Antidepressants in the Treatment of Premenstrual Dysphoric Disorder

Kimberly A. Yonkers, M.D.

Premenstrual dysphoric disorder describes a subset of women who have severe premenstrual symptoms, including at least one mood symptom. It is included in DSM-IV under "Depressive Disorders Not Otherwise Specified." Criteria differentiating premenstrual dysphoric disorder from premenstrual syndrome are the requirements that patients have at least five symptoms, including one mood symptom; have impairment associated with the illness; and prospectively confirm the symptoms. After decades of treatment research on premenstrual dysphoria, the most consistent positive results have been found for selective antidepressants, primarily those that are active at serotonin receptors. Most studies have used continuous daily treatment for acute phase therapy. Further studies should define the role of intermittent and long-term maintenance therapies with these agents.

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Premenstrual dysphoric disorder is a category new to the "Depressive Disorders Not Otherwise Specified" section of DSM-IV. This article reviews the phenomenology, psychobiology, and relevant treatment data for premenstrual dysphoric disorder. It has been informed by other works from the author, which include a more detailed literature review.[1]

The diagnostic criteria, which are elaborated in the appendix of DSM-IV [2] (see Table 1), are similar to the research criteria established in DSM-III-R,[3] except that DSM-IV added both a symptom, "the subjective sense that one is out of control," and a stipulation that one experience a symptom-free period during the week after menses. The symptoms associated with premenstrual dysphoric disorder are a subset of those found in premenstrual syndrome (PMS). As they do with PMS, women with premenstrual dysphoric disorder experience symptoms for several days to 2 weeks during the luteal phase of the cycle. Symptoms cease with the onset of menses, or shortly thereafter, which results in a symptom-free interval prior to the onset of symptoms again during the subsequent cycle. A DSM-IV workgroup reanalysis of data collected from 670 patients at four large research centers found that the most common symptoms associated with premenstrual dysphoric disorder are low mood, tension, anger, irritability, mood swings, headache, bloating, and changes in appetite and sleep.[4,5] The clinical criteria in DSM-IV stipulate a minimum of five symptoms, one of which must be a mood symptom (low mood, mood swings, tension, or irritability). These symptoms should be prospectively confirmed with some method of monitoring daily ratings. As with other mood disorders in DSM-IV, the syndrome meets criteria only if it leads to functional impairment in either work or interpersonal domains.

PREVALENCE

While the prevalence rates for milder premenstrual syndromes range from 30% to 80%,[6,7] severe symptoms such as those associated with premenstrual dysphoric disorder occur in 2% to 9% of menstruating women.[8–11] One study evaluated a non–treatment seeking university population and found a rate of 4.6%.[10] This figure coincides nicely with results from a second prospective study that found a rate of 3.4%.[11] Both these estimates are within the range found in retrospective community studies that approximate rates for women who are severely afflicted with premenstrual symptoms.[6]

While premenstrual symptoms have been investigated in subgroups of nonwhites and in other cultures, prevalence data on a syndrome consistent with premenstrual dysphoric disorder are sparse. A reanalysis of data from the Epidemiologic Catchment Area study, which is retrospective in nature, found a rate in black women equivalent to that in white women.[12] A community study of 120 Nigerian women[13] found at least one premenstrual complaint

From the University of Texas Southwestern Medical Center, Dallas.

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Reprint requests to: Kimberly A. Yonkers, M.D., The University of Texas Southwestern Medical Center, St. Paul Professional Building I, Suite 520, 5959 Harry Hines Boulevard, Dallas, TX 75235-9070.

in 68% of women. However, premenstrual symptoms led to regular loss of work in 7.5% of women. High prevalence rates (26%) of women reporting premenstrual symptoms were found in an Italian community study,[14] but the rates during the menstrual phase were higher than those expressed during the premenstrual phase. Women with severe mood symptoms were not independently identified in this study.

