REVIEW

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Treatment options for menopausal hot flashes

ABSTRACT

Although alternatives exist, hormone therapy remains the most effective treatment for menopausal symptoms such as hot flashes, and it is the only treatment approved by the US Food and Drug Administration (FDA) for this indication. The FDA recommends using the lowest effective dose of hormones. New low-dose preparations and new dosage forms of hormone therapy are available.

KEY POINTS

Lifestyle modifications should be the first-line approach for women with menopausal symptoms.

Nonapproved alternative agents include venlafaxine, fluoxetine, paroxetine, gabapentin, soy products, and herbs such as black cohosh.

New estrogen products include lower-dose Prempro (conjugated equine estrogen 0.3 mg and medroxyprogesterone 1.5 mg), transdermal patches, estrogen lotion, and an intravaginal ring.

PATIENT INFORMATION
Coping with the symptoms of menopause, page 583

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

WOMEN are looking for alternatives to estrogen to treat menopausal symptoms, after hearing about possible risks of hormone therapy.

Alternatives exist, but none is as effective as hormone therapy, and none is approved by the US Food and Drug Administration (FDA) for this purpose. Moreover, the risks associated with hormone therapy may not be as great as many people imagine, especially when used as currently recommended, ie, in the lowest effective dose for the shortest possible time consistent with the indication for therapy.

This paper discusses the current recommendations for hormone therapy, the alternative therapies, and the newer hormonal products—information we hope will be helpful when weighing the risks and benefits of therapy for menopausal symptoms.

WHAT CAUSES HOT FLASHES?

Most perimenopausal women experience some vasomotor symptoms such as classic hot flashes (a feeling of intense heat) and hot flushes, felt and seen as redness of the upper neck, face, and torso. These symptoms can range in severity from a minor irritation to a major disruption in the quality of life.[1]

The etiology of hot flashes is not completely understood but involves some destabilization of the thermoregulatory zone in the hypothalamus related to estrogen withdrawal.

Not all hot flashes are due to menopause; the differential diagnosis includes:

- Thyrotoxicosis
- Carcinoid
- Diabetes
- Hyperhidrosis
- Panic disorder

- Obesity (in which the extra adipose tissue acts as insulation, causing a chronic feeling of warmth)
- Pheochromocytoma.

Some medications can also cause or exacerbate hot flashes, eg, the selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene and the gonadotropin analogues leuprolide, goserelin, and nafarelin. Furthermore, some men who undergo androgen ablation for prostate cancer experience hot flashes.

HOW RISKY IS HORMONE THERAPY?

Concerns about hormone therapy come from the Women's Health Initiative,[2–4] a large prospective randomized study designed to determine if hormone therapy would reduce the incidence of cardiovascular disease and other adverse outcomes.

Of note: this study was not designed to evaluate the efficacy of hormone therapy in treating menopausal symptoms. In fact, all perimenopausal women were excluded, as were young castrated women and women with premature ovarian insufficiency.[3] Thus, the study population was not similar to most patients seeking help for menopausal symptoms.

Hormone therapy did not decrease the incidence of cardiovascular disease. In fact, at 5.2 years of follow-up, compared with women receiving placebo, the relative risk of nonfatal myocardial infarction or death due to coronary heart disease among participants receiving conjugated equine estrogen 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day was 1.24, although the difference did not quite reach statistical significance (nominal 95% confidence interval 1.00–1.54). In view of these findings, the estrogen-progestin arm of the study was stopped early.

Expert opinion[5] is now that hormone therapy should not be prescribed to prevent cardiovascular disease. The known risks of hormonal therapy remain:

- A twofold to threefold increased risk of venous thromboembolism
- A small but definite increased risk of breast cancer with estrogen-progestin use[6,7]
- An increased risk of stroke and gall bladder disease.

These risks must be balanced against the benefits of hormonal therapy: excellent menopausal symptom control, control of genitourinary atrophy, and bone preservation.

Absolute contraindications for hormone therapy include undiagnosed vaginal bleeding, active thromboembolic disease, and active breast cancer.

Recently the FDA announced its cautious support of hormone therapy for menopausal symptoms. A consumer-supported program, MenoPAUSE, has been launched nationwide to inform women about menopause, its symptoms, how to communicate with health care providers, and the treatment options.[8]

Weaning off hormone therapy

Women who have tried to wean off hormone therapy and are unable to do so can continue on it but need periodic clinical reevaluation; the North American Menopause Society consensus conference recommends at least yearly reevaluation of the indications, risks, benefits, and alternatives.

