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Roundtable Discussion

Is Premenstrual Dysphoric Disorder a Distinct Clinical Entity?

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ABSTRACT

Does the evidence now available support the concept of premenstrual dysphoric disorder (PMDD) as a distinct clinical disorder such that the relative safety and efficacy of potential treatment can be evaluated? In a roundtable discussion of this question, a wealth of information was reviewed by a panel of experts. The key characteristics of PMDD, with clear onset and offset of symptoms closely linked to the menstrual cycle and the prominence of symptoms of anger, irritability, and internal tension, were contrasted with those of known mood and anxiety disorders. PMDD displays a distinct clinical picture that, in the absence of treatment, is remarkably stable from cycle to cycle and over time. Effective treatment of PMDD can be accomplished with serotinergic agents. At least 60% of patients respond to selective serotonin reuptake inhibitors (SSRIs). In comparison with other disorders, PMDD symptoms

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respond to low doses of SSRIs and to intermittent dosing. Normal functioning of the hypothalamic-pituitary-adrenal (HPA) axis, biologic characteristics generally related to the serotonin system, and a genetic component unrelated to major depression are further features of PMDD that separate it from other affective (mood) disorders. Based on this evidence, the consensus of the group was that PMDD is a distinct clinical entity. Potential treatments for this disorder can now be evaluated on this basis to meet the clear need for effective therapy.

INTRODUCTION

THIS MEETING WAS CONVENED to present and discuss current knowledge and perceptions regarding premenstrual dysphoric disorder (PMDD) and in particular to address the question, "Is there adequate evidence that PMDD is a distinct clinical disorder such that the relative safety and efficacy of potential treatments can be evaluated?"

Jean Endicott; M.D., opened the meeting by briefly outlining the history behind efforts to more clearly define this disorder, which started with a workshop on premenstrual syndrome (PMS) convened jointly by the National Institute of Mental Health (NIMH) Center for Studies of Affective Disorders and the Psychobiological Processes and Behavioral Medicine Section in 1983. (It recommended that there should be a clear contrast between late luteal phase symptoms and complaints and those of the follicular phase [days 6–10 of the menstrual cycle], with a symptom change between phases of at least 30% by whatever scale was being used.) By 1987, criteria for a late luteal phase dysphoric disorder (LLPDD) were proposed and published in the Appendix of the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R).[1]

Subsequently, the term premenstrual dysphoric disorder was adopted and listed as an example of "depressive disorder not otherwise specified" in DSM-IV,[2] published in 1994. The research criteria for the diagnosis were given in the Appendix. The work group behind these changes had undertaken an extensive review of the literature up to 1993 and reached good agreement on the proposed diagnostic criteria for PMDD. There was, however, some lack of consensus within the group, and its members recommended that more studies were needed in this area.

The discussants around the table in Washington, DC, on October 14, 1998, came together, therefore, to determine if additional evidence now available, combined with prior evidence, supports the concept of PMDD as a distinct clinical entity. This meeting involved presentations by individual experts, followed by open discussion of the points raised. This report summarizes the day's proceedings.

To systematically review the available literature, data were presented and discussed in the following areas: diagnostic criteria, epidemiology, symptom profile, family history and genetics, psychosocial functioning, longitudinal course, lifetime comorbidity, biologic characteristics, treatment outcomes, and safety considerations of alternative treatments.

CRITERIA AND DIFFERENTIAL DIAGNOSIS

The diagnostic criteria for PMDD (Table 1) appear more stringent than for any other condition listed in DSM-IV,[2] said Dr. Endicott. Key components of the criteria include onset of symptoms during the luteal phase of the cycle and offset during the early follicular phase, with marked change in at least one dysphoric mood and the presence of at least four additional symptoms. These syndrome changes must be associated with marked impairment in functioning. Dr. Endicott emphasized the need to rule out other mood and mental disorders and to confirm the diagnosis by prospectively recording the timing of the syndrome, the nature and severity of symptoms, and the severity of impairment over two cycles.

In much of the literature, terms other than PMDD, such as severe premenstrual syndrome (PMS), are used. However, by reference to these criteria, which provide a clear description of the samples being studied, it can be seen that there is often considerable overlap and agreement.

EPIDEMIOLOGY

Population

Sally Severino, M.D., confirmed that women who meet the criteria for PMDD, in terms of the

TABLE 1. DSM-IV DEPRESSIVE DISORDER NOT OTHERWISE SPECIFIED: PREMENSTRUAL DYSPHORIC DISORDER

A. In most menstrual cycles during the past year, at least five of the following symptoms (which markedly interfered with functioning) 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 and 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, 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 home and at work or school).

C. The disturbance is not an exacerbation of the symptoms of another disorder, such as Major Depressive, Panic, Dysthymic, or Personality Disorders (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.)

From DSM-IV.[2]

amount of change in their symptoms and the pattern of change across the menstrual cycle, can be identified. However, she cautioned that this finding is not proof that PMDD exists as a valid diagnosis and reiterated previous criticism that "PMDD is an operationally defined construct that is method dependent for diagnosis."[3]

Prevalence

The findings since DSM-IV[2] largely substantiate earlier views that, overall, prevalence rates are remarkably similar. In 1987, Johnson[4] reported that premenstrual changes are experienced by most women to some degree and that severe changes are limited to <20%. A subsequent retrospective epidemiologic survey by Johnson et al.[5] showed that only 3.2% of 996 women experienced severe symptoms.

