Diagnosis and Treatment of Premenstrual Dysphoric Disorder

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From 2 to 10 percent of women of reproductive age have severe distress and dysfunction caused by premenstrual dysphoric disorder, a severe form of premenstrual syndrome. Current research implicates mechanisms of serotonin as relevant to etiology and treatment. Patients with mild to moderate symptoms of premenstrual syndrome may benefit from nonpharmacologic interventions such as education about the disorder, lifestyle changes, and nutritional adjustments. However, patients with premenstrual dysphoric disorder and those who fail to respond to more conservative measures may also require pharmacologic management, typically beginning with a selective serotonin reuptake inhibitor. This drug class seems to reduce emotional, cognitive-behavioral, and physical symptoms, and improve psychosocial functioning. Serotoninergic antidepressants such as fluoxetine, citalopram, sertraline, and clomipramine are effective when used intermittently during the luteal phase of the menstrual cycle. Treatment strategies specific to the luteal phase may reduce cost, long-term side effects, and risk of discontinuation syndrome. Patients who do not respond to a serotoninergic antidepressant may be treated with another selective serotonin reuptake inhibitor. Low-dose alprazolam, administered intermittently during the luteal phase, may be considered as a second-line treatment. A therapeutic trial with a gonadotropin-releasing hormone agonist or danazol may be considered when other treatments are ineffective. However, the risk of serious side effects and the cost of these medications limit their use to short periods. (Am Fam Physician 2002;66:1239-48,1253-4. Copyright© 2002 American Academy of Family Physicians.)

A patient information handout on premenstrual dysphoric disorder, written by the authors of this article, is provided on page 1253.

Millions of women of reproductive age have recurrent emotional, cognitive, and physical symptoms related to their menstrual cycles. These symptoms often recur discretely during the luteal phase of the menstrual cycle and may significantly interfere with social, occupational, and sexual functioning.

Premenstrual dysphoric disorder (PMDD), a severe form of premenstrual syndrome (PMS), is diagnosed by the pattern of symptoms. According to a report by the Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists,[1] up to 80 percent of women of reproductive age have physical changes with menstruation; 20 to 40 percent of them experience symptoms of PMS, while 2 to 10 percent report severe disruption of their daily activities. Menstruation-related physical discomfort, such as dysmenorrhea, may begin with menarche. Often this condition is superseded by PMS in late adolescence or the early 20s. These syndromes generally remain stable over time.

In the Diagnostic and Statistical Manual of Mental Disorders, *4th ed., premenstrual dysphoric disorder is classified as "depressive disorder not otherwise specified," emphasizing emotional and cognitive-behavioral symptoms.*

Diagnosis

In the *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (DSM-IV), PMDD is classified as "depressive disorder not otherwise specified" and emphasizes emotional and cognitive-behavioral symptoms.[2] At least five of the 11 specified symptoms must be present for a diagnosis of PMDD *(Table 1)*.[2] These symptoms should be limited to the luteal phase and should not represent amplification of preexisting depression, anxiety, or personality disorder. In addition, they must be confirmed prospec-

tively by daily rating for at least two consecutive menstrual cycles. A symptom-free period during the follicular phase of the menstrual cycle is essential in differentiating PMDD from preexisting anxiety and mood disorders.

Researchers have developed a reliable and valid self-reporting scale called the Daily Symptom Report *(see patient information handout)*.[3] The report consists of 17 common PMS symptoms, including 11 symptoms from the DSM-IV PMDD diagnostic criteria. Patients rate each symptom on a five-point scale, from zero (none) to 4 (severe). The scale provides guidance for scoring the severity of each symptom and may be used in the office setting by primary care physicians for diagnosis and assessment of PMDD.