There are no evidence-based strategies for weaning off hormone therapy, but there are several low-dose formulations to choose from for vasomotor symptom control (see below).

Women on hormone therapy need reevaluation at least yearly

ALTERNATIVE TREATMENTS

While hormone therapy remains the gold standard for menopause-related vasomotor symptoms, a number of women cannot or will not take it in spite of significant menopausal symptoms.

Nonpharmacologic treatments

First-line treatments for hot flashes include nonpharmacologic lifestyle adjustments (see patient information, **Coping with the symptoms of menopause,** page 583), such as:

- Avoiding triggers such as warm environments, alcohol, and caffeine
- Wearing layered cotton clothing[9]
- Practicing deep, slow diaphragmatic breathing and relaxation therapy.

Exercise, although important for a number of health benefits, has not specifically been shown to reduce vasomotor symptoms.[9] Alternative and integrative strategies such as

TABLE 1

Vasomotor symptom reduction with various therapies

THERAPY	% REDUCTION
Hormone therapy	≥ 90%
Venlafaxine	60%–75%
Gabapentin	50%–60%
Selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline)	50%
Vitamin E/soy	25%
Placebo	20%–30%

acupuncture, nutraceuticals, and herbal products have not been studied enough to assess their risks and benefits.[10]

Antidepressants

Venlafaxine is our first-line nonhormonal alternative in symptomatic menopausal women. Norepinephrine is thought to be integral for controlling the thermoregulatory set point[11]; therefore, serotonin-norepinephrine reuptake inhibitors such as venlafaxine are prime candidate drugs for nonhormonal treatment.

Studies of antidepressants for hot flashes were not as rigorous as studies of hormone therapy

In a study in breast cancer survivors, venlafaxine reduced vasomotor symptoms by 60% to 75%.[12,13] The most effective doses, as reflected in diminished hot flash scores and improved quality-of-life indicators, were 37.5 to 75 mg/day.

Side effects include dry mouth, nausea, anorexia, and constipation at higher doses.[12]

Selective serotonin reuptake inhibitors (SSRIs). Fluoxetine and paroxetine have been studied in women with and without breast cancer.[14–16]

In a recent study that received wide attention,[15] controlled-release paroxetine 25 mg/day was compared with placebo. At 6 weeks, the paroxetine group reported a 64.6% reduction in hot flashes vs 37.8% with placebo.

Dry mouth was the predominant side effect noted in these studies. Other adverse effects common to SSRIs include nausea, diarrhea, headache, insomnia, jitteriness, fatigue, and sexual dysfunction.[16]

Of note, the studies were not as rigorous (requiring at least seven to eight hot flashes per day) as the studies of estrogens seeking FDA approval for vasomotor symptom control.[9] Furthermore, studies of hot flash reduction generally show a significant placebo effect, so all studies need to have a placebo group.

A recent study in women with the CYP2D6 genotype who were receiving tamoxifen for breast cancer demonstrated that paroxetine reduces the active metabolite of tamoxifen.[17] Thus, drug interactions should be considered in women on tamoxifen and SSRIs. Pending further study, we do not recommend the concurrent use of paroxetine in women requiring tamoxifen therapy.

Other agents

Gabapentin has undergone investigation for treating hot flashes, after patients taking it for other indications incidentally noted improvement of hot flashes.

Although it is an analogue of gamma-aminobutyric acid (GABA) and is used to treat neurologic disorders such as seizures and neuropathic pain, gabapentin does not affect GABA receptors directly, and its mechanism of action remains unclear. Proposed mechanisms include modification of adrenergic and serotonergic pathways in the pituitary-hypothalamic areas.[11]

A randomized trial showed gabapentin in doses of 200 to 1,600 mg/day to reduce hot flashes by 50% to 60%.[18] Side effects included dizziness and fatigue, which tended to dissipate over time, and less often, peripheral edema.

Clonidine is a centrally acting alpha adrenergic agonist. Various doses and delivery routes have been tested, and several small randomized controlled trials showed statistically significant reductions in hot flashes; in one study, at 8 weeks the frequency of hot flashes had declined by 38% with clonidine vs 24% with placebo.

