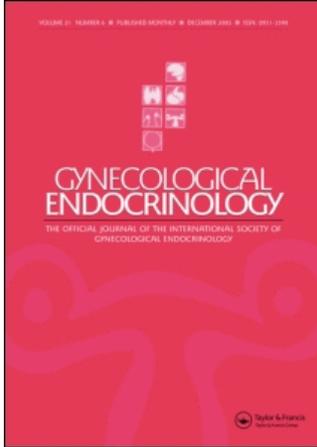


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Clinical diagnostic criteria for premenstrual syndrome and guidelines for their quantification for research studies

Uriel Halbreich ^a; Torbjorn Backstrom ^b; Elias Eriksson ^c; Shawn O'Brien ^d; Helena Calil ^e; Eva Ceskova ^f; Lorraine Dennerstein ^g; Saida Douki ^h; Ellen Freeman ⁱ; Andrea Genazzani ^j; Isabella Heuser ^k; Nadia Kadri ^l; Andrea Rapkin ^m; Meir Steiner ⁿ; Hans-Ulrich Wittchen ^o; Kimberly Yonkers ^p

^a Departments of Psychiatry and Obstetrics and Gynecology, State University of New York at Buffalo, Buffalo, New York, USA

^b Department of Obstetrics and Gynaecology and Umea Neurosteroid Research Center, Department of Clinical Sciences, Norrland University Hospital, Umeå, Sweden

^c Department of Pharmacology and Department of Clinical Neuroscience,

Sahlgrenska Academy, Göteborg University, Göteborg, Sweden

^d Academic Unit of Obstetrics and Gynaecology, Keele University Medical School, Stoke-on-Trent and Royal College of Obstetricians and Gynaecologists, UK

^e Department of Psychobiology, Federal University of Sao Paulo, Sao Paulo, Brazil

^f Department of Psychiatry of the Medical Faculty, Masaryk University and Faculty Hospital, Brno, Czech Republic

^g Department of Psychiatry, Office for Gender and Health, The University of Melbourne, Parkville, Victoria, Australia

^h Department of Psychiatry, Faculty of Medicine, Hospital Razi, Tunis, Tunisia

ⁱ Departments of Ob/Gyn and Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA

^j Division of Gynecology and Obstetrics 'P. Fioretti', S. Chiara Hospital, University of Pisa, Pisa, Italy

^k Department of Psychiatry, Charité- University Medicine, Campus Benjamin Franklin, Berlin, Germany

^l Department of Psychiatry, Ibn Rushd University Psychiatric Centre, Casablanca, Morocco

^m Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

ⁿ Departments of Psychiatry & Behavioural Neurosciences and Obstetrics & Gynecology, McMaster University, Hamilton, Ontario, Canada

^o Technical University of Dresden Institute of Clinical Psychology and Max-Planck Institute of Psychiatry, Munich, Germany

^p Departments of Psychiatry, Ob/Gyn, Epidemiology and Public Health, Yale School of Medicine, New Haven, Connecticut, USA

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ORIGINAL ARTICLE

Clinical diagnostic criteria for premenstrual syndrome and guidelines for their quantification for research studies

URIEL HALBREICH¹, TORBJORN BACKSTROM², ELIAS ERIKSSON³, SHAWN O'BRIEN⁴, HELENA CALIL⁵, EVA CESCOVA⁶, LORRAINE DENNERSTEIN⁷, SAIDA DOUKI⁸, ELLEN FREEMAN⁹, ANDREA GENAZZANI¹⁰, ISABELLA HEUSER¹¹, NADIA KADRI¹², ANDREA RAPKIN¹³, MEIR STEINER¹⁴, HANS-ULRICH WITTCHEN¹⁵, & KIMBERLY YONKERS¹⁶