Age distribution

It has generally been believed, said Dr. Severino, that the average age for clinically significant symptoms is the early to mid-30s, but there are conflicting reports about the relationship between age and premenstrual symptomatology. Freeman et al.[6] found that the severity of symptoms decreased with age in 332 women with LLPDD and was not associated with the duration of symptoms. The peak period for distressing symptoms occurred during their late 20s to mid-30s. The Zurich cohort study[7] revealed a gradual increase in menstrually related problems from ages 21 to 30 years. However, significant premenstrual symptoms have also been identified in adolescents,[8,9] in young women ages 17–29 years,[10] and in those over 40 years of age.[11]

Relatively few conclusions can be drawn at this time regarding age and premenstrual disturbances, said Dr. Severino. Although the majority of women who meet diagnostic criteria for severe PMS, LLPDD, or PMDD and participate in research studies are in their early to mid-30s, it appears that women from menarche to menopause may report clinically significant menstrually related symptoms. There is, therefore, a need for more extensive epidemiologic and longitudinal studies to determine the true course of this condition.

Gender

PMDD solely concerns women. Whether there is any correlation between PMDD and the prevalence of depression, which is twice as high in women as in men, is as yet unknown. However, the biology of the condition must be questioned. Even though there are many overlapping biologic issues between women with PMDD and women with depression, in Dr. Severino's opinion, this implies no more than the possibility of shared pathways that produce the symptoms.

Cross-cultural considerations

A review of the literature since DSM-IV[2] reveals that most of the research on premenstrual symptoms and disorders continues to be conducted in the United States. Studies adopting the LLPDD/PMDD criteria have been conducted exclusively with North American or European subjects.

In their book, Severino and Moline[12] concluded that "premenstrual symptoms are not culture-specific although particular symptoms may be reported more frequently in one culture compared to another." Since then, two publications have addressed this issue, and each relied exclusively on retrospective reports and small samples of either Indian nursing students[13] or Chinese clerical workers.[14] In each study there were more reports of somatic than of affective symptoms. Similarly, in an epidemiologic cohort study of young adults in Switzerland,[7] there were more retrospective reports of somatic than of emotional symptoms.

While remembering that the diagnoses of LLPDD and PMDD require the presence of dysphoric affect during the premenstrual phase, it would appear that women in the United States are far more likely than women from other cultures to complain of affective symptoms premenstrually. If affective premenstrual distress cannot be identified consistently in non-United States or European populations, said Dr. Severino, consideration must be given to the criticism that PMDD is a culturally bound syndrome or an unnecessary pathologizing of cyclical changes in women. Further epidemiologic work in other cultures is warranted to resolve this issue.

Parity

There are no recent publications on the role of parity. The review by Johnson[4] suggested that as age and parity are closely related, it is difficult to assess the effect of each separately on premenstrual symptomatology.

Discussion points

In the subsequent discussion, Dr. Endicott commented that 80% of women seeking treatment at her clinic report worsening of symptoms with time, yet a cross-sectional review of data obtained using a 95-item questionnaire shows no correlation with age (in those with regular menstrual cycles). A 10-year follow-up study of over 250 women revealed considerable stability; very few demonstrated an increase in symptoms. If the PMDD criteria are strictly applied, a prevalence rate of 3%–5% is currently accepted. Use of prospective daily ratings produces a lower rate than retrospective recall.

On the cross-cultural issue, although the Indian women[13] and the Chinese women[14] most frequently complained of somatic symptoms, there was a subset of the population in both studies that reported mood changes. An additional study from Nigeria showed that although more women complained of physical symptoms, on questioning, many women also endorsed mood changes.[15]

Gender was included to emphasize that men can have mood disorders, anxiety disorders, and similar conditions but not PMDD. The contribution of PMDD to the different incidence of depression between men and women is difficult to determine because the sex difference for lifetime prevalence for major depression differs from the point prevalence. The reasons for this have been subject to much discussion.

Researchers into PMDD are aware that application of different methods for assessing severity of symptoms results in somewhat different study populations. A consistent measure is still required to improve reliability in the women identified for studies. The application of an objective rating scale at both the late luteal and midfollicular phases of the cycle, administered by interview, can improve reliability.

False positives

As PMDD is essentially a self-diagnosis through daily ratings, said one participant, does it ever generate false positives, that is, normal women who appear severely dysphoric? No one present was aware of any data on this. However, as with any mental disorder, there is no external validity. Confirmation of suspected PMDD is unique in that the patient is required to complete daily ratings before a formal diagnosis can be made, and this should reduce the likelihood of false positives. The possibility of false positives is not an issue in the clinic, as all the women experience symptoms, and none is likely to deny having the problem if she acknowledges disruption to her daily life.

The issue of false positives has not been documented systematically. If false positives do exist, they might result in (1) treating women not wanting treatment and (2) labeling women falsely.

However, this same problem applies throughout psychiatry.

False negatives

Many more women think they are suffering from severe PMS than actually meet the criteria for PMDD when daily rating scales are used. Is this worrying? Are they false negatives? asked one delegate. False negatives do arise, as strict application of the criteria means that even women seeking treatment and demonstrating cyclic changes may not be diagnosed as having PMDD. Also, among women with the most severe symptoms, the requirement of completing a daily rating scale over two cycles can be a major problem that precludes them from formal diagnosis.

There are, in addition, women who do not meet the criteria but who may still need treatment for premenstrual problems or other disorders.

