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# VASOMOTOR SYMPTOMS

Managing the transition  
from perimenopause to  
postmenopause

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# Vasomotor symptoms: Managing the transition from perimenopause to postmenopause

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## OVERVIEW

This journal supplement outlines the factors that contribute to menopausal vasomotor symptoms, discusses the available treatment options and the risks/benefits associated with each, and evaluates the latest data available to formulate patient-specific treatment plans.

## LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Recognize menopause-related vasomotor symptoms to establish the clinical stages of menopausal transition
- Discuss the underlying physiology of climacteric symptoms
- Outline the various treatment options that are available for women with vasomotor symptoms and the risks/benefits associated with each
- Evaluate the evidence-based data on hormone therapy and formulate a patient-specific treatment plan for menopausal vasomotor symptoms
- Counsel women and their partners on the risks/benefits of alternative therapies to treat menopausal vasomotor symptoms

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# Vasomotor symptoms: Managing the transition from perimenopause to postmenopause

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## HIGHLIGHTS

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Menopause, defined as the permanent cessation of ovulation and menstruation, is a physiological event that occurs over time and involves a complex endocrine process resulting in the cessation of ovarian activity. Natural menopause is diagnosed after 12 consecutive months of amenorrhea that is not associated with either a physiological (eg, lactation) or a pathological cause.<sup>1</sup> Menopausal symptoms vary among women at each stage of the transition, and vary for each woman as she transits through the menopausal stages over time. Typically, it is diagnosed retrospectively after the onset of symptoms and after the physician has been able to evaluate the constellation of symptoms over time.<sup>2</sup> In the United States, most women experience menopause between 40 and 58 years of age, with a median age of 52 years.<sup>3</sup> Thus, with increasing life expectancy for women worldwide, most women will still have one-third of their lifetime remaining at the point of menopause. This monograph reviews the etiology and physiological mechanisms of vasomotor symptoms, and provides a comprehensive, evidence-based overview of the various treatment options that are available for the management of menopausal symptoms.

## Menopause and vasomotor symptoms: An overview

Perimenopause, the transition that precedes menopause, most commonly lasts for up to 5 years.<sup>1</sup> Many of the manifestations of perimenopause are caused by underlying ovarian changes, rather than by the cessation of menstruation. As the number of ovarian follicles continues to diminish during perimenopause, the cascade of hormone signaling that leads to the maturation of estrogen-producing follicles becomes irregular.<sup>4</sup> Menopause occurs when there are no more follicles left for stimulation, thus ending ovarian estrogen production and the menstrual cycle. Menstrual irregularity is the hallmark sign of perimenopause, which includes changes in cycle length and menstrual flow.<sup>4</sup> According to the nomenclature proposed by the Stages of Reproductive Aging Workshop (STRAW), perimenopause can be divided into 2 phases<sup>5</sup> (FIGURE 1). Early menopausal transition is characterized by increases in menstrual cycle length greater than 7 days, whereas late menopausal transition refers to a period of at least 2 skipped cycles and at least 1 period of amenorrhea exceeding

**FIGURE 1** Menopause terminology: STRAW staging system Final menstrual period

Stages	-2	-1	0	+1	+2
Terminology	<i>Menopausal transition</i>			<i>Postmenopause</i>	
	Early	Late <sup>a</sup>		Early <sup>a</sup>	Late
	<i>Perimenopause</i>				
Duration of stage	Variable			Ⓐ 1 yr	Ⓑ 4 yr
Menstrual cycles	Variable cycle length (>7 days different from normal)	≥2 skipped cycles and an interval of amenorrhea (≥60 days)	Amen x 12 mo	None	

Amen, amenorrhea; STRAW, Stages of Reproductive Aging Workshop.  
<sup>a</sup>Stages most likely to be characterized by vasomotor symptoms.  
 Adapted from Soules et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Fertil Steril.* 2001;76: 874-878.

**TABLE 1** Current recommendations for the use of hormone therapy

<ul style="list-style-type: none"> <li>Individualize therapy according to the needs, preferences, and risk factors of each patient.</li> </ul>
<ul style="list-style-type: none"> <li>Treatment should be patient specific and appropriate for the symptoms of menopause.</li> </ul>
<ul style="list-style-type: none"> <li>Treatment should be administered using the lowest effective dose.</li> </ul>
<ul style="list-style-type: none"> <li>Hormone therapy may not be prescribed as a preventive treatment for cardiovascular disease.</li> </ul>
<ul style="list-style-type: none"> <li>Treatment should be reviewed periodically for poor symptom control and side effects and, if needed, adjusted.</li> </ul>

Adapted from the National Institutes of Health State-of-the-Science Conference, The North American Menopause Society Position Statements 2004 and 2008.

60 days.<sup>6</sup> Several factors may influence the age at which women experience menopausal symptoms. These include habitual smoking, genetic predisposition, and the incidence of ovarian cystectomies. Although menopause is typically diagnosed after 12 months of amenorrhea, for some women, 3 consecutive months of missed cycles or a mean cycle length longer than 42 days can be predictors of impending menopause.<sup>1</sup>

**Vasomotor symptoms**

Most women experience an increased frequency of vasomotor symptoms and other physiological changes during the transition from late perimenopause to menopause. These include reduced ovarian activity, an

elevated level of follicle-stimulating hormone, reduced stamina, and changes in the skin, vagina, and hair.<sup>7</sup> Results from a community-based study of 110 Caucasian women aged 43 to 55 years showed sleep difficulties (95%), forgetfulness (92%), irritability (87%), night sweats (86%), and hot flashes (83%) were the most prevalent menopause-related symptoms.<sup>8</sup> Among those who experienced symptoms, hot flashes, night sweats, irritability, and sleep difficulties scored higher ratings for severity.<sup>8</sup>

Vasomotor symptoms that occur frequently may have a profound effect on quality of life because of increased fatigue, irritability, headaches, muscle and joint pain, and in some cases depression. As women go through the transition to menopause, an estimated 85% report more than one symptom, including hot flashes and night sweats, which prompt nearly 10% of women to seek medical help.<sup>9</sup> In addition to the typical symptoms, women also report other changes during the menopausal transition, such as anxiety, moodiness, cognitive deficits, somatic symptoms, sleep disturbance, sexual dysfunction, and genitourinary changes.<sup>1</sup>

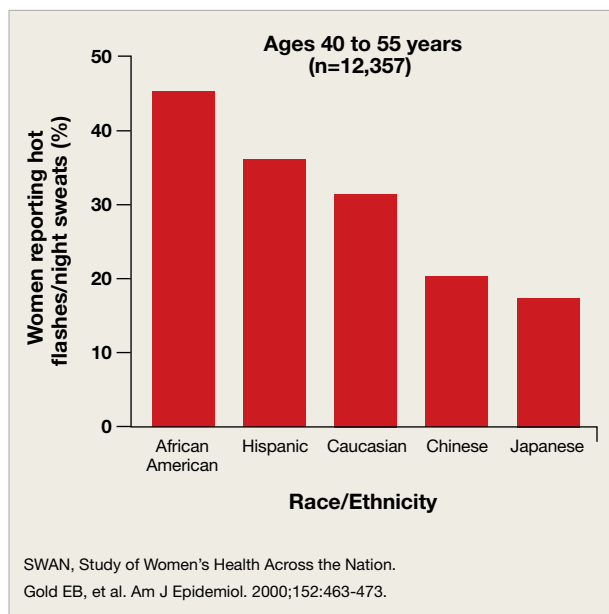
Hot flashes are not unique to menopause and could be caused by thyroid disease, infection, epilepsy, insulinoma, carcinoid syndromes, leukemia, pulmonary tuberculosis, pancreatic tumors, autoimmune disorders, and mast cell disorders.<sup>10</sup> Occurrence of hot flashes can be assessed either through direct physiological recordings or by self-report questionnaires. Of the physiological methods, sternal skin conductance is the leading measure currently used.<sup>11</sup> However, this method has 2 principal disadvantages: first, it is cumbersome and difficult to use in long-term studies, and second, the measure may not accurately reflect the patient's experience.

For this reason, self-administered questionnaires were designed to stratify women based on quality of life, and to measure changes in their quality of life. The Menopause-Specific Quality of Life questionnaire (MENQOL) is one such example that was developed based on the experiences of women who were between 2 and 7 years postmenopause.<sup>12</sup> More recently, the Menopausal Vasomotor Symptoms (MVS) survey was developed as a tool for a comprehensive and subjective assessment of hot flashes, which provided a simple and effective means to evaluate hot flash frequency and other vasomotor symptoms.<sup>13</sup>

Data from the US-based Study of Women's Health Across the Nation (SWAN), which screened 16,065 women from various ethnicities, suggested that race/ethnicity, weight, lifestyle, and socioeconomic factors may exacerbate the risk of developing vasomotor symptoms<sup>14,15</sup> (FIGURE 2). According to the SWAN data, African American women reported vasomotor symptoms more often (45.6%) than Caucasian women (31.2%) did, and hot flashes and night sweats were experienced by 37% of women in the early stages of perimenopause, which increased in prevalence (57%) as women transitioned to late perimenopause. In addition, SWAN data also revealed that vasomotor symptoms were prevalent in women with a high body mass index (BMI), those who smoked, and those who were physically less active. Previously it was thought that the risk of hot flashes was inversely related to BMI because excess adipose tissue sustains the levels of estrogen through a process of aromatization. However, data from SWAN indicated that a high BMI ( $\geq 27$ ) is a predictor of hot flash frequency. In this context, a recent study using bioelectrical impedance measurements in a group of perimenopausal and postmenopausal women reported that having a higher percentage of body fat was associated with an increased risk of developing vasomotor symptoms.<sup>16</sup> In agreement with this view, data from a recent study that used computed tomography (CT) scans to assess adiposity showed that increased body fat, specifically subcutaneous abdominal adiposity, increases the odds ratio of developing vasomotor symptoms.<sup>17</sup>

High levels of physical activity, although correlated with reduced levels of anxiety, stress, and depression, had no apparent association with the occurrence of hot flashes, even after adjusting for the variability in hormonal changes.<sup>18</sup> In fact, a recent study showed that women who engage in a high level of strenuous physical exercise were significantly more likely to report moderate-to-severe hot flashes than those who are minimally active.<sup>19</sup> In addition, women with psychiatric comor-

**FIGURE 2** SWAN: Reported prevalence of vasomotor symptoms



bidities, including higher perceived stress, depression, elevated anxiety symptoms, and a history of premenstrual complaints, have a higher risk of developing hot flashes.<sup>10,20,21</sup>

Management of vasomotor symptoms for many women has become increasingly complex—and at times, confusing—because of the increasing awareness of the risks associated with hormone therapy reported in the consumer and medical media. Thus, many women seek to use a range of symptom management options, including the use of over-the-counter preparations, complementary herbal therapies, exercise programs, and lifestyle modifications.

