Managing Menopause: Current Therapeutic Options for Vasomotor Symptoms

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Conflict of Interest: Dr Miller has served on the speakers’ bureau for Pfizer Pharmaceuticals and Wyeth-Ayerst Laboratories. Dr Ashar reports no financial or advisory relationships with corporate organizations related to this activity.

Off-Label Product Discussion: The authors include information on off-label use of venlafaxine, paroxetine, fluoxetine, gabapentin, clonidine, and methyldopa for the treatment of vasomotor symptoms.

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ABSTRACT

Purpose: To describe and evaluate the available hormonal, nonhormonal pharmacologic, and dietary supplement preparations used for the treatment of menopausal vasomotor symptoms.

Epidemiology: More than 75% of women experience hot flashes during perimenopause and more than 25% remain symptomatic for longer than 5 years. Vasomotor symptoms constitute the primary reason women seek medical care during this time.

Review Summary: Menopause brings a unique set of issues, including hot flashes, depressed mood, and vaginal dryness. Of these, vasomotor symptoms are often the most debilitating for women and create a challenge for physicians. Coping mechanisms are a reasonable treatment choice for women with mild symptoms but are frequently inadequate to restore functionality to women with moderate to severe symptoms. Hormone therapy is the most effective management option for hot flashes. Other proven, albeit less efficacious, pharmacologic options do exist. These include serotonin reuptake inhibitors, gabapentin, and alpha2-adrenergic agents. Finally, “natural” alternatives have surged in popularity, as many women have turned to over-the-counter vitamins and herbal products. Scant short-term data exist for few of these popular dietary supplements.

Type of Available Evidence: Systematic reviews; randomized controlled trials; cohort studies; case-control series; nationally recognized treatment guidelines.

Grade of Available Evidence: Poor to good.

Conclusion: Many useful modalities exist for the treatment of menopausal vasomotor symptoms, with hormone therapy being the most effective. Future research should focus on the identification and evaluation of alternatives, including lower doses or different formulations of hormone therapy and other agents, with attention to long-term beneficial and adverse outcomes.

Clinical Relevance: This review provides information on the management of menopausal vasomotor symptoms and the available therapeutic options. It highlights the importance of patient education and the potential for off-label use of certain medications in treating these symptoms.

Menopause is an inevitable part of every woman’s life. Currently, 42 million women in the United States are over the age of 50 years and potentially menopausal. With the aging of the population, this number is expected to grow to 52 million by the year 2010. Physician familiarity with treatment options for symptoms associated with menopause will be a necessity.

The definition of menopause is the permanent cessation of menses following the loss of ovarian activity. Menopause is a clinical diagnosis. In female patients in their mid-40s to mid-50s, a lack of menses for 12 months confirms the diagnosis. Most often, menses do not end abruptly but rather become irregular (shortened cycles, skipped cycles, spotting) for 2 to 5 years preceding the menopause. This interval is known as the perimenopause.
The average age at menopause is 51 years (range 45-55 years). Menopause often occurs earlier in smokers and nulliparous women. Given an increasing life expectancy of well into the ninth decade, the average woman can expect to spend one third to one half of her life in the postmenopausal years.

Measuring hormone levels, such as follicle-stimulating hormone (FSH), is not necessary or useful in the diagnosis of menopause because the levels fluctuate widely throughout perimenopause. If the clinical scenario is atypical for some reason (e.g., a young woman with possible premature ovarian failure or a hysterectomized woman without hot flashes), an elevated FSH may be helpful in establishing the diagnosis.

CLINICAL PRESENTATION

The symptoms of menopause are primarily those of estrogen deficiency. Of these, hot flashes are often the most debilitating and are the most common reason women seek medical care during the perimenopause. These vasomotor symptoms may be only a minor nuisance or may be severe enough to affect a woman’s quality of life, including her ability to work and maintain social functioning. Significant variability in the prevalence and severity of vasomotor symptoms among women exists, which may be related to genetic, dietary, and cultural factors. In the United States and Europe, up to 75% of women experience hot flashes, whereas only 20% of Asian women do. Yet, when Japanese women migrate to the United States, their incidence of hot flashes rises within 1 to 2 generations. Other predictors of vasomotor symptoms include tobacco use, decreased physical activity, lack of an occupation, high body mass index, and low estradiol levels. Hot flashes are generally most debilitating in the first 2 to 3 years and then gradually decline in frequency and severity. Unfortunately, up to 25% of women remain symptomatic for more than 5 years.

