



## Complete Summary

---

### GUIDELINE TITLE

Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society.

### BIBLIOGRAPHIC SOURCE(S)

The North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause 2004 Jan-Feb;11(1):11-33. [PubMed](#)

### GUIDELINE STATUS

This is the current release of the guideline.

## \*\* REGULATORY ALERT \*\*

### FDA WARNING/REGULATORY ALERT

**Note from the National Guideline Clearinghouse:** This guideline references a drug(s) for which important revised regulatory information has been released.

- [May 2, 2007, Antidepressant drugs](#): Update to the existing black box warning on the prescribing information on all antidepressant medications to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.
- [October 25, 2006, Effexor \(venlafaxine HCl\)](#): Published retrospective studies report that venlafaxine overdose may be associated with an increased risk of fatal outcome.
- [May 12, 2006, Paxil \(paroxetine\) and Paxil CR](#): Changes to the Clinical Worsening and Suicide Risk subsection of the WARNINGS section in the prescribing Information related to adult patients, particularly those who are younger adults.

## COMPLETE SUMMARY CONTENT

\*\* REGULATORY ALERT \*\*

SCOPE

METHODOLOGY - including Rating Scheme and Cost Analysis

RECOMMENDATIONS

EVIDENCE SUPPORTING THE RECOMMENDATIONS

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

CONTRAINDICATIONS

QUALIFYING STATEMENTS

## SCOPE

### **DISEASE/CONDITION(S)**

Vasomotor symptoms associated with menopause

### **GUIDELINE CATEGORY**

Management  
Treatment

### **CLINICAL SPECIALTY**

Endocrinology  
Family Practice  
Geriatrics  
Internal Medicine  
Obstetrics and Gynecology

### **INTENDED USERS**

Advanced Practice Nurses  
Allied Health Personnel  
Health Care Providers  
Health Plans  
Managed Care Organizations  
Physician Assistants  
Physicians

### **GUIDELINE OBJECTIVE(S)**

To provide a review of clinical data relating to treatment of peri- and postmenopausal vasomotor symptoms and to recommend the most effective treatments

### **TARGET POPULATION**

Peri- and postmenopausal women in North America

### **INTERVENTIONS AND PRACTICES CONSIDERED**

1. Lifestyle modifications
  - Environmental manipulation to keep core body temperature as cool as possible

- Behavioral changes
  - regular exercise
  - avoiding hot flash "triggers"
  - paced respiration
  - lowering body mass index
  - smoking cessation
- 2. Nonprescription therapies
  - Soy- or red-clover-derived isoflavones
  - Dietary supplements (black cohosh, Vitamin E)
  - Topical progesterone creams and other treatments (dong quai, evening primrose oil, acupuncture)
- 3. Prescription therapies – hormonal options
  - Systemic estrogen therapy (ET) (conjugated equine estrogens, 17beta-estradiol, synthetic conjugated estrogens, ethinyl estradiol, estradiol acetate, esterified estrogens, estropipate, and estriol)
    - oral
    - transdermal
    - vaginal ring (estradiol acetate)
  - Estrogen plus systemic progestogen therapy (EPT) (medroxyprogesterone acetate [MPA], norethindrone, norethindrone acetate, norgestrel, and micronized progesterone)
    - transdermal (17beta-estradiol with norethindrone acetate, 17beta-estradiol with levonorgestrel)
  - Progestogen (progesterone, progestin)
    - oral (MPA, megestrol acetate)
    - intramuscular (depot MPA)
  - Oral contraceptives (for perimenopausal women needing contraception)
- 4. Prescription therapies – nonhormonal options
  - Antidepressants (venlafaxine, paroxetine, fluoxetine)
  - Gabapentin
  - Clonidine Methyl dopa
  - Bellergal

## **MAJOR OUTCOMES CONSIDERED**

- Relief of vasomotor symptoms
- Risk-to-benefit ratio of treatments used to relieve hot flashes including lifestyle modifications, non-prescription remedies and prescription therapies

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Searches of Electronic Databases

### **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

A search was conducted of the medical literature for clinical trials that presented data specific to the treatment of vasomotor symptoms using the database MEDLINE. Priority was given to evidence from randomized, controlled clinical trials

as well as systematic reviews and meta-analyses of such trials, using criteria described elsewhere for evaluating the evidence levels. Conclusions from other evidence-based guidelines also were reviewed.

