The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

NUMBER 141, JANUARY 2014

(Replaces Practice Bulletin Number 28, June 2001)
(See also Committee Opinion Number 565, Committee Opinion Number 556)

Management of Menopausal Symptoms

Vasomotor and vaginal symptoms are cardinal symptoms of menopause. Vasomotor symptoms can be particularly troubling to women and are the most commonly reported menopausal symptoms, with a reported prevalence of 50–82% among U.S. women who experience natural menopause (1, 2). The occurrence of vasomotor symptoms increases during the transition to menopause and peaks approximately 1 year after the final menstrual period (3–5). The purpose of this document is to provide evidence-based guidelines for the treatment of vasomotor and vaginal symptoms related to natural and surgical menopause. (Treatment of menopausal symptoms in cancer survivors is discussed in the American College of Obstetricians and Gynecologists' Practice Bulletin Number 126, Management of Gynecologic Issues in Women With Breast Cancer.)

Background

Menopause is the permanent cessation of menstruation that occurs after the loss of ovarian activity. By definition, menopause cannot be determined to have occurred until 1 year after the last menstrual period. In North America, the median age of menopause is 51 years. Most women begin to undergo the physiologic changes associated with menopause in the years preceding the final menstrual period. This interval is often referred to as perimenopause, the climacteric, or—more recently—the menopausal transition (6).

The menopausal transition is marked by fluctuations in hormone levels as ovarian function begins to slow down. Serum levels of estradiol and progesterone decrease and follicle-stimulating hormone levels increase, resulting in physiologic changes and clinical symptoms. Although women report experiencing a variety of menopausal symptoms, vasomotor (hot flushes) and vaginal symptoms are the most closely associated with the hormonal changes of the menopausal transition (6, 7).

Vasomotor Symptoms

The sudden sensation of extreme heat in the upper body, particularly the face, neck, and chest, is referred to as a hot flush. These episodes, which typically last 1–5 minutes (8), can be characterized by perspiration, flushing, chills, clamminess, anxiety, and, on occasion, heart palpitations (9). Vasomotor symptoms may also interfere with sleep and cause chronic sleep disruption in some women (10).

Vasomotor symptom episodes vary in frequency and duration. Studies show that 87% of women who report hot flushes experience these symptoms on a daily basis, with approximately 33% experiencing more than 10 hot flushes per day. Published reports also indicate that symptoms may persist longer than the previous estimate

Committee on Practice Bulletins—Gynecology. This Practice Bulletin was developed by the Committee on Practice Bulletins—Gynecology with the assistance of Clarisa Gracia, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

of 6 months to 2 years, although the overall duration of hot flushes remains unclear (5). Median durations of 4 years and 10.2 years have been reported, along with the observation that vasomotor symptoms commence around entry into the menopausal transition for some women and are not limited to the years immediately around the final menstrual period (5, 11). This finding may be one explanation for the wide variation in reported symptom duration.

The pathophysiology of the hot flush is not fully understood and is likely related to multiple factors. Changes in reproductive hormones appear to play a critical role, given that these symptoms occur during the menopausal transition and improve with the administration of estrogen. Although observational studies suggest that decreased estrogen levels and elevated follicle-stimulating hormone levels are associated with vasomotor symptoms, these changes cannot be solely responsible for these symptoms because the occurrence and severity of symptoms varies greatly among women during the menopausal transition (12). There also is evidence that thermoregulatory mechanisms change during the transition so that the thermoregulatory zone is narrowed and becomes more sensitive to subtle changes in core body temperature. Small increases in temperature trigger thermoregulatory mechanisms causing the sensation of a hot flush (vasodilation, sweating, and decreased skin resistance). Physiologic studies exploring hot flushes have confirmed that fluctuations in core body temperature are more pronounced in postmenopausal women compared with premenopausal women and that administration of estrogen widens the regulatory zone (9). Other central physiologic mechanisms that play a role in vasomotor symptoms include the serotonergic, noradrenergic, opioid, adrenal, and autonomic systems (9). Evidence for a genetic predisposition to vasomotor symptoms stems from studies that have found a link between symptoms and several polymorphisms related to sex steroid metabolism (13).

Epidemiologic studies have been performed to identify risk factors for vasomotor symptoms. Racial and ethnic differences have been shown to be important in vasomotor symptom reporting in several observational studies. The Study of Women's Health Across the Nation assessed menopausal symptoms in 14,906 women with diverse ethnic backgrounds aged 40–55 years in the United States and demonstrated that African American women reported the most vasomotor symptoms and Asian women reported the fewest symptoms compared with other groups (3, 14). Such racial and cross-cultural variability in the prevalence of self-reported hot flushes is substantiated by other literature (15, 16). It is possible that physiologic differences or diets high in soy products may account for variable symptomatology. However, it also may be that ethnic variations are due to differing cross-cultural perceptions and reporting of vasomotor symptoms (17).

Several studies have reported that hot flushes are more common in obese women (16, 18). Although the mechanism of this association is not understood, it has been hypothesized that adipose tissue functions as an insulator and interferes with normal thermoregulatory mechanisms of heat dissipation. Adipose tissue also may have an endocrine function that mediates vasomotor symptoms. Other factors related to vasomotor symptoms include mood symptoms such as depression and anxiety, low socioeconomic status, and smoking (4, 19).

There are emerging data to suggest that vasomotor symptoms may be associated with adverse health outcomes including, cardiovascular health and bone health (20, 21). However, recent data from The Kronos Early Estrogen Prevention Study noted that self-reported menopausal symptoms in recently menopausal women are not strong predictors of subclinical atherosclerosis (22).

Vaginal Symptoms

Vaginal atrophy is a direct consequence of the hypoestrogenic state associated with menopause resulting in anatomic and physiologic changes in the genitourinary tract. The North American Menopause Society estimates that 10–40% of menopausal women will experience one or more symptoms of vaginal atrophy. Vaginal atrophy causes bothersome vaginal symptoms commonly associated with menopause including, vaginal or vulvar dryness, discharge, itching, and dyspareunia (23). A loss of superficial epithelial cells in the genitourinary tract causes thinning of tissue. Loss of vaginal rugae and elasticity occur with a narrowing and shortening of the vagina. Epithelial tissues are more fragile and may tear, leading to bleeding and fissures. There also is a loss of subcutaneous fat in the labia majora. These changes result in narrowing of the introitus, fusion of the labia minora, and shrinking of the clitoral prepuce and urethra. Vaginal pH becomes more alkaline, which may alter the vaginal flora and increase the risk of urogenital infection (24, 25). Vaginal secretions, largely transudate from the vaginal vasculature, may decrease. These changes from vaginal atrophy can lead to significant dyspareunia, which can impair sexual function (26). Measures of sexual dysfunction are noted to be present at higher rates in women with vaginal atrophy than in unaffected menopausal women (27). Collectively these symptoms may have a detrimental effect on a woman's quality of life, self-esteem, and sexual intimacy (treatment of sexual dysfunction is also discussed in Practice Bulletin Number 119, *Female Sexual Function*) (28). Genital examination and microscopic examination of vaginal smears can confirm atrophic vaginitis.

Clinical Considerations and Recommendations

▶ ***What hormonal medications are effective in treating vasomotor symptoms?***

Systemic hormone therapy (HT), with estrogen alone or in combination with progestin, is the most effective therapy for vasomotor symptoms related to menopause. Data do not support the use of progestin-only medications, testosterone, or compounded bioidentical hormones for the treatment of vasomotor symptoms (see Table 1).