SYMPTOM PROFILE

The five criteria for validating a psychiatric diagnosis, as proposed by Robins and Guze in 1970,[16] were reviewed by Ellen Frank, Ph.D., in the context of evidence available for PMDD:

- Course and prognosis: good evidence exists.
- Family history: information is still lacking.
- Biologic studies: weak (as in all psychiatry); there are no biologic markers.
- Treatment response: good evidence exists.
- Epidemiology: data exist on point prevalence only.

The symptom lists for PMDD and for major depressive disorder (MDD), as given in DSM-IV,[2] show many similarities (Table 2), but this does not imply that they are necessarily related. The main differences in the research criteria (Table 3) for these two conditions, explained Dr. Frank, are that MDD can be unremitting over a long period, whereas, by definition, the symptoms of PMDD remit completely in the follicular phase. Also, brief or long periods of depressive episodes cause severe functional impairment. PMDD can cause functional impairment, but it may be less severe or of shorter duration. PMDD may produce premenstrual exacerbation of other affective disorders or clinical conditions, such as asthma.

Dr. Frank then described a study to determine symptom types and patterns in 180 women with LLPDD[10] that revealed that of 33 symptoms rated daily over two cycles, there are 4 similar underlying factors that accounted for 64%–88% of the variance. These were negative affect, physical symptoms, agitation, and positive arousal. These findings were similar to those reported else-

TABLE 2. DSM-IV SYMPTOMS LIST FOR PREMENSTRUAL DYSPHORIC DISORDER (PMDD) AND MAJOR DEPRESSIVE DISORDER (MDD)

PMDD symptom list	*MDD symptom list*
Markedly depressed mood	Depressed mood most of the day nearly every day
Marked anxiety or tension	Markedly diminished interest/pleasure in all activities most of the day, nearly every day
Marked affective lability	Significant weight change (± 5%)
Persistent and marked anger/irritability	Insomnia or hypersomnia nearly every day
Decreased interest in usual activities	Psychomotor agitation/retardation nearly every day (observable by others)
Subjective sense of difficulty in concentrating	Fatigue or loss of energy nearly every day
Lethargy, fatigability, or marked lack of energy	Feelings of worthlessness or excessive guilt nearly every day
Marked change in appetite, overeating, or specific food cravings	Diminished ability to think/concentrate, or indecisiveness, nearly every day (subjective or observable)
Hypersomnia or insomnia	Recurrent thoughts of death, suicidal ideation, or suicide attempt or specific plan
Subjective sense of being overwhelmed/out of control	
Physical symptoms (e.g., breast tenderness, headache, joint/muscle pain, bloating, weight gain)	

From DSM-IV.[2]

TABLE 3. DSM-IV RESEARCH CRITERIA FOR PREMENSTRUAL DYSPHORIC DISORDER (PMDD) AND DSM-IV CRITERIA FOR MAJOR DEPRESSIVE DISORDER (MDD)

PMDD research criteria	*MDD criteria*
At least 5 of 11 symptoms present in most menstrual cycles in past year and for most of the late luteal phase, remitting with onset of follicular phase, absent in the week postmenses	Five or more of 9 symptoms must be present in the same 2 week period; at least one must be either depressed mood or loss of interest/pleasure
At least one symptom must be affective (i.e., one of first 4 of 11 symptoms[a])	Symptoms do not meet criteria for a mixed expisode
Must interfere with functioning or performance at work, school, or usual social activities and relationships with others	Symptoms cause clinically significant distress or impairment (social, occupational, or other)
Must not be merely an exacerbation of symptoms of another disorder (e.g., MDD), but it may be superimposed on another disorder	Symptoms are not due to effects of a substance or medical condition
Criteria must be confirmed by prospective daily ratings for 2+ consecutive symptomatic cycles	Symptoms are not better accounted for by bereavement; the symptoms persist ≥2 months or are characterized by marked impairment; morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

[a]See Table 1 for list of symptoms.

where. Dr. Frank commented that most women seeking treatment have had symptoms for an average of 24 weeks. In her experience, negative mood, particularly irritability/anger, is most often the symptom that brings a patient to treatment. A high level of mood symptomatology is generally associated with a high level of physical symptoms, but rarely are severe physical symptoms associated with minor mood changes.

Discussion points

It was generally agreed in the ensuing discussion that this syndrome appears to be well defined, as women usually have multiple premenstrual symptoms. Not all women, however, have somatic symptoms, and this gives rise to differences of opinion on the nomenclature. Some consider PMS to relate principally to physical symptoms and PMDD to concern dysphoria. Others firmly believe that both PMS and PMDD embrace both somatic and psychological symptoms. To them, the false dichotomy is reinforced by the name PMDD. There is concern that focusing on dysphoria runs the risk of dismissing the other symptoms of a global syndrome.

Several times in the discussion, it was emphasized that lack of symptoms postmenses is an important aspect of the differential diagnosis. One person voiced the view that if a patient remained symptomatic postmenses, she was not suffering from PMDD. However, most present accepted that patients with PMDD are not all completely symptom free during the follicular phase. Indeed, even controls can have some symptoms postmenses. The important issue appears to be the degree of change in severity of symptoms between phases of the menstrual cycle and the severity of symptoms postmenses.

There was general consensus that recognizing an appropriate diagnosis for this syndrome will be filling a need that currently exists. From a practical viewpoint, a diagnosis of PMDD (using current DSM-IV[2] criteria) can tell the clinician much about the patient in terms of suitable management, prognosis, and likely response to treatment. The absence of an appropriate diagnosis means not that women are being treated unnecessarily for major depression but they are not being treated at all. The absence of a diagnosis keeps women away from the doctor's office and, therefore, away from needed treatment.

