical safety evaluations

4.5.1. General considerations

For reference to the relevant safety guidance, see Section 3.

4.5.2. Specific adverse events

Identified adverse events (AE) should be characterized in relation to the duration of treatment, the dose and/or plasma level, the recovery time, age and other relevant variables. Assessment of adverse events, especially those predicted by the pharmacodynamic properties of the investigational product should be performed using a systematic and planned methodology.

All adverse events occurring during the course of clinical trials should be fully documented with separate analysis of adverse drug reactions, drop-outs and patients who died while on therapy. Depending on the substance studied relevant guidelines with specific safety topics should be taken into account.

4.5.3. Rebound/Withdrawal phenomena/Dependence

When pharmacological treatment is stopped, rebound and/or withdrawal phenomena may occur. Therefore, rebound and/or withdrawal phenomena should be systematically investigated.

Animal studies will be needed to investigate the possibility of dependence in new classes of compounds or when there is an indication that dependence may occur. Depending on the results of these studies further studies in humans may be needed.

4.5.4. Long-term safety

Since PMDD is a chronic disorder expected to last until menopause, long-term safety of therapeutic interventions has to be established. The total clinical experience should generally include data on a large and representative group of patients in line with the guideline on population exposure (ICH E1). Depending on the mode of action of the examined treatment special attention should be paid to long-term effects on endocrinium. Intermittent versus continuous treatment strategies might have different impacts on long-term adverse events (see 1.3) (15). For new chemical entities, long-term safety data of at least 12 cycles are needed. Safety should be covered by risk management plans.

LIST OF ABBREVIATIONS

Abbreviations and Terms	Definition
ACOG	American College of Obstetricians and Gynaecologists
C-CASA	Columbia Classification Algorithm of Suicide Assessment
C-SSRS	Columbia Suicide Severity Rating Scale
COC	Combined oral contraceptive
COPE	Calendar of Premenstrual Experience
DRSP	Daily Record of Severity of Problems
DSR	Penn Daily Symptom Rating
DSM-III/IV	Diagnostic and Statistical Manual of Mental Disorders Version III/IV
GAD	Generalised Anxiety Disorder
GnRH	Gonadotropin-releasing hormone
ICD-10	International Classification of Diseases, version 10
LLPDD	Late Luteal Phase Dysphoric Disorder (LLPDD)
MDD	Major Depressive Disorder
MDQ	Menstrual Distress Questionnaire
NSRI	Norepinephrine and Serotonin Reuptake Inhibitor
PD	Panic Disorder
PMDD	Premenstrual dysphoric disorder
PMS	Premenstrual syndrome
PMSD	Premenstrual Symptom Diary
SSRI	SelectiveSerotonin Reuptake Inhibitor

Definitions

Table 1: DSM-IV criteria for PMDD

TABLE 1
Research Criteria for Premenstrual Dysphoric Disorder

A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):
   1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
   2. Marked anxiety, tension, feelings of being "keyed up" or "on edge"
   3. Marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection)
   4. Persistent and marked anger or irritability or increased interpersonal conflicts
   5. Decreased interest in usual activities (e.g., work, school, friends, hobbies)
   6. Subjective sense of difficulty in concentrating
   7. Lethargy, easy fatigability, or marked lack of energy
   8. Marked change in appetite, overeating, or specific food cravings
   9. Hypersomnia or insomnia
   10. A subjective sense of being overwhelmed or out of control
   11. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," or weight gain

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work or school).

C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).

D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

NOTE: *In menstruating females, the luteal phase corresponds to the period between ovulation and the onset of menses, and the follicular phase begins with menses. In nonmenstruating females (e.g., those who have had a hysterectomy), the timing of luteal and follicular phases may require measurement of circulating reproductive hormones.*

Table 2: 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. (1)

Table 3: Daily Record of Severity of Problems: psychological/physical and functional impairment items

Distinct items	PMDD symptoms from DSM-IV	Individual items (symptoms)	Physical items	Mood items
Psychological/physical items				
1a*	Felt depressed, sad, 'down,' or 'blue'	1		+
1b*	Felt hopeless	2		+
1c*	Felt worthless or guilty	3		+
2*	Felt anxious, tense, 'keyed up' or 'on edge'	4		+
3a*	Had mood swings (e.g. suddenly felt sad or tearful)	5		+
3b*	Was more sensitive to rejection or my feelings were easily hurt	6		+
4a*	Felt angry, irritable	7		+
4b*	Had conflicts or problems with people	8		+
5	Had less interest in usual activities e.g. work, school, friends, hobbies)	9		
6	Had difficulty concentrating	10		
7	Felt lethargic, tired, fatigued, or had a lack of energy	11	+	
8a	Had increased appetite or overate	12	+	
8b	Had cravings for specific foods	13		
9a	Slept more, took naps, found it hard to get up when intended	14		
9b	Had trouble getting to sleep or staying asleep	15	+	
10a	Felt overwhelmed or that I could not cope	16		+
10b	Felt out of control	17		+
11a	Had breast tenderness	18	+	
11b	Had breast swelling, felt 'bloated,' or had weight gain	19	+	
11c	Had headache	20	+	
11d	Had joint or muscle pain	21	+	
Functional impairment items				
1	At work, at school, at home, or in daily routine, at least one of the problems noted above caused reduction of productivity or inefficiency	22		
2	At least one of the problems noted above interfered with hobbies or social activities (e.g. avoid or do less)	23		
3	At least one of the problems noted above interfered with relationships with others	24		

* items characterized as core symptom

Each of the items is rated on a scale from 1 (not at all) to 6 (extreme); thus a maximum sum score of 126 is possible on the first 21 items (8).

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