Estrogen Alone or Combined With Progestin

The results of multiple studies support the effectiveness of HT for the management of menopausal vasomotor symptoms. A Cochrane meta-analysis of 24 randomized controlled trials (RCTs), which included 3,329 participants found a 75% reduction in weekly hot flush

Table 1. Treatment Options for Menopausal Vasomotor Symptoms ⇦

Treatment	Dosage/Regimen	Evidence of Benefit*	FDA Approved
	Hormonal		
Estrogen-alone or combined with progestin			
• Standard Dose	Conjugated estrogen 0.625 mg/d	Yes	Yes
	Micronized estradiol-17β 1 mg/d	Yes	Yes
	Transdermal estradiol-17β 0.0375–0.05 mg/d	Yes	Yes
• Low Dose	Conjugated estrogen 0.3–0.45 mg/d	Yes	Yes
	Micronized estradiol-17β 0.5 mg/d	Yes	Yes
	Transdermal estradiol-17β 0.025 mg/d	Yes	Yes
• Ultra-Low Dose	Micronized estradiol-17β 0.25 mg/d	Mixed	No
	Transdermal estradiol-17β 0.014 mg/d	Mixed	No
Estrogen combined with estrogen agonist/antagonist	Conjugated estrogen 0.45 mg/d and bazedoxifene 20 mg/d	Yes	Yes
Progestin	Depot medroxyprogesterone acetate	Yes	No
Testosterone		No	No
Tibolone	2.5 mg/d	Yes	No
Compounded bioidentical hormones		No	No
	Nonhormonal		
SSRIs and SSNRIs		No	No
Paroxetine	7.5 mg/d	Yes	Yes
Clonidine	0.1 mg/d	Yes	No
Gabapentin	600–900 mg/d	Yes	No
Phytoestrogens		No	No
Herbal Remedies		No	No
Vitamins		No	No
Exercise		No	No
Acupuncture		No	No
Reflexology		No	No
Stellate-ganglion block		Yes	No

Abbreviations: FDA, U.S. Food and Drug Administration; SSRIs, selective serotonin reuptake inhibitors; SSNRIs, selective serotonin norepinephrine reuptake inhibitors.
*Compared with placebo.

frequency in users of oral estrogen or oral estrogen plus progestin compared with placebo (95% confidence interval [CI], 64.3–82.3) and a reduction in symptom severity (odds ratio [OR], 0.13; 95% CI, 0.07–0.23) (29). One of the largest studies investigating the effect of oral HT on vasomotor symptoms was the Postmenopausal Estrogen/Progestin Interventions trial, an RCT of 875 women treated with oral conjugated equine estrogen alone or in combination with continuous or cyclic progestin versus placebo, which found a significant reduction in self-reported vasomotor symptoms in women in both the estrogen-alone arm (OR, 0.42; 95% CI, 0.28–0.62) and the estrogen-plus-progestin arm (OR, 0.38; 95% CI, 0.25–0.58) compared with placebo (30).

Routes of Administration

There are a variety of preparations available for systemic estrogen therapy. Estrogen with or without progestin can be administered orally or transdermally in the forms of patches, gels, or sprays (31, 32). All of these delivery methods have been shown to relieve vasomotor symptoms, and also include other delivery methods, such as intranasal and buccal systems that are not available in the United States (33–35).

Dose

Studies of the efficacy of HT for the treatment of vasomotor symptoms have principally investigated standard doses of HT. Although HT is well tolerated by most women, standard doses may cause adverse effects, such as breast tenderness, vaginal bleeding, bloating, and headaches. Low-dose and ultra-low systemic doses of estrogen may be associated with a better adverse effect profile than standard doses and may reduce vasomotor symptoms in some women.

Examples of low-dose systemic estrogen therapy formulations include 0.3–0.45 mg/d of oral conjugated equine estrogen, 0.5 mg/d of oral micronized estradiol, 5 micrograms/d of ethinyl estradiol, and 0.025–0.0375 mg/wk of transdermal estradiol (patch). There also are low-dose formulations of estradiol available in topical gels, creams, and sprays that are approved by the U.S. Food and Drug Administration (FDA). There is good evidence that oral and transdermal low-dose estrogen regimens effectively alleviate vasomotor symptoms in women (36–38). The Heart Outcomes Prevention Evaluation, a large trial that assessed the efficacy of different doses of HT on vasomotor symptoms in more than 2,500 postmenopausal women, found a similar reduction in vasomotor symptoms with a conjugated equine estrogen dosage of 0.625 mg/d and all lower combination doses (38). Another study of 333 women randomized to receive various doses of estradiol or placebo found that a dosage as low as 0.5 mg/d of oral estradiol is effective in treating hot flushes (39).

The results of studies that assessed the efficacy of ultra-low doses of estrogen (0.25 mg of oral micronized estradiol and 0.014 mg of transdermal estradiol) to treat vasomotor symptoms have been mixed, and currently these doses are not FDA approved for this indication. Some studies have shown improvement in vasomotor symptoms with ultra-low dose estrogen alone or in combination with progestin (36, 40, 41). For example, an RCT of 425 women demonstrated that 41% of women experienced a reduction in moderate and severe hot flushes with ultra-low dose estradiol therapy (0.014 mg/d estradiol patch) compared with placebo (36). However, other studies have not shown a benefit for the treatment of vasomotor symptoms (42). In an RCT of 333 women, a 0.25-mg dose of oral estradiol was not more effective than placebo in treating hot flushes (39).

The degree of improvement of vasomotor symptoms from low-dose and ultra-low dose preparations has not been as extensively studied as with standard-dose preparations. Although women will experience improvement in symptoms with low and ultra-low doses of HT, lower doses do not appear to be as effective as traditional doses of HT in alleviating vasomotor symptoms. Nonetheless, given the variable response to HT and the associated risks, it is recommended that health care providers individualize care and treat women with the lowest effective dose for the shortest duration that is needed to relieve vasomotor symptoms.

Risks

The risks of systemic combined HT include thromboembolic disease and breast cancer. The majority of trials that analyzed the safety of HT have assessed preparations containing conjugated equine estrogen alone or in combination with medroxyprogesterone acetate. The Women's Health Initiative (WHI) study, a large RCT of healthy menopausal women aged 50–77 years, demonstrated a slightly increased risk of breast cancer, coronary heart disease, stroke, and venous thromboembolic events and a decreased risk of fractures and colon cancer after an average of 5 years of combined HT (43). Among women receiving estrogen only, there was an increased risk of thromboembolic events, but not an increased risk of cardiovascular events or breast cancer (44). It is difficult to generalize these findings to younger women who are recently menopausal because the WHI was aimed at assessing HT for primary coronary heart disease prevention in women, many of whom were past the menopausal transition.

A reanalysis of the WHI results in women younger than 60 years and within 10 years of menopause has suggested a possible cardioprotective effect of HT for women in this group (45). However, a follow-up study of the WHI with 13 years of cumulative follow-up data confirmed that the risk of conjugated equine estrogen and medroxprogesterone acetate outweighed the benefits (46). Similarly, a 2012 Cochrane review of HT that included 23 studies and more than 42,000 participants concluded that HT should not be used for primary or secondary disease prevention because the risks of use outweigh the benefits (47).

The use of alternative forms of estrogen and progestin may be associated with a different risk profile (48). For example, observational studies suggest that transdermal estrogen may have a lower risk of venous thromboembolism compared with oral regimens (49). Additional data from RCTs are needed to compare the safety and efficacy of various regimens.

Discontinuation

Discontinuation of HT may be associated with recurrent vasomotor symptoms in approximately 50% of women, regardless of age and duration of use (50–52). There is insufficient evidence to recommend one method of HT discontinuation (abrupt or tapering) over the other to prevent recurrent symptoms (53, 54). The decision to continue HT should be individualized and be based on a woman's symptoms and the risk–benefit ratio, regardless of age. Because some women aged 65 years and older may continue to need systemic HT for the management of vasomotor symptoms, the American College of Obstetricians and Gynecologists recommends against routine discontinuation of systemic estrogen at age 65 years. As with younger women, use of HT and estrogen therapy should be individualized based on each woman's risk–benefit ratio and clinical presentation.

