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Strategies for managing hot flashes

Hormone therapy—at the lowest possible dose for the shortest period of time—remains the best option for menopausal women with moderate to severe vasomotor symptoms.

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PRACTICE RECOMMENDATIONS

› *Use hormone therapy (HT) at the lowest effective dose and for the shortest duration possible (preferably ≤5 years) in women for whom the potential benefits outweigh the potential risks.* (A)

› *Counsel patients that the effectiveness of phytoestrogens (soy), exercise routines, yoga, acupuncture, vitamin E, evening primrose oil, and other herbal preparations has not been established.* (B)

› *When HT is refused or contraindicated by a patient's risk profile, consider antidepressants (selective norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors), gabapentin, or clonidine.* (B)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence
(B) Inconsistent or limited-quality patient-oriented evidence
(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Hot flashes are the most prevalent and most bothersome symptoms of the menopausal transition and the leading cause for seeking medical attention during that period of a woman's life.[1] They may last for a few seconds or for several minutes and may occur as frequently as every hour to several times per week. On average, women experience hot flashes for a period of 6 months to 2 years, but the symptoms may last up to 10 years or more.[2,3]

Hot flashes have been reported by up to 70% of women undergoing natural menopause, and by almost all women undergoing surgical menopause.[4] For many women, these symptoms are mild and can be managed with reassurance and counseling. For others, the symptoms are severe, overwhelming, last for many years, and impair the quality of life.

According to a community-based survey of 16,000 women, hot flashes occur most often in late perimenopause and among those with a body mass index ≥27. Hot flashes are also more common among African Americans and women who are less physically active and have a lower income.[5]

Since the publication of the Women's Health Initiative study in 2002 raised concerns about the long-term safety of hormone therapy (HT), nonhormonal remedies have emerged as potential alternative treatments.[6,7] A wealth of evidence has accumulated on the efficacy and safety of these, and various other approaches to the management of hot flashes. This review will summarize that evidence to help you provide optimal care and assist patients in making informed choices about their treatment.

Hormone replacement therapy

HT, given as estrogen alone in women without a uterus or estrogen plus progestin in women with a uterus, is the most stud-

ied and most effective therapy for vasomotor symptoms attributable to menopause. Data from one Cochrane review showed a significant reduction in the frequency of weekly hot flashes for oral estrogen compared with placebo, with a weighted mean difference (WMD) of -17.92 (95% confidence interval [CI], -22.86 to -12.99).[8] This was equivalent to a 75% reduction in frequency (95% CI, 64.3-82.3) for HT relative to placebo. Results were similar for both opposed and unopposed estrogen regimens.[8]

Transdermal vs oral therapy. Another review compared oral estradiol, transdermal estradiol, and placebo in terms of reduction of hot flash frequency or severity, or both.[9] The review revealed a pooled WMD in hot flashes of -16.8 per week (95% CI, -23.4 to -10.2) for oral estradiol and -22.4 per week (95% CI, -35.9 to -10.4) for transdermal estradiol. Results were similar for opposed and unopposed estrogen regimens.[9]

Transdermal delivery of estrogen as patches, gels, and sprays delivers unmetabolized estradiol directly to the blood stream, so that lower doses can achieve similar efficacy to doses administered orally.[10] Thus, the transdermal route would be in keeping with current guidelines to prescribe the lowest effective dose that relieves symptoms. Emerging research should provide more insight regarding safety and the potential for fewer health risks with transdermal HT compared with oral therapy.