TABLE 1
Research Criteria for Premenstrual Dysphoric Disorder

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

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

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

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

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

Etiology

Currently, there is no consensus on the cause of PMDD. Biologic, psychologic, environmental and social factors all seem to play a part. Genetic factors are also pertinent: 70 percent of women whose mothers have been affected by PMS have PMS themselves, compared with 37 percent of women whose mothers have not been affected.[4] There is a 93 percent concordance rate in monozygotic twins, compared with a rate of 44 percent in dizygotic twins.[4] Genetic influences mediated phenotypically through neurotransmitters and neuroreceptors seem to play a significant role in the etiology.

Features of PMDD and depressive disorders—specifically atypical depression—overlap considerably. Symptoms of atypical depression (i.e., depressed mood, interpersonal rejection hypersensitivity, carbohydrate craving, and hypersomnia) are similar to those of PMDD. Thirty to 76 percent of women diagnosed with PMDD have a lifetime history of depression,[5] compared with 15 percent of women of a similar age without PMDD. A family history of depression is common in women diagnosed with moderate to severe PMS.[6] There is significant comorbidity between depression and PMDD. Despite this relationship, many patients with PMDD do not have depressive symptoms; therefore, PMDD should not be considered as simply a variant of depressive disorder.[7]

The effectiveness of selective serotonin reuptake inhibitors (SSRIs), administered only during the luteal phase of the menstrual cycle,[8-14] highlights the difference between PMDD and depressive disorder. Acute treatment with SSRIs

increases synaptic serotonin without the down-regulation of serotonin receptors needed for improvement in overt depression. This finding suggests that PMDD is possibly caused by altered sensitivity in the serotoninergic system in response to phasic fluctuations in female gonadal hormone. Other studies also favor the serotonin theory as a cause of PMDD. In particular, the efficacy of L-tryptophan,[15] a precursor of serotonin, and of pyridoxine,[16] which serves as a cofactor in the conversion of tryptophan into serotonin, also favors serotonin deficiency as a cause of PMDD. Carbohydrate craving, often a symptom of PMDD, is also mediated through serotonin deficiency.

Because PMDD only affects women of reproductive age, it is reasonable to assume that female gonadal hormones play a causative role, possibly mediated through alteration of serotoninergic activity in the brain. Estrogen and progesterone seem to modulate levels of monoamines, including serotonin. Eliminating the effect of ovarian gonadal hormones through the use of a gonadotropin-releasing hormone (GnRH) agonist relieves PMDD symptoms.[17] Subsequent administration of estrogen and progesterone causes symptoms to return in women with PMS but not in those without PMS symptoms.[18]

Treatment

The goals of treatment in patients with PMDD are (1) symptom reduction and (2) improvement in social and occupational functioning, leading to an enhanced quality of life. Available treatment options are summarized in *Tables 2 through 6*.

LIFESTYLE CHANGES

Lifestyle changes may be valuable in patients with mildly severe symptoms and benefit their overall health. Aerobic exercise and dietary changes often reduce premenstrual symptoms.[19,20] Decreasing caffeine intake can abate anxiety and irritability, and reducing sodium decreases edema and bloating. Many patients prefer to try lifestyle changes and/or nutritional supplements as a first step in the treatment of PMDD.

The goals of treatment of premenstrual dysphoric disorder are symptom reduction and improvement in social and occupational functioning, leading to an enhanced quality of life.

NUTRITIONAL SUPPLEMENTS

Many of the nutritional supplements described in *Table 2*[4,15,16,19-22] have proven efficacy. A meta-analysis[16] of nine randomized, placebo-controlled trials was conducted to ascertain the effectiveness of vitamin B_6 in PMS management. The researchers concluded that vitamin B_6, in dosages of up to 100 mg per day, is likely to benefit patients with premenstrual symptoms and premenstrual depression. In another study,[21] research literature (from January 1967 to September 1999) was reviewed to evaluate the effectiveness of calcium carbonate in patients with PMS. The reviewers concluded that calcium supplementation in a dosage of