As an alternative to the use of a progestin for preventing endometrial hyperplasia with estrogen therapy, preparations combining estrogen and an estrogen agonist/antagonist have been investigated. Recently, a combined daily oral preparation of conjugated estrogen and bazedoxifene has been approved by the FDA for treatment of vasomotor symptoms and to prevent osteoporosis in postmenopausal women with a uterus. This preparation has been shown to significantly reduce the number of vasomotor symptoms and significantly increase bone mineral density compared to placebo (55).

Progestin

Although progestin is primarily used as an add-on agent to estrogen therapy to prevent endometrial hyperplasia and endometrial cancer in women with a uterus, there is some evidence that progestin may also improve vasomotor symptoms (56). Some studies suggest that improvement in vasomotor symptoms is greater compared with placebo when progestin is added to estrogen (OR, 0.10; 95% CI, 0.06–0.19) compared with estrogen alone (OR, 0.35; 95% CI, 0.22–0.56) (29). Moreover, there is some evidence that progestin-only therapy is effective in reducing vasomotor symptoms. In an RCT of 109 women treated with a single dose of depot medroxyprogesterone acetate (400 mg) or venlafaxine 37.5 mg/d for 1 week and then 75 mg/d, those in the depot medroxyprogesterone acetate arm had a greater reduction in vasomotor symptoms (79% versus 55%) and less toxicity than those in the venlafaxine arm (57). Although progestin may improve vasomotor symptoms, there are limited data on the safety of progestin alone compared with combined estrogen and progestin preparations for the treatment of vasomotor symptoms. Because the risk of breast cancer was increased in the conjugated equine estrogen and medroxprogesterone acetate arm of WHI and not in the conjugated equine estrogen-alone arm, there is concern that the risk of breast cancer may be related to progestin use. Therefore, progestin alone is not considered a first-line therapy for the management of vasomotor symptoms.

Testosterone

Testosterone in combination with HT has been investigated for the treatment of menopausal symptoms. A Cochrane meta-analysis reviewed 35 trials with 4,768 postmenopausal women to determine the efficacy of testosterone therapy in this population (58). Testosterone for the treatment of vasomotor symptoms has shown no benefit and potential adverse effects including, detrimental effects on lipid parameters, clitoromegaly, hirsutism, and acne (58–60). However, in the Cochrane meta-analysis, the pooled estimate suggested that the addition of testosterone to HT regimens improved sexual function scores and number of satisfying sexual episodes for postmenopausal women (58). Testosterone alone is currently not FDA-approved for use in women.

Tibolone

Tibolone is a synthetic steroid with tissue-specific estrogenic and progestogenic effects that has been studied for the management of menopause. Tibolone is not FDA-approved and is not available in the United States. Tibolone appears to have a beneficial effect on bone density, vasomotor symptoms, and vaginal symptoms without estrogenic effects on the uterus or breasts (61, 62). However, given its limited safety and efficacy data

compared with HT, tibolone is not considered a first-line therapy for menopausal symptoms.

Compounded Bioidentical Hormones

Bioidentical hormones are plant-derived hormones that are chemically similar or structurally identical to those produced by the body. Bioidentical hormones include commercially available products approved by the FDA, such as micronized progesterone and estradiol, as well as compounded preparations that are not regulated by the FDA. Because of a lack of FDA oversight, most compounded preparations have not undergone any rigorous clinical testing for either safety or efficacy, so the purity, potency, and quality of compounded preparations are a concern. In addition, both underdosage and overdosage are possible because of variable bioavailability and bioactivity. Evidence is lacking to support superiority claims of compounded bioidentical hormones over conventional menopausal HT (this is also discussed in Committee Opinion Number 532, *Compounded Bioidentical Menopausal Therapy*). Conventional HT is preferred given the available data (63).

▶ ***What nonhormonal medications are effective for the treatment of vasomotor symptoms?***

Selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SSNRIs), clonidine, and gabapentin are effective alternatives to HT for the treatment of vasomotor symptoms related to menopause (see Table 1).

Selective Serotonin Reuptake Inhibitors and Selective Serotonin-Norepinephrine Reuptake Inhibitors

There is increasing evidence that the antidepressant agents SSRIs and SSNRIs are effective for the treatment of vasomotor symptoms associated with menopause. Although data are mixed, the results from RCTs support the effectiveness of these medications for the treatment of menopausal hot flushes in healthy, nondepressed women (64–71). In an RCT of 365 women, 62% of those treated with the SSNRI, desvenlafaxine (100 mg/d), had a reduction of 5.35 moderate-to-severe hot flashes per day compared with only 41% of women with placebo, and the treatment effect was maintained for 1 year (69, 70). The results of a meta-analysis of earlier studies of SSRIs or SSNRIs for the management of vasomotor symptoms demonstrated a significant reduction compared with placebo (mean difference, −1.13; 95% CI, −1.70 to −0.57) (72). Reported adverse effects included nausea, dizziness, dry mouth, nervousness, constipation, somnolence, sweating, and sexual dysfunction, but these generally resolved with time or dose adjustment.

Although the available evidence indicates that SSRIs and SSNRIs appeared to be less effective than HT for the treatment of vasomotor symptoms, it is difficult to draw definitive conclusions because direct comparisons with estrogen are limited. Paroxetine (7.5 mg/d) is the only nonhormonal therapy that is approved by the FDA for the treatment of vasomotor symptoms.

Clonidine

Clonidine, a centrally acting alpha 2-agonist, is an antihypertensive agent that has been used to treat vasomotor symptoms, but is not FDA-approved for this indication. Safety and efficacy data on this preparation for the management of vasomotor symptoms are limited. A systematic review and meta-analysis reported a small benefit of clonidine (0.1 mg/d) compared with placebo, but less benefit compared with HT (72). Common adverse effects reported were dry mouth, insomnia, and drowsiness. Blood pressure was not adversely affected by clonidine.

Gabapentin

Gabapentin, a gamma aminobutyric acid analogue, is an anticonvulsant agent that has been shown to reduce vasomotor symptoms in several studies but is not FDA-approved for this indication. An RCT of gabapentin (900 mg/d) demonstrated a 45% reduction in hot flush frequency and a 54% reduction in symptom severity (73). Another trial of 45 women with moderate-to-severe hot flushes randomized to receive gabapentin (600 mg/d) versus a low-dose transdermal estradiol (25 micrograms/d) showed symptom relief in both groups, but estrogen was more effective (74). Common adverse effects from gabapentin include dizziness, somnolence, and peripheral edema. Gabapentin, SSRIs, and SSNRIs appear to have similar treatment efficacy for vasomotor symptoms, but the majority of women who were administered both venlafaxine and gabapentin in a crossover trial preferred venlafaxine (75).

▶ ***What complementary and alternative therapies are effective for the treatment of vasomotor symptoms?***

Complementary Botanicals and Natural Products

Several natural products have been used for the management of vasomotor symptoms. In the United States, none of these complementary therapies are regulated by

the FDA and have not been tested for safety, efficacy, or purity because they are considered nutritional supplements. Data do not show that phytoestrogens, herbal supplements, and lifestyle modifications are efficacious for the treatment of vasomotor symptoms.

Phytoestrogens

Phytoestrogens are plant-derived substances with estrogenic biologic activity. Examples include the isoflavones genistein and daidzein, which are found in high amounts in soybeans, soy products, and red clover. Initial interest in using phytoestrogens for the treatment of menopausal symptoms stemmed from the observation that Asian women, whose diets are rich in phytoestrogens from soy, experience fewer vasomotor symptoms and have a lower risk of estrogen-sensitive cancer compared with Caucasian women. Although multiple studies have been conducted to assess the efficacy of these substances on the management of menopause related vasomotor symptoms, most of the data are limited by small sample size, assessment of various forms of phytoestrogen products, and variability in dose and duration of trials. A 2010 Cochrane meta-analysis of 30 placebo-controlled trials of high levels of phytoestrogens for the treatment of vasomotor symptoms found no evidence of benefit (76). In particular, there was no significant difference in the frequency of hot flushes between red clover extract and placebo (weighted mean difference, −0.6; 95% CI, −1.8 to 0.6). There was no evidence of detrimental effects, such as overstimulation of the endometrium, with use up to 2 years. Nonetheless, long-term safety data are lacking.