A hot flash is an intense feeling of warmth that typically begins in the head and neck area and gradually spreads to the face, chest, and arms. It may be accompanied by significant diaphoresis, visible flushing (“hot flush”), anxiety, and palpitations. The entire episode usually lasts 1 to 5 minutes and is often followed by a period of feeling cool or chilly. Hot flashes occur more frequently at night, leading to insomnia and chronic fatigue.

The pathophysiology behind a hot flash is not well established, but it is probably related to dysregulation of the hypothalamic thermoregulatory center precipitated by the decline in estradiol and rise in gonadotropin levels. In fact, evidence supports that the withdrawal of estrogen, rather than low circulating levels, may be the crucial determinant of hot flashes and may explain why women with the abrupt onset of menopause (oophorectomy, chemotherapy) experience more severe symptoms. Freedman and colleagues have used skin conductance techniques to document a frequent, small decline in core body temperature preceding a hot flash that may then precipitate normal heat loss mechanisms, such as perspiration and vasodilation. In this pathway, norepinephrine is thought to be a key neurotransmitter in triggering the temperature rise, and serotonin receptor activation may trigger heat loss mechanisms. Interestingly, estrogen withdrawal can be associated with loss of inhibition of norepinephrine as well as decreased serotonin levels and upregulation of serotonin receptors. This may partially explain the effectiveness of newer nonestrogenic hot flash therapies.

TREATMENT OPTIONS

Therapeutic options for vasomotor symptoms are numerous and of varying efficacy. The choice of treatment should be based on symptom severity, an analysis of the risks and benefits of the various alternatives, and a close dialogue between physician and patient.

COPING MECHANISMS

For the woman with mild to moderate vasomotor symptoms, simple coping mechanisms are often adequate for treatment. Women should be instructed to wear layered clothing to accommodate fluctuations in temperature. Avoidance of triggers can greatly ameliorate hot flash frequency. Common triggers include spicy foods, alcohol, caffeine, stress, warm or humid environments, and sexual activity. Exercise can decrease the incidence of hot flashes. Slow rhythmic breathing, biofeedback, and other relaxation techniques can aid in coping with symptoms on a daily basis.
HORMONE THERAPY

Hormone therapy (HT), in the form of estrogen or estrogen plus progestin, is clearly the most effective and the only Food and Drug Administration (FDA)-approved treatment for menopausal vasomotor symptoms. Numerous oral formulations are available (Table 1). The Cochrane Database of Systematic Reviews, a meta-analysis of double-blind, randomized, placebo-controlled trials of oral HT, documented a significant 80% reduction in hot flash frequency and severity over placebo, although no agent achieved 100% effectiveness.15 Oral HT has a rapid onset of efficacy, usually within a few days to a week, but may require up to 4 weeks before maximal effectiveness is attained. Contraindications to HT use in newly menopausal women include a history of breast or uterine cancer, thromboembolic disease, and severe liver disease.

Publication of the results of the Women's Health Initiative (WHI) in 2002 greatly impacted the role of HT in the prevention of chronic disease.16 Prior to the WHI, observational data demonstrated a decrease in cardiac and all-cause mortality in women who used HT.17,18 The WHI was the first large randomized, controlled trial of conjugated equine estrogens (CEE) and continuous medroxyprogesterone acetate (MPA) vs placebo. It enrolled more than 16,000 women, with an average of 5.2 years of follow-up. The results did not document a protective effect of HT on the prevention of cardiovascular morbidity or mortality and found a borderline significant increased risk of breast cancer in this group of women (mean age 62 years), the vast majority of whom had never taken HT before. It also confirmed a 2x to 3x increased risk of thromboembolic disease and a protective effect on bone mineral density and fracture prevention in HT users.16 More recently, the estrogen-only arm of the WHI was published, with the only significant outcomes being increased thromboembolic events, increased cerebrovascular disease, and decreased osteoporotic fractures, with a surprising trend toward breast cancer protection.19 It is important to remember that neither arm of the WHI was designed to study newly menopausal women with vasomotor symptoms, and, in fact, women with severe hot flashes were excluded from the trial, resulting in an older mean age for the study subjects.20 Because of this, the results are difficult to extrapolate to a younger, perimenopausal popula-

