# Hormonal and Nonhormonal Treatment of Vasomotor Symptoms

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**KEYWORDS**

• Menopause • Vasomotor symptoms • Estrogen • Progestogen • SSRI • SNRI

**KEY POINTS**

- Hot flashes are the most common complaint of perimenopause.
- Treatment has to be individualized based on the risk/benefit ratio.
- Systemic hormone therapy is the most effective treatment.
- Nonhormonal pharmacologic therapies include selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, clonidine, and gabapentin.
- Nonpharmacologic therapies are considered less effective and include behavioral changes and possibly acupuncture.

## GENERAL HEALTH MAINTENANCE AND CARE OF MENOPAUSAL WOMEN

The American College of Obstetricians and Gynecologists (ACOG) recommends an annual history and physical examination including breast and pelvic examination. **Box 1** lists guidelines specifically for the health maintenance and care of perimenopausal and postmenopausal women. **Table 1** summarizes terms helpful in describing menopausal events.

## HOT FLASHES/VASOMOTOR SYMPTOMS

### *What Are Hot Flashes?*

Hot flashes and hot flushes can be used as synonyms. If they occur at night, they are often called night sweats. They are characterized by the sudden onset of heat, intense sweating, and flushing of the face and chest, often accompanied by palpitations and

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**Box 1**
**Health care of perimenopausal and postmenopausal women**

Evaluate sexuality, fitness, psychosocial factors, cardiovascular factors, and health risk behaviors annually

Physical examination including breast and pelvic examination annually

Pap test (per ACOG guidelines, can be discontinued at age 65 years after 3 consecutive negative cytology results or 2 consecutive negative cotest results (cytology and HPV) within the previous 10 years, and the most recent test no longer than 5 years ago, and no history of CIN2 or CIN3)

Mammogram every 1 to 2 years between the ages of 40 and 50 years, then yearly

Colonoscopy every 10 years starting at age 50 years (age 45 years for African American patients) unless risk factors present (other screening options available but not preferred)

Fasting glucose every 3 years starting at age 45 years

Fasting lipid panel every 5 years starting at age 45 years

Thyroid-stimulating hormone every 5 years starting at age 50 years

Aspirin prophylaxis at age 55 to 79 years if no contraindications (and no concern for gastrointestinal bleeding)

Herpes zoster vaccine once at age 60 years, if not previously immunized

DEXA (starting at age 65 years unless risk factors, repeat no sooner than after 2 years)

Pneumococcal vaccine once at age 65 years

HCV testing (once if born between 1945 and 1965 and not yet assessed)

HIV testing (offer annually based on risk factors)

Influenza vaccine annually

TDaP (substitute 1 dose of TDaP with TD, followed by booster every 10 years)

Varicella vaccine (1 series if no evidence of immunity)

*Abbreviations:* CIN, cervical intraepithelial neoplasia; DEXA, dual-energy x-ray absorptiometry; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papilloma virus; TD, tetanus diphtheria; TDaP, tetanus diphtheria acellular pertussis.

Additional recommendations exist for high risk patients. For more details, visit www.acog.org/~/media/Departments/Annual Womens Health Care/PrimaryAndPreventiveCare.pdf.

anxiety.[1] Hot flashes are considered the cardinal symptom of menopause[1] and, although they cause no inherent health hazard, they are the most bothersome symptom caused by estrogen withdrawal for most women. Therefore, they are clinically relevant in the everyday gynecologic practice. Furthermore, vasomotor symptoms

**Table 1**
**Menopausal terms**

| Term (WHO) | Definition |
|---|---|
| Perimenopause | Time period with a break in regular menstrual cycles with the break lasting no longer than 3 mo |
| Late perimenopause | Amenorrhea between 4 and 11 mo |
| Menopause | Amenorrhea for 12 mo or longer<br>Median age in the United States: 51 y |

*Abbreviation:* WHO, World Health Organization.

are among the clear indications for US Food and Drug Administration (FDA)–approved hormone therapy.