### Neuroendocrine changes, menopausal transition, and mood disorder

Evidence from clinical and epidemiological studies has shown that women are at significantly greater risk of developing unipolar depression than are men. The lifetime prevalence of unipolar depression is 21% in women, compared with 13% in men.<sup>22</sup> Of note, the increased prevalence in women becomes evident after puberty and continues through midlife, thus approximately corresponding to the reproductive life phase. However, after menopausal transition, the incidence of depression in postmenopausal women is comparable with men.<sup>22</sup> Further, several longitudinal, community-based studies have found that depressive symptoms occur more

## Multiple roles of estrogen in health and disease

Because of the varying outcomes noted in menopausal women, it is reasonable to assume that estrogen exerts multiple physiological roles. In premenopausal women, endogenous estrogen upregulates the vascular anti-inflammatory response, as well as stabilizes the vascular endothelium, a favorable physiological role that may contribute to the cardioprotection in these women.<sup>1</sup> The Postmenopausal Estrogen Intervention (PEPI) trial evaluated the effects of estrogen alone, or in combination with progestin, on serum lipids and found a consistent increase in high-density lipoprotein cholesterol (HDL-C) with a lowering of low-density lipoprotein cholesterol (LDL-C) over a 3-year period; the study also found overall improvement in total cholesterol levels, suggesting a reduced risk of coronary heart disease.<sup>2</sup>

The potential role of estrogen as a coagulation cascade activator, which can lead to an increased risk of embolic events, has been highlighted in a number of studies. The Heart and Estrogen/progestin Replacement Study (HERS) was one of the first large-scale randomized trials that assessed the potential effects of estrogen on cardiovascular disease.<sup>3</sup> As a secondary prevention trial, menopausal women with a previous history of coronary artery disease were treated with either combined hormone therapy (conjugated equine estrogen and medroxyprogesterone) or placebo. Although there were favorable changes in the lipid profile of those who received hormone therapy, with significant improvement in serum cholesterol levels, a subset of women experienced coronary events during the first year and had an overall increased risk of thromboembolic events throughout the 4-year course of the study.<sup>3</sup>

The loss of steroid sex hormones during menopause and thereafter causes a number of changes in the female body, of which atherosclerotic lesion formation and inflammation are of serious concern. In this context, angiographic coronary artery disease in premenopausal women has been associated with low concentrations of plasma 17 $\beta$ -estradiol.<sup>4</sup> Given that the use of oral contraceptives interferes with the release of 17 $\beta$ -estradiol, low levels of endogenous estrogens during the premenopausal years may increase cardiovascular risk in the years to come. Thus, the duration of past use of oral contraceptives might be used as an independent predictor for coronary atherosclerosis in postmenopausal women.<sup>5</sup> This risk may be compounded by the presence of other known risk factors, such as hypertension, hyperlipidemia, obesity, smoking, or hyperglycemia, and contribute to an increased burden of atherosclerosis.<sup>5</sup>

Although HERS found that estrogen therapy significantly improved lipid profiles, there was no decrease in cardiovascular morbidity.<sup>1</sup> This clearly suggests that estrogen was incapable of reversing the vascular disease process in women who were in a prolonged estrogen-deficient state.<sup>1</sup> In support of this view, data from the Estrogen Replacement and Atherosclerosis (ERA) trial indicated that estrogen therapy was ineffective in repairing damaged vessels in an advanced disease state.<sup>6</sup> By contrast, data from the Estrogen in Prevention of Atherosclerosis Trial (EPAT) demonstrated that estrogen therapy was effective in attenuating the progression of atherosclerotic plaque formation, as measured by invasive monitoring at an early subclinical disease stage.<sup>7</sup> Taken together, these studies have established a cardioprotective role for estrogen in preventing atherosclerotic plaque formation early in the disease process.

Despite estrogen's discordant roles as both a cardioprotective and a thromboembolic agent, it has been associated

frequently in perimenopausal women compared with those who are postmenopausal.<sup>23</sup> Data from a primary care clinic showed that perimenopausal women with vasomotor symptoms are 4 times more likely to develop depression than are those without symptoms.<sup>22</sup> Therefore, although genetic, psychosocial, and environmental factors all contribute to the risk of depression, available evidence now indicates that endocrine changes during perimenopause are additional factors that may contribute to depressive symptoms.<sup>22</sup>

Neuroendocrine changes in the hypothalamic-pituitary-gonadal axis have been associated with alterations in serotonin function, which may potentially account for the higher prevalence of depression noted in women. For example, administration of estrogen or progesterone to postmenopausal women resulted in

an increased density of serotonin 5-HT<sub>2A</sub> receptors in the cerebral cortex<sup>24</sup>; the 5-HT<sub>2A</sub> receptor is often implicated in the pathophysiology of depressive disorders. Another serotonin receptor that is apparently influenced by neuroendocrine changes is 5-HT<sub>1A</sub>. Using radioligand (radioactive biochemical substance) labeling together with positron emission tomography, serotonin 5-HT<sub>1A</sub> receptors have been shown to be gender specific, with more density in females compared with age-matched males.<sup>21</sup> Measurement of 5-HT<sub>1A</sub> density during the follicular phase in women with premenstrual dysphoric disorder showed small changes compared with asymptomatic controls.<sup>22,25,26</sup> In addition, estrogen therapy is effective in the treatment of perimenopausal and postmenopausal depression in placebo-controlled studies.<sup>23,27</sup>

with demonstrable positive physiological effects on other organ systems. A number of studies have shown that estrogen is important for maintaining bone vitality. In observational studies, the use of estrogen therapy has decreased the rates of vertebral, nonvertebral, and wrist fractures that often occur secondary to osteoporosis.<sup>1,8</sup> In addition to an increase in the incidence of fractures associated with osteoporosis, estrogen withdrawal also coincides with the rapid onset of osteoarthritis in the upper and lower extremities.<sup>9</sup> Of note, prior to 50 years of age, the incidence of osteoarthritis is greater in men; however, after age 50, the incidence and the rapidity of functional decline is significantly greater in women compared with their male counterparts.<sup>9</sup>

Estrogen is also active in the central nervous system.<sup>10</sup> The identification and mapping of estrogen receptors in the brain has shown abundance in regions such as the hypothalamus, pituitary, cerebral cortex, brain stem, and hippocampus.<sup>10</sup> Because of the widespread prevalence of estrogen receptors (alpha and beta) in many brain regions, it is assumed that estrogen will affect multiple neuronal functions and several neurotransmitter pathways, including the cholinergic, serotonergic, and GABAergic systems, among others.<sup>10</sup> Given that estrogen, a neuroactive hormone, increases the levels of choline acetyltransferase, it is posited that the hormone may play a role in memory.<sup>10</sup> Although currently there is a paucity of data detailing the correlation between estrogen activity in the brain and the resultant cognitive effects, outcomes from recent studies do provide some insights. In a randomized controlled study, healthy postmenopausal women were assigned to receive either a transdermal patch containing estradiol designed to deliver 0.1 mg 17 $\beta$ -estradiol per day, or placebo for 3 weeks.<sup>11</sup> Assessment of cognitive function showed a selective improvement in performance relating to learning and memory

tasks after estrogen treatment. Interestingly, estrogen therapy improved the performance on mental rotations (a test of spatial ability), whereas planning and executive skills related to frontal lobe functions were not influenced. In another randomized controlled study, postmenopausal women who received transdermal applications of estradiol for 2 weeks showed improved scores only on tests of verbal memory.<sup>10</sup> In this context, it is noteworthy that Yaffe and colleagues conducted a meta-analysis that showed that the risk of developing Alzheimer disease was significantly decreased by a factor of 29% in estrogen users compared with nonusers.<sup>12</sup>

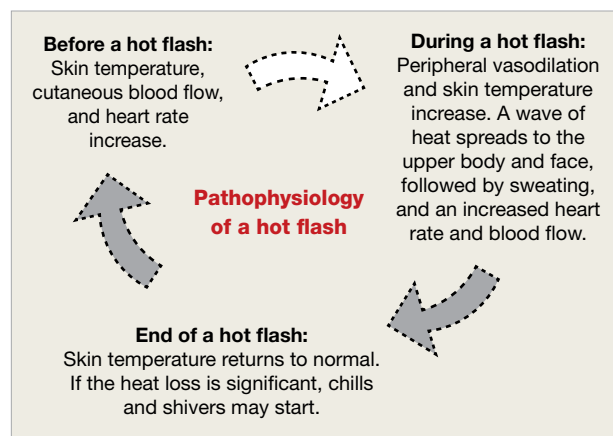
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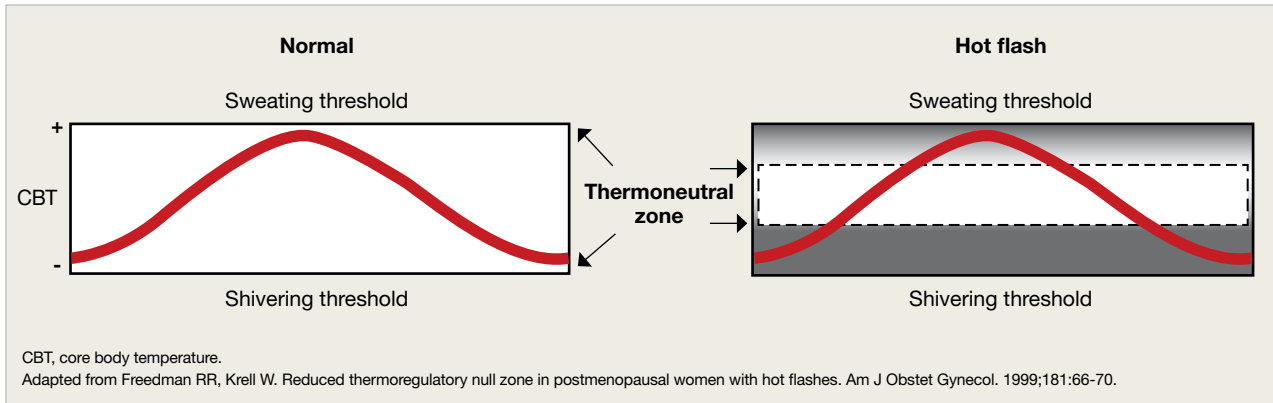
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### Thermoregulation and hot flashes