COURSE

Symptoms of premenstrual dysphoric disorder may begin at any age after menarche, but the average age at onset appears to be around 26 years[5,15,16] and several researchers[17,18] but not all[19] found that symptoms associated with the premenstrual phase gradually become worse, and perhaps more protracted, over time. It has been suggested that worsening could occur because of the recurring increases and decreases in ovarian hormones.[20] This is supported by data from other cultures: when menstruation is infrequent, premenstrual symptoms are rare. It is also supported by data associating low parity with the risk of premenstrual dysphoric disorder.[16,17,21] Low parity yields a greater number of hormonal cycles, and, thus, a woman has more exposure to and withdrawal from massive amounts of progesterone. Further, several studies find lower rates of premenstrual symptoms among users of oral contraceptives,[16,17,22] again suggesting that briefer exposure to peaks and troughs of endogenous progesterone is protective against premenstrual dysphoric disorder.

Age at onset, progression, and duration of illness are important aspects of the disorder since they speak to its accumulated morbidity. If a woman's average age at onset of premenstrual dysphoric disorder is 26 years[5,15,16] and if symptoms are not relieved during multiple gestations, she will have more than 200 symptomatic cycles or 1400 to 2800 symptomatic days (3–8 years) before she reaches menopause. During that time, several areas of her life may be adversely affected by the illness. Some studies find that patients with premenstrual dysphoric disorder experience luteal phase functional impairment most profoundly in relation to their interactions with spouses and children.[23,24] The impairment affecting social and pleasurable activities that occurs during the luteal phase of the cycle is similar to that found among patients with major depression, thus underscoring the need for effective treatments.

Other aspects of the illness argue for early intervention and treatment. It appears that compared with women without premenstrual symptoms, women with PMS[25] or premenstrual dysphoric disorder[26] are at higher risk for developing a subsequent episode of major depression. It remains to be seen whether aggressive treatment of premenstrual dysphoric disorder can reduce future risk of non–menstrually entrained mood disorders.

DETECTION AND DIAGNOSIS

As noted above, a stipulation for both late luteal phase dysphoric disorder criteria and the revised premenstrual dysphoric disorder criteria is that retrospective reports of symptomatology be prospectively confirmed. This requirement arose from earlier research findings showing that only 20% to 50% of women who retrospectively report severe PMS will confirm ratings prospectively.[27] A number of instruments are commonly used to monitor daily symptoms including visual analog scales (VAS), the Daily Rating Form (DRF), the Calendar of Premenstrual Experiences (COPE), the Moos Menstrual Distress Questionnaire (MDQ), and the Daily Rating Scale (DRS). On the basis of prospective charting, several groups[22,27] found that women who present with premenstrual complaints will show symptom patterns (1) limited to the luteal phase, (2) intermittently during the cycle but not related to the luteal phase, or (3) throughout the cycle with worsening during the luteal phase. The latter is particularly likely to happen in women who suffer from dysthymia or generalized anxiety disorder. Whether individuals confirm symptoms, current and past comorbid psychiatric illnesses are common in women with premenstrual complaints.[28–31] In a study comparing DSM-III diagnoses in women presenting for evaluation of PMS to diagnoses found in a community epidemiologic study, Stout and colleagues[28] found much higher lifetime rates of dysthymia, phobia, mania, obsessive-compulsive disorder, alcohol abuse, and substance abuse in women with premenstrual complaints. In addition, it has been suggested that 50% to 60% of menstruating women with major depressive disorder (MDD) experience premenstrual worsening,[25,30] although the only report of women with MDD that used prospective ratings found premenstrual worsening in about 30% of patients.[32] The effect of premenstrual worsening is particularly important since the rate of emergency room visits and hospitalization increases during the premenstrual and menstrual phases of the cycle.[33,34]

PSYCHOBIOLOGY OF PREMENSTRUAL DYSPHORIC DISORDER

Theories that attempt to explain what causes premenstrual symptoms have been reviewed by a number of authors[35,36] and include (1) a deficit of progesterone, (2) an excess of estrogen, (3) a decrease in the progesterone:estrogen ratio, (4) alterations in progesterone metabolism, (5) an excess of testosterone, (6) a deficiency of or decrease of apparent availability of the vitamin B_6, (7) a deficiency of the prostaglandin PGE_2, (8) an excess of prolactin, (9) a deficiency of β endorphin, and (10) abnormal neurotransmitter—particularly serotonergic—functioning. It is unclear whether these theories are relevant to the pathogenesis of premenstrual dysphoric disorder, which is more severe

than PMS and which emphasizes mood symptoms. To date, levels of progesterone, estrogen, or the ratio of the two have not been definitively shown to differ in patients with premenstrual symptoms versus controls.[35,36] Given the hypothesized association between mood symptoms and neurotransmitter systems, this section reviews the data on markers of neurotransmitter functioning and premenstrual dysphoric disorder. The reader is referred to other sources for reviews of hormonal investigations into PMS.[35–37]