### *Cause of hot flashes*

The cause of hot flashes is not well understood and most likely multifactorial. The menopausal transition coincides with declining estrogen levels, and treatment with estrogen improves or even relieves vasomotor symptoms. The decline in estrogen levels seems more relevant than the absolute estrogen levels.[2] Women who have never been exposed to estrogens, such as women with Turner syndrome, do not report hot flashes because of the absence of estrogen priming, because these women are hypogonadal at birth. During the perimenopause, the ratio of specific types of estrogens changes: estradiol levels decrease and levels of estrone, a weaker estrogen, increase.[3]

In addition, beginning with the perimenopause, narrowing of the thermoneutral zone occurs[4]: The thermoneutral zone describes a homeostatic range of body temperature. Sweating occurs when the body core temperature increases above the upper threshold of the thermoneutral zone, and chills occur with dipping of the core temperature below the lower threshold. A smaller thermoneutral zone leads to greater likelihood of crossing both the upper and lower thresholds, and therefore puts a woman at higher propensity for developing sweating and chills.[4] Neurotransmitters are involved in the regulation of the thermoneutral zone: as estrogen levels decline, norepinephrine levels increase, which causes an increase in hypothalamic serotonin receptors, and further narrowing of the thermoneutral zone.[5–7] The exact mechanism of action of selective serotonin reuptake inhibitors (SSRIs) on the improvement of hot flashes is unknown but seems to be related to this. In theory, the increase in the number of serotonin receptors leads to a decrease in circulating serotonin levels in the brain. When women use SSRIs, levels of serotonin increase within the brain, with an expected widening of the thermoneutral zone and, as a consequence, improvement in vasomotor symptoms.

Estrogen depletion also stimulates central alpha-2 receptors, which causes a further increase in norepinephrine levels and, as a consequence, further narrowing of the thermoneutral zone (**Fig. 1**).

### *Risk factors for hot flashes*

African American women are most likely to report vasomotor symptoms, whereas Chinese and Japanese women are the least likely. Women of different ethnic backgrounds show genetic polymorphisms for the estrogen receptor alpha and enzymes involved in the sex-steroid pathways. These polymorphisms can have an effect on estrogen metabolism, circulating estrogen concentration, and severity of vasomotor symptoms.[8]

Obesity was originally thought to be protective secondary to the higher conversion of androgens to estrogens in the adipose tissue, but this has not proved correct. Adipose tissue acts as a heat insulator and can make hot flashes worse.

Nicotine is another risk factor. Women who smoke enter menopause on average 2 to 3 years earlier than nonsmokers, and have a 60% higher risk for hot flashes because of the antiestrogenic effects of nicotine.

Negative mood and affect and a history of child abuse or neglect are also risk factors, possibly because of a lack of coping skills when presented with social and lifestyle stress. Lower socioeconomic position may either present a true risk factor or be a confounder. Lower socioeconomic position is associated with smoking, higher body mass index, and higher stress levels, which are all risk factors for more vasomotor symptoms.[1]

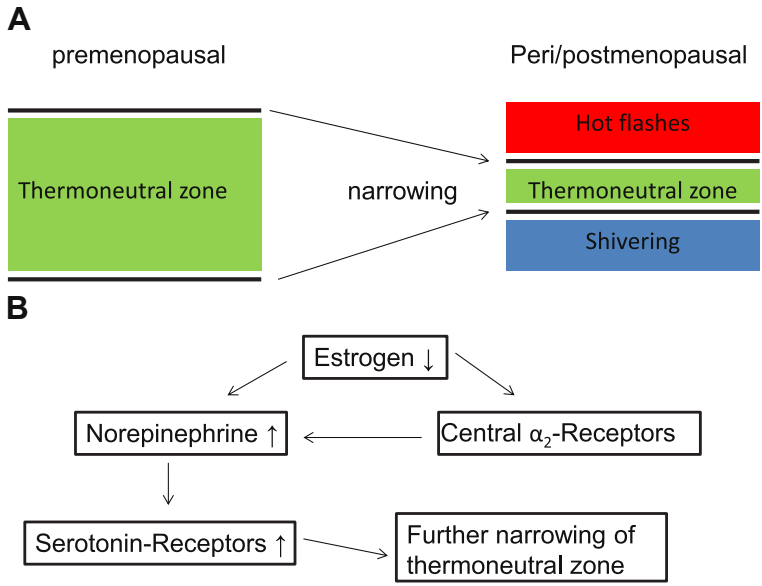


**Fig. 1.** Thermoneutral zone (*A*) and involved neurotransmitter (*B*). (*Modified from* [*A*] Pachman DR, Jones JM, Loprinzi CL. Management of menopause-associated vasomotor symptoms: current treatment options, challenges and future directions. Int J Womens Health 2010;2:123–35; and [*B*] Refs.[5–7])