Temperature regulation is a complex, integrated network of neuroendocrine, autonomic, and somatomotor responses that involves 3 major communication centers: thermosensitive afferent pathways that provide information about core body temperature, central processing areas in the central nervous system, and peripheral vasculature.<sup>28</sup> Thus, when body temperature rises above the preset limits (upper threshold) of the thermoneutral zone, peripheral vasodilation is triggered.<sup>28</sup> In the 5 to 60 seconds that precede a hot flash, a number of physiological changes occur, including a rise in skin temperature, increased cutaneous blood flow, and increased heart rate (FIGURE 3).<sup>10</sup> Typically, a hot flash lasts between 1 and 5 minutes. During this time, the

**FIGURE 3 Pathophysiology of a hot flash: A schematic illustration**



**FIGURE 4** Mechanism of a hot flash: Thermoregulatory dysfunction

skin temperature will continue to rise due to peripheral vasodilation, with a notable change in the extremities. Most women experience a wave of heat sensation that spreads to the upper body and face. The sensation of heat can be mild or intense, and may be accompanied by reddening of the skin throughout the head and upper body. The next pronounced physiological change is sweating, which closely corresponds in time with the increase in skin conductance. Nighttime sweating may lead to serious sleep disturbances, although studies on this are somewhat conflicting. In addition to sweating, heart rate and skin blood flow may rise, usually reaching a peak within 3 minutes of the onset of a hot flash. At the end of a hot flash, skin temperature will eventually return to baseline, which can take up to 30 minutes. If the loss of heat is significant, vasoconstriction of peripheral blood vessels may occur as a means of retaining heat, in addition to shivers to generate heat.<sup>10</sup>

### Three hypotheses provide potential mechanisms

Vasomotor symptoms are believed to result from a dysfunction in the temperature-control circuitry, leading to an exaggerated activation of heat dissipation mechanisms such as peripheral vasodilation and perspiration.<sup>28</sup> There are 3 principal hypotheses that have been proposed as potential mechanisms of vasomotor symptoms: (1) dysregulation of the hypothalamic control of core body temperature leading to anomalies in temperature homeostasis; (2) supersensitivity of peripheral thermoregulatory effectors; and (3) neurochemical imbalances.<sup>28</sup> All 3 hypotheses likely play a role in the development and characterization of menopausal vasomotor symptoms.

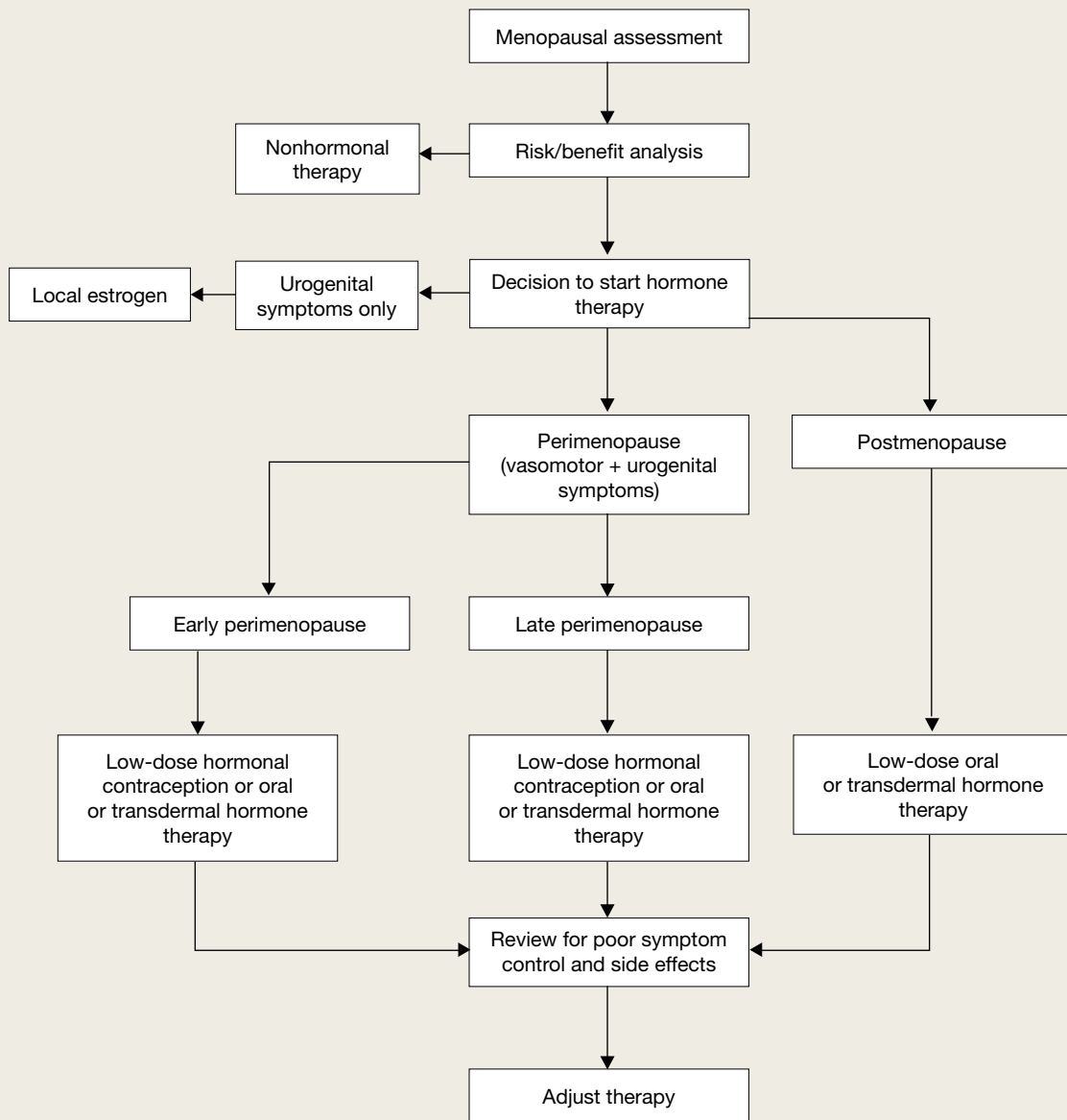
The first hypothesis is supported by the observation that during the menopausal transition, the thermoneutral zone is narrowed (FIGURE 4). This may be due

to elevated levels of norepinephrine, so that even small increases in temperature may trigger a hot flash. In this context, Freedman and Krell reported that postmenopausal women who experienced hot flashes had significantly smaller thermoneutral zones compared with those without symptoms.<sup>29</sup> Sweat rates were also significantly higher in women with symptoms compared with women who did not have symptoms.

The second hypothesis posits that hot flashes may result from altered sensitivity of cutaneous blood vessels. In addition to central thermoregulation, peripheral effectors are involved in the regulation of vasodilation and constriction of the cutaneous blood vessels.<sup>30</sup> It has been proposed that due to the altered sensitivity of cutaneous vessels, the response time to hypothalamic thermoregulatory signals may be delayed, resulting in an exaggerated response such as a hot flash.<sup>28,30</sup>

The third hypothesis relating to the mechanisms of vasomotor symptoms suggests that hot flashes may be a consequence of the changes that occur in the levels of circulating gonadotropic hormones during the perimenopausal period, which may alter the neurochemical balance in a number of brain regions that involve dopaminergic, serotonergic, and noradrenergic systems.<sup>31</sup> Thus, although estrogen withdrawal is the primary cause of vasomotor symptoms, evidence suggests that changes in estrogen levels may alter the norepinephrine and serotonin systems in regions of the hypothalamus.<sup>32</sup> For example, several studies have demonstrated the ability of estrogen to modulate the synthesis and breakdown of monoaminergic neurotransmitters such as serotonin and norepinephrine.<sup>33-36</sup> Notably, increased central noradrenergic activity has been found in menopausal women after a hot flash event.<sup>37</sup> Moreover, stimulation of norepinephrine levels with yohimbine (an alpha-2 adrenergic antagonist) triggers hot flashes,<sup>32</sup> whereas

**FIGURE 5** Treatment algorithm for hormone therapy\*



Regimen	Estrogen	Progestogen
Cyclic	Days 1 to 25	Last 10 to 14 days of ET cycle
Continuous cyclic or sequential	Daily	10 to 14 days/month
Continuous cyclic or long cycle	Daily	14 days every 2 to 6 months
Continuous combined	Daily	Daily

\*For women with an intact uterus, use estrogen with continuous or sequential progestogen.  
 North American Menopause Society position statement, 2008; adapted from Currie and Guttinger, 2007.

## Individualizing the treatment plan for hormone therapy

Current guidelines recommend the use of hormone therapy for the relief of vasomotor and urogenital symptoms associated with climacteric symptoms and menopause<sup>1-3</sup> (TABLE 1, page S4). Although clinicians and policy makers recognize that women generally live one-third of their lives after menopause, and they agree on the potential benefits that estrogen-based therapies can render, there is less consensus on the dosing and duration of therapy required to optimize treatment benefits with minimal health concerns. Thus, clinicians need to weigh the individual risks and benefits for each patient, taking into account the complex nature of the mechanisms of action of these steroid hormones and their effect on almost every organ system.

Standard methods of risk assessment start with a detailed patient history, complemented by a physical examination and laboratory findings to establish differential diagnoses. To formulate a comprehensive treatment plan, it is important for the clinician to ascertain the patient's attitude toward menopausal transition and preference for a specific treatment, and learn about any concerns that the patient may have regarding a specific treatment option. Thus, standardized questionnaires, such as the Greene Climacteric Scale, the Women's Health Questionnaire, the Menopause Rating Scale, and the Utian Quality of Life Score, have been successfully implemented in health care decision making to assess quality of life and attitudes concerning physical, psychological, and social parameters of women's health.<sup>4</sup> A study by Schapira and

colleagues clearly documented the importance of integrating patient attitudes and views when formulating individualized treatment plans.<sup>5</sup> One survey compared the opinions of hormone therapy users versus nonusers on various aspects of treatment. The questions were designed to address the long-term health benefits of hormone therapy, quality of life, and menopausal attitudes of those surveyed. For the current users of hormone therapy, relief from vasomotor symptoms, osteoporosis, and coronary heart disease were the most important issues, whereas former users showed greater concerns about side effects from the therapy. Among the nonusers, the fear of an increased risk of breast cancer was a major reason for abstaining from hormone therapy.<sup>5</sup>

Given the media publicity that hormone therapy received after the publication of the Women's Health Initiative study, women who seek treatment for relief of vasomotor symptoms are burdened with a double-edged decision-making process—a decision that has to consider the benefits of hormone therapy in reducing vasomotor/urogenital symptoms and providing protection against degenerative diseases that may result from thromboembolic events vs an increased risk of cancer.