#### **NUMBER OF SOURCE DOCUMENTS**

Not stated

#### **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Expert Consensus

#### **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

#### **METHODS USED TO ANALYZE THE EVIDENCE**

Review  
Review of Published Meta-Analyses

#### **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

Not stated

#### **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

#### **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

An Editorial Board composed of experts from both clinical practice and research was enlisted to review the published data, compile supporting statements and conclusions, and reach consensus on which recommendations to endorse. If the evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was established.

#### **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

#### **COST ANALYSIS**

A formal cost analysis was not performed and published cost analyses were not reviewed.

#### **METHOD OF GUIDELINE VALIDATION**

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

The North American Menopause Society (NAMS) Board of Trustees was responsible for the final review and approval of this document. It was edited, modified, and subsequently approved by the Board in October 2003.

## **RECOMMENDATIONS**

### **MAJOR RECOMMENDATIONS**

#### **Clinical Management**

The treatment of menopause-associated vasomotor symptoms is a common clinical challenge. Before treatment begins, a detailed patient history of hot flashes is needed, including frequency and severity as well as the effect they have on activities of daily living. Women differ in their attitude toward hot flashes. No treatment is needed unless the hot flashes are bothersome to the woman. Some women seek only to reduce their symptoms slightly while others request more complete amelioration.

The decision to undertake treatment should be based on the severity of the symptoms, an assessment of treatment-related risks, and the woman's personal attitudes about menopause and medication. The clinical goal is to tailor therapy to each individual woman's needs using the various options. Clinicians are advised to enlist women's participation in decision making when weighing the benefits, harms, and scientific uncertainties of options.

In most women, hot flashes will abate over time without any intervention. When therapy is desired, various nonpharmacologic and pharmacologic options are available. The recommended clinical management approach includes lifestyle modification followed by nonprescription and/or prescription therapies, when needed.

#### **Lifestyle Changes**

In women who need relief from mild menopause-related hot flashes, The North American Menopause Society (NAMS) recommends first considering lifestyle changes, which include environmental manipulations and behavioral changes, such as keeping the core body temperature as cool as possible, participating in regular exercise, and avoiding hot flash triggers. Use of paced respiration is another option to consider, based on its effectiveness in studies, ease of use, and lack of side effects. Because both obesity and a sedentary lifestyle are linked to increased hot flashes, a strategy to maintain a healthy weight and to exercise regularly may be helpful.

#### **Nonprescription Remedies**

When lifestyle changes are not adequate to achieve the desired level of relief from mild hot flashes, adding a nonprescription remedy may be considered. A trial of

dietary isoflavones or supplements containing black cohosh or vitamin E may be an option, primarily because these remedies are not associated with serious side effects. However, because of inconclusive efficacy data, this is not a consensus recommendation.

#### *Soy foods and Isoflavone supplements*

Efficacy in clinical trials of both soy foods and isoflavone supplements (from either soy or red clover) has been mixed, possibly because it is limited to the subset of women who are equol producers. Nevertheless, for women with frequent hot flashes, clinicians may consider recommending soy foods or soy isoflavone supplements. Most hot flash studies used isoflavone amounts of 40 to 80 mg/day. Whole foods may be a better choice than isoflavone supplements or fortified foods, based on lack of potential isoflavone "overdose" with soy foods. Effects, if any, may take several weeks. Isoflavones exhibit a low incidence of side effects, although caution is advised when estrogenicity is a concern. Whether these foods or supplements can treat hot flashes effectively and safely in women who have had or are at risk for breast cancer is unknown.

Additional studies are needed to determine whether there are differences among whole food, soy protein, and isoflavone extracts. Whole soy foods have been consumed for thousands of years and are presumed safe, but supplements and fortified foods may contain high levels of isolated isoflavones, the long-term effects of which are unknown.