**Coping Mechanisms for Hot Flashes**

- Wear layered, cotton clothing
- Avoid triggers:
  - Spicy foods
  - Caffeine
  - Alcohol
  - Stress
  - Warm, humid environments
- Pursue regular exercise
- Use relaxation, deep-breathing techniques, biofeedback

### Table 1. Hormonal Therapy Options for Vasomotor Symptoms*

<table>
<thead>
<tr>
<th>Oral Preparations</th>
<th>Standard-dose estrogen</th>
<th>Low-dose estrogen</th>
<th>Progestin only</th>
<th>Standard-dose estrogen + standard-dose progestin</th>
<th>Low-dose estrogen + low-dose progestin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE 0.625, 0.9, 1.25</td>
<td>E2 1.0, 2.0</td>
<td>CEE 0.3, 0.45</td>
<td>MPA 2.5, 5.0, 10</td>
<td>CEE 0.625 + MPA 5.0 (continuous or sequential)</td>
<td>CEE 0.45 + MPA 1.5</td>
</tr>
<tr>
<td>Esterified estrogens 0.625, 1.25</td>
<td>Estropipate 0.75, 1.5</td>
<td>E2 0.5</td>
<td>Micronized progesterone 100</td>
<td>E2 1.0 + Norgestimate 0.09 (intermittent dosing)</td>
<td>CEE 0.3 + MPA 1.5</td>
</tr>
<tr>
<td>CE, synthetic 0.625</td>
<td>CE2 synthetic 20</td>
<td>Esterified estrogens 0.3</td>
<td>Mestrol acetate 20</td>
<td>E2 1.0 + NETA 0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EE 0.005 + NETA 1.0</td>
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<table>
<thead>
<tr>
<th>Alternative Delivery Preparations</th>
<th>Transdermal</th>
<th>Topical</th>
<th>Vaginal</th>
<th>Intramuscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE 0.025, 0.0375, 0.05, 0.075, 0.1</td>
<td>E2 3.48 (2 packets) qd</td>
<td>E2 0.05, 1.0, 0, 0 3 months</td>
<td>Estradiol cypionate 1-5, q 3-4 wks</td>
<td>Estradiol valerate 10-20, q 4 wks</td>
</tr>
<tr>
<td>1-2x/week (depending on brand)</td>
<td>Estradiol 0.05 + NETA 0.14, 2x/week</td>
<td>Estradiol 0.05 + NETA 0.25, 2x/week</td>
<td>Estradiol cypionate 1-5, q 3-4 wks</td>
<td>Estradiol valerate 10-20, q 4 wks</td>
</tr>
<tr>
<td></td>
<td>Estradiol cypionate 20 mg qd</td>
<td>Estradiol cypionate 20 mg qd</td>
<td>Estradiol cypionate 20 mg qd</td>
<td>Estradiol cypionate 20 mg qd</td>
</tr>
<tr>
<td></td>
<td>Alora, Climara, Estral, Estraderm</td>
<td>N/A (must be compounded)</td>
<td>N/A (must be compounded)</td>
<td>N/A (must be compounded)</td>
</tr>
<tr>
<td></td>
<td>CombiPatch®</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Estrasorb®</td>
<td>Femring®</td>
<td>Femring®</td>
<td>Femring®</td>
</tr>
</tbody>
</table>

Note: Not intended to be all-inclusive.