Serotonergic System

Basic research has found important interactions between sex steroids and serotonin. For example, in vitro studies that used platelets to measure serotonin uptake have found that estradiol and testosterone inhibit the process.[38] The physiologic relevance for understanding the pathophysiology of premenstrual dysphoric disorder is suggested by clinical research. The first investigation of platelet serotonin uptake in PMS patients reported that uptake was decreased in the luteal versus the follicular phase of the cycle.[39] Similar findings were reported in two additional studies[40,41] although a third investigation failed to find differences between groups at either time of the cycle.[42] By using a different ligand, tritiated imipramine, Rojansky and colleagues[43] found a difference in V_{max} between groups during both phases of the cycle, but the difference was significant during only the midluteal phase. By using the same ligand, another group[44] found differences during the follicular phase of the cycle. While strict diagnostic criteria were not used for all these studies, patients in the last two studies met rigorous criteria for premenstrual dysphoric disorder.

Functioning of the serotonergic system has been probed in other ways. Subsensitivity of the 5-HT_{1A} receptor is thought to cause blunting when an agonist challenge agent is administered. Two studies showed blunting when serotonin agonists were given to women with premenstrual dysphoric disorder. In the first,[45] buspirone was administered during the follicular phase only. The prolactin response was blunted in premenstrual dysphoric disorder patients compared with controls. A second study[46] evaluated several markers twice during the menstrual cycle after L-tryptophan was given. The prolactin response was blunted during the luteal phase in women with premenstrual dysphoric disorder compared with controls, but growth hormone and cortisol responses were blunted in patients during both phases of the cycle.

Another method for probing the involvement of serotonin or serotonin neurotransmission entails the acute depletion of the neurotransmitter precursor, tryptophan, by administering an amino acid cocktail that has all the necessary neutral amino acids except tryptophan. These other amino acids monopolize the transporter that conveys neutral amino acids from the periphery into the central nervous system. In patients with major depression, this technique has been used to precipitate acute relapse of the mood disorder. When women with premenstrual dysphoric disorder were subjected to this protocol, premenstrual symptoms were provoked during the follicular phase and exacerbated during the luteal phase.[47] In sum, the evidence reviewed above suggests that the pathophysiology of premenstrual dysphoric disorder involves changes in serotonergic functioning or response.

Adrenergic System

An increase in α_2 receptor binding has been found in individuals with depressive disorders.[48] Similarly, one study[48] found that α_2 receptor binding is significantly higher during both phases of the cycle in women with premenstrual dysphoric disorder versus controls. Binding at the imidazoline receptor shows even larger binding differences between these groups. In a preliminary report, Gurguis and colleagues[49] also found differences in platelet α_2 and neutrophil β_2 receptor binding in symptomatic versus control women, but this did not hold in a larger sample (Yonkers KA. Unpublished data).

Gamma Aminobutyric Acid (GABA) System

Low plasma GABA levels are found in a subset of patients with major depression.[50] A recent report[51] also found low GABA levels in premenstrual dysphoric disorder patients compared with controls. Although this decrease occurred during both phases of the cycle, levels were lower during the luteal versus the follicular phase in the patient group.

Neurotransmitter systems do not act in isolation but rather influence each other. It appears that some medications that block the reuptake of serotonin also increase binding at the GABA-benzodiazepine receptor. Thus, in addition to their direct action at serotonergic sites, serotonin reuptake inhibitors may modulate other systems that are implicated in the pathophysiology of premenstrual dysphoric disorder.