#### *Black cohosh*

In the most recent trials of black cohosh, the results have been negative. However, some older and smaller trials from Germany have shown some efficacy for hot flashes. With its low incidence of side effects, a black cohosh supplement (two 20-mg tablets daily of a 27-deoxyactein standardized preparation) taken for less than 6 months is likely to do no harm and may provide relief of mild hot flashes.

#### *Vitamin E*

Vitamin E, 800 IU/day, is another nonprescription option to try for hot flash relief, although clinical evidence is mixed. A statistically significant but not clinically significant decrease in hot flashes among breast cancer survivors was noted in one clinical trial, although older trials found no benefit for vitamin E over placebo. Because vitamin E seems to be nontoxic at low doses, inexpensive, and available without a prescription, it is a reasonable option for a trial. Effects, if any, may take weeks.

#### *Topical progesterone creams*

Scientific data are lacking regarding the efficacy and safety of topical progesterone creams for relief of hot flashes. Contents and concentrations vary widely in different brands of nonprescription progesterone creams. Additionally, safety concerns regarding systemic progestogen preparations may also apply to

topical progesterone preparations. Therefore, NAMS does not recommend use of progesterone creams for hot flash relief.

#### *Other treatments*

Given the lack of efficacy data, NAMS also does not recommend dong quai, evening primrose oil, ginseng, licorice, Chinese herb mixtures, acupuncture, or magnet therapy for hot flash relief.

### **Prescription Therapies: Hormonal Options**

When lifestyle changes and nonprescription approaches do not provide the desired relief, prescription options are available. Hormonal approaches, primarily systemic estrogen therapy/estrogen-progestogen therapy (ET/EPT), are most often prescribed and are the only government-approved therapies in the United States and Canada for treating moderate to severe hot flashes. During perimenopause, follicle-stimulating hormone and estradiol levels fluctuate. Dosing estrogen at this time provides uncertain results. After menopause is reached and ovarian activity ceases, response to estrogen therapy will be more predictable.

#### *Systemic estrogen therapy and estrogen-progestogen therapy*

NAMS considers treatment for moderate to severe menopause-related hot flashes to be a primary indication for systemic ET and EPT. Use of ET and EPT should be limited to the shortest duration consistent with treatment goals, benefits, and risks for the individual woman.

NAMS recommends considering lower-than-standard doses of ET and EPT (i.e., daily doses of 0.3 mg conjugated estrogens tablet, 0.25-0.5 mg 17beta-estradiol tablet, 0.025 mg 17beta-estradiol patch, or the equivalent). Many studies have demonstrated that these doses provide similar vasomotor symptom relief. Lower EPT doses are better tolerated and may or may not have a more positive safety profile than standard doses; however, lower doses have not been tested for outcomes (including endometrial safety) in long-term trials.

For all women with an intact uterus who are using estrogen therapy, NAMS recommends that they receive adequate progestogen, either in a continuous combined or continuous sequential EPT regimen. However, there is insufficient evidence regarding long-term endometrial safety to recommend use of long-cycle progestogen (i.e., progestogen every 3-6 months for 12-14 days), a progestin-containing intrauterine device (IUD), or low-dose estrogen without progestogen as an alternative to standard EPT regimens. If utilizing any of these approaches, close surveillance of the endometrium is recommended, pending more definitive research. Some women with an intact uterus who choose EPT may experience undesirable side effects from the progestogen component.

If the initial ET/EPT dose is not effective, it may be increased. For women who are not obtaining symptom relief with once-daily dosing of oral ET due to the possibility of their metabolizing the hormone more rapidly, twice-daily dosing with half doses may be advised or they may be switched to transdermal ET. There is often no need to increase the total daily oral dose in women suspected of having

rapid or irregular metabolism of exogenous estrogen. In such women, stability of the circulating estrogen level may be more important than attainment of an absolute level. The route of administration can also be switched. Transdermal ET may provide more stable levels of circulating estrogen than oral therapies. Another option is the vaginal estrogen ring (Femring) that is FDA-approved for treating hot flashes.

There are few clinical trial data on custom hormone preparations. For most women, NAMS does not recommend these preparations for hot flash relief, due to lack of efficacy and safety data on the specific compounded prescriptions.