Herbal Remedies

Herbal treatments that have been studied for the relief of vasomotor symptoms include Chinese herbal medicine, black cohosh, ginseng, St. John's wort, and ginkgo biloba. There are currently insufficient data to support the use of herbal remedies for menopausal–vasomotor symptoms.

Chinese herbal medicine treatments, often containing the plant dong quai (*Angelica sinensis*), have been used to treat vasomotor symptoms, with limited data to support safety and effectiveness. In one RCT, dong quai was not found to be more effective than placebo, and potential adverse effects included photosensitivity and an increased risk of bleeding in patients using warfarin (77). Another Chinese herb, dang gui bu xue tang, has been found to be more effective than placebo for the management of mild vasomotor symptoms (78). In one study, Chinese herbal medicine plus acupuncture was found to be as effective as HT at relieving menopausal symptoms (79).

Black cohosh (also known as *Actaea racemosa* or *Cimicifuga racemosa*) is a plant that is widely used to treat vasomotor symptoms, although data are conflicting regarding its efficacy and safety, due in part to limited study quality. In particular, liver toxicity has been reported (80–83). There is currently insufficient evidence to support the use of black cohosh for menopausal symptoms, although further study is warranted (84).

Studies have not shown that other herbs including, ginseng, St. John's wort, and ginkgo biloba, either alone or in combination, are superior to placebo for the treatment of vasomotor symptoms (85–88).

Vitamins

There are limited data on the effectiveness of vitamin supplements for the treatment of vasomotor symptoms (89, 90). One less hot flush per day, a marginal reduction, has been reported with the use of vitamin E (800 international units/d) (89).

Alternative Techniques

Several studies have been conducted to assess the effectiveness of acupuncture for the management of vasomotor symptoms. A meta-analysis of six RCTs showed no benefit over placebo for vasomotor symptoms (91). Similarly, reflexology has not been shown to significantly reduce vasomotor symptoms compared with nonspecific foot massage (92). There are some preliminary data to suggest that local injection of anesthetic into the stellate ganglion may reduce vasomotor symptoms in women with contraindications to HT (93, 94). However, additional studies are needed to assess the safety and effectiveness of this novel technique.

▶ *What behavioral and lifestyle changes are effective in treating vasomotor symptoms?*

Despite limited supporting data, common sense lifestyle solutions such as layering of clothing, maintaining a lower ambient temperature, and consuming cool drinks are reasonable measures for the management of vasomotor symptoms. Women also may be advised to avoid consumption of alcohol and caffeine, which have been associated with increased severity and frequency of vasomotor symptoms (95).

Although there is some evidence that aerobic exercise may improve quality of life and mood in women with vasomotor symptoms, there are insufficient data to recommend exercise for the treatment of vasomotor symptoms (96). A meta-analysis of six small RCTs that evaluated exercise interventions for vasomotor symptoms revealed no significant improvement compared

with placebo (standard mean difference, –0.14; 95% CI, –0.54 to 0.26) (97). A systematic review of studies that compared exercise interventions with HT showed a greater benefit for HT, but the difference was not statistically significant (standard mean difference, 0.49; 95% CI, –0.27 to 1.26) (98).

▶ ***What hormonal medications are effective in treating vaginal symptoms?***

Estrogen

Estrogen therapy effectively alleviates atrophic vaginal symptoms related to menopause. Local therapy is advised for the treatment of women with only vaginal symptoms. All low-dose systemic estrogen formulations are FDA-approved for the treatment of atrophic vaginitis. Oral dosages of conjugated equine estrogen as low as 0.3 mg/d and transdermal estradiol dosages of 12.5 micrograms/d have demonstrated improvements in vaginal atrophy (38, 98).

Local vaginal estradiol and local conjugated equine estrogen, which can be administered in cream, ring, and tablet formulations, are effective in treating atrophic vaginitis in menopausal women (99–101). The results of RCTs show that even low-dose (10 micrograms) vaginal estradiol tablets improve vaginal symptoms (102, 103). Typically, vaginal estrogen formulations are administered daily for 1–2 weeks as induction therapy and then may be used indefinitely at low doses for maintenance therapy. Studies indicate that the 3-month estradiol-releasing vaginal ring is preferred to cream because of greater comfort, ease of use, and satisfaction (101).

Systemic absorption of vaginal estrogen has been documented in postmenopausal women with atrophy using a daily low-dose vaginal estrogen preparation with 25 micrograms of estradiol (104). There is a theoretic concern that systemic absorption may increase the risk of endometrial cancer. However, a Cochrane meta-analysis of 19 trials with 4,162 women found that local estrogen therapy was not associated with an increased risk of endometrial hyperplasia compared with placebo and, therefore, the addition of progestion for endometrial protection is not needed (102). Use of progestin or local estrogen therapy does not require endometrial surveillance, unless women experience postmenopausal bleeding, which would require diagnostic evaluation.

Because of variable rates of estrogen absorption associated with local estrogen therapy, there has been concern about the use of this treatment in women with a history of breast cancer (105). Because of the lack of data to determine whether transient increases in estradiol are clinically significant, and whether the effects of long-term exposure pose increased risk, nonhormonal methods should be considered first-line treatment for vaginal atrophy in women with a history of hormone-sensitive breast cancer (106). Short-term use of hormonal methods may be considered for women with severe or refractory symptoms in whom other options have failed, following appropriate counseling with their oncologists about the potential risks (105).

Estrogen Agonists and Estrogen Antagonists

Estrogen agonists and estrogen antagonists are synthetic compounds that selectively stimulate or inhibit the estrogen receptors of different target tissues. Such selectivity is possible because estrogen receptors in different target tissues vary in chemical structure (105). The physiologic effects of estrogen agonists and estrogen antagonists are not uniform and vary depending on the type of estrogen agonist or estrogen antagonist. Because estrogen agonists and estrogen antagonists selectively stimulate or inhibit the estrogen receptors of different target tissues, their effects in some tissues can have a deleterious physiologic effect, including an increased risk of thromboembolic events, endometrial and vulvovaginal abnormalities, and vasomotor problems. Studies demonstrate that two currently available FDA-approved agents, raloxifene and tamoxifen, are not effective for the treatment of menopausal vaginal symptoms (107). The current evidence does not suggest an important effect of either agent for the treatment of vasomotor symptoms. However, studies suggest that ospemifene, a novel estrogen agonist and estrogen antagonist improves vaginal atrophy without stimulating the endometrium. A study of 826 postmenopausal women randomized to receive 30 mg/d or 60 mg/d of ospemifene showed that the 60-mg dose was effective for improving vulvovaginal atrophy (108). Common adverse effects of ospemifene reported during clinical trials included hot flushes, vaginal discharge, muscle spasms, genital discharge, and excessive sweating. The FDA approved ospemifene for treating moderate-to-severe dyspareunia in postmenopausal women (see Table 2).