TREATMENT

Identifying efficacious treatments for women suffering from severe premenstrual symptoms has been hampered by several factors. First, older clinical trials included a heterogeneous group of women in terms of both the constellation of symptoms experienced (i.e., primarily somatic symptoms vs. affective symptoms) and the level of severity.[37] The failure to exclude women with concurrent psychiatric conditions such as mood disorders or anxiety disorders added to the heterogeneity. The second factor hampering treatment investigations was the assumption that premenstrual dysphoric disorder was caused by either an excess or a deficit of one or another ovarian hormone (usually progesterone). Consequently, many trials evalu-

Table 1. DSM-IV Proposed Criteria for Premenstrual Dysphoric Disorder*

A. During the past year in most cycles, at least five symptoms, including minimally one mood symptom, are present during the last week of the luteal phase and are absent in the week of postmenses.
   - Depressed mood, feelings of hopelessness
   - Anxiety, tension, feeling "keyed up"
   - Affective lability
   - Lack of energy, lethargy
   - Persistent and marked anger or irritability
   - Decreased interest in usual activities
   - Difficulty concentrating
   - Changes in appetite
   - Changes in sleep
   - A subjective sense of being overwhelmed
   - Physical symptoms such as breast tenderness, bloating or muscle pain

B. Symptoms must markedly interfere with work or interpersonal relationships.
C. Disturbance is not merely an exacerbation of another disorder.
D. Criteria A, B, and C are confirmed by daily ratings for two cycles.

*Data adapted from reference 2.

ated the efficacy of progesterone or its optical isomer dydrogesterone, even though few had positive results. Other problems with earlier trials included high placebo response rates, difficulty in replicating prior positive findings, and the failure of these treatments after they were removed from clinical trials and prescribed in clinical settings. Two developments advanced research for women with more severe premenstrual symptoms such as those with premenstrual dysphoric disorder: (1) standardized criteria were developed and incorporated into DSM-III-R and then DSM-IV (see Table 1), and (2) investigators turned to the use of psychotropic compounds that target the core symptoms of premenstrual dysphoric disorder (mentioned above).

Psychotropic Drug Treatment

The recurrent nature of the illness, and the fact that many women convert from an intensely productive, high-energy state (during the follicular phase) to a lethargic, less productive condition associated with low mood suggested to some that severe disorders such as premenstrual dysphoric disorder may be a type of bipolar mood disorder. To test this hypothesis, two groups investigated the utility of lithium.[52,53] The first trial[52] did not stipulate that women prospectively confirm their symptomatology. Thus, even though a placebo arm was included in this study, the patient population was probably a heterogeneous one. This trial failed to find benefit for lithium. A second open study[53] did carefully define the study population, but even in this open trial, lithium benefited only 3 of 15 women.

The next psychotropic agent to receive research attention was alprazolam. Alprazolam was a reasonable treatment choice since it has the benefit of both anxiolytic and antidepressant properties. In addition, it is sedating for those women who have difficulty with irritability and poor sleep. To date, five trials have investigated the therapeutics of alprazolam.[54–58] Although they were small, all five studies used solid research designs and included women who prospectively confirmed premenstrual symptomatology. Alprazolam was prescribed during only the luteal phase for all of these investigations in dosages that ranged between 0.75 mg/day to 4 mg/day across studies. The length of study was between two and four cycles. Alprazolam was beneficial in four of five studies. In the negative study,[58] alprazolam was superior to placebo on analyses of the Beck Depression Inventory and self-rated Rating Scale for Premenstrual Tension, but failed to show any difference from placebo according to daily self-ratings. An additional study deserves mention. Berger and Presser[57] included two groups of women in their study: those who had severe premenstrual symptoms and were symptom-free during the follicular phase and those who had severe premenstrual symptoms accompanied by mild follicular phase symptoms. The latter group did not benefit from alprazolam treatment. Thus, it may be that patients who have residual symptomatology do poorly on a drug that is administered during only the follicular phase. Given the degree of improvement in alprazolam responders, it appears that this agent is more helpful for women who have a relatively brief period of symptomatology and have somewhat less severe symptoms than women with longer and more severe symptomology.

Experience at my center mirrors what the data show. Alprazolam appears to be more beneficial for women with only a few days of symptoms, particularly if symptoms are not severe. I start patients at a dose of 0.25 mg twice to three times daily and increase it as needed. I rarely find difficulties with abuse in this patient population.