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4. Vitiello D, Naftolin F, Taylor HS. Menopause: developing a rational treatment plan. *Gynecol Endocrinol.* 2007;23:682-691.
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inhibition with clonidine (an alpha-2 adrenergic agonist) has shown efficacy in the treatment of vasomotor symptoms.<sup>32</sup> Interestingly, menopausal women with low levels of serum serotonin reportedly have experienced the most severe climacteric symptoms.<sup>38</sup> Another neural pathway that has been implicated in the pathophysiology of vasomotor symptoms is the opiate system, insofar as hot flashes have been associated with changes in plasma endorphin concentrations.<sup>39,40</sup>

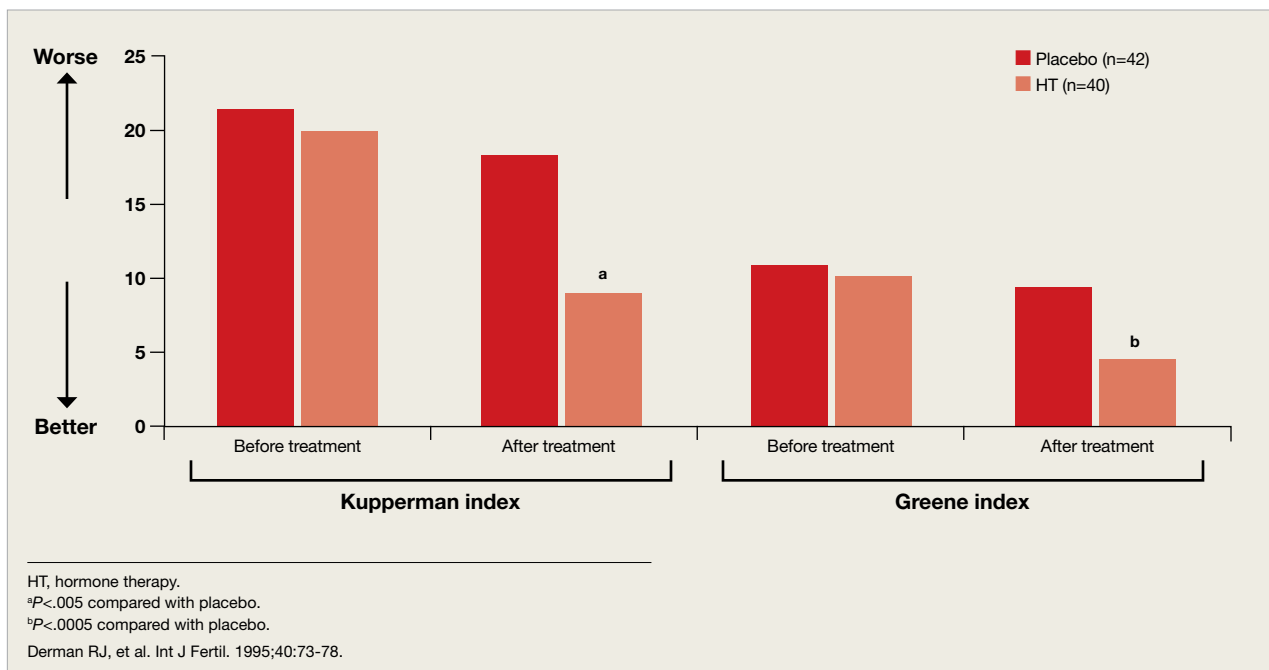
## Management of menopause-related symptoms

The management of vasomotor and other menopausal symptoms is complex, and the treatment remains contentious. It is noteworthy that most women can tolerate menopausal symptoms, if the symptoms are mild and transient; an estimated 30% to 50% of women have

improved hot flashes within several months, and many have resolved hot flashes within 4 to 5 years.<sup>41</sup> Results from large-scale trials now recommend that an individualized risk/benefit analysis must be carried out for each patient before instituting patient-specific treatment plans<sup>42</sup> (FIGURE 5). Clinicians are advised to enlist their patients' participation in decision making when weighing the benefits, harms, and scientific uncertainties of options.<sup>10</sup> Nonetheless, surveys in the United States indicate that physicians often underestimate their patients' attitudes about menopausal symptoms and hormone therapy.<sup>43</sup>

A number of conditions contraindicate the use of any estrogen-based hormone therapy. These include estrogen-dependent neoplasms, endometrial carcinoma, hyperplasia, breast cancer, venous or arterial thrombosis, high risk of cardiovascular disease, and/or liver disorders.<sup>1</sup> In addition, as indicated in a pooled

**FIGURE 6** Hormone therapy relieves vasomotor symptoms and improves quality of life

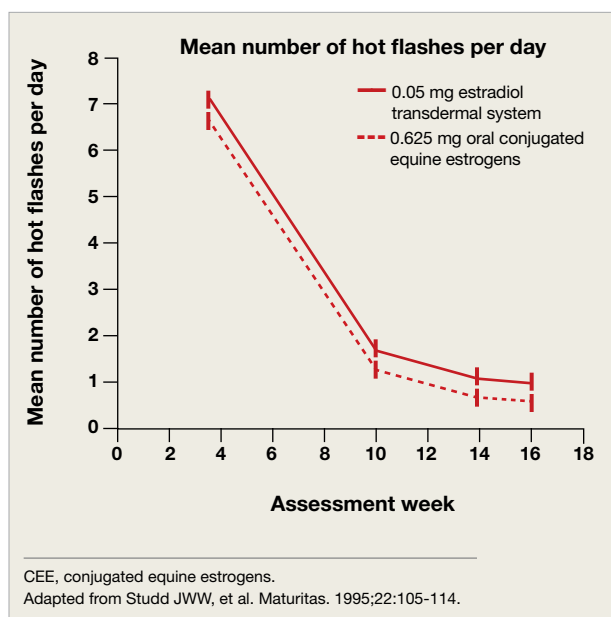


analysis of prospective studies, oral conjugated equine estrogen (CEE) significantly increases triglyceride levels.<sup>44</sup> Thus, oral estrogen therapy is not optimal for women with elevated triglycerides; however, these patients may benefit from transdermal estradiol therapy. Because smoking upregulates the P450 or CYP3A4 liver enzymes, which increase the metabolism and excretion of estrogen, oral estrogen therapy is also not recommended for heavy smokers.<sup>45</sup> Although the routine use of combined hormone therapy is no longer recommended for prevention of chronic conditions in postmenopausal women,<sup>46</sup> it is effective and approved for the prevention of postmenopausal osteoporosis at higher doses.

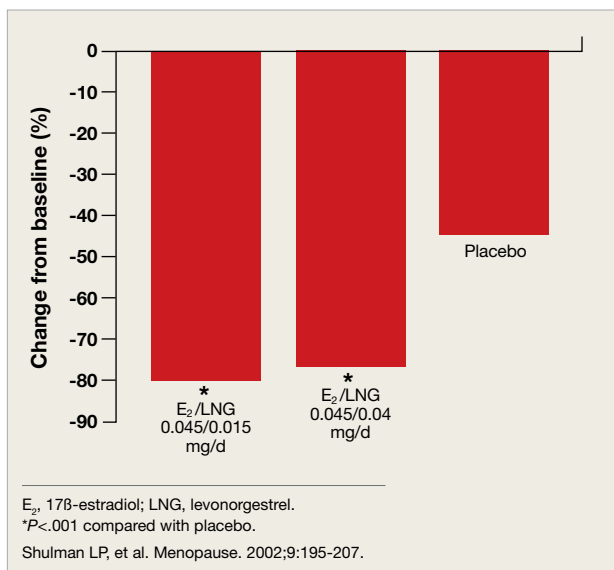
### Hormone therapy: Benefits and risks

**Benefits:** Estrogen therapy is the gold standard in the treatment of hot flashes.<sup>45</sup> Among users, symptom control and perceived improvement in quality of life are the main reasons for initiating hormone therapy and for the high continuation rates.<sup>47</sup> In a Cochrane meta-analysis, MacLennan and colleagues found that vasomotor symptoms improved with either oral estrogen alone, or in combination with progestogen, and with transdermal estrogen.<sup>48</sup> The majority of the trials included in the analysis were of 12 weeks' duration and comprised healthy menopausal women who were approximately

**FIGURE 7** Impact of hormone therapy on hot flashes: Transdermal estradiol vs oral CEE



50 years of age. Treatment with estrogen significantly reduced the number of hot flashes, with a pooled equivalent reduction of 17.9 per week compared with placebo (75.3% reduction in frequency).<sup>48</sup> In a separate study,

**FIGURE 8** Effect of transdermal E<sub>2</sub>/LNG treatment on hot flash frequency

relieving vasomotor symptoms with hormone therapy significantly improved the quality of life of women, as assessed by the measures of the Kupperman and Greene indices<sup>49</sup> (FIGURE 6).

Currently, there is no clear benefit of oral hormone formulations vs transdermal regimens for systemic estrogen therapy.<sup>51</sup> Although a long-term benefit/risk ratio has not been demonstrated, there have been suggestions that transdermal regimens afford some advantages over oral hormone formulations.<sup>50</sup> These include stable levels of circulating estrogen; circumventing first-pass metabolism; nonelevation of triglycerides or high-density lipoproteins; comparable efficacy at lower concentrations; reduced frequency of dosing; and a suitable alternative for women who choose not to use oral medication.<sup>51</sup> In the absence of data from large, head-to-head studies that compare the efficacy, dosing, and safety of oral formulations with the equivalent transdermal regimens, it is important to note that hormone therapy, whether transdermal or oral, may not be recommended to those women with known risks. Thus, risks and benefits need to be assessed on an individual basis and each patient should be made aware of the potential risks of hormone therapy, regardless of the route of administration.