### *How Do Hot Flashes Affect Women?*

The Study on Women's Health Across the Nation (SWAN), one of the largest and most ethnically diverse longitudinal studies of the perimenopausal transition, enrolled 3302 midlife women across 5 racial/ethnic groups and followed these for more than 10 years, with yearly assessment of menopause-related symptoms, health behaviors, and social/psychological functioning. The SWAN study showed the following results: hot flashes are most common in postmenopausal women (50%–85%), and least common in premenopausal women (20%–40%). In general, 15% to 20% of women report daily flashes. The usual duration of vasomotor symptoms is 1 to 10 years on average, but some women experience them for up to 30 years. This wide range in frequency is thought to be related to different cross-cultural perceptions, which can lead to underreporting as well as overreporting.

Vasomotor symptoms affect sleep quality and quantity. Sleep disorders are subjective and therefore difficult to measure. Per the SWAN study, perimenopausal sleep disorders are most common in white women (40.3%) and least common in Japanese women (28.2%). Sleep disturbances occur even in the absence of vasomotor symptoms, so estrogen withdrawal is not the only factor to blame. Confounding factors include depressed mood, anxiety, back aches, joint pain, low income and financial worries, as well as marital discord, all of which can cause problems sleeping.

### *Differential diagnoses of hot flashes*

In premenopausal women, in whom vasomotor symptoms are the least common, other causes for vasomotor instability have to be considered. Differential diagnoses, and tests to consider after a thorough history and physical examination, are listed in **Table 2**.

**Table 2**
**Differential diagnoses of hot flashes and tests to order**

| Differential Disease State | Diagnostic Test |
|---|---|
| Thyroid disease | Thyroid-stimulating hormone |
| Subacute/chronic infection | Complete blood count, C-reactive protein |
| Psychosomatic disorder and stress | Stress questionnaire (eg, Patient Stress Questionnaire) |
| Leukemia | Complete blood count |
| Pheochromocytoma | Urine vanillylmandelic acid |
| Carcinoid | Chromogranin A, urine 5-hydroxy indole acetic acid |
| Other malignancies | CT or MRI |

*Abbreviation:* CT, computed tomography.

### *Estrogen (Plus Progestogen) Therapy*

Several updates have been published since the controversial Women's Health Initiative (WHI) publication in 2002 reported an association between hormone therapy and breast cancer as well as cardiovascular events. Many of the WHI participants were older women, asymptomatic with regard to hot flashes, postmenopausal when starting hormone therapy, and had significant comorbidities. These characteristics are in contrast with the young, healthy perimenopausal women requesting hormone therapy for hot flashes.

#### *Estrogen therapy*

Estrogen therapy is considered the most effective therapy for hot flashes. Guidelines have been published by ACOG, the North American Menopause Society (NAMS), the United States Preventative Services Task Force (USPSTF) and the American Association of Clinical Endocrinologists (AACE). The recommendation is to use "the lowest effective dose for the shortest duration possible in women for whom the potential benefits outweigh the potential risks."

Risks and benefits of estrogen therapy are listed in **Table 3**, with contraindications in **Table 4**. **Table 5** lists the different estrogen formulations with starting doses and routes of administration. Patients should be started on the lowest dose possible, with an increase in the dose if no improvement in symptoms is noted.

The transdermal route should be considered to avoid the hepatic first-pass effect and possibly decrease the risk for venous thromboembolism.[9,10] Lower doses usually require longer duration of treatment until the maximal benefit for vasomotor symptoms is reached. The ultralow dose of estrogen therapy is not FDA approved for the treatment of vasomotor symptoms.