¹Departments of Psychiatry and Obstetrics and Gynecology, State University of New York at Buffalo, Buffalo, New York, USA and World Psychiatric Association, Section on Interdisciplinary Collaboration, ²Department of Obstetrics and Gynaecology and Umea Neurosteroid Research Center, Department of Clinical Sciences, Norrland University Hospital, Umeå, Sweden, ³Department of Pharmacology and Department of Clinical Neuroscience, Sahlgrenska Academy, Göteborg University, Göteborg, Sweden, ⁴Academic Unit of Obstetrics and Gynaecology, Keele University Medical School, Stoke-on-Trent and Royal College of Obstetricians and Gynaecologists, UK, ⁵Department of Psychobiology, Federal University of Sao Paulo, Sao Paulo, Brazil, ⁶Department of Psychiatry of the Medical Faculty, Masaryk University and Faculty Hospital, Brno, Czech Republic, ⁷Department of Psychiatry, Office for Gender and Health, The University of Melbourne, Parkville, Victoria, Australia, ⁸Department of Psychiatry, Faculty of Medicine, Hospital Razi, Tunis, Tunisia, ⁹Departments of Ob/Gyn and Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA, ¹⁰Division of Gynecology and Obstetrics 'P. Fioretti', S. Chiara Hospital, University of Pisa, Pisa, Italy, ¹¹Department of Psychiatry, Charité – University Medicine, Campus Benjamin Franklin, Berlin, Germany, ¹²Department of Psychiatry, Ibn Rushd University Psychiatric Centre, Casablanca, Morocco, ¹³Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, Los Angeles, California, USA, ¹⁴Departments of Psychiatry & Behavioural Neurosciences and Obstetrics & Gynecology, McMaster University, Hamilton, Ontario, Canada, ¹⁵Technical University of Dresden Institute of Clinical Psychology and Max-Planck Institute of Psychiatry, Munich, Germany, and ¹⁶Departments of Psychiatry, Ob/Gyn, Epidemiology and Public Health, Yale School of Medicine, New Haven, Connecticut, USA

Abstract

Premenstrual syndrome (PMS) encompasses a variety of symptoms appearing during the luteal phase of the menstrual cycle. Although PMS is widely recognized, the etiology remains unclear and it lacks definitive, universally accepted diagnostic criteria. To address these issues an international multidisciplinary group of experts evaluated the current definitions and diagnostic criteria of PMS and premenstrual dysphoric disorder (PMDD). Following extensive correspondence, a consensus meeting was held with the aim of producing updated diagnostic criteria for PMS and guidelines for clinical and research applications. This report presents the conclusions and recommendations of the group. It is hoped that the criteria proposed by the group will become widely accepted and eventually be incorporated into the next edition of the World Health Organization's *International Classification of Diseases* (ICD-11). It is also hoped that the proposed guidelines for quantification of criteria will be used by clinicians and investigators to facilitate diagnostic uniformity in the field as well as adequate treatment modalities when warranted.

Keywords: *Premenstrual syndrome, PMS, diagnosis, research*

Introduction

The existence of clinically significant premenstrual symptoms has been acknowledged from antiquity. In the modern era, the broad diagnostic concept of

premenstrual syndrome (PMS) has been recognized for over 70 years [1,2]. PMS encompasses a wide variety of cyclic and recurrent physical, emotional, behavioral and cognitive symptoms that occur during the luteal phase of the menstrual cycle and remit

shortly following the beginning of menses [3–5]. The majority of women of reproductive age usually experience one or more premenstrual symptoms during most of their menstrual cycle [6–8]. The severity and frequency of symptoms experienced may differ between each cycle but their nature is usually stable within each woman. The most prevalent severe symptoms are emotional and behavioral – irritability, mood lability, depressed moods, anxiety, impulsivity, social friction and feelings of ‘loss of control’ as well as fatigue; cognitive – decreased concentration; and physical – bloatedness, breast swelling and tenderness, and general aches [5,9,10]. Symptoms may cause impairment and distress that warrant treatment in up to 20% of women of reproductive age [4,7,11–13].

Furthermore, it is estimated that up to 8% of women experience premenstrual dysphoric disorder (PMDD), a debilitating emotional condition at the severe end of the spectrum of premenstrual symptoms [7,14–16].

Premenstrual symptoms may be severe enough to have a substantial negative impact on the individual’s daily life activities and her relationships with family members and partners [17,18]. Social and personal functions may be impaired; work performance, family and social activities, and sexual relationships are often negatively affected [17–27].