Studd and colleagues compared the efficacy and safety of transdermal estradiol with oral CEE in reducing hot flashes in a randomized, multicenter, double-blind, and double-dummy study<sup>51</sup> (FIGURE 7). In this study, 214

women aged 40 to 65 years with moderate-to-severe hot flashes were administered a continuous regimen of Menorest 50 (transdermal formulation) twice weekly or Premarin (oral CEE) 0.625 mg daily for 12 weeks after an initial treatment-free washout period (4 weeks). Results showed that the transdermal formulation, at a lower dose, was equally as efficacious as the oral therapy.<sup>51</sup> A statistically significant reduction in the mean number of hot flashes occurred during the 12-week period of therapy, with no significant difference between the treatment groups.

A more recent corroborative analysis systematically reviewed a number of clinical studies that used oral and transdermal formulations to evaluate their efficacy in reducing hot flash frequency and severity.<sup>1,41</sup> Accordingly, both oral and transdermal estradiol reduced hot flashes by 2.4/day and 3.2/day, respectively, compared with placebo. Similar results were obtained for opposed and unopposed estrogen regimens. Interestingly, the same study reported that a comparison of head-to-head trials that employed various estrogen formulations (CEE, oral estradiol, and transdermal estradiol) showed a reduced number and severity of hot flashes in all treatment groups, with no significant differences among them.

Combination therapies of estrogen with progesterone have also been examined. In this regard, oral medroxyprogesterone acetate is the most frequently prescribed agent for endometrial protection.<sup>10</sup> Other oral formulations include norethindrone, norethindrone acetate, micronized progesterone, and drospirenone. Among these, medroxyprogesterone combined with CEE is commonly prescribed for the management of vasomotor symptoms. Among non-oral options, vaginal progesterone gel and off-label use of a levonorgestrel-releasing intrauterine system (LNG-IUS) can be used to deliver small doses of intrauterine progestin, particularly for perimenopausal women.<sup>52</sup> Indicated as a contraceptive, LNG-IUS prevents endometrial hyperplasia.<sup>53</sup> Transdermal delivery systems could also include combination hormone therapy to relieve vasomotor symptoms, while providing protection against hyperplasia in postmenopausal women. In this context, low doses of 17β-estradiol (E<sub>2</sub>) and levonorgestrel (LNG), a well-characterized synthetic progestogen that possesses 5- to 10-fold greater potency than norethindrone, can be delivered using an adhesive-based matrix transdermal system.<sup>54</sup>

To investigate the efficacy and safety of 3 separate dosing regimens of LNG in combination with estradiol for the treatment of vasomotor symptoms and the prevention of estrogen-induced endometrial hyperplasia

in healthy postmenopausal women, a prospective, multicenter, randomized, double-blind, placebo-controlled study was undertaken.<sup>54</sup> Results showed that all 3 dosing regimens (estradiol 0.045 mg/day with LNG 0.015, 0.030, and 0.040 mg/day) of transdermal combination therapy were effective in significantly reducing the number and severity of hot flashes when compared with placebo.<sup>54</sup> Symptom relief was evident as early as 2 weeks after the start of treatment. Participants also showed significant improvement on the Women's Health Questionnaire for vasomotor symptoms, sleep problems, sexual function, and cognitive difficulties (FIGURE 8).<sup>54</sup> Of interest was the marked decrease in the levels of total cholesterol, low-density lipoprotein (LDL), and triglycerides with the use of combined transdermal estradiol and LNG therapy.<sup>44,54</sup> The reductions in the blood lipids found in this study suggest possible reduced risk of coronary heart disease with the use of these (treatments).<sup>54</sup> Moreover, the reduction noted in triglyceride levels after 1 year of transdermal therapy was remarkable and differs markedly from oral estradiol/norethindrone formulations, which are associated with increased triglyceride levels after 1 to 2 years of treatment<sup>54</sup> (FIGURE 9).

Common side effects of short-term estrogen therapy include breast tenderness, uterine bleeding, nausea and vomiting, headache, weight change, dizziness, rash and pruritus, cholecystitis, liver disorders, venous thrombotic events, and cardiovascular events.<sup>1</sup>

**Risks:** Data from the Collaborative Group on Hormone Factors in Breast Cancer provided strong evidence from an analysis of 51 epidemiological studies that breast cancer risk was increased in women receiving hormone therapy.<sup>55</sup> Nonetheless, the relative role of estrogen and estrogen/progestogen combination therapy with regard to the increased risk of breast cancer was less evident. The best evidence came from the Women's Health Initiative (WHI), the large randomized, controlled trial of postmenopausal women aged 50 to 79 years (mean, 63.2 years), all of whom had an intact uterus at baseline. The trial was designed to investigate whether estrogen, with or without progestin therapy, could prevent chronic conditions such as heart disease and breast/colorectal cancer.<sup>56</sup> As stated, initial data from the combined treatment arm showed that 5 years of estrogen and progestin therapy resulted in a significant reduction in fractures. However, there was an increased occurrence of breast cancer and thromboembolic events, with no overall cardiovascular benefits (FIGURES 10 AND 11). These findings raised serious health concerns about the safety of hormone therapy in the treatment of menopausal symp-

**FIGURE 9** Effect of oral vs transdermal hormone therapy on lipid levels in postmenopausal women

	TRANSDERMAL			
	E	E + P	E	E + P
Total cholesterol	↓	↓	↓	↓
LDL-cholesterol	↓	↓	↓	↓
HDL-cholesterol	↑	(↑)	↑	(↑)
Triglycerides	↑	(↑)	↓	↓

E + P, estrogen + progestin combination.  
 Parentheses indicate blunted effect relative to unopposed estrogen.  
 Adapted from Godsland IF. *Fertil Steril.* 2001;75:898-915. Shulman LP, Yankov V, Uhl K. *Menopause.* 2002;9:195-207.

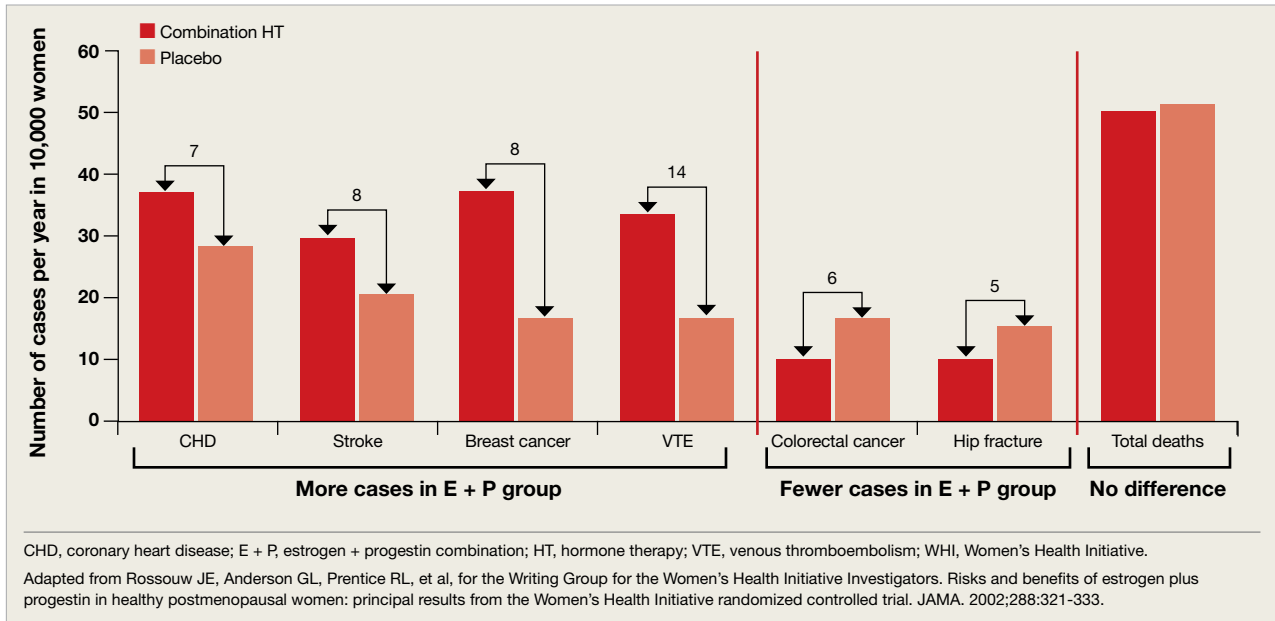
oms. This and subsequent negative data eventually led to the premature termination of the study.<sup>56</sup> As a consequence, in the year immediately following the publication of the WHI data, annual prescriptions for hormone therapy decreased by 50% in the United States. Many women stopped taking hormones to treat menopausal symptoms.<sup>57</sup>

A surprising outcome from the WHI study, which was evident from the preliminary analyses but was not addressed by the study investigators in the years after initial publication, was that age and years after menopause are important determinants of the benefits and risks of hormone therapy.<sup>58</sup> Problems in the interpretation of data arose because of inappropriate extrapolation and generalization of data gathered mainly from older women (mean age, 63 years)—who typically did not seek hormone therapy for the relief of menopausal symptoms—to those younger women who were transitioning through the perimenopausal stage.<sup>58</sup> More recently, detailed evaluation and subgroup analyses of the WHI data have revealed that for younger women (aged <60 years) who are in the early postmenopausal period, estrogen therapy may confer a cardioprotective effect.<sup>59,60</sup> According to the new analyses, treatment with CEE alone reduced the following events per 10,000 treated women annually: coronary artery disease by 11, strokes by 2, diabetes cases by 14, fractures by 56, breast cancer diagnoses by 8, and deaths by 10.<sup>58</sup>