Best way to discontinue? When HT is discontinued, hot flashes may return—sometimes immediately, sometimes after a few months. No evidence-based guidelines exist on the best way to discontinue HT with the least recurrence and severity of hot flashes. No optimal tapering regimen (either by dose or number of days per week that HT is taken) has yet been described in any studies, nor have any randomized controlled trials (RCTs) revealed a significant difference between tapered or abrupt discontinuation.[11,12]

The breast cancer connection. The relationship between HT and breast cancer has generated considerable controversy. In the Women's Health Initiative (WHI) trial, which included participants on estrogen-only and estrogen plus progesterone regimens, an overall increased risk (hazard ratio [HR]=1.26; 95% CI, 1.00-1.59) was reported. The increased risk fell short of statistical significance, and varied with the duration of exposure.[6]

In subsequent studies, the magnitude of the associated risk was substantially greater for the estrogen-progestogen preparation, and also higher for longer-term exposure.[13] Additionally, a meta-analysis of 8 studies of the risk of breast cancer with combination HT resulted in an odds ratio (OR) of 1.39 (95% CI, 1.12-1.72). Estimates were higher for more than 5 years of use (OR=1.63; 95% CI, 1.22-2.18) when compared with estimates for less than 5 years of use (OR=1.35; CI, 1.16-1.57).[14] Recent studies have reported a decline in the incidence of breast cancer in the United States, which has been attributed to a parallel reduction in HT use.[15]

In contrast to the findings for women taking combination HT, the estrogen-only arm of the WHI study showed a decrease in the overall risk of breast cancer.[16] A new analysis of data on participants in the estrogen-only arm of the study shows that, 10 years after the intervention ended, a decreased risk of breast cancer persists. In addition, the increased risk of stroke and deep vein thrombosis found in the original study had dissipated, and the decreased risk of hip fracture was not maintained.

Ten years after the end of the Women's Health Initiative, follow-up data show participants in the estrogen-only arm continued to exhibit a decreased risk of breast cancer.

Age matters. Health outcomes in this new analysis were more favorable for younger women for coronary heart disease, heart attack, colorectal cancer, total mortality, and a global index of chronic diseases.[17] Pooled results of systematic reviews and meta-analyses on HT risks are available in **TABLE 1**.[14,16,18-21]

Progestins

Progesterone in the form of injections (Depo-Provera 150 mg, for example) or oral medroxyprogesterone acetate 20 mg daily has shown a significant reduction in hot flashes compared with placebo.[22] However, associated side effects (withdrawal bleeding and weight gain) and concerns about breast cancer often limit the use of this medication.[23] Because of the paucity of evidence, transdermal progesterone creams should not be recommended.[24]

Tibolone

Tibolone is a synthetic steroid that is structurally related to 19-nortestosterone derivatives. It has weak estrogenic, progestogenic, and

TABLE 1
Pooled results of HT risks from recent systematic reviews and meta-analyses

Harm associated with HT	OR or RR (95%CI)	Study
Breast cancer		
Overall	OR=1.39 (1.12-1.72)	Shah et al[14]
<5 years	OR=1.35 (1.16-1.57)	
>5 years	OR=1.63 (1.22-2.18)	
VTE		
Overall	OR=2.5 (1.9-3.4)	Canonico et al[18]
<1 year	OR=4.0 (2.9-5.7)	
>1 year	OR=2.1 (1.3-3.8)	
Overall	RR=2.15 (1.61-2.86)	Gabriel et al[19]
Overall	OR=2.05 (1.44-2.92)	Sare et al[20]
Stroke		
Overall	OR=1.29 (1.13-1.47)	Bath et al[21]
Fatal	OR=1.56 (1.11-2.20)	
Nonfatal	OR=1.23 (1.06-1.44)	
Overall	RR=1.44 (1.10-1.89)	Gabriel et al[19]
Overall	OR=1.32 (1.14-1.53)	Sare et al[20]
Coronary heart disease		
Incidence (all groups)	RR=0.88 (0.64-1.21)	Nelson et al[16]
Mortality (all groups)	RR=0.74 (0.36-1.45)	
Overall	OR=1.02 (0.90-1.11)	Sare et al[20]

CI, confidence interval; HT, hormone therapy; OR, odds ratio; RR, relative risk; VTE, venous thromboembolism.

androgenic properties and has shown significant reduction in hot flashes and night sweating compared with placebo.[25] Tibolone has also been shown to enhance mood and sexual function.[26] However, evidence of its safety on outcomes such as breast cancer and cardiovascular events is obscure and has shown conflicting results, especially for breast cancer.[25,26]

A recent double-blinded trial on women with breast cancer found that although tibolone significantly improved vasomotor symptoms, it was associated with an increased risk of breast cancer recurrence (HR=1.40; 95% CI, 1.14-1.70]; *P*=.001).[27] Tibolone is not approved for sale in the United States.