With cyclic ET regimens (i.e., estrogen only for 3 weeks followed by 1 week off therapy), hot flashes may return by the end of the hormone-free week. This is especially true with 17beta-estradiol, due to its rapid clearance from the body. Thus, NAMS recommends using continuous ET regimens before cyclic regimens when treating hot flashes.

If hot flashes persist after an adequate trial (i.e., 2-3 months) of hormone therapy (HT), other conditions associated with hot flashes should be considered in the differential diagnosis.

When ET/EPT is discontinued abruptly, hot flashes often return within several days, depending on the type and route of estrogen therapy. No specific protocols can be recommended for discontinuing therapy to avoid rebound hot flashes. Some clinicians gradually decrease the dose, whereas others lengthen the time between doses. There are no data to suggest that one method is better than the other. If hot flashes recur, ET/EPT may be reinstated then discontinued at a later time.

#### *Prescription progestogen*

Prescription progestogen alone can be used to treat hot flashes of varying severity. In clinical trials, DMPA, MPA, and megestrol acetate have demonstrated efficacy. Short-term use of these drugs seems reasonable in women without contraindications who do not wish to try estrogen but who are not opposed to trying another hormone, although progestogens have been linked to breast cancer risk in some studies.

#### *Oral contraceptives*

Perimenopausal women who need both hot flash relief and contraception may achieve both goals with low-dose, combined estrogen-progestin oral contraceptives (OCs). NAMS supports this use for otherwise healthy women who do not smoke or have other contraindications. The potential side effects of nausea, mood swings, and headaches can usually be decreased or eliminated by altering the regimen or dose. Relief of hot flashes should be achieved within 2 to 3 months of starting therapy. If hot flashes occur during the placebo week, adding a low dose of supplemental estrogen or shortening or eliminating the placebo interval may provide relief. DMPA offers another option for hot flash relief and contraception, although adverse effects are greater than with OCs. Standard menopausal doses of ET/EPT have not been well studied with respect to protection from an unwanted pregnancy and, thus, should not be relied on for contraception.

If EPT is needed postmenopause, transitioning from a combination OC to EPT should be done as soon as appropriate. Even OCs with very low hormone doses still provide significantly more hormone than in standard EPT, which may increase exposure to unnecessary risks from long-term use.

### **Prescription Therapies: Nonhormonal Options**

In women with hot flashes for whom hormones are not an option, nonhormonal prescription drugs have shown some effectiveness in relieving hot flashes. However, there are no comparative trials in similar patient populations to guide clinicians in selecting a particular option.

#### *Antidepressants*

If there are no contraindications, NAMS recommends the antidepressants venlafaxine (at dosages of 37.5-75 mg/day), paroxetine (12.5-25 mg/day), or fluoxetine (20 mg/day) as options for women with hot flashes who are not candidates for hormone therapy, including breast cancer survivors. The additional antidepressant effect may benefit some women who suffer from mood disorders.

Hot flash relief, if any, is almost immediate with these therapies, whereas for depression, effects often are not observed for 6 to 8 weeks. This rapid onset of action can be a powerful reinforcement for women who do not find relief from other, simpler methods. A brief trial of 1 week may determine if these agents are going to be effective.

Side effects, especially nausea and sexual dysfunction, should be monitored. Women who experience drowsiness should take the drug at night. Venlafaxine is the most likely in its class to promote weight loss (by causing anorexia), and may be preferred by overweight women. Paroxetine has similar side effects, although less nausea and anorexia. It can also cause blurred vision, although this is rare. Fluoxetine is less likely to cause acute withdrawal side effects because of its longer half-life.

To minimize side effects, very low doses of these antidepressants can be used when starting therapy. If not effective, the dose can be increased after 1 week. Higher doses than those used in trials do not seem appropriate, given the lack of additional efficacy and the potential for increased toxicity. Taking the drugs with food may lessen nausea.

These antidepressant medications should not be stopped abruptly, as sudden withdrawal has been associated with headaches and anxiety. Women who have been using an antidepressant for at least 1 week should taper off the drug. Tapering may require up to 2 weeks, depending on the initial dosage.