As suggested by the psychobiological evidence reviewed above, efficacy data consistently find benefit for a number of the newer antidepressants, and in particular, antidepressants that are active at serotonin receptors. These include the 5-HT reuptake inhibitors clomipramine,[59] fluoxetine,[60–66] paroxetine,[67,68] and sertraline[23]; the reuptake and 5-HT_2 antagonist nefazodone[69]; the 5-HT agonist fenfluramine[70]; and the dual reuptake inhibitor venlafaxine (Yonkers KA. Unpublished data).

Four randomized, placebo-controlled trials evaluating fluoxetine have found this agent beneficial.[60–63] The initial studies were small; they had fewer than 20 patients. The most recent trial was a large multicenter trial that persisted for six cycles and evaluated daily doses of 20 mg and 60 mg.[61] Self-ratings of premenstrual symptomatology significantly improved with treatment. Dropouts were substantial (44%) in the 60-mg cell but less problematic (11%) in the 20-mg cell, which implies that the drug should be started at lower dosages. Physicians at my center start fluoxetine at either 5 mg or 10 mg/day to avoid any activating side effects that may lead to noncompliance. The dose can be increased as needed. I prescribe the

medication to be taken daily, but after they experience improvement, some patients find that it can be taken during the luteal phase only.

Acute phase efficacy for paroxetine is shown by one small randomized, double-blind, placebo-controlled trial[67] and one open trial.[68] These studies used prospective ratings to define patients eligible for the study, and in both instances, the participants met rigorous criteria for premenstrual dysphoric disorder. These results indicate that paroxetine is a promising compound for this disorder, although a more thorough evaluation is required.

A recently presented multicenter study[23] of over 200 patients found that sertraline is significantly more beneficial than placebo on both self-rating measures and observer ratings. This study used DSM-IV criteria for premenstrual dysphoric disorder and a flexible dose of sertraline, which was begun at 50 mg/day and was increased, if needed, to 150 mg/day over three cycles. The mean dose by Cycle 3 was 80 mg/day. On the basis of response as defined by the Clinical Global Impressions–Improvement scale, 65% of those who received active treatment responded, while 34% of those in the placebo cell responded.

The new dual reuptake inhibitor, venlafaxine, shows promise for the treatment of premenstrual dysphoric disorder. This agent appears to have a very rapid onset of action, which is advantageous for a disorder that is intermittent. It is currently being evaluated in a large multicenter trial that is employing very rigorous standards, including DSM-IV criteria, and both subjective and objective measures. This trial is unique in that these measures are obtained during both the follicular phase and the luteal phase of the cycle. Physicians at my center (which is participating in the study) have found that women have very few side effects when venlafaxine is started at a dose of 25 mg twice daily, which can be increased by 25 mg per day each cycle if needed. During treatment, daily ratings show clear stabilization in symptoms of mood, irritability, and anger as well as in somatic symptoms.

Other serotonergic compounds tested in small clinical trials have yielded promising results. Clomipramine was effective in an open, five-cycle treatment study[71] and a double-blind study.[72] Symptom severity cutoffs (50% decrease in the Hamilton Rating Scale for Depression and daily ratings) and tests of statistical significance were used to define response for an open trial of the 5-HT_2 antagonist and reuptake inhibitor, nefazodone.[69] Buspirone significantly improved daily symptoms over placebo, but other measures such as observer ratings were not reported.[73] The 5-HT indirect agonist, d-fenfluramine, was more helpful than placebo for symptoms of depression and appetite in a trial of 17 patients.[70]

Despite the effectiveness of agents reviewed above, antidepressants do not appear to be equally effective for premenstrual dysphoric disorder. The placebo-controlled study evaluating paroxetine included a maprotiline treatment arm to compare the relative efficacy of a noradrenergic compound with a serotonergic medication.[67] Paroxetine was more effective than maprotiline, which was slightly more beneficial than placebo. Similarly, a recent study comparing fluoxetine with bupropion and placebo found that fluoxetine led to greater improvement than either bupropion or placebo.[74] These studies imply that compounds active in blocking 5-HT reuptake are particularly efficacious.