A strong correlation between PMS symptom severity and impairment of social and work performance has been demonstrated [26,28]. Women with PMS are almost nine times more likely to report over a week of impairment to partnership and family activities, hobbies and work productivity, compared with women without PMS. As many as 80% of women with PMS report at least one week per month of reduced work productivity as a result of premenstrual symptoms; furthermore, women with PMS have higher levels of absenteeism as a result of their symptoms than women without PMS. An increase in the use of healthcare resources by women with PMS is reflected in a greater number of visits to ambulatory healthcare providers compared with women without PMS [17]. In the USA, a diagnosis of PMS was found to be associated with significantly increased direct (cost of medical care) and indirect (loss of work productivity; \$4333 per patient) costs [29].

PMS has been reported in many culturally diversified developed as well as developing countries [30–34]. PMS/PMDD results in a similar burden of illness (disability-adjusted life years, DALYs) as major dysphoric disorders [22]. It has been estimated that 14 492 465 years of productivity in the USA and 17 534 579 years in the European Union countries are lost for the limited number (5%) of women meeting the criteria for just PMDD alone (strict definition according to the *Diagnostic and Statistical*

Manual of Mental Disorders, fourth edition; DSM-IV) [4,22]. The global DALYs for women suffering from PMS may well be astonishing, if calculated.

Accurate prevalence rates of PMS and the impact of symptoms are, however, difficult to determine, mainly due to a lack of universally accepted operational diagnostic criteria for PMS.

Current diagnostic criteria for premenstrual syndrome

The World Health Organization (WHO) and the American College of Obstetricians and Gynecologists (ACOG) have both published diagnostic guidelines for PMS [35,36]. In the tenth edition of the WHO’s *International Classification of Diseases (ICD-10)*, the definition of premenstrual tension syndrome is included in the Gynaecology Section and requires at least one symptom to be present from a range of physical and emotional symptoms. Severity of symptom(s) is not specified [35]. The ACOG has proposed a stricter definition of PMS that requires at least one of a list of emotional and physical symptoms to be experienced by women during the five days before menses and remit within 4 days of onset of menses, with no recurrence at least until day 13 of the cycle, in each of three prior menstrual cycles. Identifiable dysfunction in social or economic performance and prospective confirmation for two cycles are required.

PMDD has emerged as a separate clinical entity, defined in the DSM-IV [37]. To fulfill the DSM-IV criteria, premenstrual symptoms must occur in the last week before menses and remit within a few days of onset of follicular phase, and they must reach a level of severity that interferes with functioning in work, family and social relationships. At least five symptoms (including at least one major dysphoric symptom) out of a list of 11 symptoms must have been present in the majority of cycles in the preceding 12 months. Symptoms must be confirmed prospectively by daily monitoring for at least two consecutive symptomatic menstrual cycles and cannot be merely an exacerbation of another disorder.

Why new diagnostic criteria are needed

The diagnosis and effective management of PMS and PMDD present several challenges to clinicians. This starts with the lack of a universal consensus on the nature of PMS and PMDD, as well as the lack of universal and interdisciplinary acceptance of the current diagnostic criteria; nor are any criteria applied in everyday clinical practice. As the clinical and public health impact of PMS and PMDD is substantial, internationally accepted diagnostic criteria and guidelines are required.

An accurate diagnostic entity with specific and accepted criteria is required for prescription of

specifically targeted efficacious treatment, for drug labeling, for clinical trials, and for any meaningful research on underlying mechanisms and associated conditions of the diagnostic entity.

From the research perspective, the absence of a universally accepted and implemented diagnostic tool for PMS and PMDD has contributed to the diverse range of outcomes measured in clinical trials. Different studies use different methodologies and criteria to assess the symptoms of PMS and PMDD and the severity of their impact on normal daily life. As a result, the prevalence rates of PMS and PMDD vary widely among different studies, with estimates of the prevalence of moderate or severe PMS ranging from 8 to 32% [10,19]. Furthermore, the issue of PMDD being a separate diagnostic entity independent of PMS is still unresolved.

The three most commonly acknowledged diagnostic guidelines/criteria for PMS or PMDD are associated with several limitations. The WHO's ICD-10 description of the syndrome is somewhat vague; it does not specify a required level of impairment or severity of symptoms, it lists few specific symptoms and does not require prospective confirmation. Essentially, it merely acknowledges the existence of the condition. The ACOG criteria for PMS and the DSM-IV criteria for PMDD are the outcome of elaborate work by organized American gynecologists (for PMS) and the American Psychiatric Association (for PMDD), and represent significant advances towards more specific diagnoses. However both do not specify the number of days that premenstrual symptoms should be experienced. The DSM-IV PMDD criteria specify a threshold number of symptoms; however, their selection-specific emphasis and the specific numerical threshold (five of 11 symptoms) still need to be substantiated as is the ACOG list of symptoms.