#### *Gabapentin*

Gabapentin is another nonhormonal option recommended by NAMS for treating hot flashes. Therapy can be initiated at a daily dose of 300 mg (although starting at 100 mg/day may be advisable in women older than age 65). Bedtime administration is advised, given the initial side effect of dizziness. In women who

continue to have hot flashes, the dose can be increased to 300 mg twice daily and then to three times daily, at 3- to 4-day intervals. Increased efficacy may be seen at even higher doses, although this has not been well studied. Antacids may reduce the bioavailability of gabapentin; the drug should be taken at least 2 hours after antacid use.

### *Clonidine*

Clonidine is sometimes used to treat mild hot flashes, although it is less effective than the newer antidepressants or gabapentin. In addition, clonidine has a side effect profile that limits its use in many women. The initial oral dose for hot flash treatment is 0.05 mg twice daily, but women may require at least 0.1 mg twice daily. The clonidine patch, delivering 0.1 mg/day, can also be considered. When discontinuing higher-dose therapy, the dose should be gradually tapered to avoid adverse side effects.

### *Methyldopa/Bellergal*

Given their toxicity, NAMS does not recommend methyldopa or Bellergal as hot flash treatments for most women.

Any hot flash treatment may need to change over time because of gradually lowering levels of ovarian hormones through perimenopause and the possible appearance of medical conditions unrelated to menopause or menopause treatments. New research and changing ideas about treatments may have an impact on health decisions. Before switching from one therapy to another, a washout period may be required.

## **CLINICAL ALGORITHM(S)**

None provided

## **EVIDENCE SUPPORTING THE RECOMMENDATIONS**

### **TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS**

The position statement was supported by evidence from randomized, controlled clinical trials and meta-analysis of such trials, conclusions from other evidence-based guidelines. If the evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was made.

## **BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS**

### **POTENTIAL BENEFITS**

#### **Lifestyle Modifications**

#### **Core Body Temperature**

- Observational studies have shown that lowering air temperature reduces hot flashes.

### **Exercise**

- In observational studies, physically active women reported fewer and less severe hot flashes than an age-matched control group with sedentary lifestyles; significant decreases of more than 50% were noted.

### **Paced Respiration**

- In three randomized, prospective clinical trials, paced respiration lowered hot flash frequency by approximately 50% more than the controls, a significant difference from baseline. Hot flashes were objectively measured by ambulatory monitoring of sternal skin conductance level.

### **Nonprescription Remedies**

**Soy foods and isoflavone supplements** exhibit a low incidence of side effects.

### **Black Cohosh**

- Some older and smaller trials from Germany have shown some efficacy for hot flashes. With its low incidence of side effects, a black cohosh supplement (two 20-mg tablets daily of a 27-deoxyactein standardized preparation) for less than 6 months is likely to do no harm and may provide relief of mild hot flashes.

### **Vitamin E**

- Because vitamin E seems to be nontoxic at low doses, inexpensive, and available without a prescription, it is a reasonable option for a trial. Effects, if any, may take weeks.

### **Prescription Therapies: Hormonal Options**

#### **Estrogen Therapy (ET) and Estrogen Plus Systemic Progestogen Therapy (EPT)**

- A meta-analysis conducted by the Cochrane Group of 21 randomized, double-blind, placebo-controlled trials enrolling 2,511 women found that systemic ET/EPT significantly reduced both hot flash frequency and severity compared with placebo. Overall, hot flash frequency was reduced by 77% relative to placebo while symptom severity was reduced by 87% (95% CI, 0.08-0.22). Among placebo recipients, a significant reduction in hot flashes of 51% from baseline to end of study was also reported. Trial durations ranged from 3 months to 3 years.

### **Progestogen**

- Studies have found that several progestogens effectively treat hot flashes, leading to the conclusion that, as with estrogens, it is a drug class effect.