Another issue for debate was who should treat women with PMDD—general practitioners, psychiatrists, or obstetrics/gynecology specialists? The view was expressed that if general practitioners refer women to the psychiatrist, this allows for a proper assessment of the patient, and subsequent return to primary care encourages education of the general practitioner. That assessment involves determining if the woman is still symptomatic postmenses. If so, this implies either comorbidity or a condition other than PMDD.

Until an ongoing condition, such as panic disorder, is treated, the physician will not know if there is overlying PMDD.

Diagnostic criteria for PMDD in DSM-IV[2]

The decision to include PMDD in the DSM-IV[2] manual with its diagnostic criteria in the Appendix is a source of controversy[3] and concern to some. Areas of disagreement relate to whether PMDD should be categorized as a mood disorder and whether the changes that were made in DSM-IV are harmful to women. One person even questioned why PMDD is considered as a mental disorder and not as a clinical condition with a spectrum of symptoms.

Dr. Endicott, Dr. Frank, and other members of the DSM-IV[2] work group indicated that placing the criteria in the Appendix did not reflect a view by the task force that the level of evidence for a mood disorder was not high enough to justify inclusion in the body of the manual. Rather, it reflected concern about the potential stigma attached to women plus the undue focus that would be attached to the diagnosis if it were moved to the body of DSM-IV[2] at this time.

One person expressed the view that the diagnostic criteria for PMDD are arbitrary and questioned whether psychiatrists are painting themselves into a corner. There was also concern that the demand (under DSM-IV[2]) for five symptoms to be present before a diagnosis of PMDD can be made is too high and that the DSM-IV[2] criteria do not specify how the daily ratings should be performed.

FAMILY HISTORY AND GENETICS

There are few systematic data in this area, said Dr. Endicott, although many patients will provide anecdotal accounts of familial patterns. In a small sample, Dalton et al.[17] reported concordance rates of 93% for monozygotic twins versus 44% for dizygotic twins. In a study by Glick et al.[18] of 80 sibling pairs, there was a good correlation in some of the physical symptoms and a small but positive correlation between some of the atypical symptoms but not in other symptoms.

In a recent genetic study looking at concordance between monozygotic and dizygotic twins,[19] lifetime major depression and three premenstrual-related symptoms (tiredness, sadness, and irritability) were assessed twice over 6 years in 1312 twins. A comparison of the concordance for the two groups of twins showed that liability to premenstrual symptoms was only modestly affected by those genetic factors that influence major depression. Conversely, the environmental factors that influence premenstrual symptoms only modestly affect the liability to major depression. The authors concluded that, "The genetic and environmental risk factors for these premenstrual-related symptoms and major lifetime depression are not closely related."[19] It therefore appears that premenstrual symptoms are independent of the risk for MDD.

IMPACT OF PMDD ON PSYCHOSOCIAL FUNCTIONING

Epidemiologic studies

"There is limited self-report or observer-confirmed information on functional impairment associated with PMDD," said Teri Pearlstein, M.D. Women appear to be more concerned with the effects on relationships than effects on work.[20,21] In the first of these studies, 70% of 310 women reported that premenstrual symptoms caused increased arguing with family and friends, whereas only 11% reported interference with going to work. This same article found no increase in absenteeism or decreased work performance in nonclinical populations of women with self-described premenstrual symptoms, even though the women perceived cognitive impairment. Similar findings have been reported in other nonclinical populations.[5,22–25] An older study had reported increased absenteeism in women with self-reported premenstrual symptoms.[26] Functional impairment has been associated with more severe symptoms[27] and with mood rather than somatic symptoms,[28] but two recent reviews were unable to confirm luteal phase impairment in attention, memory, or learning despite the women's perception of slowness.[29,30]

Sertraline and fluoxetine studies

Dr. Pearlstein then described three treatment studies in which function was assessed. Examination of data from the sample in a large multisite study by Yonkers et al.[31] confirmed that at

baseline, women with PMDD were more impaired during the luteal phase relative to the follicular phase of their cycles, and in comparison with a community norm, they showed some impairment during the follicular phase. Comparison of the social adjustment scale and quality of life scores at premenstrual baseline for this PMDD population with other, contemporary, and comparable patient samples showed marked similarities with dysthymic patients but higher function than women with chronic major depression, said Dr. Pearlstein. Significant benefits were reported from sertraline treatment of PMDD compared with placebo for nearly all measures of social adjustment, quality of life, and daily functioning.[31]

Examination of data on fluoxetine from the sample reported by Steiner et al.[32] from a large multisite study and from a smaller study by Su et al.[33] have also confirmed that the selective serotonin reuptake inhibitors (SSRIs) improve psychosocial functioning in patients with PMDD.

Discussion points

It was emphasized in the discussion that the lack of external validation of impairment applies to all disorders and studies. Anecdotes emerged during the discussion from some panelists who indicated that family members also notice the efficacy of the drugs. The benefit to PMDD sufferers from antidepressant treatment that acts on serotonin neurotransmitters is frequently endorsed by unsolicited feedback from mothers or husbands. This provides a type of external validation.

LONGITUDINAL COURSE

Age at onset of PMDD

From the studies reviewed by Donna E. Stewart, M.D., the onset of symptoms frequently seems to be at the time of menarche, gradually increasing thereafter and peaking around 30–39 years of age, although some longitudinal studies indicate symptoms may begin up to the age of meno-pause.[4,34–37] Data from Johnson et al.[5] and more recently from Campbell et al.[20] indicate that symptoms often worsen after pregnancy. In contrast, rates of depression in girls rise abruptly at menarche, are highest in women of reproductive age, and decline slightly after menopause.