Both the ACOG and DSM-IV criteria require impairment of functioning for a diagnosis. However, as is the case with most pain and emotional states, the degree of severity is subjectively described by the sufferer and therefore the assessment is heavily influenced by the individual's personality, perception, tolerance and subjective definition of what constitutes 'severe'. There is no consensus on how PMS/PMDD symptom severity should be assessed. In any method for assessment of PMS or 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 post-menstrually. A commonly used measure for these differences has been recommended by a panel convened at the US National Institute of Mental Health, which suggested 30% as the criterion for a marked difference between pre- and post-menstrual symptom level [38]. However, if the baseline is zero, a 30% increase will still be below a disorder threshold.

One review of PMS outcomes found 65 different questionnaires or scales, measuring 199 different symptoms or signs, ranging from irritability, impulsivity, depression and anxiety to headaches, mastalgia and bloatedness [39]. Since that review the number of questionnaires has proliferated further, e.g. [12,40–43]. It is, therefore, almost impossible to accurately compare findings of many PMS clinical studies. Indirect statistical measures such as the standardized mean difference or effect size [44,45] provide for only a partial solution.

This report presents the conclusions and recommendations of an international multidisciplinary group of experts who evaluated current definitions and diagnostic criteria of PMS and PMDD. The group believes that the advancement in knowledge in the multidisciplinary fields relevant to PMS calls for updated diagnostic criteria of PMS and guidelines for their clinical and research applications. It is hoped that the criteria will be widely accepted, eventually incorporated in the next edition of the *International Classification of Diseases* (ICD-11), and used by clinicians and investigators to facilitate diagnostic uniformity in the field as well as adequate treatment modalities when warranted.

The group's methods and process

Review of the literature

A comprehensive review of MEDLINE and HealthSTAR databases was undertaken. For the years 1980–2002 (Bornstein et al., unpublished) articles on research conducted on human populations and published in English – focused on PMS, PMT, PMDD or LLPDD evaluation, diagnosis, management and/or treatment – were included. The expert panel agreed upon the search terms and strategies by a unanimous vote. The panel critically appraised each article and group consensus on quality and relevance was achieved by a modified Delphi technique. The four US participants in the current consensus group also participated in this data review. Treatment-related articles were considered for the current database only if they were relevant for diagnostic criteria and their quantification. The outcome of the first panel was considered for previously published papers [4,46,47]. The literature search was expanded to other languages and updated until late 2005 as a component for the formation of statements and the consensus group deliberations.

Subsequent deliberations

The group of experts was constructed of nine women and seven men, clinicians and investigators who have published extensively on PMS and/or PMDD and/or women's mental health, with diversity of

backgrounds including gynecologists (five), reproductive endocrinologists (two), psychiatrists (eight), psychologists (two), a pharmacologist and an epidemiologist. A geographic balance and experience in regional, culturally sensitive clinical research were emphasized.

Issues and specific questions were first debated electronically, followed by a series of statements on the definition of PMS and criteria for its diagnosis. A written vote for each statement was taken. We considered a consensus when there were only two dissidents or fewer (out of 16 voters). Points of controversy were deferred for face-to-face discussion. Suggested amendments of definition and clinical criteria were presented, discussed and voted on in a face-to-face group meeting during which each question or statement was again reviewed individually and discussed until consensus was confirmed. Some points on which consensus was not achieved were recommended for future studies.

Consensus group recommendations on premenstrual syndrome

- (1) **ICD diagnostic code:** Should be incorporated in a new 'multidisciplinary diagnoses' section.
- (2) **Title:** PMS – Premenstrual syndrome (different patterns of symptoms or clusters of symptoms may appear as part of the syndrome).
- (3) **Definition:** PMS is distinguished by the timing of symptom(s). It is characterized by symptom(s) (or clusters of symptoms) that are associated with the premenstrual phase of the cycle, are recurrent, and are severe enough to cause impairment and distress.