▶ ***What nonhormonal therapies are effective in treating vaginal symptoms?***

Vaginal Lubricants

Nonestrogen water-based or silicone-based vaginal lubricants and moisturizers may alleviate vaginal symptoms related to menopause. These products may be particularly

Table 2. Treatment Options for Menopausal Vaginal Symptoms ⇦

Treatment	Dosage	Evidence of Benefit*	FDA Approved
	Hormonal		
Estrogen			
Systemic			
• Standard Dose	Conjugated estrogen 0.625 mg/d	Yes	Yes
	Micronized estradiol-17β 1 mg/d	Yes	Yes
	Transdermal estradiol-17β 0.0375–0.05 mg/d	Yes	Yes
• Low Dose	Conjugated estrogen 0.3–0.45 mg/d	Yes	Yes
	Micronized estradiol-17β 0.5 mg/d	Yes	Yes
	Transdermal estradiol-17β 0.025 mg/d	Yes	Yes
• Ultra-Low Dose	Micronized estradiol-17β 0.25 mg/d	Mixed	No
	Transdermal estradiol-17β 0.014 mg/d	Mixed	No
Vaginal/Local	Estradiol-17β ring 7.5 micrograms/d	Yes	Yes
	Estradiol vaginal tablet 25 micrograms/d	Yes	Yes
	Estradiol ring 0.05 mg/d	Yes	
	Estradiol-17β cream 2 g/d	Yes	
	Conjugated estrogen cream 0.5–2 g/d	Yes	
	Nonhormonal		
Estrogen agonists–antagonists			
• Raloxifene and tamoxifen		No	No
• Ospemifene	60 mg/d	Yes	Yes
Vaginal lubricants		Yes	No
Vaginal moisturizers		Yes	No
Herbal remedies and soy products		No	No

Abbreviation: FDA, U.S. Food and Drug Administration.

*Compared with placebo.

helpful in women who do not wish to use hormonal therapies. Vaginal lubricants are intended to be used to relieve friction and dyspareunia related to vaginal dryness during intercourse and are applied to the vaginal introitus before intercourse. Vaginal moisturizers are intended to trap moisture and provide long-term relief of vaginal dryness. Although there are limited data regarding the effectiveness of these products, prospective studies have demonstrated that vaginal moisturizers improve vaginal dryness, pH balance, and elasticity and reduce vaginal itching, irritation, and dyspareunia (109), and many women have found nonhormonal vaginal lubricants and moisturizers to be effective in managing vaginal dryness (see Table 2) (110). There are insufficient data to support the use of herbal remedies or soy products for the treatment of vaginal symptoms (111, 112).

Summary of Recommendations and Conclusions

The following recommendations and conclusions are based on good or consistent scientific evidence (Level A):

- Systemic HT, with estrogen alone or in combination with progestin, is the most effective therapy for vasomotor symptoms related to menopause.
- Low-dose and ultra-low systemic doses of estrogen are associated with a better adverse effect profile than standard doses and may reduce vasomotor symptoms in some women.

- Given the variable response to HT and the associated risks, it is recommended that health care providers individualize care and treat women with the lowest effective dose for the shortest duration that is needed to relieve vasomotor symptoms.
- The risks of combined systemic HT include thromboembolic disease and breast cancer.
- Selective serotonin reuptake inhibitors, SSNRIs, clonidine, and the gabapentin are effective alternatives to HT for the treatment of vasomotor symptoms related to menopause.
- Estrogen therapy effectively alleviates atrophic vaginal symptoms related to menopause. Local therapy is advised for the treatment of women with only vaginal symptoms.
- Paroxetine is the only nonhormonal therapy that is approved by the FDA for the treatment of vasomotor symptoms.
- The FDA approved ospemifene for treating moderate-to-severe dyspareunia in postmenopausal women.

The following conclusions are based on limited or inconsistent scientific evidence (Level B):

- Data do not support the use of progestin-only medications, testosterone, or compounded bioidentical hormones for the treatment of vasomotor symptoms.
- Data do not show that phytoestrogens, herbal supplements, and lifestyle modifications are efficacious for the treatment of vasomotor symptoms.
- Nonestrogen water-based or silicone-based vaginal lubricants and moisturizers may alleviate vaginal symptoms related to menopause.
- Common sense lifestyle solutions such as layering of clothing, maintaining a lower ambient temperature, and consuming cool drinks are reasonable measures for the management of vasomotor symptoms.

The following recommendation is based primarily on consensus and expert opinion (Level C):

- The decision to continue HT should be individualized and be based on a woman's symptoms and the risk–benefit ratio, regardless of age.

Proposed Performance Measure

Documentation of the discussion with patients about the severity of vasomotor and vaginal menopausal symptoms and therapeutic options

References

1. Feldman BM, Voda A, Gronseth E. The prevalence of hot flash and associated variables among perimenopausal women. Res Nurs Health 1985;8:261–8. (Level II-3) [PubMed] ⇦
2. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas 1992;14:103–15. (Level II-2) [PubMed] [Full Text] ⇦
3. Gold EB, Colvin A, Avis N, Bromberger J, Greendale GA, Powell L, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. Am J Public Health 2006;96:122–35. (Level II-3) [PubMed] [Full Text] ⇦
4. Gold EB, Sternfeld B, Kelsey JL, Brown C, Mouton C, Reame N, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. Am J Epidemiol 2000;152:463–73. (Level II-3) [PubMed] [Full Text] ⇦
5. Politi MC, Schleinitz MD, Col NF. Revisiting the duration of vasomotor symptoms of menopause: a meta-analysis. J Gen Intern Med 2008;23:1507–13. (Meta-analysis) [PubMed] [Full Text] ⇦
6. Grady D. Clinical practice. Management of menopausal symptoms. N Engl J Med 2006;355:2338–47. (Level III) [PubMed] [Full Text] ⇦
7. Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population-based study of menopausal symptoms. Obstet Gynecol 2000;96:351–8. (Level II-3) [PubMed] [*Obstetrics & Gynecology*] ⇦
8. Kronenberg F. Hot flashes: epidemiology and physiology. Ann N Y Acad Sci 1990;592:52–86; discussion 123–33. (Level III) [PubMed] ⇦
9. Freedman RR. Physiology of hot flashes. Am J Hum Biol 2001;13:453–64. (Level III) [PubMed] ⇦
10. Erlik Y, Tataryn IV, Meldrum DR, Lomax P, Bajorek JG, Judd HL. Association of waking episodes with menopausal hot flushes. JAMA 1981;245:1741–4. (Level III) [PubMed] ⇦
11. Freeman EW, Sammel MD, Lin H, Liu Z, Gracia CR. Duration of menopausal hot flushes and associated risk factors. Obstet Gynecol 2011;117:1095–104. (Level II-3) [PubMed] [*Obstetrics & Gynecology*] ⇦
12. Randolph JF Jr, Sowers M, Bondarenko I, Gold EB, Greendale GA, Bromberger JT, et al. The relationship of longitudinal change in reproductive hormones and vasomotor symptoms during the menopausal transition.