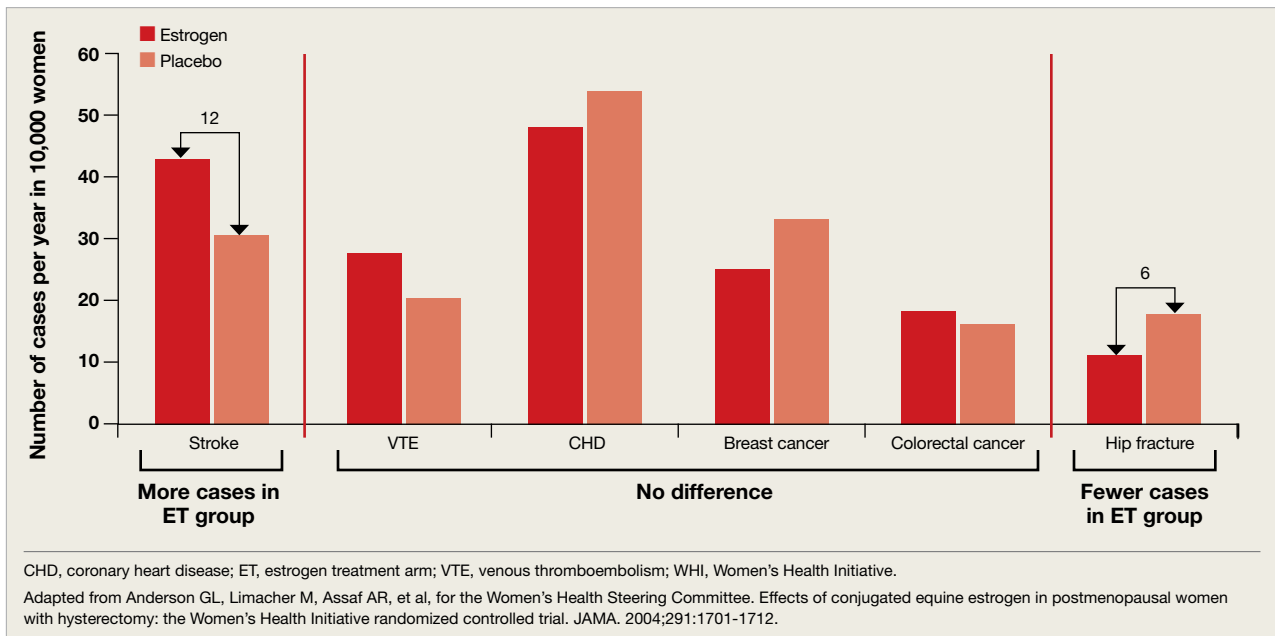
## Post-WHI study era

Given the lack of alternative treatment strategies that present a unified approach to treating women with menopausal symptoms, there has been a significant, growing interest in revisiting the evidence from the WHI study to explore ways to better stratify patient subgroups

**FIGURE 10** WHI annual disease rates: Combination hormone therapy vs placebo



**FIGURE 11** WHI annual disease rates: Estrogen monotherapy vs placebo



and to optimize the treatment period and dosage. For example, for women who continue to have regular menstrual cycles, a low dose of estrogen may offer better advantages over combination therapy, including a reduced risk of progestin-related side effects and a simpler dosing regimen.<sup>4</sup> Because of the sloughing of the

endometrium during the luteal phase of each menstrual cycle, unopposed low-dose estrogen is not likely to pose a risk to the endometrium of these women.<sup>4</sup> In this context, to study the effect of estrogen-only therapy on the risk of developing breast cancer, an observational study investigated a cohort of 84,729 Finnish postmenopausal

women aged 50 years and older.<sup>57,61</sup> The study concluded that the risk of breast cancer does not increase with systemic or transdermal application of estrogen when used for less than 5 years; however, the risk tends to increase with continued use of hormone therapy.<sup>57,61</sup>

Relief from perimenopausal vasomotor symptoms can be achieved with lower doses of estrogen than the typical high-dose formulations that are used during menopause.<sup>4</sup> Thus, in treating perimenopausal women with ovarian activity, the goal of the treatment must be to augment and stabilize the levels of circulating estrogen with low-dose exogenous hormone, such as with transdermal formulations, as these circumvent first-pass liver metabolism to provide a stable blood level of estrogen over each dosing period.<sup>4</sup> There is now evidence to support the view that oral estrogens may confer cardioprotection, if initiated around the time of menopause when vascular estrogen receptors are prone to respond to exogenous hormone.<sup>62,63</sup> In trials, estrogen therapy instituted near menopause reduced the progression of atherosclerotic plaques, whereas administration of hormone many years after menopause did not yield the expected benefits, and sometimes produced adverse outcomes due to disruption of established plaques.<sup>63</sup>

## Use of nonhormonal neuroactive therapies

Use of postmenopausal estrogen-based therapy has changed pursuant to the release of the WHI study in 2002. The US Food and Drug Administration and various professional organizations have issued recommendations against the use of estrogen and progestin or progesterone for prevention of chronic conditions.<sup>41</sup> In addition, the announcement in 2004 of the termination of the estrogen-only treatment arm of the WHI due to increased incidence of strokes among users has raised more concerns about safety.<sup>41</sup> Because estrogens are often contraindicated in patients with cancer, other pharmacologic treatment options are needed to alleviate the menopausal vasomotor symptoms in this group of women. Thus, nonhormonal neuroactive therapies may be the treatment of choice for women who seek alternatives or who are contraindicated for hormone therapy. Currently available pharmacologic agents include antidepressants, anticonvulsants, monoamine oxidase inhibitors, and antihypertensives. Among these, antidepressants are considered to be the most robust in reducing hot flashes and improving the quality of life; however, their efficacy does not compare with that of estrogen therapy.<sup>45</sup>

**Antidepressants:** Selective serotonin reuptake inhibitors (SSRIs) have been the standard treatment for the management of mood and anxiety disorders for many years. More recently, the off-label use of this class of drugs has increased, and a number of agents have been used in evidence-based studies for the treatment of menopausal vasomotor symptoms.<sup>64</sup> Although results from large-scale, long-term clinical studies are lacking, data from smaller, controlled studies support the use of antidepressants as the choice of drugs to alleviate vasomotor symptoms in patients who are contraindicated for hormone therapy because of cardiovascular disease, a history of thromboembolic events, breast or uterine cancer, or liver disease.<sup>10,65</sup> SSRIs and selective norepinephrine reuptake inhibitors (SNRIs) have been extensively studied for their efficacy, safety, and tolerability as antidepressants. The potential roles of serotonin and norepinephrine in hypothalamic thermoregulation provide the rational basis for considering these therapeutic agents for alleviating vasomotor symptoms.

In a randomized, placebo-controlled trial of 165 menopausal women, treatment with the SSRI paroxetine significantly reduced the mean frequency of hot flashes by approximately 62% compared with a reduction of 38% in the placebo group.<sup>66</sup> A subsequent corroborative study confirmed the efficacy of paroxetine 10 mg/day therapy in reducing the frequency and severity of hot flashes, while improving the sleep quality of the patients.<sup>67</sup> To investigate the efficacy and off-label use of the SSRI fluoxetine as a nonhormonal agent in the treatment of vasomotor symptoms for women with a history of breast cancer or perceived risk of breast cancer, a randomized, double-blind, crossover study was designed.<sup>68</sup> Women who met the inclusion criteria of at least 14 hot flashes per week were prescribed fluoxetine 20 mg/day. By the end of the first treatment period, hot flash scores (defined as frequency multiplied by average severity) decreased by 50% in the treatment group compared with 36% in the placebo group.<sup>68</sup> Interestingly, the effect of the drug on hot flashes occurred over the first 1 or 2 weeks after initiation of treatment.

Compared with the off-label use of fluoxetine and paroxetine, a newer SNRI, venlafaxine, has been most extensively studied as a treatment option for vasomotor symptoms.<sup>65,69</sup> Treatment with extended-release venlafaxine has been effective in reducing vasomotor symptoms in women with a history of breast cancer, or those who were concerned about the risks of breast cancer associated with hormone therapy.<sup>65</sup> Thus, in a randomized, placebo-controlled, double-blind study, women who experienced at least 14 hot flashes per week were

assigned to receive extended-release venlafaxine or placebo, adhering to a dose-escalating schedule.<sup>65</sup> After 4 weeks of treatment, median hot flash scores in the treatment group were reduced by up to 61% from baseline in a dose-dependent manner. It is thought that the dose-dependent efficacy of extended-release venlafaxine may be explained by its mechanism of action.<sup>65</sup> Because venlafaxine affects both serotonin and norepinephrine reuptake, it is posited that at a lower dose, the drug may exert its effect by inhibiting serotonin reuptake. At higher doses, the increased efficacy of venlafaxine may have been in part due to the combined inhibition of both serotonin and norepinephrine reuptake, or predominantly the latter.<sup>65</sup> As an antidepressant, extended-release venlafaxine is usually well tolerated. Nonetheless, side effects reported in the study, including dry mouth, decreased appetite, nausea, and constipation, were significantly greater in patients who received higher doses (75 mg/day and 150 mg/day).<sup>65</sup>

What effect might venlafaxine have in healthy postmenopausal women with vasomotor symptoms? Given that venlafaxine was effective in reducing vasomotor symptoms in women who were contraindicated for hormone therapy, a randomized study examined the efficacy of this drug in the symptom management of healthy menopausal women in the general population.<sup>69</sup> The results from this study are noteworthy, as they showed that venlafaxine 75 mg/day could significantly reduce the patient-perceived effects of hot flashes on the activities of daily life, compared with placebo. These include interference with work, family life, sleep, and sexual function.<sup>69</sup> Because patients' perception of hot flashes improved significantly relative to the decrease noted in the severity of the hot flashes, the authors have speculated that venlafaxine, as an effective antidepressant, may have improved the overall sense of well-being of the participants, which consequently altered their perception of hot flashes.<sup>69</sup>

In addition to the use of antidepressants as monotherapy, combination therapy with a low-dose hormone has shown to be more effective in reducing the frequency of hot flashes and improving the overall quality of life.<sup>70</sup> Accordingly, in a randomized, controlled study of oophorectomized women with hot flashes and depression, combination therapy with low-dose CEE 0.3125 mg/day and fluoxetine 50 mg/day showed significant reduction in hot flashes and improvement in depressive symptoms compared with estrogen alone.<sup>70</sup>

Therapies combining selective estrogen receptor modulators (SERMs) and estrogen have been studied for their efficacy and safety in the treatment of

postmenopausal vasomotor symptoms.<sup>71</sup> Although results were promising, with a significant improvement in hot flashes, the combination therapy posed a risk of increased thickening of the endometrial lining.<sup>71</sup>