Any symptom or cluster of symptoms qualify as PMS if they occur mostly during the luteal phase of the menstrual cycle, are alleviated shortly following menses and are not merely an exacerbation of other underlying conditions. Examples of prevalent severe symptoms are: emotional and behavioral – irritability, anxiety, depression, mood lability, impulsivity, social frictions, lack of control and fatigue; cognitive – decreased concentration; physical – bloatedness, breast swelling and tenderness, and general aches. During the symptomatic phase there is an impairment in daily functions and/or relationships, or distress that is severe enough to warrant help. This is the critical feature that distinguishes PMS from normal premenstrual experiences. Impairment, dysfunction and/or distress occur during most, but not necessarily all menstrual cycles, and are absent post-menses for at least days 6–10 of the menstrual cycle.

The timing, menstrually-related cyclicality and severity of symptom(s) as well as their absence in the follicular phase are documented by repeated

observations or monitoring. PMS may be associated with ovulation-related processes. The existence and nature of specific subtypes or phenotypes still need to be elucidated. Such subtypes may be associated with different additional underlying mechanisms that may suggest differentiated treatment responses.

Clinical diagnostic criteria of premenstrual syndrome

A woman should be diagnosed as having PMS if **all** of the following criteria are met:

- (1) The symptom(s) occur up to 2 weeks before menses in most menstrual cycles.
- (2) Symptoms(s) remit shortly following onset of menses and are absent during most of the mid-follicular phase of the menstrual cycle.
- (3) The symptom(s) are associated with impairment in daily functioning and/or relationships and/or cause suffering, emotional or physical distress.
- (4) The menstrual-related cyclicality, occurrence during the luteal phase and absence during the mid-follicular phase are documented by repeated observations by a clinician and/or daily monitoring by the patient.* (*In hysterectomized women, menstrual-related cyclicality is documented by clinical determinations.)
- (5) The symptom(s) are not just an exacerbation or worsening of another mental or physical chronic disorder. PMS may also be a concomitant condition.

Guidelines on operational quantification of diagnostic criteria for premenstrual syndrome for research studies

Operational principles

There should not be separate research diagnostic criteria for PMS. Rather, each clinical criterion should be quantified for research purposes. A quantified state of disorder or disease should be defined. When applicable, a range of normalcy is defined. Then a quantified definition of threshold beyond which the individual criteria are 'abnormal' should be provided.

For clinical trials, targeted populations and their symptoms should be specified as well as the definition of response/remission improvement.

Specific quantified criteria

- A regular menstrual cycle: The length of a regular menstrual cycle varies among individuals and varies slightly within an individual. Therefore cycles within a lower limit of 24 days and an upper

limit of 35 days are considered to be within a normal range.

- Determination of ovulatory cycles: Since lack of symptoms during the premenstrual period may be due to an anovulatory cycle, for studies of biological ovulation-related underlying mechanisms ovulation and its day should be documented. For some clinical trials, mid-luteal progesterone levels should be detected in order to exclude anovulatory cycles from analyses.

Diagnostic criterion 1

- The symptom(s): PMS is not distinguished by the nature of symptom(s). Any symptom may qualify as PMS. For specific studies, a specific list of targeted symptoms should be studied and monitored. A core symptoms list to be monitored for most studies still needs to be confirmed.
- Severity of individual symptom(s): A severity scale of 0–10 or equivalent is recommended, where 0 = no symptoms, 1–3 = mild, 4–6 = moderate, 7–10 = severe. Some studies will only include women with severe symptom(s) (>7), others will include women with moderate and severe symptom(s) (≥ 4).
- Timing of symptom(s): During the 14 days prior to onset of menstrual flow (rather than spotting) and up to 5 days during the menstrual flow.
- Pattern and length of symptomatic period: Minimum of 2 days, up to 14 days.
- ‘Most menstrual cycles’: For initial screenings, two out of last three consecutive cycles; for enrolment, two out of three monitored cycles.

Diagnostic criterion 2

- Timing and length of asymptomatic phase: Day 6 to at least day 10 of the menstrual cycle.
- Absence of symptoms: A symptom is considered ‘absent’ if its severity is rated 0–3 (‘not exist’ to ‘mild’) on the scale of 0–10. An occasional day of moderate stress due to external circumstances is accepted.

Diagnostic criterion 3

- Measurement of impairment, dysfunction and distress: An adaptation of the Sheehan Disability Scale (0–10, self-rating) should be administered at least on the first day of full menstrual flow, pertinent to ‘last week’. Most but not all experts agreed that impairment and/or distress should last for at least 2 days.