CEE = conjugated equine estrogens; E2 = estradiol; CE = conjugated estrogens (synthetic); MPA = medroxyprogesterone acetate; NETA = norethindrone acetate; EE = ethinyl estradiol; qd = every day; q = every.
Review of Oral Hormone Therapy for Hot Flashes

- Oral hormone therapy is highly effective for vasomotor symptoms relative to placebo
  - Hot flash frequency reduced by an average of 77% (95% CI, 58.2, 87.5)
  - Hot flash severity also reduced (OR 0.13, 95% CI, 0.08, 0.22)
- Onset of effectiveness within days, but may take up to 4 weeks to reach maximal efficacy
- No agent achieves 100% effectiveness
- Placebo results in 50.8% (95% CI, 41.7, 58.5) reduction in hot flashes

Data from MacLennan et al.

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A limitation of the WHI is that it evaluated only one dosing regimen and one form of estrogen and progestin (CEE + MPA). Perhaps other doses or formulations would produce different outcomes, although this is speculative at best. To this end, newer HT options have become available. In particular, low-dose estrogen has become increasingly popular, with the anticipation that lower doses will preserve the benefits of estrogen without the adverse events. The HOPE trial (Women's Health, Osteoporosis, Progestin, Estrogen Study) compared lower doses of CEE/MPA (0.3/1.5 mg and 0.45/1.5 mg) to standard doses (0.625/2.5 mg) in more than 2600 women. The results demonstrated comparable decreases in hot flashes (up to 81%) in all groups and significant gains in bone mineral density compared to losses in the placebo group. Furthermore, patients experienced less vaginal spotting and mastalgia with the lower doses.

A variety of estrogen formulations are available and may have different effects. These include 17 beta-estradiol, ethinyl estradiol, esterified estrogens, synthetic conjugated estrogens, and estropipate (Table 1). Importantly, in a woman with an intact uterus, it is recommended that a concurrent progestin to prevent endometrial hyperplasia and carcinoma be prescribed, although newer ultra-low-dose estrogen preparations could conceivably result in lower hyperplasia and cancer risk.23 Various preparations of progestins exist, both in combination with estrogens and as individual agents, and can be safely delivered cyclically, continuously, or even intermittently in a new formulation (Prevest®, Table 1).24,25 Whereas all of these estrogen preparations demonstrate significant improvement in vasomotor symptoms,26-28 large studies on long-term outcomes, such as osteoporosis, breast cancer, and cardiovascular disease, are few. The CHART study was one of the largest to examine a hormone combination different from the WHI regimen. Roughly 1200 women were assigned to varying doses of ethinyl estradiol in combination with continuous norethindrone acetate. The combination provided endometrial protection and dose-related increases in bone mineral density.29 Ultra-low doses of estradiol (0.25 mg per day) have been shown to increase bone mineral density relative to placebo in older women.30 Large head-to-head comparisons of the different hormone formulations on these important long-term outcomes are also lacking.

Some women may be interested in alternative methods of estrogen delivery other than oral, either for convenience or theoretical benefits (Table 1). Transdermal 17 beta-estradiol has documented efficacy in reducing hot flashes by 84% within 2 to 3 weeks of initiation and produces modest gains in bone mineral density.31 An ultra-low-dose transdermal estradiol that delivers 14 mcg per day (Menostar®) was recently approved for the prevention of osteoporosis, but not for treatment of vasomotor symptoms. A newer, topical estradiol preparation that is applied daily to the thighs or arms (Estraderm®) and an intravaginal estradiol ring that is inserted every 3 months (Femring®) provide still more options and are both approved for the treatment of hot flashes. These alternative delivery methods avoid the first-pass effect associated with oral estrogens and can achieve similar and possibly more stable serum levels with lower doses. However, it remains to be determined if this hepatic bypass is desirable or not. First-pass metabolism may play a beneficial role in changes to the lipid profile (eg, increases in high-density lipoprotein, decreases in low-density lipoprotein), but may also be involved in undesirable effects on coagulation factors and triglycerides. A small, case-control study suggested a decreased thrombotic risk with transdermal vs oral estrogen therapy,32 but no definitive studies exist as to the most beneficial method of estrogen delivery regarding coagulation risk or other considerations.

Progestins alone also can provide relief of menopausal symptoms (Table 1). Megestrol acetate,33 depomedroxy-progesterone acetate,37 and transdermal progesterone cream38 have all been studied and result in an 80% to 90% decrease in hot flashes. Common side effects include irregular vaginal bleeding, weight gain, mood changes, and breast discomfort. Long-term safety studies are not available, however, and many clinicians hesitate to use progestins in breast and uterine cancer patients.