Stability of the clinical picture

The recent study by Bloch et al.[28] showed considerable cycle-to-cycle stability in negative mood symptoms (anxiety, irritability, and lability) of PMDD. Both physical and mood symptoms were remarkably stable in severity across cycles, but only mood symptoms were correlated across cycles with functional impairment. The results suggest a "stable syndrome as part of a spectrum of recurrent mood disorder."[28]

Endogenous depression seems to have an unstable clinical picture,[38] with a lot more variability between episodes than is seen with PMDD.

Chronicity

PMDD is monthly and stable over the reproductive years, often with gradually increasing severity. Once symptoms begin, they rarely resolve spontaneously except during pregnancy, sometimes (but not always) while using oral contraceptives, or after oophorectomy.[5] On the other hand, depression has a more unstable and unpredictable course.

Treatment: Long-term outcome/relapse on stopping treatment

The long-term effectiveness of SSRIs in controlling symptoms of PMDD was demonstrated by Pearlstein and Stone,[39] who studied 60 women for a mean of 18.6 months. Efficacy was maintained over this period. Intermittent dosing is a particularly interesting aspect of PMDD treatment, and it appears to be efficacious in most women.[40–42] It may be interesting to assess this approach in major depression.

Dr. Stewart said that in her experience there is a very rapid recurrence of symptoms after discontinuation of treatment that is much faster than in other affective disorders. Recently, Yonkers et al.[43] reported symptom relapse rates after discontinuation of sertraline in a double-blind, placebo-controlled trial: 66% after three cycles, 66% after six cycles, and 60% after nine cycles. Likewise, De la Gandara et al.[44] found fluoxetine to be efficacious over 18 months for PMDD treatment, but patients who stopped treatment after 6 months relapsed rapidly, often within one cycle.

Pregnancy

The SSRIs appear to be relatively safe in pregnancy, with the most data existing for fluoxetine.

A study by Nulman et al.[45] demonstrated no effect on intelligence quotient, language, or behavioral development in babies exposed to fluoxetine *in utero* who were monitored up to school age. Data on fluvoxamine, paroxetine, and sertraline are more limited, with no long-term follow-up studies.

Menopause/hormone replacement therapy

Some women express psychological symptoms at the time of menopause that are similar to those of PMDD, particularly depression, anxiety, and irritability, although fatigue and memory loss can also be problems. These symptoms worsen for some women placed on hormone replacement therapy (HRT), particularly with preparations containing progestins.

It would appear, said Dr. Stewart, that there is a subpopulation of women with vulnerability to affective disorders at times of hormonal change: at the premenstruum, during oral contraceptive use, postpartum, and at the menopause. This view is supported by her study (with Boydell) of 259 women attending a menopause clinic,[46] which showed that perimenopausal women were significantly more distressed, as assessed by a global severity index and depression and anxiety scores, than menopausal women. The women showing that highest level of distress at perimenopause also reported psychological problems at all other times of hormonal change (premenstruum, during oral contraceptive use, postpartum). A longitudinal, prospective study is needed to further clarify the picture.

Discussion point

Dr. Endicott stressed and the group concurred that the clinical picture of symptom stability in PMDD from cycle to cycle is striking. This is another facet that differentiates PMDD from depression.

LIFETIME COMORBIDITY

Once current comorbidity has been established, it no longer presents a problem, said Meir Steiner, M.D. The patient is referred to the mood disorders clinic and receives appropriate treatment. Lifetime comorbidity is a different issue. There have been a number of articles on this subject that show a prevalence in terms of lifetime comorbidity for mood disorders of between 30% and 70%.

(Dr. Steiner described early work that led to the creation of the premenstrual tension syndrome [PMTS] rating scale. In the 1970s, it was thought that PMTS was just a variant, or part, of some other psychiatric disorder. Dr. Steiner's group showed this not to be the case through measuring urinary free cortisol excretion and performing dexamethasone suppression tests.)

Phenomenology and treatment of PMDD

The symptoms are not all mood or anxiety related, said Dr. Steiner, but irritability, anger, frustration, and tension dominate the picture, with at least 50% of women at their clinic complaining of such symptoms. Unlike major depression, for most but not all women, the symptoms include physical changes, such as bloating and breast tenderness. The hallmark of PMDD is spontaneous appearance and remission of symptoms during each cycle. As a consequence, most patients with PMDD can be separated from patients with MDD, general anxiety disorder, panic, and similar syndromes.

Lithium and other mood stabilizers are ineffective in treatment of PMDD, as are most tricyclic antidepressants. The exception is clomipramine, which really is a cousin of the SSRIs. Opinion on the efficacy of the benzodiazepines is mixed. Treatment with SSRIs is effective, as is abolishing the cycle using gonadotropin-releasing hormone (GnRH) agonists, whereas neither of these approaches works in major depression.