**Anticonvulsants:** In 2004, the North American Menopause Society (NAMS) recommended the use of venlafaxine, paroxetine, fluoxetine, or gabapentin as treatment options for women with moderate-to-severe vasomotor symptoms, and for those who have concerns about or contraindications to hormone therapy.<sup>10</sup> Since the initial publication of the WHI study, small-scale, short-term, controlled studies have explored the safety and efficacy of gabapentin, an analogue of  $\alpha$ -aminobutyric acid, as a potential alternative to hormone therapy in the treatment of vasomotor symptoms.<sup>72-74</sup> Thus, a randomized, double-blind, placebo-controlled study examined the efficacy of gabapentin (titrated up to 2700 mg/day) over a 12-week period in a group of 59 postmenopausal women with moderate-to-severe hot flashes (7 or more hot flashes per day).<sup>74</sup> Results showed that gabapentin was significantly more effective than placebo in reducing composite scores that reflect the frequency and severity of hot flashes: a 45% reduction in hot flash frequency and a 54% decrease in the composite score, compared with 29% and 31%, respectively, in the control group. A separate study examined the efficacy of gabapentin in reducing the frequency of vasomotor symptoms in women with breast cancer.<sup>73</sup> In a large-scale, randomized, double-blind, placebo-controlled, multi-institutional study, gabapentin was administered at 300 mg/day and 900 mg/day. Notably, the anticonvulsant drug was effective in reducing both the frequency and severity of hot flashes only at the higher dose: 41% and 49%, respectively, at week 4, compared with 18% and 21% in the placebo group.<sup>32,73</sup> Adverse events such as somnolence, dizziness, rash, and peripheral edema are often the reason for discontinuation of therapy among patients who received gabapentin for the treatment of vasomotor symptoms.<sup>32</sup>

**Antihypertensives:** Among the antihypertensives, clonidine, a centrally acting alpha-2 adrenergic agent that modulates norepinephrine release, has been examined in a number of small-scale studies of postmenopausal women and those who were being treated with tamoxifen.<sup>45</sup> Although none of these trials were considered to be of good quality, clonidine administered at 0.1 mg/day was reported to have a modest effect in reducing hot flash frequency; a reduction of 20% was noted in one study and 14% in another, compared with placebo.<sup>45,75</sup>

**FIGURE 12 Use of nonhormonal therapies in the management of vasomotor symptoms**

Agent	Dose per day	Reduction in hot flashes (%)	Placebo effect (%)
Paroxetine <sup>a</sup>	25 mg	50	27
Venlafaxine <sup>b</sup>	75 mg	51	15
Gabapentin <sup>c</sup>	900 mg	45	29
Clonidine <sup>c</sup>	0.1 mg	38	20 <sup>a</sup>

<sup>a</sup>Stearns V, et al. JAMA. 2003;289:2827-2834.  
<sup>b</sup>Evans ML, et al. Obstet Gynecol. 2005;105:161-166.  
<sup>c</sup>Guttuso T Jr, et al. Obstet Gynecol. 2003;101:337-345.

Clonidine must be used with caution because it is a potent antihypertensive.<sup>32</sup> Nonetheless, results from a controlled study indicated no adverse hemodynamic effects with an oral formulation of 0.1 mg/day in women who experienced tamoxifen-associated hot flashes.<sup>76</sup> The overall tolerability of oral clonidine is poor because of adverse events, resulting in a 40% discontinuation rate among women who were treated for menopausal symptoms.<sup>77</sup> By contrast, a transdermal formulation of clonidine has better tolerability than the oral drug, but appears to have limited usefulness in the treatment of hot flashes because it provides only a 10% reduction from baseline in symptom severity.<sup>75</sup>

Another alpha-adrenoceptor antagonist, methyl-dopa, also has been examined in 2 small trials for its effectiveness in alleviating hot flashes.<sup>78,79</sup> The active metabolite of methyl-dopa (alpha-methylnoradrenaline), like clonidine, can inhibit the release of norepinephrine from central and peripheral adrenergic terminals. Both studies reported that methyl-dopa was more effective than placebo in reducing hot flashes. Accordingly, a double-blind treatment with methyl-dopa reduced the frequency of hot flashes by 65%, compared with a decrease of 38% in the control group.<sup>78</sup> In the second double-blind, randomized, crossover trial, methyl-dopa apparently reduced both the frequency and severity of hot flashes.<sup>79</sup> Nonetheless, in other studies, the drug has been associated with potentially serious side effects that include reduced blood pressure, a positive Coombs test, hemolytic anemia, and liver disorders.<sup>10</sup> Considering the risks vs benefits of the drug, then, the modest efficacy of methyl-dopa in reducing the frequency of hot flashes may be negated against the potential harms that the drug may induce.

**Other neuroactive agents:** Veralipride, a synthetic benzamide derivative with antidopaminergic action, has

been tested in small trials. In a study comparing the effects of several treatments of veralipride on menopausal symptoms, the number and severity of hot flashes were significantly reduced compared with placebo, but to a lesser extent than estrogen therapy.<sup>80</sup> In a double-blind study of 50 patients, treatment with veralipride significantly reduced both hot flashes and excessive perspiration in 63% and 80% of the subjects, respectively.<sup>81</sup> However, in another small-scale study of 10 women, treatment with veralipride reduced the frequency of hot flashes without significant adverse effects, except for moderate weight gain; extrapyramidal symptoms were noted in 1 patient.<sup>82</sup> Thus, the safety of veralipride has been questioned because of misuse and mistakes in administration that may lead to extrapyramidal disorders even many months after treatment has ended.<sup>83,84</sup> These may include acute dyskinesias or parkinsonism, tardive symptoms, and respiratory dyskinesia.<sup>85</sup>

#### Alternative therapies and lifestyle modifications

A significant number of women use complementary or alternative therapies to manage their menopausal symptoms. In a telephone survey of 886 women aged 45 to 65 years, 22% reported the use of at least one form of alternative treatment for menopausal symptoms.<sup>86</sup> The use of alternative regimens should be assessed carefully in order to provide a risk/benefit assessment. In this context, a systematic review of 70 randomized controlled trials concluded that although many of the alternative therapies are suggestive of potential benefits, there are insufficient data thus far to recommend any one of them.<sup>45</sup>

**Herbal therapy:** Black cohosh/St. John's wort: The major concerns with herbal treatments are the general lack of regulatory control of ingredients and the relative dearth of robust scientific studies demonstrating clinical

effectiveness. As such, there is little evidence that supports the efficacy of these herbal therapies in treating vasomotor symptoms, as they either were not tested in adequately powered randomized, controlled studies, or had negative results that continue to remain unreported.<sup>45</sup> Black cohosh is a widely used over-the-counter product that is sold as an ethanolic extract. To date, a number of clinical and observational studies have reported that black cohosh is an efficacious product in relieving hot flashes, although many of these studies have significant methodological problems. For example, a recent double-blind, placebo-controlled study showed that black cohosh was comparable to estrogen therapy in reducing the overall menopausal symptoms, but did not show significant improvement over placebo in hot flash/sweat subscores.<sup>45</sup> Also, in another randomized, double-blind, crossover study, treatment with black cohosh, 20 mg twice daily for two 4-week periods, showed the supplement was no more effective in reducing hot flash frequency than placebo.<sup>87</sup>

In addition to the use of black cohosh as a monotherapy, a recent randomized, double-blind, placebo-controlled study evaluated the efficacy of black cohosh and St. John's wort extracts as a fixed combination therapy in 301 women with climacteric complaints.<sup>88</sup> After a treatment period of 16 weeks, women who received the herbal extracts showed a significant improvement in climacteric symptoms compared with the placebo group: 50% versus 20% decrease in the mean Menopause Rating Scale score. In addition, the psychological symptoms also showed significant improvement in the treatment group compared with those treated with placebo: 42% vs 13% decrease in the mean Hamilton Depression Rating Scale score.<sup>88</sup>

**Biologically based substances:** Phytoestrogens are plant constituents with a phenolic structure that is similar to estrogen. Among the phytoestrogens, isoflavones from soy protein and red clover have been studied for their potential effects in relieving climacteric symptoms. Several studies have found that soy isoflavones do not exert significant effects on hot flash frequency, whereas some have reported a small decrease in hot flash severity or a reduction in frequency: 15% reduction over placebo with a daily intake of 60 g soy protein containing 76 mg of isoflavones.<sup>45</sup> Notably, a randomized, controlled study of 75 menopausal women reported significant reductions in the number of hot flashes by 38%, 51%, and 61% after 1, 2, and 4 months of treatment, respectively, vs a 21% reduction in the placebo group.<sup>89</sup>

A critical review that evaluated the outcomes of studies that examined the efficacy of isoflavones in reducing climacteric symptoms showed that the type of isoflavone may affect hot flash response.<sup>90</sup> Thus, studies that administered more than 15 mg of the isoflavone genistein reported a statistically significant decline in hot flashes.<sup>90</sup> Of note, a large-scale, randomized, double-blind, placebo-controlled, outpatient multicenter study of 177 postmenopausal women that assessed the efficacy of soy isoflavones (total of 50 mg genistein) for 6 weeks reported significant reductions in hot flash frequency and severity compared with changes in the placebo group.<sup>91</sup> However, by 12 weeks, the difference between treatment and placebo groups was no longer statistically significant.<sup>91</sup> Taken together, these results suggest a modest effect for soy isoflavones in alleviating hot flashes.

Red clover, a legume, is a plant source rich with isoflavones. A randomized, double-blind, placebo-controlled trial of 30 women with more than 12 months of amenorrhea showed that treatment with an extract of red clover 80 mg/day resulted in a significant reduction (44%) in hot flashes after 12 weeks of treatment.<sup>92</sup> Nonetheless, other studies have been unable to demonstrate that red clover-derived isoflavones are effective in alleviating hot flashes in menopausal women. To examine the effects of isoflavones in reducing hot flashes, Nelson and colleagues reviewed 17 controlled studies that used isoflavone extracts from red clover or soy.<sup>93</sup> Of these, only 1 study from the red clover group and 3 studies from the soy treatment group showed reductions in the frequency of hot flashes.