Selective estrogen receptor modulators (SERMs) are designer estrogens that serve as both estrogen receptor agonists and antagonists, depending on the target organ. The most popular SERM in use today is raloxifene. Advantages of raloxifene include demonstrated efficacy in maintaining bone mineral density
and preventing vertebral fractures in newly menopausal women, lack of endometrial stimulation leading to hyperplasia, and potential reduction in breast cancer risk. For the woman with severe vasomotor symptoms, however, raloxifene either has no effect or may even worsen hot flashes.39,40

**Nonhormonal Pharmacologic Options**

Despite the well-documented effectiveness and minimal risk imposed by short-term HT, many women with severe vasomotor symptoms cannot take or remain hesitant to use hormonal preparations. In fact, up to 56% of women reported trying to discontinue HT after the publication of the initial WHI results in 2002, although many experienced significant recurrence of vasomotor symptoms.41 For these women, other choices are available (Table 2).

**Antidepressants.** Certain antidepressants have demonstrated efficacy in the reduction of hot flash frequency and severity. Venlafaxine, the first agent rigorously studied, inhibits reuptake of serotonin, norepinephrine, and dopamine. Its effects on norepinephrine and serotonin levels in particular may mediate a role in hypothalamic thermoregulation.9 In a study of 191 breast cancer survivors with hot flashes, venlafaxine produced a 37% to 61% reduction in hot flash score (composite of severity multiplied by frequency) at 4 weeks, depending on dose. The 37.5-mg and 75-mg doses were most effective and resulted in the fewest side effects.42

Subsequently, selective serotonin reuptake inhibitors (SSRIs) also have been studied. Fluoxetine generated a 50% decrease in hot flash score at a daily dose of 20 mg.43 Most recently, a large, multicenter trial of controlled-release paroxetine demonstrated an almost 65% reduction in hot flash score relative to placebo at both the 12.5-mg and 25-mg doses.44 In general, venlafaxine and SSRIs are well tolerated, but some women may experience nausea, diarrhea, and other gastrointestinal upset; insomnia or somnolence; headache; and sexual dysfunction. The clinician should also be aware of a potential drug-drug interaction in that paroxetine may decrease the active metabolites of tamoxifen in some women with breast cancer.45

**Gabapentin.** Gabapentin, a gamma-aminobutyric acid analog, was initially approved for the treatment of seizures but has since shown efficacy for many conditions, including neuropathic pain and migraines. The exact mechanism of action is unknown, but it is postulated to have an effect on hypothalamic tachykinin activity.46 In a 12-week, double-blind, placebo-controlled trial of 59 postmenopausal women, 900 mg of gabapentin was associated with a 45% reduction in hot flash frequency and a 54% reduction in hot flash score (severity and frequency combined).46 The most common side effects of gabapentin are somnolence and dizziness. Gradual titration of dose and consumption of the medication with meals can ameliorate these side effects.

**Alpha2-Adrenergic Agents.** Less desirable options for vasomotor therapy include clonidine and methyldopa, agents that work via stimulation of central alpha2-adrenergic receptors. Both oral and transdermal clonidine have been studied and found to have limited effectiveness in reducing hot flash frequency by 20% to 40%.47,48 Side effects significantly limit tolerance to the drug, with drowsiness, postural hypotension, and dry mouth being the most bothersome. Likewise, methyldopa has a proven, modest benefit but produces a similar adverse effect profile.49

### Table 2. Nonhormonal Pharmacologic Options for Vasomotor Symptoms

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Potential Class Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin reuptake inhibitors</td>
<td>Venlafaxine 37.5 mg - 75 mg qd</td>
<td>Gastrointestinal upset, Sexual dysfunction, Somnolence or insomnia</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine 20 mg qd</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paroxetine CR 12.5 mg - 20 mg qd</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants alpha2-adrenergic agents</td>
<td>Gabapentin 300 mg tid</td>
<td>Drowsiness, lethargy, Hypotension, dizziness, Fatigue</td>
</tr>
<tr>
<td></td>
<td>Clonidine 0.1 mg - 0.2 mg bid or transdermal 0.1 mg - 0.2 mg /24 hours</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Metyldopa 250 mg - 500 mg bid</td>
<td>Constipation</td>
</tr>
</tbody>
</table>

qd = every day; tid = 3 times a day; bid = twice daily.