Diagnostic criterion 4

- Cyclicity – measurement of the ‘off-on’ phenomenon: There should be a clear shift from no

symptoms (below threshold) to symptoms (above threshold). ‘No symptoms’ are defined as severity of 0 (not exist) to 3 (mild) during mid-follicular phase. Definition of above-threshold severe symptoms varies according to studies, from 4 (lower level of ‘moderate’) to 7 (lower level of ‘severe’).

- Repeated observations by a clinician are needed for specific research protocols: They should be performed at least twice – during symptomatic and asymptomatic phases.
- Daily monitoring by the patients: During two, not necessarily consecutive, cycles.

Diagnostic criterion 5

Fluctuations or exacerbations of disorders and conditions listed in Table I should be excluded.

Suggestions for the clinical diagnostic process

There is a need for a clinically relevant, practical diagnostic process that will focus on the unique distinction of PMS: luteally entrained repeated cyclicity. The process should reflect the reality of a busy outpatient general practice, obstetrics/gynecology or mental health clinics and the wish of the woman for an immediate treatment decision and professional help, if warranted.

There was a consensus that when a patient calls for an appointment for diagnosis of PMS and initial screening does not point to any other condition, she may be sent a daily rating form to monitor her symptoms over one menstrual cycle. She should whenever feasible get explanation and instructions over the phone and bring the daily rating form with her to the clinical visit. Preferably the clinical visit should be scheduled for the non-symptomatic mid-follicular

Table I. Differential diagnoses of premenstrual syndrome.

Mental disorders (may be with premenstrual exacerbations)	General medical conditions (with menstrual-related worsening exacerbations)
Chronic depressions	Dysmenorrhea
Major depressive episodes	Endometriosis
Bipolar disorder	Polycystic ovaries
Generalized anxiety disorder	Adverse effects of hormonal contraceptives
Panic disorder	Perimenopausal symptoms
Somatiform disorder	Seizure disorders, epilepsy
Substance abuse	Migraines
ADHD	Autoimmune diseases (e.g. MS, SLE)
	Hypothyroidism
	Hyperglycemia
	Anemia
	Allergies

ADHD, attention deficit/hyperactivity disorder; MS, multiple sclerosis; SLE, systemic lupus erythematosus.

phase of the menstrual cycle. Sending a woman with suspected PMS home with instructions to start prospective daily ratings monitoring of her symptoms may not be feasible for clinical evaluations.

During the initial visit physical and mental histories should be taken and a physical examination should be performed. As premenstrual symptoms occur in a cyclical recurring pattern, a diagnosis of PMS or any of its probable manifestations or patterns, e.g. PMDD, may be obscured by the presence of other disorders which can be associated with premenstrual magnification or exacerbation. The differential diagnosis of PMS (or PMDD) includes any medical and psychiatric condition that either presents symptoms which are similar to some of the symptoms of PMS or is subject to premenstrual exacerbation (see Table I). Only when symptoms are absent during the post-menstrual phase of the menstrual cycle may PMS be considered. It should be noted, however, that PMS may be a concomitant condition. The presence of another psychiatric or medical condition does not necessarily rule out an additional diagnosis of PMS (or PMDD), nor does it rule out a benefit of adjuvant PMS treatment.

Need for future diagnostic studies of premenstrual syndrome

Despite substantial progress in the field there are still major gaps in knowledge as well as a need to improve methodology in studies of PMS.

In order to improve methodology, first and foremost the development of a universal, widely accepted research assessment tool for PMS is needed. This tool should reflect the operational quantification of the criteria as they are recommended here. It should be flexible to allow for identification of putative diversified patterns and subtypes of PMS and be adequate for assessment of PMDD or its future DSM-V equivalent. The tool should allow for targeting specific groups of women for more selective PMS treatments. Once an English version is developed, culturally sensitive but harmonized translations – to allow for cross-cultural studies – should be developed.

Methods and tools to improve compliance and efficiency of monitoring of symptoms should be refined, including confirmation of less frequent alternatives to daily monitoring – especially for use in long-term clinical trials or epidemiologic studies. Simplified statistical analyses should be developed to measure cyclicity, repetition of symptoms and burden of disease.