**Table 3**
**Benefits and risks of hormone therapy initiated during perimenopause**

| Benefits | Future Potential Risks |
|---|---|
| Improvement of vasomotor symptoms | Breast cancer |
| Improvement of vaginal dryness | Cerebrovascular accident (age dependent) |
| Decreased risk for osteoporosis | Venous thromboembolic event |
| Decreased risk for colorectal cancer | Possible risk for epithelial ovarian cancer if used longer than 10 y[10,53] |

**Table 4**
**Contraindications to using hormone therapy**

| Absolute Contraindications | Relative Contraindications |
|---|---|
| Current, past, or suspected breast cancer | Smoking (cigarettes, marijuana) |
| Known or suspected estrogen-sensitive malignant conditions | |
| Untreated endometrial hyperplasia | |
| Undiagnosed vaginal bleeding | |
| Active liver disease | |
| Uncontrolled hypertension | |
| Thrombophilia | |
| Previous idiopathic or current venous thromboembolism (transdermal application may be acceptable) | |
| Active or recent arterial thromboembolic event (eg, myocardial infarction) | |
| Hypersensitivity to any ingredient of the formulation | |
| Porphyria cutanea tarda | |

In assessing the effectiveness of the hormone therapy, it is important for the health care provider to understand that any kind of treatment, hormonal as well as nonhormonal, has a placebo response of up to 51%.[11]

A new FDA-approved hormone combination contains 0.625 mg of conjugated estrogen as well as bazedoxifene 20 mg daily. Bazedoxifene is a selective estrogen receptor modulator (SERM) with antagonistic effects on the endometrium, thereby eliminating the need for additional progestogen therapy.[12] Side effects include muscle spasm, nausea, and diarrhea.

***Progestogen therapy***

Progestogen therapy is necessary for endometrial protection if a uterus is present, or a possible necessity if the patient has a history of endometriosis. In contrast, progestogens act as mitogens and can cause stimulation of epithelial breast cells.[13] The WHI showed an increased risk for breast cancer after 3 to 5 years of combined estrogen/progestogen therapy and after 5 to 7 years of estrogen-only therapy.

Different terms are in use to describe progestogens: progesterone is the natural hormone produced in the human ovary, whereas progestins are synthetic hormones mimicking the action of the natural progesterone. Progestogen is the summarizing term for both of them.[14]

Examples for progestogen therapy with starting doses are listed in **Table 5**. Progestogens are either commercially available as combination product with estrogen, or can be individually combined with estrogens fixed or individually matched to a given estrogen dose. In order to prevent endometrial hyperplasia, progestogens should be given for at least 10 to 14 days every month.[10] Continuous progestogen exposure is not recommended per AACE guidelines, and long-cycle progestogen therapy (14 days every 3 months) may be considered in order to reduce the risk for breast cancer.[10] The progestin intrauterine device can also be used for endometrial protection, and has been shown to be equivalent or superior to systemic therapy.[15] However, it is not FDA approved for this indication.

Although progestogen-only therapy for vasomotor symptoms has been shown to be beneficial in several studies,[16,17] because of the concern of breast stimulation, ACOG and AACE do not recommend progestogen-only therapy for hot flashes.[10,18]

Progestogens without estrogens are not FDA approved for the treatment of vasomotor symptoms.

***Bioidentical hormones***

Patients often inquire about bioidentical hormones. This term describes custom-made formulations specifically compounded for each patient according to her physician's instructions. The term indicates that bioidentical hormones are chemically similar or structurally identical to hormones produced in the ovary. Bioidentical hormones can also contain a combination of different hormones. They can be administered via nonstandard routes such as subdermal implants or pellets, and they can contain nonhormonal ingredients (eg, dyes, preservatives) that can cause allergies in the individual using the product.

Bioidentical hormones are not FDA approved for the treatment of vasomotor symptoms. Concerns with bioidentical hormones include the following: (1) no testing for efficacy and safety, (2) uncertain purity and standardization, (3) difficult assessment of dosing, and (4) no packaging insert detailing the attributes and potential risks of the hormone product.