Clonidine's side effects of dry mouth, drowsiness, postural hypotension, and constipation, together with its modest effect on vasomotor symptoms, have limited its use.[19]

Cetirizine. A recent abstract described a double-blind, randomized, placebo-controlled

trial in 50 symptomatic postmenopausal women not already on hormonal therapy. At 4 weeks, those given cetirizine 10 mg/day had a reduction in hot flash scores of 39.7%, vs 8.8% with placebo.[20]

Vitamins. Vitamin C and vitamin B complex have been advocated but not shown in any rigorous studies to reduce hot flashes. Vitamin E 800 IU is frequently recommended; however, it is not much more likely than placebo to reduce vasomotor symptoms.[5]

Megestrol acetate, a synthetic progestin, reduced hot flashes in a study in breast cancer survivors.[21] Its association with weight gain limits its use in many menopausal women.

Other options available in Europe but not in the United States include tibolone (an agent associated with an apparent increased risk of breast cancer)[22] and veralipride.

Soy products

Phytoestrogens and isoflavones are naturally occurring plant-derived estrogens that are thought to have mixed estrogen agonism and antagonism to certain estrogen receptors.

Studies of the effects of soy on hot flashes have yielded conflicting results.[5,23]

Soy is available in a variety of forms. Doses of isoflavones in multiple studies ranged from 50 to 150 mg/day.[24] Red clover (Promensil) contains isoflavones similar to soy protein isoflavones. This product has not been clearly demonstrated to be effective in reducing menopausal signs or in the prevention of osteoporosis and is therefore not recommended.[25]

The long-term safety of isoflavone or soy supplement use has not been studied in women with breast cancer. In theory, these products could pose a risk in patients with contraindications to estrogens due to their potential estrogenic agonist activity in some tissues.

However, all women can be encouraged to adopt a healthy diet, which may include 25 grams of soy protein, primarily for possible cholesterol reduction, as per American Heart Association recommendations.

Herbs

Herbs, particularly black cohosh (*Cimicifuga racemosa*), have been used for centuries to reduce hot flashes. Their mechanism of action remains unknown. The German Commission E (similar to the US FDA) approves the use of black cohosh for only up to 6 months (based on study length) for hot flash reduction.[5]

Women should be warned that some herbal products may contain other agents, including kava kava, which recently was linked to hepatotoxicity.[26]

Dong quai, a Chinese herb, was tested in a large randomized trial and was found not to reduce hot flashes; furthermore, it can increase the international normalized ratio in patients on warfarin.[27]

Wild yam contains diosgenin, used in the manufacture of steroids and progesterone. It is not, however, converted to active progesterone in the human body and has not been studied adequately to prove its efficacy in treating hot flashes.[10]

Bellergal not recommended

Bellergal-S remains available by prescription and has been used to treat hot flashes. It contains phenobarbital and belladonna and works primarily by sedation. We and others[11] discourage Bellergal-S use in view of its adverse effects, limited efficacy, and addictive potential.

NEWER ESTROGEN OPTIONS

Low-dose estrogen therapy

Because the risks and benefits of alternative agents are not fully known, and they may be much less effective than hormone therapy, attention has turned to using lower doses of hormone therapy in the hopes of maintaining the same efficacy while reducing the side effects and risks.

Of note, the results of the estrogen-only arm of the Women's health Initiative were recently released and showed no increased risk of breast cancer in women using conjugated equine estrogen 0.625 mg. The only reported increased risk in older women with hysterectomy taking estrogen was an increased risk of stroke.[28]

Low-dose Prempro (conjugated equine estrogen 0.45 mg plus medroxyprogesterone 1.5 mg) was released in the summer of 2003, after the Women's HOPE (Health, Osteoporosis, Progestin, Estrogen) trial showed it was as effective as usual-dose Prempro in hot flash control, with improved

Some herbal products contain other agents

bleeding patterns and less mastalgia compared with prior standard doses of Prempro 0.625/2.5 mg.[29] An even lower dose of Prempro (0.3/1.5 mg) is now available. Lower doses of estrogen are thought to confer similar benefit with less risk.

Ultra-low doses of estrogen (estradiol 0.025 mg/day by mouth or via a transdermal patch, changed weekly) have been shown to preserve bone status.[30]

Newer estrogen delivery systems

Femring is an intravaginal ring that is changed every 3 months and provides both local and systemic estrogen. It is approved to treat vasomotor symptoms in women who have had a hysterectomy. (In contrast, the Estring is only for early local genitourinary effects.

Estrasorb estrogen lotion is available for topical application on the thighs and arms daily and has systemic estrogenic effects. It may be an effective option for symptom control for women who do not want to take an oral estrogen, who do not like the adhesive of transdermal estrogen systems, and who do not want to use a vaginal ring. However, the FDA has not approved it for preventing or managing osteoporosis.

Of importance: any woman with a uterus who is using systemic estrogen—transdermally, orally, or topically with systemic effects—needs progestin opposition.

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