There is a need for field trials to confirm and refine the operational quantification of the recommended clinical criteria. Previous large-scale clinical trials or other studies may be re-analyzed according to these criteria. As a second step, cross-cultural epidemiolo-

gic trials, including personal and social burden of disease studies, should be conducted.

The concept of PMS and the boundaries of its domain are still not universally agreed upon. It is apparent that currently there is a controversy whether PMS is a syndrome or a group of syndromes. PMS could be an umbrella term, under which different patterns or clusters of symptoms would appear. This issue needs further studies with methods that will allow for identification of diversified phenotypes. It is also important for further clinical trials aimed at specific well-defined populations. Differential treatment responses may be studied as a component for identifying different underlying mechanisms of PMS. It is likely that there is a genetic component to the existence and severity of premenstrual symptoms [48]. Such a genetic component and its relationships with environmental inputs should be studied, preferably according to specific phenotypes, when they are demonstrated. Although PMS appears to exist across cultures, the symptoms' patterns or clusters may vary among cultures [34]. The influence of socio-cultural factors on symptoms that women notice or consider problematic should be studied.

The association between PMS and catamenial episodes should be clarified. The degree of overlap between premenstrual migraines, premenstrual epilepsy, and other premenstrual exacerbations of chronic disorders and PMS should be clarified. Some women experience cyclic symptoms that occur during the interval (withdrawal period) of combined oral contraceptives or during triphasic dosing. It is still unclear if such episodes should be considered as PMS.

Summary

The prevalence of PMS, its personal and public health impact and burden of disease call for uniform, widely accepted definitions and diagnostic criteria. In the report of an international multidisciplinary consensus group presented here such criteria are recommended. The criteria emphasize timing, impairment and distress and allow for subtypes of PMS to emerge. It is hoped that their specified quantifications will allow for improvement in targeted clinical trials and understanding of underlying mechanisms of specific symptoms, as well as culturally sensitive comparable studies of epidemiology and burden of disease.

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Conflicts of interest and disclosures

We declare that we have participated in the consensus process and that we have seen and approved the final version. We have the following conflicts of interest.

U.H. received grant/research support from Eli Lilly, Wyeth, Bristol Myers Squibb (BMS) and Pfizer. He has been a consultant for Schering, Janssen, Berlex and Wyeth.

T.B. received research/grant support from Organon, Orion Pharma and Schering. He has served as a consultant for Organon, Orion Pharma and Schering.

E.E. received research/grant support from Lundbeck, BMS and Glaxo Wellcome. He is a consultant for Lundbeck, Eli Lilly and Schering.

P.M.S.O'B. received research/grant support from British Heart Foundation and Novo Nordisk. He is a consultant for Schering.

H.C. received research/grant support from Astra-Zeneca and Eli Lilly. She is a consultant for Eli Lilly, Boehringer Ingelheim and Servier. She is also on the Speakers' Bureau for Pfizer and Eli Lilly.

E.C. stated no actual or potential conflict of interest.

L.D. received research/grant support from Organon and Wyeth. She is a consultant for Pfizer.

S.D. stated no actual or potential conflict of interest.

E.F. received research/grant support from Wyeth, Berlex and Forest. She is a consultant for Wyeth and Pfizer. She received an honorarium from Wyeth, Pfizer and Forest. She is also on the Speakers' Bureau for Wyeth, Pfizer and Werner-Chilcott.

A.G. stated no actual or potential conflict of interest.

I.H. stated no actual or potential conflict of interest.

N.K. stated no actual or potential conflict of interest.

A.R. received research/grant support from Wyeth and Berlex. She has received honoraria from TAP and is on the speaker board for Wyeth.

M.S. received research/grant support from Eli Lilly, Pfizer, Glaxo Smith-Kline (GSK), Lundbeck, Novartis and Azevan Pharma. He is a consultant for Eli Lilly, GSK, Novartis, Proctor and Gamble, Pfizer, Lundbeck, Wyeth-Ayerst and Barr Labs. He received an honorarium from Proctor and Gamble and Ortho Mc-Neil. He is on the Speakers' Bureau for Astra-Zeneca, Eli Lilly, Pfizer, GSK, Lundbeck, Wyeth and Warner-Chilcott.

H.-U.W. stated no actual or potential conflict of interest.

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