TABLE 2
Treatment Approaches to PMDD

Lifestyle changes	**Nonpharmacologic treatments**
Regular, frequent, small balanced meals rich in complex carbohydrates and low in salt, fat, and caffeine[19,20]	Stress reduction and management[20]
Regular exercise[19,20]	Anger management[4]
Smoking cessation[20]	Self-help support group[20]
Alcohol restriction[20]	Individual and couples therapy[20]
Regular sleep[20]	Cognitive-behavioral therapy[23]
Nutritional supplements	Patient education[20] about the cause, diagnosis, and treatment of PMS/PMDD
Vitamin B_6, up to 100 mg per day[16]	Light therapy[20] with 10,000 Lx cool-white fluorescent light
Vitamin E, up to 600 IU per day[20]	
Calcium carbonate, 1,200 to 1,600 mg per day[21,22]	
Magnesium, up to 500 mg per day[20]	
Tryptophan, up to 6 g per day[15]	

PMDD = premenstrual dysphoric disorder; PMS = premenstrual syndrome.

Information from references 4, 15, 16, and 19 through 23.

TABLE 3
Herbal Therapies for PMDD

Herbal product	*Dosage*	*Use recommendation*	*Comments*
Evening primrose oil[24,25]	500 mg per day to 1,000 mg three times per day	Days 17 through 28 of menstrual cycle	Most-studied of all herbs used in treatment of PMS May provide a precursor for prostaglandin synthesis Benefits breast tenderness Safety data in pregnancy and lactation lacking Not approved for this use by the FDA
Chaste tree berry[24-26]	30 to 40 mg per day	Days 17 through 28 of menstrual cycle	May benefit breast symptoms Inhibits prolactin production Safety data lacking Not approved for this use by the FDA

PMDD = premenstrual dysphoric disorder; PMS = premenstrual syndrome; FDA = U.S. Food and Drug Administration.

Information from references 24 through 26.

1,200 to 1,600 mg per day is a treatment option in women with PMS. Calcium supplementation (using Tums E-X) was found to reduce core premenstrual symptoms by 48 percent in 466 patients.[22] Vitamin E, an antioxidant, seems to reduce the affective and physical symptoms of PMS.[20] Tryptophan,[15] a substrate for serotonin, may also benefit some patients.[15]

NONPHARMACOLOGIC TREATMENTS

Almost invariably, psychosocial stressors should be addressed, either as a cause or a result of PMDD. Psychosocial stressors are known to alter brain neurochemistry and stress-related hormonal activity. Stress reduction, assertiveness training, and anger management can reduce symptoms and interpersonal conflicts. Women with negative views of themselves and the future caused or exacerbated by PMDD may benefit from cognitive-behavioral therapy.[23] This kind of therapy can enhance self-esteem and interpersonal effectiveness, as well as reduce other symptoms.[23] Educating patients and their families about the disorder can promote understanding of it and reduce conflict, stress, and symptoms.[20]

HERBAL THERAPIES

A recent study[24] reviewed efficacy and safety data on herbal supplements marketed for women. The author concluded that two herbal products, evening primrose oil and chaste tree berry, have been effective in treating PMS *(Table 3)*.[24-26] Other researchers[25] have arrived at variable conclusions about the efficacy of evening primrose oil. It is thought to provide the gamma-linolenic acid required for synthesis of prostaglandin E_1,[24] one of the anti-inflammatory prostaglandins. Chaste tree berry may reduce prolactin levels,[24,25] thereby reducing symptoms of breast engorgement. These herbal therapies have not been approved by the U.S. Food and Drug Administration (FDA) for use in PMDD, and their safety in pregnancy and lactation has not been established. Moreover, manufacturing standards for herbal products are not uniform.