The lack of accurate, verifiable dosing assessment can cause problems if not enough estrogen is present to prevent the loss of bone density, or if too much estrogen and not adequate progestogen are given, with the risk for endometrial hyperplasia. ACOG, AACE, and NAMS therefore do not recommend compounded therapy unless the patient has a proven allergy to an FDA-approved formulation.[18]

***How long should hormone therapy be continued?***

The WHI has shown increased risk for the development of breast cancer after prolonged use. Therefore the length of treatment has to be individualized and coupled with good surveillance options for breast cancer. Up to 50% of women report recurrence of vasomotor symptoms after discontinuation of hormone therapy, regardless of age and duration of prior use.[19] Because endogenous estrogen production gradually decreases over time and with age, it seems reasonable to taper therapy. Per NAMS, the decision to continue hormone therapy should be "individualized based on the severity of symptoms and current benefit-risk ratio consideration."

Hormone therapy in postmenopausal women should not be used in order to prevent chronic conditions such as coronary artery disease or dementia,[20] unless menopause was caused by surgical intervention or premature ovarian insufficiency before the age of 50 years. Hormone therapy should not be started later than 10 years after menopause, or after age 60 years,[21] because this can put the patient at higher risk for cardiovascular events or worsening of dementia.

## *Nonestrogen Pharmaceutical Therapy*

***Selective serotonin reuptake inhibitors***

SSRIs are possible alternatives to hormone therapy for the treatment of vasomotor symptoms. The exact mechanism of action for SSRIs and serotonin-norepinephrine reuptake inhibitor (SNRIs) is unknown. Both serotonin and norepinephrine can directly and indirectly influence the thermoneutral zone via a central and peripheral mechanism. The current thinking suggests that, as estrogen levels decline, norepinephrine levels increase, which causes an increase in hypothalamic serotonin receptors, and further narrowing of the thermoneutral zone. When women take SSRIs, there is an increase in serotonin levels within the brain leading to a widening of the thermoneutral zone and an improvement in vasomotor symptoms. Estrogen also stimulates alpha-2 receptors, which leads to a further increase in norepinephrine levels and, as a consequence, further narrowing of the thermoneutral zone (see **Fig. 1**). Because hot flashes

**Table 5**
**Treatment options for vasomotor symptoms**

| Treatment | Dose and Administration | Evidence | FDA Approval | References |
|---|---|---|---|---|
| **Hormonal** | | | | |
| Estrogen | | | | |
| Ultralow dose | Transdermal estradiol 17β 0.0075 mg/d | Yes | No | 54 |
| | Transdermal estradiol 17β 0.014 mg/d | — | — | — |
| | Micronized estradiol 17β 0.25 mg/d orally | — | — | — |
| Low dose | Transdermal estradiol 17β 0.025 mg/d | Yes | Yes | 55–59 |
| | Micronized estradiol 17β 0.5 mg/d orally | — | — | — |
| | Conjugated equine estrogen 0.3 mg/d orally | — | — | — |
| Standard dose | Transdermal estradiol 17β 0.05 mg/d | Yes | Yes | 55,56 |
| | Micronized estradiol 17β 1 mg/d orally | — | — | — |
| | Conjugated equine estrogen 0.625 mg/d orally | — | — | — |
| Progestogen in combination with estrogen | | | | |
| Standard dose | Medroxyprogesterone acetate 5 mg/d orally | Yes | Yes | 55,56 |
| Levonorgestrel IUD | Intrauterine levonorgestrel 20 μg/d | Yes | No | 15 |
| Estrogen + agonist/antagonist | Conjugated estrogen 0.45 mg/d + bazedoxifene 20 mg/d orally | Yes | Yes | 12 |
| Testosterone | — | No | No | 32 |
| Bioidentical hormones | Compounded | No | No | 18 |
| Progestogen only | Megestrol acetate 20 mg/d orally | Yes: prospective trial | No | 16 |
| | Depo medroxyprogesterone acetate 400 mg IM | Yes: prospective trial | No | 16 |
| **Nonhormonal pharmaceutical** | | | | |
| SSRI | — | — | No | — |