### **Oral Contraceptives**

- A randomized, double-blind, placebo-controlled Canadian study of 132 healthy, nonsmoking perimenopausal women (aged 40-55) experiencing hot flashes found that an OC containing 0.02 mg ethinyl estradiol and 1 mg norethindrone acetate (Minestrin 1/20, equivalent to Loestrin 1/20) substantially reduced both the number and severity of hot flashes, but it was statistically no more effective than placebo. A 3-year randomized study of a low-dose triphasic OC in 200 perimenopausal women found significant reductions in hot flashes compared with controls. The relatively high estrogen and progestin doses found in OCs, compared with menopausal hormone therapy, increase the likelihood that OCs might be effective.

### **Prescription Therapies: Nonhormonal Options**

#### **Antidepressants**

- Venlafaxine: A randomized, double-blind, placebo-controlled clinical trial enrolled 229 women who were experiencing at least 14 hot flashes per week (69% were taking tamoxifen) and either had a history of breast cancer or chose not to take ET/EPT. Women were randomized to 4 weeks of treatment with either placebo or one of three venlafaxine doses: 37.5, 75, or 150 mg/day. At study end, venlafaxine recipients had hot flash score reductions from baseline of 37% for the 37.5 mg/day dosage and 60% for both higher doses, as compared with a 27% reduction for placebo recipients. The effect on reducing hot flashes was relatively rapid, with full effect noted within 1 to 2 weeks. An uncontrolled pilot trial also supports this finding.
- Paroxetine: The only randomized, double-blind, placebo-controlled trial used controlled-release paroxetine in 165 women without a history of breast cancer and experiencing 2 or 3 hot flashes per day. At doses of either 12.5 or 25.0 mg/day for 6 weeks, paroxetine significantly decreased hot flash composite scores by 62.2% (12.5 mg/day) and 64.6% (25.0 mg/day), compared with a 37.8% decrease for placebo recipients. Results from two uncontrolled pilot studies also support this study.
- Fluoxetine: In a double-blind, placebo-controlled, crossover trial, 81 healthy women with a history of breast cancer or a perceived risk of breast cancer and at least 14 hot flashes per week were randomized to fluoxetine (20 mg/day) or placebo for a 4-week period, with the alternative treatment given for an additional 4 weeks. The crossover analysis found additional reductions in hot flash frequency of about 20% for fluoxetine recipients compared with placebo recipients (no difference in results based on age). The magnitude of benefit in this study, however, did not appear to be as great as was seen with venlafaxine. Fluoxetine was well tolerated in this trial.

#### **Gabapentin**

- A randomized, double-blind, placebo-controlled trial performed in 59 postmenopausal women averaging seven or more hot flashes per day found that after 12 weeks of gabapentin therapy (900 mg/day, administered in

three divided doses), hot flash frequency was reduced by 45%, with a 54% reduction in a hot flash composite score. The differences were statistically significant compared with placebo recipients, who had reductions of 29% and 31%, respectively.

### **Clonidine**

- Two randomized, placebo-controlled trials (N = 10 and 29) found that the alpha<sub>2</sub>-adrenergic agonist clonidine, given either orally or transdermally, reduced hot flash frequency by 46% (for 0.4 mg/day) and 80%, respectively, in healthy women.

## **POTENTIAL HARMS**

### **Isoflavones and Supplements**

#### **Isoflavones**

- People with soy allergies may experience adverse reactions.

#### **Black Cohosh**

- Current available data are contradictory, therefore, caution dictates that the use of black cohosh not be presumed safe in women with breast cancer.

#### **Vitamin E**

- Individuals with vitamin K deficiency may experience increased bleeding with high doses of vitamin E.

### **Estrogen Therapy/Estrogen Plus Systemic Progestogen Therapy (ET/EPT)**

- Current data from the Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS) support a link between estrogen-progestogen therapy (EPT) and increased risks for breast cancer, coronary heart disease, thromboembolism, stroke, and dementia. Data from these studies should be extrapolated only with caution to women younger than 50 years of age who initiate estrogen therapy/estrogen-progestogen therapy. WHI and HERS involved women aged 50 and over (with mean ages of 63 and 67, respectively), and HERS was conducted solely in women with known coronary artery disease. The data should not be extrapolated to women experiencing premature menopause (<40 years of age) and initiating hormone therapy (HT) at that time. Breast cancer risk is increased with estrogen therapy (ET) and, to a greater extent, estrogen-progestogen therapy use beyond 5 years.
- Potential adverse effects of estrogen therapy include uterine bleeding, breast tenderness, nausea, abdominal bloating, fluid retention in extremities, headache, dizziness, and hair loss. Additional adverse effects when progestogen is added to estrogen (EPT) include mood changes and the potential for more uterine bleeding than with estrogen alone.