PHARMACOLOGIC INTERVENTIONS

Antidepressant and Anxiolytic Medications. The serotoninergic antidepressants are the

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TABLE 4
Pharmacologic Interventions: Antidepressant and Anxiolytic Medications

Agents	*Dosage*	*Use recommendation*	*Comments*
SSRIs			
Citalopram[13,35]	10 to 30 mg per day	Full cycle or luteal phase only	Benefits physical, cognitive, and emotional symptoms Administration during luteal phase Luteal-phase use is superior to continuous treatment Not approved by FDA for this use
Fluoxetine[12,27,29,35]	20 mg per day	Full cycle or luteal phase only	Significant reduction of all symptoms Decreased libido or delayed orgasm is most common side effect in long-term, continuous use Approved by FDA for this use
Paroxetine[30,35]	10 to 30 mg per day	Full cycle	Benefits all symptoms Transient GI and sexual side effects Superior to maprotiline Not approved by FDA for this use
Sertraline[8-10,14,31-33,35]	50 to 150 mg per day	Full cycle or luteal phase only	Benefits all symptoms Transient GI and sexual side effects Approved by FDA for this use
Other serotoninergic antidepressants			
Clomipramine[11,34]	25 to 75 mg per day	Full cycle or luteal phase only	Benefits all symptoms Anticholinergic and sexual side effects Not approved by FDA for this use
Anxiolytics			
Alprazolam[28,36,37]	0.375 to 1.5 mg per day	Luteal phase	Interrupted use during the luteal phase can reduce the risk of drug dependence Use only if SSRIs are ineffective Not approved by FDA for this use

SSRIs = selective serotonin reuptake inhibitors; FDA = U.S. Food and Drug Administration; GI = gastrointestinal.

Information from references 8 through 14, and 27 through 37.

first-line treatment of choice for severe PMDD *(Table 4)*.[8-14,27-37] Fluoxetine, in a dosage of 20 mg per day, has been shown to be superior to placebo, whether used only during the luteal phase[12] or throughout the full menstrual cycle.[27-29] In a review[29] of seven controlled and four open-label clinical trials of fluoxetine, symptoms were significantly reduced in patients with PMDD.

In one placebo-controlled study,[30] paroxetine in a dosage of 10 to 30 mg per day improved mood and physical symptoms in patients with PMDD. Paroxetine was more effective than the noradrenaline reuptake inhibitor maprotiline.[30] Sertraline in a dosage of 50 to 150 mg per day was superior to placebo whether used during the full menstrual cycle[31-33] or only during the luteal phase.[8-10,14] Citalopram in a dosage of 10 to 30 mg per day was effective in one randomized, placebo-controlled trial.[13] Interestingly, intermittent administration of citalopram during the luteal phase was found to be superior to continuous treatment. Clomipramine, a serotoninergic tricyclic antidepressant that affects the noradrenergic system, in a dosage of 25 to 75 mg per day used during the full cycle[34] or intermittently during the luteal phase,[11] significantly reduced the total symptom complex of PMDD.

In a recent meta-analysis[35] of 15 random-

The serotoninergic antidepressants are the first-line treatment of choice for patients with severe premenstrual dysphoric disorder.

Alprazolam should be used as a second-line drug only if selective serotonin reuptake inhibitors fail to bring about an optimal response.

ized, placebo-controlled studies of the efficacy of SSRIs in PMDD, it was concluded that SSRIs are an effective and safe first-line therapy and that there is no significant difference in symptom reduction between continuous and intermittent dosing. Because fluoxetine, citalopram, clomipramine, and sertraline were effective if administered during the luteal phase only, these drugs may be used as first-line therapy and taken intermittently only during the luteal phase. Such an approach can reduce the risk of long-term side effects (e.g., weight gain), minimize discontinuation syndrome, and reduce the cost of care. SSRIs benefit the total symptom complex of PMDD, not only the mood-related symptoms. It should also be noted that fluoxetine and sertraline are the only two SSRIs with FDA approval for use in the treatment of PMDD.