| | | | | |
|---|---|---|---|---|
| Paroxetine | 7.5 mg/d orally | Yes: double blind, placebo, multicenter | Yes | 24 |
| | 10–25 mg/d orally | Yes: placebo, RCT | No | 7 |
| Fluoxetine | 20–30 mg/d orally | Yes: placebo, RCT | No | 8 |
| Citalopram | 20–40 mg/d orally | Yes: placebo | No | 25 |
| Sertraline | 25–250 mg/d orally | Yes: RCT | No | 60 |
| SNRI | | | | |
| Venlafaxine | 35.5–75 mg/d orally | Yes: RCT | No | 61 |
| Desvenlafaxine | 100 mg/d orally | Yes: RCT | No | 62 |
| Gabapentin | 900 mg/d orally | Yes: RCT | No | 30 |
| Clonidine | 0.1 mg/d orally | Yes: RCT | No | 63 |
| **Nonpharmaceutical** | | | | |
| Acupuncture | — | Yes: RCT | No | 42 |
| Exercise | — | No | No | 39 |
| Relaxation | — | No | No | 38 |
| Yoga | — | No | No | 37 |
| Black cohosh | — | Unclear | No | 46,47 |
| Phytoestrogens | — | Unclear | No | 51,52 |
| Vitamin E | 800 IU/d orally | No | No | 44 |
| Omega-3 fatty acids | 1.8 g/d orally | No | No | 45 |

*Abbreviations:* IM, intramuscular; IUD, intrauterine device; RCT, randomized controlled trial.

and depression seem to be connected, it is difficult to determine whether SSRIs help with the vasomotor symptoms, or depression, or both. All SSRIs can interfere with the metabolism of tamoxifen (Nolvadex, Soltamox) to its active metabolite endoxifen by inhibiting the cytochrome P (CYP) 450 (CYP2D6) enzyme system. This interference causes decreased efficacy of tamoxifen and can potentially increase reoccurrence of breast cancer.[22] SSRIs therefore should not be used in women taking tamoxifen. Bupropion (Wellbutrin, Zyban) as well can interfere with the CYP 450 system and therefore should also be avoided in these situations.[23]

The only FDA-approved nonhormonal formulation for hot flashes is a low dose (7.5 mg) of paroxetine (Brisdelle[24]). This dose is less than commonly used doses for the treatment of psychiatric diseases. Other higher doses the of paroxetine (Paxil, Pexeva), although not FDA approved, have been evaluated as well. Examples for other SSRIs with their starting doses are listed in **Table 5**. Direct comparison of SSRI use with estrogen is limited. Other SSRIs have shown efficacy in decreasing vasomotor symptoms as well. For example, citalopram (Celexa), an SSRI, seems to be effective for women with sleep difficulties.[25]

***Selective norepinephrine reuptake inhibitors***

SNRIs are only weak inhibitors of the CYP2D6 system and therefore may represent a safer alternative for women with a history of breast cancer or women who are taking tamoxifen. Examples for starting doses are listed in **Table 5**. The most common side effects of SNRIs include nausea, dizziness, and insomnia.

***Clonidine***

Clonidine (Catapres) is a centrally acting alpha-adrenergic agonist. Several trials have shown benefit in the treatment of hot flashes using doses of 0.1 mg orally daily, although not to the same extent as hormone therapy.[26,27] The use of clonidine is limited by its significant side effects, including dry mouth, constipation, and insomnia.

***Gabapentin***

Gabapentin (Neurontin) is an anticonvulsant. Its mechanism of action for vasomotor symptoms is unknown, but is thought to be related to the modulation of calcium channels. Gabapentin is a ligand of the $\alpha 2\delta 1$ and $\alpha 2\delta 2$ subunits of the voltage-gated calcium channels. The subunits increase the density of calcium channels at the plasma membrane.[28] There are no good trials available comparing gabapentin with SSRIs, and gabapentin is not as effective as hormone therapy.[29] Side effects include somnolence, disorientation, headache, and peripheral edema. Most trials evaluating gabapentin for hot flashes used a dose of 900 mg daily.[30] In one double-blinded randomized controlled trial, gabapentin in a daily dose of 2400 mg was equivalent to a standard dose (0.625 mg) of conjugated equine estrogen in alleviating hot flashes.[31]