## **Progestogen**

- In women with a history of breast or endometrial carcinoma, there are no data demonstrating safety of progestogen on the breast, although progestogen appears to contribute substantially to the increased breast cancer risk seen with estrogen-progestogen use. Mammographic density, linked in some studies to greater breast cancer risk, is increased with progestogen use, although this effect will reverse with discontinuation of use.

## **Depot Medroxyprogesterone Acetate (DMPA) and Medroxyprogesterone Acetate (MPA)**

- Adverse effects include weight gain, irregular uterine bleeding, amenorrhea, and nervousness.

## **Megestrol Acetate**

- Side effects include increased appetite and possible exacerbation of pre-existing diabetes and an increase in thromboembolic events.

## **Oral Contraceptives**

- The most common adverse effects include nausea, vomiting, abdominal bloating, breakthrough uterine bleeding, change in menstrual flow, edema, melasma, and migraine.

## **Antidepressants**

### **Venlafaxine**

- Adverse effects observed in venlafaxine trials for depression include somnolence, dizziness, constipation, and sexual dysfunction. There is also a dose-related risk of increased blood pressure affecting about 3% of those using less than 100 mg/day.

### **Paroxetine and Fluoxetine**

- Adverse effects observed in trials for depression include asthenia, sweating, nausea, decreased appetite, somnolence, insomnia, and dizziness. Caution is advised with concomitant administration of warfarin.

## **Anticonvulsants**

### **Gabapentin**

- Low dose gabapentin (100 mg/day) are typically used as starting doses for hot flashes, particularly in older women. Adverse effects observed in seizure trials include somnolence, dizziness, ataxia, fatigue, and nystagmus.

## **Antihypertensives**

## **Clonidine**

- Adverse effects observed in hypertension trials include dry mouth, drowsiness, dizziness, constipation, and sedation.

## **Subgroups Most Likely to be Harmed**

No therapy is government approved in either the United States or Canada for treating hot flashes in women who are at high risk for or have been diagnosed with breast cancer or other hormone-dependent neoplasias. However, a variety of nonprescription and nonhormonal treatments has been used to relieve hot flashes in these populations. Caution is advised when recommending therapies to these women, as some therapies may have estrogenic activity.

# **CONTRAINDICATIONS**

## **CONTRAINDICATIONS**

### **Estrogen Therapy/Estrogen Plus Systemic Progestogen Therapy (ET/EPT)**

Estrogen therapy/estrogen-progestogen therapy is contraindicated in women with a history of hormone-sensitive cancer, liver disease (oral estrogen is of particular concern), history of blood-clotting disorders, and confirmed cardiovascular disease.

### **Oral Medroxyprogesterone Acetate and Depot Medroxyprogesterone Acetate (DMPA)**

Contraindicated in women with a history of hormone-sensitive cancer, liver disease, history of blood-clotting disorders, and confirmed cardiovascular disease.

### **Oral Contraceptives (OCs)**

Contraindications include a history of blood clots, cardiovascular disease, migraine, hormone-sensitive carcinoma, jaundice, or liver disease. Smokers over age 35 should not use oral contraceptives.

## **Venlafaxine**

Contraindications to using venlafaxine include concomitant use with MAO inhibitors.

## **Paroxetine and Fluoxetine**

Contraindications to using paroxetine include concomitant use of MAO inhibitors or thioridazine.

## **Gabapentin**

Hypersensitivity to the drug is the only contraindication to gabapentin use.

## Clonidine

Contraindications include cardiac sinus node function impairment.