Discussion points

During the discussion, it was mentioned that up to 80% of patients with PMDD will have exacerbations of axis-1 disorders premenstrually. In addition, it is possible to have PMDD and comorbid psychotic disorders (e.g., schizophrenia) or concurrent PMDD and an axis-1 disorder that is unrelated to the 11 symptoms listed in DSM-IV.[2]

An important part of the differential diagnosis of PMDD, therefore, is to exclude those patients with exacerbations of another disorder. Use of daily ratings are essential for this, as symptoms postmenses suggest a condition other than, or underlying, PMDD. Likewise, it is difficult and unadvisable to make a diagnosis of PMDD in a woman with current major depression/anxiety/panic disorder. Once the episode has resolved, the presence of PMDD symptoms post-

menstrually can be determined. The value in this approach, said one speaker, is seen particularly in women treated with psychotherapy who go into clear remission for 3 of 4 weeks in every cycle.

BIOLOGIC CHARACTERISTICS

Barbara Parry, M.D., reviewed studies examining biologic differences between patient and control groups, with prospective identification of symptoms.

Gonadal steroid levels show little difference between patients with PMDD and normal controls. Any differences reported are likely to be due to individual patient variation. For neurovegetative signs, subjective sleep changes seem to show the most consistency, but there is no consistency in such objective measures as electroencephalography to allow differentiation of groups of patients. In neuroendocrine studies, the thyroid abnormalities and cortisol differences seen are sometimes consistent with those seen in major depression. Some studies of peripheral β-endorphin levels have shown differences, but Dr. Parry questioned whether they were indicative of central levels and was unsure of their accuracy. Previous studies of calcium and magnesium have not shown major differences between patient groups, but more data in this area are expected soon.[47]

In terms of biologic characteristics for PMDD, the serotonin system is probably most important. The differences in serotonin metabolism are the most consistent in the literature. Serotonin is converted to melatonin in the pineal gland, for which the rate-limiting factor is the β-adrenergic system. Parry et al. have found lowered melatonin levels in patients with PMDD, and even though the patients were effectively treated, their melatonin levels remained low throughout the menstrual cycle.[48,49]

Disruption of circadian rhythms may also be important, as desynchronized rhythms produce mood disorders. In a study of response to light, both PMDD patients and controls responded appropriately during the follicular phase, but PMDD patients had a maladaptive response during the luteal phase.[50] Dr. Parry speculated that different systems (gonadal hormones and melatonin) have to come together for a functional response to light and effective working of the body.

Discussion points

"In 5 years' time there will be phenotypic markers for this disorder, so today's discussion will be irrelevant," commented David Rubinow, M.D. This comment came at the end of far-ranging discussions concerning, for example, the relative importance of the serotonergic system in PMDD, interaction with the ovarian axis, and differences in the biologic profile of PMDD in comparison with anxiety/mood disorders.

Many centers are investigating potential biologic correlates of PMDD. At present, perturbations of the serotonin system have been shown to be most involved. Even though a large proportion of women respond to treatment with an SSRI, the exact role of serotonin in the pathophysiology of this disorder remains to be determined. Is PMDD related to absolute serotonin levels or serotonin transport? If the latter, might very low doses of a serotonin transport blocker be effective? Dose-ranging studies with very low doses of SSRIs (relative to those needed for depression) may be useful in trying to answer these questions.

The importance of gonadal steroids was also discussed. One study has demonstrated a within-patient correlation between progestin levels and severity of symptoms in women with premenstrual dysphoric changes.[51] There is also anecdotal evidence of sequential HRT causing symptoms of PMS during the progestin phase. This is apparently contradicted by the study by Kirkham et al.,[52] where progestin was given to posthysterectomized/oophorectomized patients. A past history of PMS did not predict development of dysphoria.

In PMDD, the ovarian axis is apparently functioning normally, with normal hormone levels, but the response is abnormal. In contrast, depression concerns an abnormally functioning axis. This was illustrated in a recent study in which, after the ovarian axis in women with PMS was shut off, estrogen, progestin, or placebo was added back in a double-blind manner.[53] The two hormones stimulated recurrence of PMS symptoms, whereas placebo had no effect. This response could not be replicated in women without a history of PMS. Such findings imply that a history of PMS confers on the individual a different sensitivity to perturbations of gonadal steroids from someone lacking that history, said Dr. Rubinow. The fact that a trigger (i.e., a hormone) will produce symptoms that then go away

when the trigger is removed is as solid evidence for the validity of the diagnostic construct as is available for any other psychiatric disorder.

Another type of study showing the difference between PMDD and other disorders is response to carbon dioxide inhalation,[54] lactate infusion,[55] or double breath challenges.[56] Normal people and depressives without a history of panic attack do not have increased anxiety with these challenges. However, women with PMDD show a high level of response, particularly during the luteal phase, that can be blocked with alprazolam.[56]

TREATMENT OUTCOMES

There is much empirical information on treatment response, said Ellen Freeman, Ph.D., at the beginning of her overview, and two aspects have a bearing on the question "Is PMDD a clinical entity?" These are that serotonergic antidepressants are effective in PMDD and that women with PMDD differ in their response to antidepressants.

Serotonergic agents

There is strong and consistent evidence that PMDD responds to serotonergic antidepressants. In 1990, the ability of clomipramine (a non-SSRI that is highly serotonergic) to reduce premenstrual irritability and dysphoria was demonstrated by Eriksson et al.,[57] first in an open-label study, and then by Sundblad et al.[58] against placebo control. Subsequently, many double-blind, placebo-controlled studies have shown, with one exception, the efficacy of SSRIs in the treatment of symptoms of PMDD.[31–33,59–66] The degree of improvement on SSRI treatment has been considerable, with response rates reported in the range 50%–65%.