### Lifestyle modifications

A psychophysiological basis for the occurrence of hot flashes is supported by laboratory data that showed hot flashes could be elicited readily under controlled conditions.<sup>7</sup> Based on these laboratory findings, it has been suggested that acute or chronic stress and/or the effects of midlife transitions may potentiate hot flashes by decreasing the threshold for the triggering of flushing at the hypothalamic level, similar to the proposed effects of diminishing levels of estrogen.<sup>7</sup> Psychological stress during a hot flash may also affect the frequency of symptoms. For example, a state of anxiety experienced during a hot flash is likely to exacerbate the frequency and symptoms of hot flashes.<sup>7</sup>

Reductions in hot flash intensity, anxiety, and/or depression have been reported with relaxation and psychoeducational techniques. Although many studies that

used these behavioral approaches to improve climacteric symptoms have claimed either a trend or a statistically significant improvement in vasomotor symptoms, a critical review of trial methodology has revealed that most studies were underpowered because of the small sample sizes (11 of 14 studies had fewer than 45 participants).<sup>94</sup> In addition, the risk of bias in such behavioral studies is generally high, in part due to the patient-therapist relationship. Given that 4 weeks of placebo treatment has been shown to reduce hot flashes by approximately 30%, assessment of outcome by comparing baseline observations with postintervention measures is likely to introduce a bias of placebo effect that may confound the interpretation of data.<sup>94</sup>

Among the various behavioral approaches, relaxation and paced respiration are some techniques that have reduced the severity and frequency of vasomotor symptoms.<sup>95</sup> Paced respiration for hot flash reduction requires slow, deep abdominal breathing at symptom onset, whereas applied relaxation therapy involves the use of 8 to 12 sixty-minute sessions to learn different aspects of techniques to induce relaxation in 30 to 60 seconds when a hot flash event is triggered.<sup>96</sup> Although these approaches have limited effectiveness in improving vasomotor symptoms compared with the proven efficacy of pharmacotherapy, they are likely to be more effective in women who experience comorbid stress, anxiety, or depressive symptoms that exacerbate the frequency and severity of hot flashes. A number of coping strategies and lifestyle modifications may alleviate some of the symptoms. For example, a cool environment (18°C) alone may reduce the frequency of hot flashes, particularly during those nights when hot flashes cause awakenings. It is interesting to note that women with high perceived control have better symptom management through the use of more coping strategies, such as wearing layers of clothes to speed cool-down and by maintaining a positive attitude.<sup>45</sup>

A number of studies have indicated that a moderate level of physical activity may be therapeutically effective in reducing menopausal vasomotor symptoms. A prospective study in Sweden examined the frequency and severity of hot flashes in 142 menopausal women who had never received hormone therapy.<sup>97</sup> Women who regularly exercised reported hot flashes with reduced frequency compared with those in the control group: 21.5% vs 43.8%. A subsequent survey of 1323 women in a Swedish community reported that fewer physically active women had severe vasomotor symptoms than those who led a sedentary lifestyle.<sup>98</sup> Workouts such as

jogging and swimming were considered as intense activities, whereas cycling and recreational walking were categorized as less intense and least intense activities, respectively.<sup>99</sup> In a prospective study of 438 women, factors such as age, follicle-stimulating hormone (FSH) levels, and physical activity were compared with the occurrence of hot flashes.<sup>97</sup> Results showed that the hot flash index (a combination of hot flash frequency and severity) was greater in women with higher levels of circulating FSH and decreased in relation to age and exercise levels.

## Summary

Women who experience vasomotor symptoms such as night sweats and hot flashes have smaller thermoneutral zones than those who are asymptomatic. For many women, hot flashes are mild and transient, whereas for those with moderate-to-severe symptoms, treatment may help relieve the distressing symptoms and improve their quality of life. Hormone therapy is the most effective treatment to reduce vasomotor symptoms in women; however, it is contraindicated in women with risk factors such as breast cancer, a history of endometrial carcinoma, hyperplasia, or endometriosis, a history of thromboembolic events, and a high risk of cardiovascular disease.

Current guidelines recommend the use of an individualized, patient-specific treatment strategy that takes into account of the needs, preferences, and risk factors of each patient. When instituting hormone therapy, it is essential that patients be informed of the available treatment options (dose and route of administration) and understand the risks involved. Given the risk associated with combination hormone therapy, it is recommended that the lowest effective dose be administered for the management of vasomotor symptoms and that therapy not be prescribed as a preventive treatment for long-term, chronic diseases.

For those women who prefer nonhormonal pharmacotherapies, and for those who are contraindicated for hormones, venlafaxine, paroxetine, fluoxetine, and gabapentin may offer relief from vasomotor symptoms.<sup>10</sup> However, the efficacy of these agents is modest compared with estrogen-based therapy. In addition, a number of over-the-counter plant/herbal remedies, lifestyle modifications, and coping strategies have shown some positive results in alleviating vasomotor symptoms, although the available evidence for the effectiveness of these treatments is relatively weak. ■

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## POSTTEST QUESTIONS

1. According to STRAW nomenclature, late perimenopause is described as a stage when:

- a. Changes in menstrual cycle length are greater than 7 days
- b. Menstrual flow is reduced, with changes in cycle length greater than 10 days
- c. Two or more menstrual cycles are skipped
- d. Two or more menstrual cycles are skipped and there is at least 1 period of amenorrhea exceeding 60 days
- e. b and c

2. Which of the following statements is incorrect regarding vasomotor symptoms?

- a. Vasomotor symptoms are less prevalent during the late perimenopausal stage
- b. Postmenopausal women who experience hot flashes have smaller thermoneutral zones compared with those who do not experience them
- c. The average hot flash lasts from 1 to 5 minutes
- d. Vasomotor symptoms are due to an exaggerated activation of heat dissipation mechanisms such as peripheral vasodilation and perspiration

3. Based on evidence from the SWAN study, choose the correct descending order for risk of developing hot flashes.

- a. African American > Hispanic > Caucasian > Japanese
- b. African American > Caucasian > Hispanic > Japanese
- c. Hispanic > Japanese > Caucasian > African American
- d. Caucasian > Japanese > Hispanic > African American
- e. None of the above

4. Which of these factors relate(s) to hot flash occurrence?

- a. Cold temperature
- b. BMI greater than 27
- c. Cycling and swimming
- d. Eating soy products
- e. All of the above

5. According to the WHI study, the cumulative hazard for CHD risk in the use of estrogen therapy is age dependent. Which of the following statements is/are true?

- a. Conjugated equine estrogen administered to women 50 to 59 years of age lowered the CHD risk at baseline
- b. Conjugated equine estrogen administered to women 60 to 69 years of age lowered the CHD risk at baseline
- c. Conjugated equine estrogen administered to women 70 to 79 years of age lowered the CHD risk at baseline
- d. a and b
- e. b and c

6. Transdermal hormone therapy may have particular advantages for women:

- a. With elevated triglycerides
- b. With type 2 diabetes
- c. Who smoke
- d. Who prefer nondaily therapy
- e. All of the above

7. Transdermal hormone therapy differs from oral formulations in the following aspects.

- a. Transdermal formulations avoid first-pass liver metabolism
- b. Transdermal formulations use higher doses than oral formulations
- c. Transdermal formulations cause increased thromboembolism compared with oral formulations
- d. Transdermal formulations provide more stable circulating levels of hormone
- e. All of the above

8. Among the nonhormonal neuroactive therapies, which of the following drugs offers the most effective relief for vasomotor symptoms?

- a. Venlafaxine
- b. Gabapentin
- c. Clonidine
- d. Methyldopa
- e. Bellergal

9. Which of the following statements is/are true with regard to the use of venlafaxine in the treatment of menopausal vasomotor symptoms?

- a. Although venlafaxine can decrease the frequency of hot flashes in menopausal women, the efficacy is below that observed with estrogen therapy
- b. The most common adverse effects include nausea, insomnia, dry mouth, loss of appetite, and constipation
- c. Treatment with venlafaxine may cause sexual dysfunction
- d. All of the above

10. Select the alternative treatment approach known to reduce vasomotor symptoms.

- a. Paced respiration
- b. Cooling body temperature
- c. Moderate exercise
- d. Relaxing activities
- e. All of the above

# REGISTRATION AND EVALUATION FORM

## Vasomotor Symptoms:

Managing the transition from perimenopause to postmenopause

I certify that I have completed this educational activity and posttest and claim (please check one):  Physician credit hours  Nurse contact hours

SIGNATURE

*Please print clearly*

FIRST NAME, MI

LAST NAME, DEGREE

TITLE

AFFILIATION

SPECIALTY

MAILING ADDRESS

CITY

STATE

ZIP

DAYTIME TELEPHONE

FAX

EMAIL

**Physician:** This activity is designated for a maximum of 1.5 AMA PRA Category 1 Credits™.

**Nurse:** This activity is approved for 1.5 nursing contact hours.

**Release Date:** October 1, 2008

**Expiration Date:** September 30, 2009

**To receive a statement of credit, please complete the posttest and evaluation form and mail or fax them to:**

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**EXAMINATION:** Place an X on the box under the letter that represents the best answer to each question on the previous page. There is only ONE correct answer per question. Place all answers on this form:

	A	B	C	D	E
1.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**PROGRAM EVALUATION:** So that we may assess the value of this self-study program, we ask that you please fill out this evaluation form.

### Have the objectives for the activity been met?

1. Recognize menopause-related vasomotor symptoms to establish the clinical stages of menopausal transition  YES  NO
2. Discuss the underlying physiology of climacteric symptoms  YES  NO
3. Outline the various treatment options that are available for women with vasomotor symptoms and the risks/benefits associated with each  YES  NO
4. Evaluate the evidence-based data on hormone therapy and formulate a patient-specific treatment plan for menopausal vasomotor symptoms  YES  NO
5. Counsel women and their partners on the risks/benefits of alternative therapies to treat menopausal vasomotor symptoms  YES  NO

**Was this publication fair, balanced, and free of commercial bias?**  YES  NO

IF NO, PLEASE EXPLAIN:

### 1. How often do you currently use each of the following patient care strategies for your patients with vasomotor symptoms? (Scale: 1=Never, 2=Not very often, 3=Sometimes, 4=Very often, and 5=Always)

- a. Conduct a risk/benefit analysis before instituting an appropriate therapy 1 2 3 4 5
- b. Individualize treatment plans specific to the needs and risk profile of each patient 1 2 3 4 5
- c. Counsel patients on the available treatment options, including nonpharmacologic options, to ensure they make an informed decision 1 2 3 4 5
- d. Follow up with patients periodically for symptom control, compliance, and side effects 1 2 3 4 5

### 2. Based on your participation in this CE/CME activity, how often do you now plan to use each of the following patient care strategies for your patients with vasomotor symptoms? (Scale: 1=Never, 2=Not very often, 3=Sometimes, 4=Very often, and 5=Always)

- a. Conduct a risk/benefit analysis before instituting an appropriate therapy 1 2 3 4 5
- b. Individualize treatment plans specific to the needs and risk profile of each patient 1 2 3 4 5
- c. Counsel patients on the available treatment options, including nonpharmacologic options, to ensure they make an informed decision 1 2 3 4 5
- d. Follow up with patients periodically for symptom control, compliance, and side effects 1 2 3 4 5

**Effectiveness of this method of presentation:** POOR FAIR GOOD VERY GOOD EXCELLENT

**What other topics would you like to see addressed?**

**Comments**

SUPPLEMENT TO

**THE JOURNAL OF**  
**FAMILY**  
**PRACTICE**

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# VASOMOTOR SYMPTOMS

Managing the transition  
from perimenopause to  
postmenopause



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