### QUALIFYING STATEMENTS

#### QUALIFYING STATEMENTS

- This position statement will not specifically address vasomotor symptoms associated with causes other than menopause, such as hypogonadism, low serum gonadotropin levels, or gonadotropin-releasing hormone agonist therapy. However, it will include research conducted among peri- and postmenopausal women who have had breast cancer. Although their vasomotor symptoms may be related to breast cancer treatment (e.g., tamoxifen), it is reasonable to assume that the therapeutic results may be applicable to naturally postmenopausal women, even though the physiologic mechanisms can differ. Finally, although the information is relevant internationally, the focus is limited to therapies available in clinical practice in the United States and Canada.
- Most of the clinical recommendations are based on medical evidence, and they represent areas in which the Editorial Board reached consensus. If the evidence was inconclusive, recommendations were made based on expert opinion and clinical judgments; readers should be aware that these opinions may not be shared by all healthcare clinicians. In some cases, an intervention is recommended, or not discouraged, if it appears to have a harmless side effect profile. In other cases, interventions are not recommended if they have the potential for adverse effects.

### IMPLEMENTATION OF THE GUIDELINE

#### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

#### IMPLEMENTATION TOOLS

Slide Presentation

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

### INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

#### IOM CARE NEED

Getting Better

#### IOM DOMAIN

Effectiveness  
Patient-centeredness

## IDENTIFYING INFORMATION AND AVAILABILITY

### **BIBLIOGRAPHIC SOURCE(S)**

The North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause 2004 Jan-Feb;11(1):11-33. [PubMed](#)

### **ADAPTATION**

Not applicable: The guideline was not adapted from another source.

### **DATE RELEASED**

2004 Jan

### **GUIDELINE DEVELOPER(S)**

The North American Menopause Society - Private Nonprofit Organization

### **SOURCE(S) OF FUNDING**

The development of this manuscript was supported by an unrestricted educational grant from Duramed Pharmaceuticals, Inc., a subsidiary of Barr Laboratories, Inc.

### **GUIDELINE COMMITTEE**

Expert Consensus Committee

### **COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE**

Nanette F. Santoro, MD (Chair); Thomas B. Clarkson, DVM; Robert R. Freedman, PhD; Adriane J. Fugh-Berman, MD; Charles L. Loprinzi, MD; Nancy King Reame, MSN, PhD, FAAN

### **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

Not stated

### **GUIDELINE STATUS**

This is the current release of the guideline.

### **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from [The North American Menopause Society \(NAMS\) Web site](#).

Print copies: Available from NAMS, P.O. Box 94527, Cleveland, OH 44101, USA  
Order forms are available at The North American Menopause Society [NAMS] Web site, [www.menopause.org](http://www.menopause.org)

#### **AVAILABILITY OF COMPANION DOCUMENTS**

- Key points: NAMS March 2007 position statement on hormone therapy. Slide set. 2004. 5 p. Available from [The North American Menopause Society \(NAMS\) Web site](#).
- Boggs PP, Utian WH. The North American Menopause Society develops consensus opinions. Menopause 1998 Summer;5(2):67-8. Available from the [NAMS Web site](#).

#### **PATIENT RESOURCES**

None available

#### **NGC STATUS**

This NGC summary was completed by ECRI on March 4, 2004. The information was verified by the guideline developer on April 19, 2004. This summary was updated by ECRI on May 31, 2006 following the U.S. Food and Drug Administration advisory on Paxil (paroxetine hydrochloride). This summary was updated by ECRI on November 22, 2006, following the FDA advisory on Effexor (venlafaxine HCl). This summary was updated by ECRI Institute on November 6, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs.

#### **COPYRIGHT STATEMENT**

This summary is based on content contained in the original guideline, which is subject to terms as specified by the guideline developer. Users are free to download a copy of the materials and information on a single computer for personal, noncommercial use only; provided that any copyright, trademark or other proprietary notices are not removed from any materials and information downloaded. Any other use requires written permission from the guideline developer.

### **DISCLAIMER**

#### **NGC DISCLAIMER**

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public

or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at <http://www.guideline.gov/about/inclusion.aspx> .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

© 1998-2008 National Guideline Clearinghouse

Date Modified: 9/15/2008