***Testosterone***

Testosterone (Androderm, Testim) has not shown any benefit in the treatment of vasomotor symptoms. It has potential adverse effects, including negative effects on the lipid parameters, clitoromegaly, hirsutism, and acne.[32] Testosterone is not recommended for the treatment of hot flashes. For some postmenopausal women, it may improve sexual function scores.[33]

***Tibolone***

Tibolone is a synthetic steroid with tissue-specific estrogenic and progestogenic effects. It is currently not available in the United States. It has shown to have beneficial effects on vasomotor symptoms, bone mineral density, and vaginal symptoms, with

no estrogenic effect on endometrium and breast tissue. Its use has been limited by its androgenic side effects.

### *Nonpharmaceutical Therapy*

#### *Behavioral changes*

The NAMS lists behavioral changes that can be beneficial for the treatment of mild to moderate hot flushes.[34] These changes include:

- Dressing in layers
- Consuming cold beverages and foods
- Avoiding hot and spicy foods
- Avoiding hot and alcoholic beverages
- Using a personal fan
- Smoking cessation[35]

A recent pilot study showed that losing weight helped improve the frequency of hot flashes in overweight and obese women.[36] Short-term anxiolytics such as alprazolam (Xanax, Nivaram) may help if hot flashes are caused by stressful situations.

#### *Yoga, exercise, relaxation techniques, acupuncture*

Yoga, relaxation techniques such as slow breathing, exercise, and mindfulness-based stress reduction may reduce the extent to which hot flashes interfere with a woman's daily function, although these methods have not been shown to decrease hot flashes.[37–40] Exercise can increase the severity of vasomotor symptoms in obese women, because adipose tissue acts as an insulator.[41] A recent randomized controlled trial[42] and a recent meta-analysis[43] have documented the benefit of acupuncture in decreasing daily hot flashes.

#### *Vitamin E*

Vitamin E was found to have minimal to no difference for the treatment of hot flashes compared with placebo.[44] Per NAMS, women can consider herbal remedies (eg, isoflavones or vitamin E) if desired. This suggestion is not a consensus recommendation because efficacy data are inconclusive at this point.[34]

#### *Omega-3 fatty acids*

Cohen and colleagues[45] found no effect on hot flashes after treatment with 1.8 g of omega-3 fatty acids in a randomized controlled trial over a 12-week time frame.

#### *Black cohosh*

Different studies have shown inconsistent results.[46,47] Concern exists for the development of hepatitis and myopathy with continued use of black cohosh.[48]

#### *Phytoestrogens*

Phytoestrogens are nonsteroidal components with estrogenic and sometimes antiestrogenic activity. There are 3 classes of phytoestrogens:

- Isoflavones (eg, soybeans)
- Lignans (eg, flaxseed)
- Coumestans (eg, sunflower seeds)

For all phytoestrogens, equol is the active metabolite. Setchell and colleagues[49] found that only 50% to 70% of humans are equol producers who have the intestinal microflora to transform phytoestrogens into equol. Consumption of phytoestrogens by non–equol producers may therefore have limited or no benefit. The average phytoestrogen intake in the Western world is 3 mg/d, whereas in Japan it is 50 mg/d.[50]

Overall, studies of phytoestrogens show different results[51,52] using different doses. There are no consensus recommendations, and ACOG does not recommend their use.[53]

Because it is not clear how much estrogen is generated from soy intake, women with a personal or strong family history of hormone-dependent cancers, venous thromboembolism, or cardiovascular disease should not consider soy-based treatments.[10]

## VAGINAL ATROPHY/DYSPAREUNIA

Vaginal atrophy and resulting dyspareunia are late signs of the perimenopausal transition, caused by a lack of estrogen. Details about pathophysiology and guidelines for treatment are listed in **Box 2**.

## LOW BONE DENSITY/OSTEOPOROSIS

Low bone density (previously called osteopenia) and osteoporosis are 5 times more common in women than in men. Information about screening, prevention, and treatment can be found in **Box 3**.

## CARDIOVASCULAR DISEASE

Cardiovascular disease is the leading cause of death for women in the United States, and therefore is the most dangerous consequence of menopause. Premenopausal women producing endogenous estrogen are protected compared with men, but, after menopause, because of the lack of protective estrogen, the risk for women increases significantly. **Box 4** lists risk factors and preventative measures.