Long-Term Treatment of Premenstrual Dysphoric Disorder

Only a few studies have investigated long-term treatment efficacy for agents that are beneficial in acute phase treatment. Pearlstein and Stone[66] followed 60 acute phase responders to fluoxetine for up to 2 years on an open basis and found continued well-being in at least 21, all of whom continued pharmacotherapy. Six of the larger group experienced an episode of major depression, and 1 experienced recurrent hypomanic episodes. Elks[65] treated 11 women with fluoxetine and found continued moderate-to-marked relief during 3 to 20 months of treatment. Similarly, Freeman and colleagues[69] followed a subgroup of nefazodone acute phase responders for a variable length of time up to 1 year. In 8 of 33 women who completed an additional 6 to 12 months of treatment, improvement was maintained.

FUTURE DIRECTIONS

Many treatment trials describe response in terms of continuous variables, i.e., the average amount of change in an active group compared with a control group. While this offers a sense of how an active treatment compares with placebo, it does not illustrate either how symptomatic an individual remains after treatment nor does it describe the likelihood that women who are given adequate treatment will be rendered completely or nearly asymptomatic. Categorical measures can provide this data by, for example, identifying the number of patients who have total or nearly total improvement or the number of patients who fall below a given threshold of a particular psychiatric instrument. Future studies should provide some picture of the residual symptomatology in the various treatment groups.

Premenstrual dysphoric disorder is a disorder that may respond to unique dosing patterns such as intermittent treatment during the luteal phase only. If luteal phase treatment is as effective as continuous treatment, then women can be spared medication side effects and the treatment costs during the follicular phase of the cycle.

Methods of ovulation suppression have been shown to be helpful for some women with severe PMS or premenstrual dysphoric disorder. It may be that treatments such as

oral contraceptives or gonadotropin-releasing hormone agonists would be efficacious for women with premenstrual dysphoric disorder who have failed initial therapies or lost a therapeutic response and failed to respond to other interventions.

SUMMARY

Antidepressants are likely to be beneficial for other psychiatric disorders, especially nonmajor mood disorders. As noted above, newer antidepressants have acute phase efficacy for premenstrual dysphoric disorder. Interestingly, not all antidepressants are equally efficacious since preliminary evidence finds that agents which are active at serotonin receptors (clomipramine, fluoxetine, paroxetine, sertraline, and venlafaxine) are superior to agents such as bupropion or maprotiline. Future studies should build on these new, exciting efficacy data and address issues such as intermittent treatment, long-term treatment, treatment resistance, and the need for combination therapy.

Drug names: alprazolam (Xanax), bupropion (Wellbutrin), buspirone (BuSpar), clomipramine (Anafranil), fenfluramine (Pondimin), fluoxetine (Prozac), maprotiline (Ludiomil), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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Disclosure of Off-Label Usage

The following agents mentioned in this article are *not* indicated for premenstrual dysphoric disorder: alprazolam, bupropion, buspirone, clomipramine, fluoxetine, imipramine, lithium, maprotiline, nefazodone, paroxetine, sertraline, and venlafaxine.

Discussion

Dr. Keck: During the clinical trials of the serotonin reuptake inhibitors, do you treat patients daily or during only the luteal phase?

Dr. Yonkers: Clomipramine was given during the luteal phase only. All the other agents have been administered daily.

Dr. Keck: Turning to your diagnostic and treatment algorithm, do you think it would be advantageous to use p.r.n. doses of serotonin reuptake inhibitors instead of alprazolam for patients with moderate, time-limited symptoms?

Dr. Yonkers: Possibly. This is a future area of research. We have to define the efficacy of intermittent treatment with serotonin reuptake inhibitors and the patient populations for whom this methodology will be successful.

Dr. Popper: Do you sometimes combine gonadotropin-releasing hormone agonist treatment with a serotonin reuptake inhibitor?

Dr. Yonkers: Certainly. In my group's stepwise protocol, we start with the least invasive treatment and reserve gonadotropin-releasing hormone agonist treatment for patients who have failed at least two to three other agents and are seriously contemplating a surgical alternative. We not only treat these patients with the gonadotropin-releasing hormone agonist, but we also continue treatment with either a dual reuptake inhibitor or a serotonin reuptake inhibitor to minimize the symptoms that are likely to occur when menopause is induced. After the hypothalamic-pituitary-ovarian axis has essentially been shut off, we withdraw the antidepressant. This is a relatively rare treatment; three women have required surgery for severe premenstrual symptoms in the 3 years I have been running the University of Texas Southwestern Medical Center program.

