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Guideline on the treatment of Premenstrual Dysphoric Disorder (PMDD)

Draft

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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 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, 13, 14, 22, 37, 41). 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 Gynecology 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).

These DSM-IV diagnostic criteria define the most severe subpopulation of the broader concept of PMS and were accepted by regulatory bodies outside Europe to grant marketing authorisations for the PMDD 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 recommended criteria defining moderate to severe PMS (see Definitions Table 2). The criteria are 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 can be recruited with the DSM-IV diagnostic criteria for PMDD for clinical trials. These DSM-IV criteria are in the process of updating and further validation, particularly with regard to better quantification of the different domains affected.

1.3. Pathophysiology of PMDD

The exact pathophysiology of PMDD has not been understood and clarified. The etiology is considered multi-factorial and many research data have shown abnormalities in the hypothalamus-pituitary-ovary axis and brain serotonergic system in this patient population.

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 (39). Studies on PMDD rather favour abnormal hypothalamic-pituitary regulation across the menstrual cycle and abnormal luteal phase cortical excitability as underlying mechanism (25). 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 (17).

1.4. Treatment

Based on these theories for the underlying causes until now two main methods of treating PMDD have been under development (1) treatment options targeting the hypothalamus-pituitary-ovary axis by abolishing fluctuations in gonadal hormone levels (e.g. GnRH analogues, oestradiol, combined oral contraceptives (COCs)) and (2) treatment options targeting brain serotonergic synapses by increasing central serotonergic transmission (e.g. SSRI, NSRI).

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

1.5. Differential diagnosis

It is mandatory to separate PMDD from other diagnoses including both psychiatric and nonpsychiatric disorders (see DMS-IV criterion C, Table 1).

Most chronic psychiatric or medical conditions will be apparent throughout the whole menstrual cycle. 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 must be experiencing PMDD. The underlying mechanism of this increase in symptoms is not understood.

Dysthymia, Major Depressive Disorder (MDD), panic disorder and generalised anxiety disorder 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, 22).

Medical disorders that may demonstrate a premenstrual increase in symptoms further include migraines, asthma, seizure disorders, irritable bowel syndrome, diabetes, chronic fatigue symptom, allergies and autoimmune disorders. The diagnosis of these conditions is usually straightforward because the key symptoms are not part of the typical PMDD set of symptoms and emotional symptoms are not prominent (22).

2. Scope

The scope of the present document is to provide guidance in the definition 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 focused on 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 adequate target for the development of pharmacological treatment, however, careful considerations on the adequate trial design of clinical studies are required.

3. Legal basis

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

- 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 (ICH11);
- Adjustment for Baseline covariate – CHMP/EWP/2863/99;
- Missing data – CPMP/EWP/177/99;
- Extent of Population Exposure to Assess Clinical Safety – CPMP/ICH/375/95 (ICH E1A);
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A);
- Note for guidance on the investigation of drug interactions EMEA/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 Rev1.

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, 27, 28). Premenstrual symptoms seem to affect women irrespective of cultural background or socioeconomic status, although specific symptoms may vary in frequency by culture background.

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 research 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. Several assessment instruments to establish diagnosis of PMDD are available: e.g. the DRSP (Daily record of severity of problems) (29), the DRS (Penn daily symptom rating), and the MDQ (menstrual Distress Questionnaire) (10).

PMDD requires prospective reporting of symptoms. Skilled and reliable screening methods should be used. In advance and if necessary during the study raters (e.g. physicians) 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). Retrospective reporting is not acceptable as retrospective recall of symptoms is unreliable (26).

PMDD specifies the number and types of symptoms but not the degree of increase required during the luteal phase. The presence of five out of 11 possible symptoms, 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”. The method of standardizing and operationalizing DSM-IV criteria should be described in studies of PMDD (32). A minimum duration of 4 days for symptom presence in the last week of the luteal phase should be required.

There is no consensus on how symptom severity should be assessed. 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.

Presence and acceptance of co-morbidities

PMDD may be a co-morbid condition with other axis I disorders, 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 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 and that symptoms of PMDD tend to persist beyond successful pharmacological treatment of MDD in women diagnosed with both (40). 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 (18).