Alprazolam, a high-potency benzodiazepine with mood-enhancing and anxiolytic effects, has been shown to be somewhat effective in patients with PMS.[28,36,37] Because of the potential for drug dependence, alprazolam should be considered a second-line drug and used only if SSRIs fail to achieve an optimal response. Therapy should be limited to the luteal phase, and the agent should be given in low dosages—0.375 to 1.5 mg per day. The risk of drug dependence with alprazolam can be minimized by administering it only during

TABLE 5
Hormonal Therapies for PMDD

Drug	*Dosage*	*Use recommendation*	*Comments*
Leuprolide depot[38,40]	3.75 mg IM per month	Up to six cycles	Pregnancy category X Significant relief from symptoms but can induce menopausal syndrome
Leuprolide depot with ovarian hormone supplements[18]	3.75 mg IM per month with estrogen and progesterone	Can exceed six cycles	Less likely to induce menopause; PMDD symptoms may return, making this combination less effective
Goserelin with estrogen supplementation[39]	3.6 mg SC every 28 days with estrogen	Can exceed six cycles	Less likely to induce menopause; PMDD symptoms may return, making this combination less effective Pregnancy category X Use nonhormonal contraception during therapy and for 12 weeks after discontinuation of drug or until menses resume
Danazol[41]	100 mg twice a day	Up to six cycles	May cause masculinization from weak androgenic properties Pregnancy category X
OCPs[20]	OCPs with varying amounts of estrogen and progesterone, once a day	Full cycle	Variable response; may not benefit patients with significant mood symptoms; in some patients, may make mood symptoms worse
Progesterone[42,43]	Vaginal suppositories, 200 to 400 mg per day	Not recommended for this use	Questionable efficacy

PMDD = premenstrual dysphoric disorder; IM = intramuscularly; SC = subcutaneously; OCPs = oral contraceptive pills.

Information from references 18, 20, and 38 through 43.

TABLE 6
Miscellaneous Pharmacologic Interventions for PMDD

Agents	*Dosage*	*Use recommendation*	*Comments*
Diuretics			
Spironolactone[44]	100 mg per day	Luteal phase	Aldosterone antagonist Potassium-sparing diuretic Could improve physical and psychologic symptoms
Dopamine agonist			
Bromocriptine[4,20,45]	Up to 2.5 mg three times per day	Days 10 through 26 of menstrual cycle	May relieve cyclic mastalgia; evaluate hepatic and renal functions before initiation
NSAIDs			
Ibuprofen[20]	500 to 1,000 mg per day	Days 17 through 28 of menstrual cycle	Take with food May relieve mastalgia

PMDD = premenstrual dysphoric disorder; NSAIDs = nonsteroidal anti-inflammatory drugs.

Information from references 4, 20, 44, and 45.

the luteal phase of the menstrual cycle in patients without a history of substance abuse.

Hormonal Therapies. It has been shown that by inducing anovulation and amenorrhea, GnRH agonists, leuprolide, histrelin, and goserelin provide significant relief of symptoms in patients without comorbid depression.[38-40] However, these medications can induce menopausal symptoms such as hot flushes, vaginal dryness, fatigue, irritability, cardiac problems, and osteopenia. In women with a history of PMDD, treatment of induced menopause with estrogen[39] or estrogen plus progestational agents[18] can induce recurrent symptoms of PMDD. This finding supports the theory of an etiologic role for female gonadal hormones in PMDD.

Danazol (Danocrine), a weak androgen prescribed for patients with endometriosis, fibrocystic breast disease, and hereditary angioneurotic edema, is sometimes used to treat PMDD. The typical dosage is 100 mg twice a day. Such treatment can reduce symptoms but may result in anovulation and masculinization, either of which may limit regular use.[41] Because of the potential for serious side effects and significant costs, GnRH agonists and danazol should be tried as a last resort. These medications must be initiated during menstruation to prevent teratogenicity if there is an unintended pregnancy.

Although oral contraceptive pills (OCPs) suppress ovulation, they are not reported to be consistently effective in the treatment of PMDD (perhaps because the studies had variable samples). OCPs may not suffice if mood symptoms are prominent and, in some patients, these drugs may worsen dysphoria (a known side effect of some birth control pills) in many women without PMDD.