**Box 2**
**Vaginal atrophy/dyspareunia**

Hypoestrogenism causes loss of epithelial cells, loss of elasticity, loss of subcutaneous fat, and increase in vaginal pH

Common symptoms are vaginal and vulvar dryness, pruritus, dyspareunia, and vaginal infections

Treatment options:

- Water-based or silicone based vaginal lubricants (mostly used before and during intercourse)
- Any of the systemic estrogen formulations (except ultralow dose) are FDA approved for vaginal atrophy
- Local estrogen: estradiol 17β cream 2 g/d, conjugated equine estrogen cream 0.5 to 2 g/d, estradiol ring 0.05 mg/d. Ultralow dose: 17β-estradiol tablet 0.01 mg/d vaginally[64]
  - Use daily for 1 to 2 weeks, then once or twice weekly for maintenance
  - Theoretic concern for endometrial hyperplasia, but not proved
- Ospemifene 60 mg/d
  - FDA approved for moderate-severe dyspareunia in postmenopausal women
  - No stimulatory effect on endometrium[65]
  - Side effects include hot flashes, vaginal discharge, and muscle spasm

**Box 3**
**Low bone density/osteoporosis**

Fastest bone loss occurs within 3 years after menopause (reduction in estrogen level increases osteoclast activity)

Recommended intake (IOM)

Calcium 1200 mg/d and vitamin D 600 IU/d (ages 51–70 years)

Calcium 1200 mg/d and vitamin D 800 IU/d (age 71 years and older)

DEXA bone scan recommended at age 65 years; should be performed at younger age if:

- Personal history of fragility fracture
- Smoking
- Alcohol abuse
- Body weight less than 58 kg (127 lb)
- Medical causes of bone loss: endocrine disease, gastrointestinal disease
- History of hip fracture in parents
- Rheumatoid arthritis

Lifestyle changes include:

- Regular weight-bearing exercise
- Optimization of eyesight
- Decrease fall risk in homestead

Treatment options include:

- Bisphosphonates
- SERMs (eg, Raloxifene)
- Calcitonin
- Parathyroid hormone
- Systemic estrogen

*Abbreviation:* IOM, Institute of Medicine.

**Box 4**
**Cardiovascular disease**

- Atherosclerosis in major vessels
- Risk factors are the same for women and men: family history, hypertension, smoking, diabetes, abnormal lipid panel, increased homocysteine level, and obesity (mainly central adiposity indicating hyperandrogenic state)
- Endothelial damage and high low-density lipoprotein–cholesterol cause foam cells, fatty streaks, and eventually atherosclerotic fibrous plaques
- Estrogen protects premenopausal women against cardiovascular disease because of vasodilatory effects (via nitric oxide) and antithrombotic effects (via prostacyclin)
- Risk for cardiovascular disease is higher in men than in premenopausal women, but after menopause risk is the same in men and women
- Estrogen given after menopause in preexisting atherosclerosis induces matrix metalloproteinase activity, which makes plaques unstable and can worsen disease
- Strongest predictor in women: high-density lipoprotein–cholesterol less than 50 mg/dL
- Decrease in risk factors is the most important preventative measure

## SUMMARY/DISCUSSION

Hot flashes are primarily caused by a decrease in estrogen levels and change in neurotransmitters occurring during the menopausal transition, leading to narrowing of the thermoneutral zone. Known risk factors include ethnicity, obesity, and cigarette smoking. The most effective treatment of hot flashes is hormone therapy using estrogen with or without a progestogen depending on the presence of a uterus, followed by nonhormonal pharmacologic therapies (SSRIs, SNRIs, clonidine, gabapentin) and nonpharmacologic therapy options (behavioral changes, acupuncture). The major risks associated with hormone therapy include development of breast cancer, venous thromboembolism, and cerebrovascular disease. Hormone therapy is not indicated for the prevention of chronic conditions. SSRIs should not be used in women with a history of breast cancer, or women who are taking tamoxifen. The best treatment option for vasomotor symptoms often is individualized therapy for each patient.

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