PMDD versus depression

The ways in which PMDD and depression differ in their response to serotonergic antidepressants and other treatments were listed by Dr. Freeman as follows:

- Efficacy of intermittent dosing
- Rapid onset of response
- Maximal response at low doses
- Serotonin selective (other antidepressants are not equally effective)
- History of depression does not account for the response
- Rapid recurrence of symptoms with discontinuation of treatment
- Responds to ovulation suppression and other drugs

Each point was illustrated in turn.

There are a number of preliminary published studies on intermittent dosing (10–14 days per cycle) that are totally consistent. For example, Halbreich and Smoller[41] showed that patients responding to continuous sertraline treatment were equally responsive to sertraline given only during the luteal phase. Freeman et al.[42] similarly found half-cycle treatment to be at least as effective as full-cycle treatment in women with PMDD. Similar studies exist for clomipramine,[67] fluoxetine,[40] and citalopram.[68]

The majority of studies show that response to SSRIs is in the first month of treatment, often with some additional increment in the second month with dose adjustment. There is little change thereafter. This has been shown with fluoxetine[32] and sertraline,[31,69] but in the latter study desipramine, a tricyclic antidepressant, was no different in effect from placebo.

PMDD responds to relatively low doses of SSRIs when compared with doses required in depression. End point mean doses that have been reported for PMDD patients are: sertraline 85 mg/day,[69] desipramine 110 mg/day,[67] nefazodone 319 mg/day,[70] fluoxetine 20 mg/day,[32,71] and fluvoxamine 100 mg/day.[72] These doses tend to be at the low end of the range for treatment of depression.

Yonkers et al.[43] showed rapid recurrence of symptoms (within 2 months) in >60% of women after discontinuation of sertraline treatment and transfer to placebo in a blinded fashion. Those continuing treatment showed only a 10% recurrence rate.

There are no studies showing lithium and non-serotonergic antidepressants, such as bupropion, desipramine, and maprotiline, to be more effective than placebo. This implies that the response of PMDD to treatment involves a serotonergic effect. Freeman et al. (unpublished data, 1999) found no evidence that history of depression was a factor in the treatment response.

PMDD/severe PMS does respond to other medications, but the effect is much smaller than

that with the SSRIs. Alprazolam produces a modest effect over placebo in some but not all studies.[73–77]

The GnRH agonists are effective, particularly if the symptoms of PMDD are severe, implying some involvement of ovarian hormones in the condition.[78,79] Freeman et al.[78,79] found that patients with severe PMS had a strong positive response to leuprolide, whereas patients with premenstrual exacerbations of major depression had none.[78,79] This difference in treatment response to suppression of ovulation again suggests there is a clear difference in the underlying mechanisms of PMDD and major depression.

Discussion points

There was general agreement that the DSM-IV[2] diagnostic criteria have been of considerable value in the conduct of treatment studies and in the interpretation of the resulting data. Women diagnosed with PMDD who have been included in treatment trials can be described far more clearly than those in trials for major depression and other disorders. This lends weight to subsequent clinical application of the findings.

Dr. Rubinow, however, cautioned that depending on which thresholds are set for determining premenstrual presence or postmenstrual absence of symptoms or degree of impairment, entirely different patients/controls are identified. Although this is less relevant for determining whether the diagnosis exists, it is important for researchers to identify the means by which they operationalize the criteria they are using.

Experience shows that if patients with both MDD and PMDD are treated with tricyclic antidepressants, the major depression will respond but not the PMDD. When the same patients receive SSRIs for their depression, however, most lose the premenstrual exacerbation of their symptoms. On the basis that PMDD responds to lower doses of SSRIs than major depression, one would expect the PMDD to remit, although it must be remembered that around 40% of PMDD patients do not respond to SSRIs. This area warrants further investigation.

As the etiology and physiology are still unknown, the whole spectrum of symptoms must be considered, said one participant, and not just those of dysphoria. For example, premenstrual headache/migraine can cause psychosocial dysfunction or impairment. This aspect was endorsed by another speaker, who stressed that it is important to define which symptoms are amenable to treatment from the point of view of future licensing. He suggested that further research is needed, particularly with regard to the effect of SSRIs on somatic symptoms. The view was expressed also that focusing on the mental symptoms is not neglecting the physical ones, even though there are likely to be differences in the pathophysiology. Each symptom warrants individual study, particularly in terms of response to treatment.

Other treatments

Reference was made in the discussion to a large study giving women with PMS 1200 mg/day calcium, which showed that 55% had a >50% response (17 symptoms were monitored) within 3 months.[80] The area of calcium is not well explored, and both low and high levels can be associated with abnormal mood. It may be that disturbances in calcium regulation affect the symptoms of PMDD. It is known that Ca^{2+} is essential for neurotransmitter synthesis and release and, therefore, may be linked in some way to serotonin.

SAFETY CONSIDERATIONS

Various issues concerning the safety of treatment with SSRIs in patients with PMDD were raised around the table.

Does tolerance develop with pulsed treatment?

In the opinion of Elias Eriksson, M.D., (who has been treating patients for the longest time), tolerance to treatment may develop over time, and this may differ with different compounds. He suggested that the only way to explain the finding that intermittent dosing with SSRIs is more effective than continuous dosing is on the basis that continuous dosing causes slight tolerance, which is avoided with intermittent dosing.

What are the long-term effects of treatment?

The long-term effects of SSRI treatment are not known. This toxicologic issue is particularly important because healthy women could be exposed to treatment for most of their reproductive lifetime, up to 30 years. This situation is unlike that seen with depression. Although nearly all de-

pression is recurrent, patients rarely stay on antidepressant therapy forever. In panic disorders, patients may be treated for a very long time, but there are no data from long-term controlled trials.