Efficacy studies of progesterone have shown limited benefits. One study[42] found progesterone to be superior to placebo; however, another study[43] reported efficacy equal to or less than that of placebo. Currently, ovarian gonadal hormones are thought to be of limited usefulness in the treatment of PMDD, and none of the drugs has FDA approval for this indication *(Table 5)*.[18,20,38-43]

Miscellaneous Pharmacologic Interventions. In a double-blind, placebo-controlled, crossover study,[44] spironolactone in a dosage of 100 mg per day was more effective than placebo in reducing irritability, depression, somatic symptoms, feelings of swelling, breast tenderness, and craving for sweets. Bromocriptine in a dosage of up to 2.5 mg three times per day may be beneficial in patients with cyclic mastalgia,[4,20] although in one study[45] it was not found to be effective. Ibuprofen, in a dosage of up to 1,000 mg per day, can reduce breast pain, headaches, back pain, and other pain symptoms,[20] but seems to have limited effect on mood symptoms *(Table 6)*.[4,20,44,45]

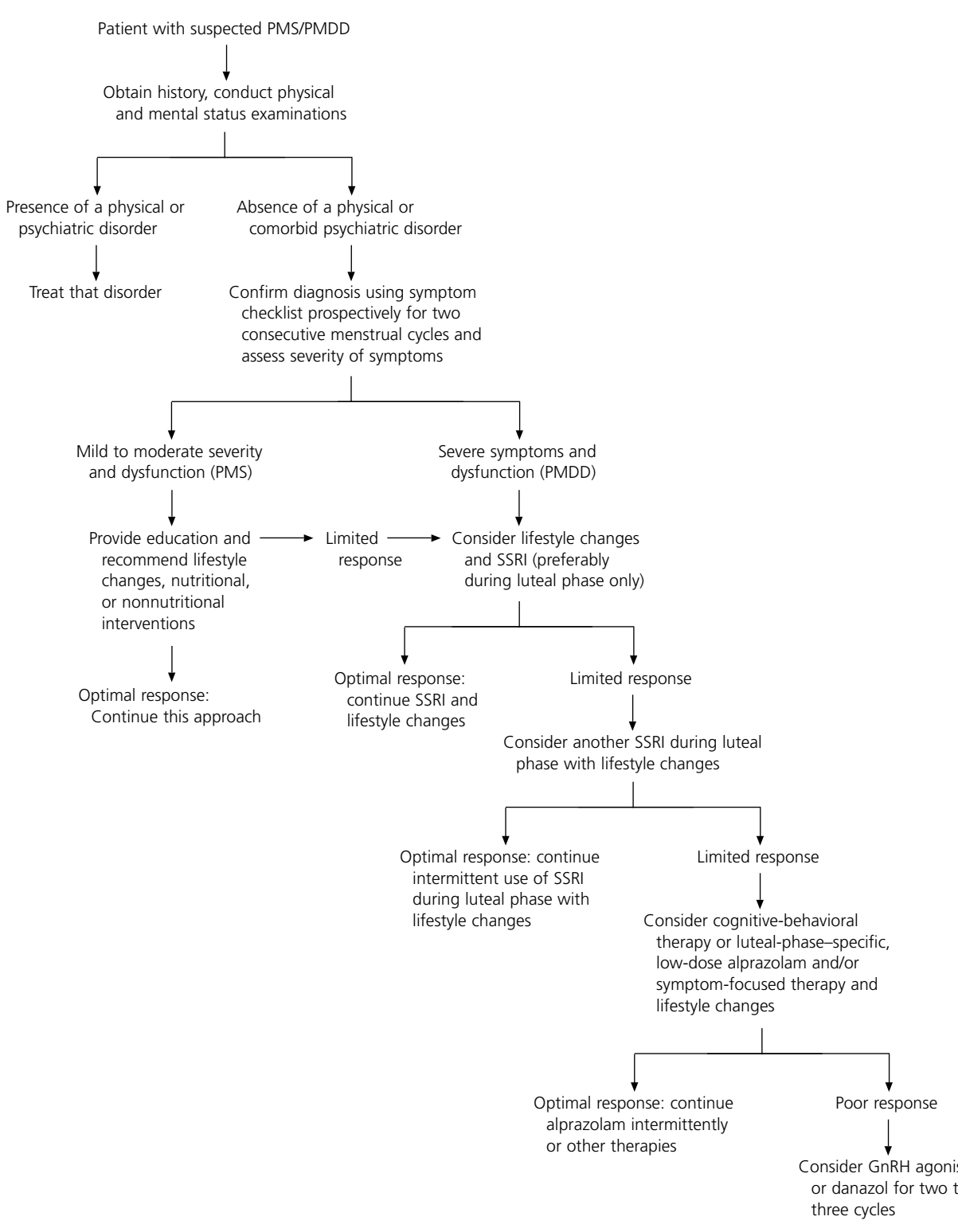

FIGURE 1. Algorithm for the management of PMS/PMDD. (PMS = premenstrual syndrome; PMDD = premenstrual dysphoric disorder; SSRI = selective serotonin reuptake inhibitor; GnRH = gonadotropin-releasing hormone.)

TABLE 7
Efficacy Rating of Current Treatments for PMS/PMDD

Recommended treatment	*Efficacy in PMS/PMDD*	*Efficacy rating**	*Comments/evidence*
Lifestyle changes[19,20]	PMS or PMDD	G	Health benefits without risks
Vitamin B_6[16]	PMS or PMDD	B	Dosage > 100 mg per day may cause peripheral neuropathy
Vitamin E[20]	PMS or PMDD	E	Antioxidant without significant risk
Calcium carbonate[21,22]	PMS or PMDD	B	Placebo-controlled study supports benefits in moderate to severe PMS
Tryptophan[15]	PMS or PMDD	B	Supported by a placebo-controlled study