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 chronic or severe major mental disorder, alcoholism or substance abuse during the last 2 years prior to the trial
- Any formal psychotherapeutic counselling within 1 month before 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), anxiolytics, and antidepressants during the 3-month period prior to screening and during the study. In case contraceptives are used before the start of the trial as baseline therapy, 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 baseline and end of treatment scores in symptomatology. 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. A clinically relevant treatment response has been defined in PMDD treatment trials, as a 50% reduction in symptom ratings post-treatment versus baseline (2).

Several valid and reliable daily rating forms are available for the prospective recording of PMDD symptoms (10, 13).

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 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 data are available for the 'Daily Record of Severity of Problems' (DRSP) that was developed for diagnosing and evaluating PMDD (see Definitions Table 3; 6, 8, 40). 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).

4.2.2 Definition of secondary endpoints

Secondary outcome measures should be the change from baseline of the components of the PMDD criteria which include physical, affective and functional symptoms. Cyclicity of symptoms should be an outcome measure, especially in clinical trials in which the main demonstrated action of the active compound is elimination of hormonal cyclicity by suppression of ovulation..

Important secondary endpoints:

- Change from baseline in items of the DRSP scale describing psychological and physical impairment.
- Change from baseline in items of the DRSP scale describing functional impairment:

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

For rating scales that rely on self-ratings the validity of the outcome scales should be confirmed by observer-ratings. Therefore, in research studies, clinician rating scales should be used in addition to the patient´s symptom reports. Clinician ratings are based on patient interview, including the patient´s symptom reports and global assessment of symptom severity, improvement and adverse events. Physicians must be trained for using the different rating scales (see 4.1).

Additional secondary endpoints used in clinical trials might include the Clinical Global improvement Scale (CGI scale), the Hamilton Depression Rating scale, the Beck Depression Index (BDI II), the Profile of Mood States (POMS), the State-Trait Anxiety Inventory (STAI), the SF-36 (General Health Survey), the Endicott Q-Les-Q (Quality of Life Enjoyment and Satisfaction Questionnaire), the SAS (Social Adjustment scale). Used tools should be justified and adjusted for multiplicity (4, 20).

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

Due to the subjective nature of the primary endpoint, two well-conducted therapeutic studies are required for a specific claim in this indication. Both, short term-efficacy and maintenance of effect have to be proven. Confirmatory studies should be randomised, double-blind, parallel group and placebo controlled and designed to demonstrate superiority over placebo. In case of inclusion of an active control the choice and dose of the comparator should be justified on the basis of placebo-controlled evidence of efficacy of the comparator. However, there is no established gold standard for the time being.

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

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

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

Blinding

In placebo-controlled studies investigating treatment options which may influence the menstrual bleeding pattern (e.g. COCs), special attention should be paid to blinding.

Data analyses

Longitudinal data analyses of the repeatedly measured outcome (e.g. the daily recorded DRSP score) can provide a more detailed insight in the time course of primary and secondary endpoint variables. These analyses should consider the cyclic nature of the disease. Summary measures might be given per cycle and subject allowing for a longitudinal analysis of these measures over several cycles. Cycles should clearly be defined. Different cycle lengths induced by study medication may be an issue. The proposed analyses should be guided by clinical relevance.

For details on the statistical analysis refer to the statistical guideline (ICH 9) as well as the Points to consider document concerning missing values.

4.3.3 Study duration

Since PMDD is a chronic condition clinical studies should be long enough to provide information about the effectiveness, tolerability and patient compliance associated with a treatment. 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).

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. Studies indicate that 14% to 88 % of adolescent girls have moderate to severe symptoms of PMS, respectively (5, 27, 28). Though the diagnosis is not frequently made, the literature suggests that a similar proportion of teens 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 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, suicidal ideation and behaviour should be monitored carefully. Special attention should be paid to attempted and completed suicides. The Columbia Suicide severity Rating Scale by Posner et al. (24) or alternative rating scales may be used.

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. 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 E1A). Special attention should be paid to long-term effects on endocrinium. For new chemical entities, long term safety data of at least 12 cycles are needed. Safety should be covered by risk management plans.

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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