What medications are effective for treating symptoms of premenstrual syndrome (PMS)?

EVIDENCE-BASED ANSWER Vitamin B6 (50–100 mg/d) and elemental calcium (1200 mg/d) are safe, inexpensive, and moderately effective (Table) (grade of recommendation: B). Selective serotonin reuptake inhibitors (SSRIs) and some other antidepressants are more effective, but are also more costly and more likely to cause side effects or treatment dropout (grade of recommendation: A). Antidepressant dosing only during the luteal phase may be effective and more tolerable (grade of recommendation: B). Alprazolam (generally 0.25–0.5 mg 3 times a day during luteal phase) may be effective for treating mood or anxiety symptoms (grade of recommendation: B). Hormonal therapies (oral contraceptives, gonadotropin-releasing hormone agonists, danazol, estrogen) lack convincing evidence of efficacy and cause many side effects; progesterone is no more beneficial than placebo (grade of recommendation: B). There is no convincing evidence of benefit from diuretics, magnesium, beta-blockers, or lithium (grade of recommendation: C).

TABLE

Agents for treating symptoms of premenstrual syndrome

Medication	Sample drug and dose	Adverse effects	Benefit
Vitamin B6[1]	50–100 mg/d	Peripheral neuropathy	OR = 2.32 (95% CI 1.95–2.54)
Elemental calcium[2]	1200 mg/d	Same as placebo	NNT = 6 for 50% symptom reduction
SSRIs[3]	Fluoxetine 20 mg/d	Insomnia, headache, nausea, dizziness	NNT = 4–11
Benzodiazepines[4]	Alprazolam 0.25–0.5 mg tid/qid in luteal phase	Habituation	NNT = 3 for 50% symptom reduction
GnRH agonists[5]	Danazol 200–400 mg/d	Hypoestrogenic Androgenic	Benefit unclear Benefit unclear

GnRH, gonadotropin-releasing hormone; NNT, number needed to treat; SSRIs, selective serotonin reuptake inhibitors.

EVIDENCE SUMMARY Pooled results of 9, generally poor-quality studies of Vitamin B6 show some benefit.[1] Doses higher than 100 mg/d may cause peripheral neuropathy. Three small studies in the 1980s suggested possible benefit of Vitamin E; however, these studies have not been further replicated. One well-designed, randomized controlled trial of calcium therapy showed > 50% decrease in symptom complex scores after 3 months in more than half of subjects taking 1200 mg/d supplemental elemental calcium (NNT=6).[2]

Among SSRIs, fluoxetine (20 mg/d) is well-studied and effective.[3] Other SSRIs, including sertraline, paroxetine, fluvoxamine, and venlafaxine, and clomipramine (a tricyclic with serotonin reuptake inhibitor activity), also show benefit but are less well studied. Luteal phase-only dosing may be equally or more effective than continuous dosing for some SSRIs. Benzodiazepines have shown mixed results in treating PMS, and overall their benefit appears smaller than that of SSRIs.[4] Luteal phase-only dosing theoretically reduces the risk of benzodiazepine withdrawal or dependence, but published data are rare.

Gonadotropin-releasing hormone agonists may be effective, but troublesome anti-estrogenic side effects limit their utility. Estrogen and progesterone "add-back" therapy to counter side effects further complicates this approach. The gonadotropin inhibitor danazol has a high treatment dropout rate at higher doses (200–400 mg/d continuously), but can be effective in individuals who are able to tolerate it[3,5]; however, danazol is expensive and causes significant androgenic side effects. Lower-dose danazol (200 mg/d luteal phase only) is better tolerated but ineffective.[6] A meta-analysis of progesterone found no evidence to support its efficacy.[7] Oral contraceptives are ineffective for global symptoms, and may actually cause PMS symptoms in some women.

RECOMMENDATIONS FROM OTHERS The American College of Obstetricians and Gynecologists recommend that patients with mild to moderate PMS should receive supportive, lifestyle, and dietary interventions. For severe PMS, SSRIs are the initial drug of choice. Alprazolam may be useful when these interventions are ineffective. Consider oral contraceptives for primarily physical symptoms and reserve gonadotropin-releasing hormone for severe cases unresponsive to other treatments.[8]

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Clinical Commentary by Peter Danis, MD, at http://www.fpin.org.

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