**Dietary Supplements**

The popularity of dietary supplements for the treatment of menopausal symptoms began to increase long before the results of the WHI were available. The passage of the Dietary Supplement Health and Education Act (DSHEA) of 1994 effectively deregulated the supplement industry by permitting manufacturers to market their products without providing evidence of safety or efficacy. Additionally, DSHEA expanded the definition of a dietary supplement to include vitamins, minerals, amino acids, herbs, and biological metabolites. Overall, there are very limited safety and efficacy data for most of these products. There is also currently no quality assurance for supplements. Patients cannot be certain that the product that they are ingesting actually contains the active ingredient that is described on the product label. Despite these concerns, manufacturing, marketing, and use of supplements have surged. Surveys have suggested that as many as 40% of peri- and
postmenopausal women use dietary supplements regularly.50,51 The most popular of these are discussed below and in Table 3.

**Phytoestrogens.** Phytoestrogens are compounds derived from plants that exhibit some estrogenic activity. They are typically classified as isoflavones, lignans, or coumestans. Isoflavones and lignans are thought to have the most potential for amelioration of menopausal symptoms. They can be found in various foods or in over-the-counter products (Table 4).

**Soy Isoflavones.** Observational studies have suggested that women from certain Asian countries have a lower incidence of menopausal symptoms compared with white populations.52,53 High dietary intake of soy has been proposed as one possible explanation for this discrepancy. Dietary surveys of Japanese women have supported the hypothesis that a diet rich in soy has a protective effect against vasomotor symptoms.54,55 Clinical data, however, are conflicting. Even though some small studies do show an improvement in symptoms with the administration of either soy supplements or soy-based foods compared to placebo, a majority of completed trials have yielded negative results.56-58 Only 3 studies to date have extended beyond 16 weeks in duration. All of these have failed to show a distinct benefit from soy.59-60 Additionally, ingestion of soy supplements has been recently shown to induce endometrial hyperplasia when taken long-term (5 years).61 Given this information, it is difficult to enthusiastically endorse soy supplements for long-term treatment of moderate to severe menopausal symptoms.

**Red Clover (Trifolium pratense).** Dietary supplements derived from red clover contain the isoflavones formononetin and biochanin A, in addition to the daidzein and genistein found in soy. There have been few published studies on the effects of these supplements on menopausal symptoms. In the largest trial completed to date, Tice and colleagues randomized 252 menopausal women to placebo or 1 of 2 red clover–containing supplements, Promensil™ (82 mg of total isoflavones) or