Dr. Hirschfeld: Have mood stabilizers been tried for severe premenstrual symptoms?

Dr. Yonkers: Lithium is the only mood stabilizer that has been systematically studied, and the results of the trials were negative. Carbamazepine and valproate have not been systematically evaluated, but one case report showed that valproate was helpful. My clinical impression is that a substantial number of women who are treated with antidepressants for premenstrual dysphoric disorder are ultimately diagnosed with a bipolar II disorder.

Dr. Hirschfeld: Is psychosurgery an option?

Dr. Yonkers: It hasn't been used.

Dr. Leonard: Is there a seasonal component to premenstrual dysphoric disorder? Has light therapy been tried?

Dr. Yonkers: Many patients with premenstrual dysphoric disorder complain of a winter worsening of their symptomatology, and their symptoms are consistent with those for seasonal affective disorder. In an investigation conducted at the University of California at San Diego, Parry et al. showed efficacy for both bright and dim light treatment administered during the premenstrual phase of the menstrual cycle [Am J Psychiatry 1993;150:1417–1419].

Dr. Keck: What is the long-term diagnostic stability of premenstrual dysphoric disorder? In how many women is this a tip-of-the-iceberg presentation that becomes full-blown, noncyclic, major depression or bipolar illness?

Dr. Yonkers: Pearlstein and Stone reported [J Clin Psychiatry 1994;55:332–335] that of 60 patients treated with fluoxetine for a mean of 18.6 months for late luteal phase dysphoric disorder, 6 experienced major depressive episodes and 1 experienced bipolar II disorder. In terms of the validity of the long-term diagnosis, Peter Schmidt, M.D., and David Rubinow, M.D., have been following a group of women with premenstrual dysphoric disorder for a decade; some of these women are now entering menopause.

Dr. Popper: What percentage of women with premenstrual dysphoric disorder would you estimate are completely free of psychiatric comorbidity?

Dr. Yonkers: We generally accept 1 of 20 women who apply for studies at our research facility. Most are excluded because they have a concurrent disorder; they have symptomatology that is not limited to the late luteal phase, i.e., brief full depression, or they have symptoms that don't meet the threshold severity criteria or are not associated with functional depression. Between 30% and 50% of the women who are included in one of our protocols have a previous history of a mood disorder.

My guess is that more than 50% of the women who go to a doctor because of premenstrual syndrome (PMS) will have a concurrent psychiatric disorder. The most likely comorbid diagnoses are dysthymia and generalized anxiety disorder, but women often have phobias or more severe psychiatric disorders.

Dr. Popper: Are you estimating that 50% of these patients have a comorbid mood disorder or are you also including anxiety disorders in your figures?

Dr. Yonkers: Mood and anxiety disorders.

Dr. Hirschfeld: Dr. Yonkers, has tryptophan been tried to treat premenstrual dysphoric disorder?

Dr. Yonkers: Tryptophan was evaluated in one well-designed, open trial [Steinberg S, Annable L, Young SN, et al. J Psychiatry Neurosci 1994:19:114–119]. Fewer

than 30% of patients responded according to the criterion, which was a 50% decrease on the Hamilton Rating Scale for Depression.

Dr. Keck: Do women who have premenstrual dysphoric disorder tend to have a maternal history of this condition?

Dr. Yonkers: Twin—both monozygotic and dizygotic—studies [Van den Akker OB, Eves FF, Stein GS, et al. J Psychosom Res 1995;39:477–487; Kendler KS, Silberg JL, Neale MC, et al. Psychol Med 1992;22: 85–100] found that the concordance rate ranges between 0.3 and 0.5. Interestingly, Kendler et al. reported that the diagnosis of severe PMS did not correlate with the diagnosis of dysmenorrhea. Glick, Endicott, and Nee [Acta Psychiatr Scand 1993;88:149–155] also found low correlations for the symptom profile of premenstrual dysphoric disorder between women with premenstrual dysphoric disorder and their sisters, although atypical symptoms tend to run in sister pairs. The data on mother-daughter transmission are shaky because we lack prospective ratings for both mother and daughter.

Dr. Leonard: I think many disorders will ultimately be linked to multisystems, which have many different neurotransmitter interactions. Since you mentioned the GABA system, has baclofen been tried?