J Clin Endocrinol Metab 2005;90:6106–12. (Level II-3) [PubMed] [Full Text] ⇦

13. Rebbeck TR, Su HI, Sammel MD, Lin H, Tran TV, Gracia CR, et al. Effect of hormone metabolism genotypes on steroid hormone levels and menopausal symptoms in a prospective population-based cohort of women experiencing the menopausal transition. Menopause 2010;17:1026–34. (Level II-2) [PubMed] [Full Text] ⇦
14. Avis NE, Stellato R, Crawford S, Bromberger J, Ganz P, Cain V, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. Soc Sci Med 2001;52:345–56. (Level II-3) [PubMed] ⇦
15. Dennerstein L, Smith AM, Morse C, Burger H, Green A, Hopper J, et al. Menopausal symptoms in Australian women. Med J Aust 1993;159:232–6. (Level II-3) [PubMed] ⇦
16. Freeman EW, Grisso JA, Berlin J, Sammel M, Garcia-Espana B, Hollander L. Symptom reports from a cohort of African American and white women in the late reproductive years. Menopause 2001;8:33–42. (Level II-3) [PubMed] ⇦
17. Crawford SL. The roles of biologic and nonbiologic factors in cultural differences in vasomotor symptoms measured by surveys. Menopause 2007;14:725–33. (Level III) [PubMed] ⇦
18. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, Crandall CJ, Gold E, Sternfeld B, et al. Are vasomotor symptoms associated with alterations in hemostatic and inflammatory markers? Findings from the Study of Women's Health Across the Nation. Menopause 2011;18:1044–51. (Level II-2) [PubMed] [Full Text] ⇦
19. Freeman EW, Sammel MD, Lin H, Gracia CR, Kapoor S, Ferdousi T. The role of anxiety and hormonal changes in menopausal hot flashes. Menopause 2005;12:258–66. (Level II-2) [PubMed] ⇦
20. Crandall CJ, Tseng CH, Crawford SL, Thurston RC, Gold EB, Johnston JM, et al. Association of menopausal vasomotor symptoms with increased bone turnover during the menopausal transition. J Bone Miner Res 2011;26:840–9. (Level II-3) [PubMed] [Full Text] ⇦
21. Thurston RC, Sowers MR, Chang Y, Sternfeld B, Gold EB, Johnston JM, et al. Adiposity and reporting of vasomotor symptoms among midlife women: the study of women's health across the nation. Am J Epidemiol 2008;167:78–85. (Level II-2) [PubMed] [Full Text] ⇦
22. Wolff EF, He Y, Black DM, Brinton EA, Budoff MJ, Cedars MI, et al. Self-reported menopausal symptoms, coronary artery calcification, and carotid intima-media thickness in recently menopausal women screened for the Kronos early estrogen prevention study (KEEPS). Fertil Steril 2013;99:1385–91. (Level I) [PubMed] [Full Text] ⇦
23. Castelo-Branco C, Cancelo MJ, Villero J, Nohales F, Julia MD. Management of post-menopausal vaginal atrophy and atrophic vaginitis. Maturitas 2005;52(suppl 1): S46–52. (Level III) [PubMed] [Full Text] ⇦
24. Caillouette JC, Sharp CF Jr, Zimmerman GJ, Roy S. Vaginal pH as a marker for bacterial pathogens and menopausal status. Am J Obstet Gynecol 1997;176:1270–5; discussion 1275–7. (Level III) [PubMed] [Full Text] ⇦
25. Nyirjesy P, Leigh RD, Mathew L, Lev-Sagie A, Culhane JF. Chronic vulvovaginitis in women older than 50 years: analysis of a prospective database. J Low Genit Tract Dis 2012;16:24–9. (Level II-3) [PubMed] ⇦
26. Nappi RE, Lachowsky M. Menopause and sexuality: prevalence of symptoms and impact on quality of life. Maturitas 2009;63:138–41. (Level III) [PubMed] [Full Text] ⇦
27. Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. Menopause 2008;15:661–6. (Level II-3) [PubMed] ⇦
28. Nappi RE, Kokot-Kierepa M. Women's voices in the menopause: results from an international survey on vaginal atrophy. Maturitas 2010;67:233–8. (Level II-3) [PubMed] [Full Text] ⇦
29. MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD002978. DOI: 10.1002/14651858.CD002978.pub2. (Meta-analysis) [PubMed] [Full Text] ⇦
30. Greendale GA, Reboussin BA, Hogan P, Barnabei VM, Shumaker S, Johnson S, et al. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. Obstet Gynecol 1998;92:982–8. (Level I) [PubMed] [*Obstetrics & Gynecology*] ⇦
31. Adler G, Young D, Galant R, Quinn L, Witchger MS, Maki KC. A multicenter, open-label study to evaluate satisfaction and menopausal quality of life in women using transdermal estradiol/norethindrone acetate therapy for the management of menopausal signs and symptoms. Gynecol Obstet Invest 2005;59:212–9. (Level II-2) [PubMed] ⇦
32. Al-Azzawi F, Buckler HM. Comparison of a novel vaginal ring delivering estradiol acetate versus oral estradiol for relief of vasomotor menopausal symptoms. United Kingdom Vaginal Ring Investigator Group. Climacteric 2003;6:118–27. (Level I) [PubMed] ⇦
33. Davis SR, Davison SL, Wilson S, Shepherd J, Lawton B. Intranasal versus transdermal matrix oestrogen replacement in Australasian women. Maturitas 2005;51: 163–71. (Level II-3) [PubMed] [Full Text] ⇦
34. Gass MS, Rebar RW, Cuffie-Jackson C, Cedars MI, Lobo RA, Shoupe D, et al. A short study in the treatment of hot flashes with buccal administration of 17-beta estradiol. Maturitas 2004;49:140–7. (Level I) [PubMed] [Full Text] ⇦
35. Castelo-Branco C, Coloma JL. The role of intranasal estradiol spray in the management of moderate to severe vasomotor symptoms in menopausal women. Gynecol Endocrinol 2010;26:23–9. (Level III) [PubMed] [Full Text] ⇦
36. Bachmann GA, Schaefers M, Uddin A, Utian WH. Lowest effective transdermal 17beta-estradiol dose for

relief of hot flushes in postmenopausal women: a randomized controlled trial. Obstet Gynecol 2007;110:771–9. (Level I) [PubMed] [*Obstetrics & Gynecology*] ⇦

37. Honjo H, Taketani Y. Low-dose estradiol for climacteric symptoms in Japanese women: a randomized, controlled trial. Climacteric 2009;12:319–28. (Level I) [PubMed] [Full Text] ⇦

38. Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. Fertil Steril 2001; 75:1065–79. (Level I) [PubMed] [Full Text] ⇦

39. Notelovitz M, Lenihan JP, McDermott M, Kerber IJ, Nanavati N, Arce J. Initial 17beta-estradiol dose for treating vasomotor symptoms. Obstet Gynecol 2000;95:726–31. (Level I) [PubMed] [*Obstetrics & Gynecology*] ⇦

40. Haines C, Yu SL, Hiemeyer F, Schaefers M. Microdose transdermal estradiol for relief of hot flushes in postmenopausal Asian women: a randomized controlled trial. Climacteric 2009;12:419–26. (Level I) [PubMed] [Full Text] ⇦

41. Panay N, Ylikorkala O, Archer DF, Gut R, Lang E. Ultra-low-dose estradiol and norethisterone acetate: effective menopausal symptom relief. Climacteric 2007; 10:120–31. (Level I) [PubMed] [Full Text] ⇦

42. Diem S, Grady D, Quan J, Vittinghoff E, Wallace R, Hanes V, et al. Effects of ultralow-dose transdermal estradiol on postmenopausal symptoms in women aged 60 to 80 years. Menopause 2006;13:130–8. (Level I) [PubMed] ⇦

43. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. Writing Group for the Women's Health Initiative Investigators. JAMA 2002;288:321–33. (Level I) [PubMed] [Full Text] ⇦

44. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. Women's Health Initiative Steering Committee. JAMA 2004;291:1701–12. (Level I) [PubMed] [Full Text] ⇦

45. Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, et al. Estrogen therapy and coronary-artery calcification. WHI and WHI-CACS Investigators. N Engl J Med 2007;356:2591–602. (Level I) [PubMed] [Full Text] ⇦

46. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 2013;310:1353–68. (Level II-1) [PubMed] [Full Text] ⇦

47. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD004143. DOI: 10.1002/14651858.CD004143.pub4. (Meta-analysis) [PubMed] [Full Text] ⇦

48. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study [published erratum appears in Breast Cancer Res Treat 2008;107:307-8]. Breast Cancer Res Treat 2008;107:103–11. (Level II-3) [PubMed] [Full Text] ⇦

49. Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Levesque H, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Estrogen and Thromboembolism Risk (ESTHER) Study Group. Circulation 2007;115:84–5. (Level II-2) [PubMed] [Full Text] ⇦

50. Aslan E, Bagis T, Kilicdag EB, Tarim E, Erkanli S, Kuscu E. How best is to discontinue postmenopausal hormone therapy: immediate or tapered? Maturitas 2007;56:78–83. (Level I) [PubMed] [Full Text] ⇦