### Table 3. Popular Dietary Supplements Used for the Treatment of Menopausal Symptoms

<table>
<thead>
<tr>
<th>Herb</th>
<th>Potential Toxicity</th>
<th>Potential Drug Interactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black cohosh (Cimicifuga racemosa)</td>
<td>Gastrointestinal discomfort</td>
<td>None known</td>
<td>See text</td>
</tr>
<tr>
<td>Chaste tree berries (Vitex agnus-castus)</td>
<td>Pruritus</td>
<td>May have dopaminergic activity; therefore, avoid with use of dopamine-receptor antagonists (eg, neuroleptics)</td>
<td>May have estrogenic activity but no clinical studies for vasomotor symptoms to date</td>
</tr>
<tr>
<td>Dong quai (Angelica sinensis)</td>
<td>Rash</td>
<td>Increased international normalized ratio (INR) in patients taking warfarin</td>
<td>No clinical evidence of efficacy 87</td>
</tr>
<tr>
<td>Evening primrose (Oenothera biennis)</td>
<td>Nausea, vomiting, diarrhea, flatulence</td>
<td>Possible lowering of seizure threshold in patients taking antiepileptic medication</td>
<td>One study completed showing no benefit beyond placebo 63</td>
</tr>
<tr>
<td>Flaxseed</td>
<td>Hypersensitivity reactions</td>
<td>May impair absorption of drugs given high fiber content</td>
<td>One small study completed showing equivalence to HT for mild vasomotor symptoms 84</td>
</tr>
<tr>
<td>Ginseng (Panax species)</td>
<td>Generally considered safe; rare reports of hypertension, insomnia, headache, and mastalgia</td>
<td>May interact with monoamine oxidase inhibitors and warfarin (decreased prothrombin time)</td>
<td>Only 1 study completed showing no benefit beyond placebo 86</td>
</tr>
<tr>
<td>Kava kava (Piper methysticum)</td>
<td>Rash, sedation, liver toxicity</td>
<td>May potentiate effects of benzodiazepines; best to avoid with other anxiolytics or alcohol</td>
<td>Small, short-term studies suggest efficacy over placebo 66; risk of potential toxicity and dependence</td>
</tr>
<tr>
<td>Red clover (Trifolium pratense)</td>
<td>Generally well tolerated</td>
<td>Theoretical risk of interaction with warfarin and tamoxifen</td>
<td>See text</td>
</tr>
<tr>
<td>Soy isoflavones</td>
<td>Constipation, bloating, nausea, rash</td>
<td>Potential decreased INR in patients on warfarin; theoretical risk of competition with tamoxifen</td>
<td>See text</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Generally well tolerated</td>
<td>Theoretical increased risk of bleeding in patients on anticoagulants</td>
<td>Scant data to support its use 87</td>
</tr>
<tr>
<td>Wild yam (Dioscorea villosa) cream</td>
<td>None known</td>
<td>None known</td>
<td>Only 1 study completed showing no benefit beyond placebo 67</td>
</tr>
</tbody>
</table>
Rimostil™ (57 mg of total isoflavones). After 12 weeks, the reduction in the hot flash count was similar for all 3 groups, although patients in the higher-dose Promensil group had a faster rate of symptom reduction. No statistically significant adverse events were noted in this study. There are currently no data on safety and efficacy of red clover extract beyond 3 months.

Black Cohosh (Cimicifuga racemosa). Black cohosh is a plant that has been used by Native Americans for a number of gynecologic conditions. Currently, it is one of the most popular supplements used for the treatment of menopausal symptoms. The mechanism of action of black cohosh remains unclear. Studies on its effect on estrogen receptors have been conflicting. Recent animal data have suggested a possible effect on serotonin receptors.

Four studies on the use of black cohosh for menopausal symptoms have been completed and have yielded mixed results. Most of these studies used the black cohosh product Remifemin®, contained small sample sizes, and were of short duration (6 months or less). Of the trials enrolled women with breast cancer (most of whom were on tamoxifen). This study failed to show a positive treatment effect compared with results from placebo.

Black cohosh has been associated with mild gastrointestinal side effects that may be self-limited. Overdose can lead to dizziness, tremors, headaches, nausea, and vomiting. Case reports of hepatic failure with black cohosh do exist, but direct causality has not been established. No clinically significant drug interactions are known.

Table 4. Sources and Biologic Activity of Phytoestrogens

<table>
<thead>
<tr>
<th>Isoflavones</th>
<th>Lignans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food sources</td>
<td></td>
</tr>
<tr>
<td>• Legumes (eg, soybeans, lentils, chick peas)</td>
<td>• Whole-grain cereals (eg, wheat, barley, rye)</td>
</tr>
<tr>
<td>• Soybean products (eg, tofu, soy milk, soy flour)</td>
<td>• Fruits, vegetables (eg, cherries, apples, pears, onion)</td>
</tr>
<tr>
<td>Popular supplements</td>
<td>Seeds (eg, fennel, sunflower)</td>
</tr>
<tr>
<td>• Soy extracts, red clover</td>
<td>Flaxseed</td>
</tr>
<tr>
<td>Biologically active ingredients</td>
<td>Genistein, daidzein</td>
</tr>
<tr>
<td></td>
<td>Enterodiol, enterolactone</td>
</tr>
</tbody>
</table>