Nonhormonal options

Lifestyle modifications

According to recent reviews, exercise is less effective than HT in relieving hot flashes, but does seems to have beneficial effects on mood, sleep, and overall quality of life.[28,29] Other lifestyle modifications such as smoking cessation and weight loss may also be of use.[5]

Antidepressants

Data from one meta-analysis showed that selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) were significantly more effective than placebo in reducing daily frequency of hot flashes (WMD=-1.13; 95% CI, -1.70 to -0.57).[30] Efficacy varied for individual drugs.

Venlafaxine, an SNRI, has been shown to be more effective than placebo in managing hot flashes.[31] The effect on hot flashes was noticed after 4 weeks of treatment with the 75- and 150-mg doses, but the higher dosage was associated with more adverse effects such as dry mouth, sleeplessness, and decreased appetite.[32] Even so, 93% of the participants in the venlafaxine group chose to continue treatment, because the reduc-

Progesterone alone reduces frequency of hot flashes, but withdrawal bleeding and concerns about breast cancer risk limit its usefulness.

tion in hot flashes had significantly improved their daily lives.[31] Desvenlafaxine, a metabolite of venlafaxine, has been shown to reduce the number of hot flashes by almost 65% from baseline at Weeks 4 and 12, with dosages of 100 and 150 mg/d.[33]

The SSRIs fluoxetine, citalopram, and paroxetine in 10-, 20-, and 30-mg doses and paroxetine CR (12.5 and 25 mg) have been studied in many RCTs. All have demonstrated a significant decrease in hot flashes compared with placebo with various dosages used. SSRIs reduce hot flashes by as much as 50% to 60%, compared with 80% for estrogen.[34] The duration of treatment ranged from 4 weeks to 6 months.

SSRIs, SNRIs, gabapentin, and clonidine have also been shown to reduce the frequency and severity of hot flashes, although not as effectively as hormone therapy.

Gabapentin

Gabapentin is approved by the FDA for the treatment of partial seizures and postherpetic neuralgia.[35] A meta-analysis of multiple studies published in 2006 showed that gabapentin reduced the mean number of daily hot flashes by 2.05 (95% CI, -2.80 to -1.30).[30] Two recent reviews evaluated the efficacy and safety of gabapentin in the treatment of hot flashes in menopausal women and reported that gabapentin in daily doses ranging from 900 to 2400 mg and titration periods lasting 3 to 12 days was well tolerated and effective.[35,36]

A meta-analysis published in 2009 that included 4 RCTs reported significant heterogeneity from one study to another, but comparisons of gabapentin and placebo showed reductions of 20% to 30% in the frequency and severity of hot flashes with gabapentin.[36] The most commonly reported adverse effects included somnolence, dizziness, ataxia, fatigue, nystagmus, and peripheral edema.

Clonidine

Clonidine has been studied in oral and transdermal forms for the treatment of hot flashes in menopausal women, especially in women with breast cancer.[37-39] Data from one meta-analysis revealed significant reductions in daily hot flashes in the clonidine group compared with placebo at 4 weeks (mean difference [MD]=-0.95; 95% CI, -1.44 to -0.47) and at 8 weeks (MD=-1.63; 95% CI, -2.76 to -0.50).[30] Adverse effects included dry mouth, drowsiness, and dizziness. The transdermal route may avoid some of these side effects.[40]

Alternative remedies

Phytoestrogen and isoflavones. Phytoestrogens are sterol molecules produced by plants. They are similar in structure to human estrogens and have been shown to have estrogen-like activity.[40] They are available as dietary soy, soy extract, and red clover extracts. Isoflavones are a type of phytoestrogen.