Dr. Yonkers: My group has applied for a grant to study baclofen in patients with major depressive disorder and premenstrual dysphoric disorder. Since two major metabolites for progesterone are active at the benzodiazepine GABA receptor, we can expect that dysfunction may be precipitated by the withdrawal of these metabolites. Medications that increase affinity and binding at the GABA benzodiazepine receptor complex could correct this deficit.

Dr. Leonard: Do serotonin reuptake inhibitors vary in ability to affect the GABA system?

Dr. Yonkers: Not to my knowledge.

Dr. Popper: If onset of premenstrual dysphoric disorder is generally around age 20 years, what might the prodromal or preadolescent picture look like?

Dr. Yonkers: Many of my patients report a history of milder symptomatology that progressively worsened. However, I have seen patients who started experiencing symptomatology when they began to cycle, and I have patients who have premenstrual dysphoric disorder and report seeing similar symptomatology in their daughters.

Dr. Keck: Does pregnancy change the course?

Dr. Yonkers: Patients retrospectively say that their symptoms worsened after pregnancy and after tubal ligation, but it is unclear whether these pivotal events in a woman's reproductive cycle are simply a marker or whether an actual physiologic change can be attributable to these events. It makes sense biologically that pregnancy could worsen the disorder, but there is no physiologic explanation for worsening after tubal ligation.

Paul McDonald, M.D., a reproductive endocrinologist and one of my mentors at the University of Texas Southwestern campus, argues that recurrent exposure to and withdrawal from large amounts of progesterone "primes" women, and large amounts of hormone could exacerbate the recurrent, repetitive pattern of premenstrual dysphoric disorder. On the other hand, pregnancy could be beneficial because, instead of having 9 cycles, women have a consistent hormone level for 9 months. Historically, women had far fewer menstrual cycles because they were either pregnant or lactating most of the time.

Dr. Popper: Does menstrual cycling trigger early mood disorders in women who experience premenstrual dysphoric disorder later in their reproductive years?

Dr. Yonkers: That could be examined by comparing the rate of depression in women who have and have not been treated with oral contraceptives. While I have not conducted this comparison for depression, I have found that oral contraceptives are somewhat protective against the eventual development of premenstrual dysphoric disorder.

Dr. Leonard: The diagnosis of and even the name of this disorder has changed in each subsequent DSM, and the criteria in the DSM-IV have been narrowed dramatically. How have the changes in the diagnostic criteria affected general issues in women's health?

Dr. Yonkers: The diagnostic criteria for premenstrual dysphoric disorder were included in the appendix of the DSM-III-R as a disorder requiring further study, and the criteria in DSM-IV changed very little from those in DSM-III-R. The goal in changing the diagnostic criteria is to decrease the heterogeneity in study populations and target the most problematic symptoms so we can find effective treatments. In fact, 90 of 100 patients would report depressed mood, irritability, and anger as their worst symptoms. Interestingly, research also shows that somatic symptoms improve when mood symptoms are treated.

In terms of the general issues related to women's health, many women have sought treatment for premenstrual dysphoric disorder, and their degree of suffering was often trivialized (they were told to exercise more or to stay away from chocolate). Narrowing the criteria allows us to identify and find treatments for patients with the more severe syndrome. It is also important for us to distinguish treatment for premenstrual dysphoric disorder from treatment for the 80% of the population who have one or two mild premenstrual symptoms.

Dr. Leonard: Is the term PMS still used and is there a consensus in the field on the definition of PMS?

Dr. Yonkers: The ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) code for PMS is not accompanied by a rigorous definition. Neither the particular symptoms nor the totally

asymptomatic follicular phase interval are defined in the ICD-9-CM criteria.

Dr. Keller: Dr. Yonkers, suggest two or three research studies that are needed.

Dr. Yonkers: It is critical for us to begin evaluating long-term treatment (both continuation and maintenance phases). We have few placebo-controlled data that last beyond the acute phase of treatment. We don't know for how long these medications are efficacious and for how long patients should be treated. We also need to evaluate novel treatment designs. Venlafaxine has an acute onset of action, which may make it an optimal medication for brief, luteal-phase treatment of premenstrual dysphoric disorder.