51. Grady D, Ettinger B, Tosteson AN, Pressman A, Macer JL. Predictors of difficulty when discontinuing postmenopausal hormone therapy. Obstet Gynecol 2003;102:1233–9. (Level II-3) [PubMed] [*Obstetrics & Gynecology*] ⇦

52. Ockene JK, Barad DH, Cochrane BB, Larson JC, Gass M, Wassertheil-Smoller S, et al. Symptom experience after discontinuing use of estrogen plus progestin. JAMA 2005;294:183–93. (Level II-3) [PubMed] [Full Text] ⇦

53. Cunha EP, Azevedo LH, Pompei LM, Strufaldi R, Steiner ML, Ferreira JA, et al. Effect of abrupt discontinuation versus gradual dose reduction of postmenopausal hormone therapy on hot flushes. Climacteric 2010;13:362–7. (Level I) [PubMed] [Full Text] ⇦

54. Lindh-Astrand L, Bixo M, Hirschberg AL, Sundstrom-Poromaa I, Hammar M. A randomized controlled study of taper-down or abrupt discontinuation of hormone therapy in women treated for vasomotor symptoms. Menopause 2010;17:72–9. (Level I) [PubMed] ⇦

55. Tella SH, Gallagher JC. Bazedoxifene + conjugated estrogens in HT for the prevention of osteoporosis and treatment of vasomotor symptoms associated with the menopause. Expert Opin Pharmacother 2013;14:2407–20. (Level III) [PubMed] ⇦

56. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD000402. DOI: 10.1002/14651858.CD000402.pub4. (Meta-analysis) [PubMed] [Full Text] ⇦

57. Loprinzi CL, Levitt R, Barton D, Sloan JA, Dakhil SR, Nikcevich DA, et al. Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group Trial N99C7. J Clin Oncol 2006;24:1409–14. (Level I) [PubMed] [Full Text] ⇦

58. Somboonporn W, Bell RJ, Davis SR. Testosterone for peri and postmenopausal women. Cochrane Database of

Systematic Reviews 2005, Issue 4. Art. No.: CD004509. DOI: 10.1002/14651858.CD004509.pub2. (Meta-analysis) [PubMed] [Full Text] ⇦

59. Matthews KA, Owens JF, Salomon K, Harris KF, Berga SL. Influence of hormone therapy on the cardiovascular responses to stress of postmenopausal women. Biol Psychol 2005;69:39–56. (Level I) [PubMed] ⇦
60. Warnock JK, Swanson SG, Borel RW, Zipfel LM, Brennan JJ. Combined esterified estrogens and methyltestosterone versus esterified estrogens alone in the treatment of loss of sexual interest in surgically menopausal women. ESTRATEST Clinical Study Group. Menopause 2005;12:374–84. (Level I) [PubMed] ⇦
61. Formoso G, Perrone E, Maltoni S, Balduzzi S, D'Amico R, Bassi C, et al. Short and long term effects of tibolone in postmenopausal women. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD008536. DOI: 10.1002/14651858.CD008536.pub2. (Meta-analysis) [PubMed] [Full Text] ⇦
62. Modelska K, Cummings S. Tibolone for postmenopausal women: systematic review of randomized trials. J Clin Endocrinol Metab 2002;87:16–23. (Level III) [PubMed] [Full Text] ⇦
63. Compounded bioidentical menopausal hormone therapy. Committee Opinion No. 532. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120:411–5. (Level III) [PubMed] [*Obstetrics & Gynecology*] ⇦
64. Freedman RR, Kruger ML, Tancer ME. Escitalopram treatment of menopausal hot flashes. Menopause 2011;18:893–6. (Level I) [PubMed] [Full Text] ⇦
65. Bouchard P, Panay N, de Villiers TJ, Vincendon P, Bao W, Cheng RJ, et al. Randomized placebo- and active-controlled study of desvenlafaxine for menopausal vasomotor symptoms. Climacteric 2012;15:12–20. (Level I) [PubMed] [Full Text] ⇦
66. Grady D, Cohen B, Tice J, Kristof M, Olyaie A, Sawaya GF. Ineffectiveness of sertraline for treatment of menopausal hot flushes: a randomized controlled trial. Obstet Gynecol 2007;109:823–30. (Level I) [PubMed] [*Obstetrics & Gynecology*] ⇦
67. Archer DF, Seidman L, Constantine GD, Pickar JH, Olivier S. A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause. Am J Obstet Gynecol 2009;200:172.e1–172.e10. (Level I) [PubMed] [Full Text] ⇦
68. Barton DL, LaVasseur BI, Sloan JA, Stawis AN, Flynn KA, Dyar M, et al. Phase III, placebo-controlled trial of three doses of citalopram for the treatment of hot flashes: NCCTG trial N05C9. J Clin Oncol 2010;28:3278–83. (Level I) [PubMed] [Full Text] ⇦
69. Pinkerton JV, Archer DF, Guico-Pabia CJ, Hwang E, Cheng RF. Maintenance of the efficacy of desvenlafaxine in menopausal vasomotor symptoms: a 1-year randomized controlled trial. Menopause 2013;20:38–46. (Level I) [PubMed] ⇦
70. Pinkerton JV, Constantine G, Hwang E, Cheng RF. Desvenlafaxine compared with placebo for treatment of menopausal vasomotor symptoms: a 12-week, multicenter, parallel-group, randomized, double-blind, placebo-controlled efficacy trial. Study 3353 Investigators. Menopause 2013;20:28–37. (Level I) [PubMed] ⇦
71. Speroff L. Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms. Obstet Gynecol 2003;102:823–34. (Level I) [PubMed] [*Obstetrics & Gynecology*] ⇦
72. Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA 2006;295:2057–71. (Meta-analysis) [PubMed] [Full Text] ⇦
73. Guttuso T Jr, Kurlan R, McDermott MP, Kieburtz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. Obstet Gynecol 2003;101:337–45. (Level I) [PubMed] [*Obstetrics & Gynecology*] ⇦
74. Aguirre W, Chedraui P, Mendoza J, Ruilova I. Gabapentin vs. low-dose transdermal estradiol for treating post-menopausal women with moderate to very severe hot flushes. Gynecol Endocrinol 2010;26:333–7. (Level I) [PubMed] [Full Text] ⇦
75. Bordeleau L, Pritchard KI, Loprinzi CL, Ennis M, Jugovic O, Warr D, et al. Multicenter, randomized, crossover clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol 2010;28:5147–52. (Level II-3) [PubMed] [Full Text] ⇦
76. Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for vasomotor menopausal symptoms. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD001395. DOI: 10.1002/14651858.CD001395.pub3. (Meta-analysis) [PubMed] [Full Text] ⇦
77. Hirata JD, Swiersz LM, Zell B, Small R, Ettinger B. Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial. Fertil Steril 1997;68:981–6. (Level I) [PubMed] [Full Text] ⇦
78. Haines CJ, Lam PM, Chung TK, Cheng KF, Leung PC. A randomized, double-blind, placebo-controlled study of the effect of a Chinese herbal medicine preparation (Dang Gui Buxue Tang) on menopausal symptoms in Hong Kong Chinese women. Climacteric 2008;11:244–51. (Level I) [PubMed] [Full Text] ⇦
79. Azizi H, Feng Liu Y, Du L, Hua Wang C, Bahrami-Taghanaki H, Ollah Esmaily H, et al. Menopause-related symptoms: traditional Chinese medicine vs hormone therapy. Altern Ther Health Med 2011;17:48–53. (Level I) [PubMed] ⇦
80. Frei-Kleiner S, Schaffner W, Rahlfs VW, Bodmer C, Birkhauser M. Cimicifuga racemosa dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial. Maturitas 2005;51:397–404. (Level I) [PubMed] [Full Text] ⇦
81. Nappi RE, Malavasi B, Brundu B, Facchinetti F. Efficacy of Cimicifuga racemosa on climacteric complaints: a randomized study versus low-dose transdermal estradiol. Gynecol Endocrinol 2005;20:30–5. (Level I) [PubMed] ⇦

82. Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. Ann Intern Med 2006;145:869–79. (Level I) [PubMed] [Full Text] ⇦

83. Pockaj BA, Gallagher JG, Loprinzi CL, Stella PJ, Barton DL, Sloan JA, et al. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC1. J Clin Oncol 2006;24:2836–41. (Level II-3) [PubMed] [Full Text] ⇦

84. Leach MJ, Moore V. Black cohosh (Cimicifuga spp.) for menopausal symptoms. Cochrane Database Syst Rev. 2012 Sep 12;9:CD007244. doi: 10.1002/14651858.CD007244.pub2. (Meta-analysis) [PubMed] [Full Text] ⇦

85. Al-Akoum M, Maunsell E, Verreault R, Provencher L, Otis H, Dodin S. Effects of Hypericum perforatum (St. John's wort) on hot flashes and quality of life in perimenopausal women: a randomized pilot trial. Menopause 2009;16:307–14. (Level I) [PubMed] ⇦

86. Heyerick A, Vervarcke S, Depypere H, Bracke M, De Keukeleire D. A first prospective, randomized, double-blind, placebo-controlled study on the use of a standardized hop extract to alleviate menopausal discomforts. Maturitas 2006;54:164–75. (Level I) [PubMed] [Full Text] ⇦

87. van Die MD, Bone KM, Burger HG, Reece JE, Teede HJ. Effects of a combination of Hypericum perforatum and Vitex agnus-castus on PMS-like symptoms in late-perimenopausal women: findings from a subpopulation analysis. J Altern Complement Med 2009;15:1045–8. (Level I) [PubMed] ⇦

88. Wiklund IK, Mattsson LA, Lindgren R, Limoni C. Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. Swedish Alternative Medicine Group. Int J Clin Pharmacol Res 1999;19:89–99. (Level I) [PubMed] ⇦

89. Barton DL, Loprinzi CL, Quella SK, Sloan JA, Veeder MH, Egner JR, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. J Clin Oncol 1998;16:495–500. (Level 1) [PubMed] ⇦

90. Biglia N, Sgandurra P, Peano E, Marenco D, Moggio G, Bounous V, et al. Non-hormonal treatment of hot flushes in breast cancer survivors: gabapentin vs. vitamin E. Climacteric 2009;12:310–8. (Level I) [PubMed] [Full Text] ⇦

91. Lee MS, Shin BC, Ernst E. Acupuncture for treating menopausal hot flushes: a systematic review. Climacteric 2009;12:16–25. (Level III) [PubMed] [Full Text] ⇦

92. Williamson J, White A, Hart A, Ernst E. Randomised controlled trial of reflexology for menopausal symptoms. BJOG 2002;109:1050–5. (Level I) [PubMed] [Full Text] ⇦

93. Kontos M, Agbaje OF, Rymer J, Fentiman IS. What can be done about hot flushes after treatment for breast cancer? Climacteric 2010;13:4–21. (Level III) [PubMed] [Full Text] ⇦

94. Lipov EG, Joshi JR, Sanders S, Wilcox K, Lipov S, Xie H, et al. Effects of stellate-ganglion block on hot flushes and night awakenings in survivors of breast cancer: a pilot study. Lancet Oncol 2008;9:523–32. (Level II-3) [PubMed] ⇦

95. Greendale GA, Gold EB. Lifestyle factors: are they related to vasomotor symptoms and do they modify the effectiveness or side effects of hormone therapy? Am J Med 2005;118(suppl 12B):148–54. (Level I) [PubMed] ⇦

96. Daley AJ, Stokes-Lampard HJ, Macarthur C. Exercise to reduce vasomotor and other menopausal symptoms: a review. Maturitas 2009;63:176–80. (Level III) [PubMed] [Full Text] ⇦

97. Daley A, Stokes-Lampard H, MacArthur C. Exercise for vasomotor menopausal symptoms. Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD006108. DOI: 10.1002/14651858.CD006108.pub3. (Meta-analysis) [PubMed] [Full Text] ⇦

98. Johnson SR, Ettinger B, Macer JL, Ensrud KE, Quan J, Grady D. Uterine and vaginal effects of unopposed ultralow-dose transdermal estradiol. Obstet Gynecol 2005;105:779–87. (Level I) [PubMed] [*Obstetrics & Gynecology*] ⇦

99. Rioux JE, Devlin C, Gelfand MM, Steinberg WM, Hepburn DS. 17beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. Menopause 2000;7:156–61. (Level I) [PubMed] ⇦

100. Simon JA. Vulvovaginal atrophy: new and upcoming approaches. Menopause 2009;16:5–7. (Level III) [PubMed] ⇦

101. Suckling JA, Kennedy R, Lethaby A, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD001500. DOI: 10.1002/14651858.CD001500.pub2. (Meta-analysis) [PubMed] [Full Text] ⇦

102. Bachmann G, Lobo RA, Gut R, Nachtigall L, Notelovitz M. Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. Obstet Gynecol 2008;111:67–76. (Level I) [PubMed] [*Obstetrics & Gynecology*] ⇦

103. Simon J, Nachtigall L, Gut R, Lang E, Archer DF, Utian W. Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet [published erratum appears in Obstet Gynecol 2008;112:1392]. Obstet Gynecol 2008;112:1053–60. (Level I) [PubMed] [*Obstetrics & Gynecology*] ⇦

104. Labrie F, Cusan L, Gomez JL, Cote I, Berube R, Belanger P, et al. Effect of one-week treatment with vaginal estrogen preparations on serum estrogen levels in postmenopausal women. Menopause 2009;16:30–6. (Level I) [PubMed] ⇦

105. Management of gynecologic issues in women with breast cancer. Practice Bulletin No. 126. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;119:666–82. (Level III) [PubMed] [*Obstetrics & Gynecology*] ⇦

106. Files JA, Ko MG, Pruthi S. Managing aromatase inhibitors in breast cancer survivors: not just for oncologists. Mayo Clin Proc 2010;85:560–6; quiz 566. (Level III) [PubMed] [Full Text] ⇦

107. Shelly W, Draper MW, Krishnan V, Wong M, Jaffe RB. Selective estrogen receptor modulators: an update on recent clinical findings. Obstet Gynecol Surv 2008;63:163–81. (Level III) [PubMed] ⇦

108. Bachmann GA, Komi JO. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Ospemifene Study Group. Menopause 2010;17:480–6. (Level I) [PubMed] ⇦

109. Bygdeman M, Swahn ML. Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. Maturitas 1996;23:259–63. (Level I) [PubMed] [Full Text] ⇦

110. Bachmann GA, Leiblum SR. The impact of hormones on menopausal sexuality: a literature review. Menopause 2004;11:120–30. (Level III) [PubMed] ⇦

111. Nikander E, Rutanen EM, Nieminen P, Wahlstrom T, Ylikorkala O, Tiitinen A. Lack of effect of isoflavonoids on the vagina and endometrium in postmenopausal women. Fertil Steril 2005;83:137–42. (Level II-3) [PubMed] [Full Text] ⇦

112. Reed SD, Newton KM, LaCroix AZ, Grothaus LC, Grieco VS, Ehrlich K. Vaginal, endometrial, and reproductive hormone findings: randomized, placebo-controlled trial of black cohosh, multibotanical herbs, and dietary soy for vasomotor symptoms: the Herbal Alternatives for Menopause (HALT) Study. Menopause 2008;15:51–8. (Level I) [PubMed] ⇦

The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000–April 2013. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

The American College of Obstetricians and Gynecologists
409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920

Management of menopausal symptoms. Practice Bulletin No. 141. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;123:202–16.