Comparing trials of effects of soy or isoflavone is difficult, as various formulations and amounts of these products have been used. Combining the data from these trials yielded nonsignificant results for Promensil, a red clover extract (WMD=-0.6; 95% CI, -1.8 to 0.6), and inconsistent results (sometimes favoring the intervention, other times the placebo) for soy food and soy extracts.[41-43]

There is no evidence of estrogenic stimulation of the endometrium with phytoestrogens used for up to 2 years.[41] Nevertheless, in the absence of evidence on the safety of long-term use, women with a personal or strong family history of hormone-dependent cancers (breast, uterine, or ovarian) or thromboembolic events should be cautious about using soy-based therapies.[42] Long-term safety of these products has to be established before any evidence-based recommendations can be made.

Black cohosh. *Actaea racemosa* (formerly *Cimicifuga racemosa*) is the most studied and perhaps the most widely used herbal remedy for hot flashes. It is commonly known as black cohosh and has been used traditionally by Native Americans for the treatment of various medical conditions, including amenorrhea and menopause.[44,45]

Remifemin is an available standardized extract. Evidence for effectiveness is limited and contradictory. Data from a recent meta-analysis showed that although there was significant heterogeneity between included trials, preparations containing black cohosh improved vasomotor symptoms overall by 26% (95% CI, 11%-40%).[45]

A recent well-conducted RCT concluded that neither black cohosh nor red clover significantly reduced the frequency of symptoms compared with placebo.[46] The same study found that both botanicals were safe as administered for a 12-month period. Some case reports have identified serious adverse events including acute hepatocellular damage, which

TABLE 2

Nonhormonal therapies: An evidence-based comparison

Agent (Tx duration)	Dose	Number of hot flashes per day vs placebo (95% CI)	Adverse effects	Level of evidence*
Gabapentin[30,36] (12 wk)	100-300 mg, 3 times a day[30]	MD=-2.05 (-2.80 to –1.30)	Dizziness, unsteadiness, fatigue, somnolence	A
	300-800 mg, 3 times a day[36]	WMD=23.72 (16.46-30.97)		
Antidepressants[30,48] (4 wk-6 mo)			Headache, nausea, dizziness, dry mouth	A
Paroxetine	10-20 mg (12.5-25 mg for CR) daily	MD=-1.66 (-2.43 to -0.89)		
Fluoxetine	20-30 mg daily	MD=-1.37 (-3.03 to 0.29)		
Venlafaxine	37.5-150 mg daily	MD=-0.49 (-2.40 to 1.41)		
Citalopram	20-30 mg daily	MD=-0.20 (-1.45 to -1.05)		
Clonidine[30] (4-8 wk)	Oral 0.025-0.075 mg 2 times a day, or transdermal 0.1 mg weekly	MD=-0.95 (-1.44 to -0.47) at 4 weeks; MD=-1.63 (-2.76 to -0.50) at 8 weeks	Dry mouth, drowsiness, dizziness	A
Isoflavones[30,41] (6-12 wk)			May cause adverse GI effects (eg, constipation or diarrhea), itching, rash	B
Soy extract	40-164 mg daily	MD=-1.15 (-2.33 to 0.03)		
Red clover	40-164 mg daily	WMD=-0.6 (-1.8 to 0.6)		
Black cohosh[47,49-51] (3-12 mo)	40-160 mg daily	No quantitative data reported. Efficacy is established in qualitative studies, however	GI upset, rashes. Long-term safety is unknown	B
Vitamin E, ginseng, primrose oil;[52] acupuncture;[53,55] yoga[54] (6 wk-6 mo)	Vitamin E, 400-800 IU daily Primrose oil, 500 mg daily	No quantitative data reported. Qualitative data show that evidence for efficacy is limited or lacking.	**Vitamin E:** nausea, diarrhea, abdominal pain. May increase the chance of hemorrhagic stroke **Ginseng:** sleep difficulty, nausea, diarrhea. May induce a manic attack in patients taking antidepressants **Primrose oil:** nausea, diarrhea, stomach upset **Acupuncture:** slight discoloration at acupuncture site	C

CR, controlled release; GI, gastrointestinal; MD, mean difference; WMD, weighted mean difference (the sum of the differences in individual studies weighted by the individual variances for each study).