Is there any evidence of changes in cycle length?

Dr. Steiner reported that dose-dependent changes in cycle length do occur, but their relevance or importance has yet to be determined. In a large study by Steiner et al.,[32] cycle length increases/decreases of 4 or more days were observed in about 10% of patients receiving a high dose (60 mg/day fluoxetine), but no changes were observed in the placebo group. It is unlikely that this would happen with intermittent dosing, said Dr. Steiner.

What are the discontinuation effects?

The effect of discontinuing SSRI treatment in these patients is different from that seen in depression. Symptoms recur rapidly but at the expected time in the menstrual cycle. The advantage of intermittent dosing is that any withdrawal effects that might be seen on stopping long-term treatment are avoided.

What are the effects on sexual function?

According to Dr. Eriksson, sexual side effects, such as reduced libido and anorgasmia, are relatively common. These side effects are probably considerably less burdensome when the medication is restricted to the luteal phase of the cycle.

Pregnancy

There are no issues unique to this population that do not apply to any other sample taking medication. The absence of cycles during pregnancy obviates the need for medication, so exposure during pregnancy would be minimal.

GENERAL POINTS FROM THE DISCUSSIONS

The debate was unresolved as to whether the terms PMDD and severe PMS essentially represent the same groups of women, although for most of the discussion, the terms were being used interchangeably. This suggests that PMDD and PMS were being considered as part of the same disorder spectrum, with severe PMS being regarded as PMDD.

"There is no terminology that could be used with impunity," commented Dr. Rubinow. This view underlines some of the difficulties that are still to be overcome. Other comments were as follows: "PMDD is not a disorder that lends itself to conceptualization in typical medical terms—it is not a disorder with a specific set of symptoms. It is the temporal association of symptoms that defines PMDD, not any specific symptom or constellation of symptoms. There is no constellation of symptoms that can be developed that will not be accused of being overinclusive or underinclusive. PMDD is a time-orientated [*sic*] diagnosis."

Operational definitions for the treatment of PMDD along the following lines were proposed from the floor:

1. These drugs are indicated for the treatment of severe premenstrual disorders, which consist of the cyclic occurrence during the luteal phase of a variety of mood symptoms, including depression, anxiety, anger, and mood liability.
2. These drugs are indicated for the treatment of severe premenstrual problems that are associated with impairment in psychosocial functioning.

Both DSM-IV[2] and International Statistical Classification of Diseases and Related Health Problems (ICD-10)[81] definitions of PMDD could be used as a guide to clinicians, but, said Dr. Endicott, it must be remembered that none of the treatment studies in PMDD have used ICD. Currently, in the labeling for treatments of conditions, such as major depression or panic disorder, physicians are referred to DSM-IV[2] for definitions.

The group considered the regulatory dilemma associated with PMDD and its treatment. The fact that there is a condition in the community that is recognized, can be identified by clinicians, and for which effective treatments are available is probably more important than terminology. When a potential treatment becomes the subject of a product license application, regulators are likely to be dealing with assessments relating to quality of life while trying to respond to public needs. Given the controversy over mental disorders and the related apparent stigma, their position may be difficult.

Even so, there was a general feeling that SSRIs should be made more readily available for the treatment of premenstrual symptoms, as there is considerable evidence in support of their efficacy. There was little concern that a product license for the indication of PMDD would result in overuse of SSRIs, as the diagnostic criteria are very operational. Women without negative affective symptoms are unlikely to receive such medication.

SUMMING UP

Dr. Endicott made the following points in her summation at the end of the meeting:

- Most present are convinced (maybe in different ways) that PMDD is a distinct entity.
- The typical clinical picture for PMDD is not the typical picture for depression.
- In terms of symptom profile, PMDD differs from other mood or anxiety disorders.
- In particular, internal tension, anger, and irritability are characteristic of PMDD.
- The key difference between PMDD and other disorders is the clear onset and clear offset of symptoms, both linked to the menstrual cycle.
- The genetic component of PMDD is not related to depressive disorders (limited data).
- There is considerable stability in the course of PMDD from cycle to cycle and over time in the absence of treatment.
- PMDD is a chronic condition that can worsen in some women.
- Age at onset appears to be any time after regular menstrual cycles have been established.
- At present, most women seeking treatment are in their late 20s/early 30s.
- After pregnancy, symptoms return once cycles have been reestablished.
- There can be lifetime comorbidity with other mental disorders.
- Women with PMDD and without any comorbid disorders can be identified.
- Biologic characteristics in PMDD differ from those of control samples, but there are few comparisons with other mood/panic disorders.
- Biologic characteristics outside the normal range tend to be related to the serotonin system.
- In PMDD, the hypothalamic-pituitary-adrenal axis often functions normally, unlike its functioning in major depression.
- Symptoms of PMDD can be treated effectively; around 60% of women respond to SSRIs.
- PMDD differs in response to treatment in comparison with other disorders.
- Blocking the menstrual cycle will cure women with PMDD but not those with other mood disorders.
- There is good diagnostic validity for PMDD.

CONCLUSIONS

The group reached the consensus that PMDD is a distinct entity with clinical and biologic profiles dissimilar to those seen in other disorders. Thus, the relative safety and efficacy of potential treatments for PMDD can be evaluated, and, indeed, many of those present thought that sufficient evidence is now available to support the use of SSRIs in this disorder.

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Other attendees

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