CLINICAL GUIDELINES

The North American Menopause Society (NAMS) has issued an evidence-based position statement on the treatment of vasomotor symptoms associated with menopause. It is a useful guide for the practicing clinician. For women with mild hot flashes, NAMS recommends an initial strategy of lifestyle changes as outlined in the sidebar on page 486. Among nonprescription remedies, soy foods, isoflavone supplements, black cohosh, and vitamin E appear to lack serious side effects and may demonstrate some efficacy, although sufficient data are lacking. Nonhormonal prescription options that show efficacy include the antidepressants venlafaxine, paroxetine, fluoxetine, and the anticonvulsant gabapentin. High rates of adverse effects render clonidine and methyldopa less useful. For women with moderate to severe hot flashes, however, systemic therapy with either estrogen or estrogen and progestin (as appropriate) has clearly been shown to be most effective in alleviating symptoms and remains the gold standard. Short-term use appears to have little risk and is very acceptable.

Other professional organizations have reached similar conclusions. The Medical Association of Clinical Endocrinologists issued a statement that menopausal HT considerations must be individualized and that, in the absence of contraindications, HT remains appropriate for moderate to severe vasomotor symptoms associated with estrogen deficiency. Likewise, the American College of Obstetrics and Gynecology (ACOG) Task Force on Hormone Replacement Therapy plans to publish a full report in late 2004, but preliminarily suggests that HT still plays an important role in menopause management. However, the ACOG Task Force notes that HT therapy should not be used without physician consultation and should be taken for the shortest time and in the smallest dose needed. Finally, the US Preventive Services Task Force recommends against the routine use of estrogen and progesterin for the prevention of chronic conditions (grade D recommendation), but makes no statement regarding short-term use for vasomotor symptoms.

Since the publication of WHI, investigators have attempted to quantify the risks and benefits of HT using Markov decision models that incorporate WHI data to help guide choices. Kim and Kwok examined quality-adjusted life expectancy (QALE) and concluded that HT minimally decreased life expectancy if vasomotor symptoms were not considered. If even mild vasomotor symptoms (comparable in severity to seasonal allergies) were taken into account, HT use for 5 years produced equivalent QALE. Col and colleagues found that short-term use (2 years) of HT in asymptomatic women resulted in net losses in QALE of 1 to 3 months, depending on cardiovascular risk. Women with mild vasomotor symptoms gained 3 to 4 months of QALE, and women with severe symptoms gained 7 to 8 months. These models emphasize the small size of the life-expectancy changes in populations as a whole and are limited by the many assumptions in the models. Nonetheless, they may provide a useful perspective for clinicians.
**CONCLUSION**

Many questions are left unanswered regarding both HT in general and treatment of vasomotor symptoms specifically; the WHI created a need for more research, not less. Perhaps lower doses or different preparations of estrogen will prove effective in controlling hot flashes while maintaining bone mineral density and lacking the undesirable associations with breast cancer and thromboembolic disease. Alternatively, different formulations of progestins may afford endometrial protection yet avoid unwanted side effects. Furthermore, the WHI studied women of an average age of 62; conceivably, HT may show a different risk-benefit profile when used in younger, perimenopausal women. The Kronos Early Estrogen Prevention Study and others will attempt to answer this question in the coming years by enrolling newly menopausal women with vasomotor symptoms. Newer SERMs, currently under development, are also being designed to provide vasomotor relief plus the other benefits of estrogen without the attendant risks. The future is promising.

For now, physicians and patients should be comforted that effective options do exist for the treatment of hot flashes during menopause. Women with mild symptoms may choose coping mechanisms alone or use of certain dietary supplements. In women with moderate to severe symptoms, short-term use of HT is safe and appropriate. The lowest dose of HT that achieves symptom control should be the goal. The optimal duration of therapy is much less clear, as good evidence for a uniform recommendation is lacking. For women who wish to avoid HT, a serotonin reuptake inhibitor or gabapentin is a reasonable first-line pharmacologic option. Regardless of choice, successful treatment of menopausal vasomotor symptoms hinges on the initiation and yearly continuation of a close dialogue between physician and patient.

**REFERENCES**


**VASOMOTOR SYMPTOMS**