*Grading system from the American Association of Clinical Endocrinologists Ad Hoc Task Force for Standardized Production of Clinical Practice Guidelines (http://www.endocrinologia.org.mx/descargas/guias_endos/Clinical%20Practice%20Guidelines.pdf):

A=Homogenous evidence from multiple well-designed, randomized controlled trials with sufficient statistical power.

B=Evidence from at least one large well-designed clinical trial, cohort or case-controlled analytic study, or meta-analysis.

C=Evidence based on clinical experience, descriptive studies, or expert consensus opinion.

D=Not rated.

warrants further investigation, although no causal relationship has been established.[47]

Evidence for safety and efficacy of antidepressants, gabapentin, clonidine, isoflavones, black cohosh, yoga, acupuncture, and herbal remedies is summarized in **TABLE 2**.[30,36,41,47-55]

For more on the treatment of hot flashes, see "Clinical approach to managing hot flashes" on page 338.[40]

What the future holds

The selective estrogen receptor agonist MF-101, which can induce tissue-specific estrogen-like effects, has been shown to be effective in reducing menopausal hot flashes

Clinical approach to managing hot flashes

Start with a detailed history: Ask about the nature of your patient's symptoms, her past gynecologic and medical history, and her family history. Take a baseline blood pressure, measure body mass index (BMI), and order a lipid profile. Exclude other possible causes of hot flashes: hyperthyroidism, panic disorder, diabetes, and medications such as antiestrogens or selective estrogen receptor modulators.

Assess the severity of hot flashes and explain their typical clinical course. Discuss lifestyle modifications that may help: losing weight, quitting smoking, wearing lighter clothing, and cutting down on caffeine intake, alcohol, and spicy foods. Tell your patient that hormone therapy (HT) has been shown to be the most effective treatment for women without contraindications. These include current, past, or suspected breast cancer, other estrogen-sensitive malignant conditions, undiagnosed genital bleeding, untreated endometrial hyperplasia, venous thromboembolism, angina, myocardial infarction, uncontrolled hypertension, liver disease, porphyria cutanea tarda (absolute contraindication), or hypersensitivity to the active substances of HT.[40]

If contraindications can be ruled out, find out whether she is receptive to HT or would prefer alternatives. If she is interested in HT, discuss the risks and benefits involved and the different dosages and routes of administration that are available. If she prefers to explore nonhormonal remedies, discuss the various options and present the evidence for their safety and efficacy. Tell her that the safety of some herbal remedies that contain estrogenic compounds has not been established.

Efficacy and safety studies of phytoestrogens, isoflavones, black cohosh, and other herbal remedies are inconclusive. Case reports have connected black cohosh with liver damage.

compared with placebo in a phase II trial.[56] A larger phase III trial is in progress.

Lower and ultra-lower doses of systemic estrogen are now available and approved by the FDA, and were found effective in relieving vasomotor symptoms.[57-59] The drawback of these preparations is that they may take longer than standard-dose estrogen to achieve maximum relief of symptoms (8-12 weeks vs 4 weeks, respectively). The lower doses have been associated with fewer adverse effects (such as vaginal bleeding and breast tenderness) compared with the standard doses.[58,59] Their long-term effects on the cardiovascular system, bone, and breast are still being tested and need to be established.

Newer selective estrogen receptor modulators, especially in combination with estrogen, are another approach to menopausal symptoms currently in testing.[60] **JFP**

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Lower and ultra-lower doses of systemic estrogen are now available and approved by the FDA, and were found effective in relieving vasomotor symptoms.