Cognitive-behavioral therapy[23]	PMS PMDD	A B	Benefits documented; not many studies —
Herbal therapies[24,25]	PMS or PMDD	E	Safety in pregnancy and lactation not documented; not FDA-approved
Selective serotonin reuptake inhibitors[8-10,12-14,29-33,35]	Nonresponsive PMS or PMDD	A	Well-designed, randomized, placebo-controlled studies and meta-analyses
Clomipramine[11,34]	PMDD	B	Anticholinergic side effects
Alprazolam[28,36-37]	PMDD	B	Low-dose, luteal phase treatment; long-term use may cause tolerance
GnRH agonists or danazol[18,38,39,41,42]	PMDD	C	Menopausal syndrome/masculinization/cost limit its use
Spironolactone, bromocriptine, or ibuprofen[41,44,45]	PMS or PMDD	D	Symptom-focused efficacy; spironolactone efficacy supported by double-blind study
Oral contraceptives or progesterone[42,43]	PMDD	E	Anecdotal efficacy or not consistently effective
Surgical or radiation oophorectomy	PMDD	F	Not recommended

PMS = premenstrual syndrome; PMDD = premenstrual dysphoric disorder; FDA = U.S. Food and Drug Administration; GnRH = gonadotropin-releasing hormone.

**—Efficacy rating key: A = first line; B = second line; C = third line; D = symptomatic efficacy; E = efficacy anecdotal or not consistently effective; F = not recommended; G = general or adjunctive treatments.*

Information from references 8 through 16, 19 through 25, 28 through 39, and 41 through 45.

Other Medical Interventions. Historically, surgical and radiation oophorectomies have been used to treat severe PMS, but these modalities have no role in the current management of PMDD.

Evidenced-based efficacy ratings of currently available treatments for PMS and PMDD are described in *Table 7*,[8-16,19-25,28-39,41-45] while an algorithm for the management of these conditions is outlined in *Figure 1*.

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