

Hormone therapy and venous thromboembolism in menopausal women

► Janet F. McLaren, MD, and Kurt Barnhart, MD, MSCE

Venous thromboembolism (VTE) is a significant disease entity with an estimated annual incidence of approximately 1 per 1000 adults in the US population.¹ VTE is the formation of a blood clot in the veins, which can travel from the site where it formed and block blood flow at other locations in the body. VTE is the collective term for 2 forms of thrombosis: deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT refers to the formation of a blood clot in one of the deep veins within the body, such as in the leg or pelvis. PE is the blockage

of the pulmonary artery or one of its branches, typically from a blood clot that travels from its original location to the arterial supply of the lung.

Established risk factors

Among the list of established risk factors for VTE is exposure to sex hormones. In fact, numerous studies have shown that exposure to estrogen in the form of hormonal contraceptives or menopausal hormone therapy (HT), with or without progestin, increases the risk of clot formation.

Still, for menopausal women, estrogen remains the primary therapy for vasomotor symptoms, used in conjunction with progesterone or progestins to protect the endometrium in women with an intact uterus. An understand-

ing of the risk of VTE associated with HT is important to best prescribe and manage these medications in our patients.

Possible inherited predisposition

A growing number of recognized heritable thrombophilias exist, which result in a predisposition to VTE. These include, but are not limited to:

- Factor V polymorphisms (the most common form being factor V Leiden)
- Prothrombin G20210A mutation
- Antithrombin III deficiency
- Deficiencies of protein C and protein S

The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study included a systematic review and meta-analysis of 9 studies to assess the risk of VTE in women with thrombophilias.² It reported an increased risk of VTE in women with thrombophilia compared with women who did not carry a mutation; specifically it found an odds ratio (OR) of 3.8 (95% confidence interval [CI], 2.2-6.4) for women with the factor V Leiden mutation, an OR of 1.34 (95% CI, 0.8-2.2) for prothrombin G20210A, an OR of 3.2 (95% CI, 0.8-12.3) for

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FROM THE EDITOR



A magnified look at symptoms and risks of hormone therapy

This issue of *Menopausal Medicine* addresses 2 evolving areas of research. Both involve taking a closer look at aggregates of data to better determine benefits and risks of hormone therapy.

As I often mention in these editorials, each woman is different and brings a unique set of genes, vulnerabilities, and healthy and unhealthy habits to her menopause. When confronted by an individual patient, we must continue to stretch our knowledge, examine the 3-dimensional being before us, and come up with a private and personal set of recommendations that are the most likely to help our patient and keep her as healthy as possible.

We are now fortunate enough to have aggregate data on the overall risks and benefits of our most frequent intervention—hormone therapy—to alleviate symptoms. We are even beginning to accumulate some data on alternatives to hormones, although the bulk of the data suggest inferiority to hormones, if not outright ineffectiveness of these treatments.

Drs Goldsmith and Weiss point out that we may be helping less when our patient is African American. Women of African American ethnicity are more likely to experience hot flashes than are any other ethnic group, and they are more likely to report more severe symptoms.¹ By re-analyzing existing data by race, Drs Goldsmith and Weiss make a persuasive argument that symptoms are not only worse for African American women, but commonly used remedies for menopausal symptoms are less effective. Clearly, such a situation warrants careful examination, as it will change the risk-to-benefit equation for African American women in general.

Drs McLaren and Barnhart return to a series of large studies of venous thromboembolism to provide not only an overview but a closer look at which women are most likely to be at risk of VTE from hormone therapy. It is likely that we will learn over time how best to risk-stratify women to reduce the likelihood of this rare but life-threatening complication of hormone therapy. These authors point the way to the next series of studies that will allow us to provide better care for patients.

Epidemiological studies provide all-important information that we can apply to big questions, but without training a magnifying glass on the data, we will fail to identify the next question that needs to be answered. And there will always be a “next question!”

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antithrombin deficiency, an OR of 2.4 (95% CI, 1.2-5.1) for protein C deficiency, and an OR of 5.3 (95% CI, 2.5-11.4) for protein S deficiency.² Of note, heterozygote and homozygote populations were pooled in these calculations. Thus, women with thrombophilia have an elevated baseline tendency toward VTE on which other risk factors are imposed.

Additional risk factors

A number of additional factors affect the risk of venous thromboembolic disease (TABLE 1). Surgery and the immobilization of hospitalization are known risk factors for VTE; as a result, prophylactic therapy and policies exist to prevent VTE in these scenarios. The Sirius study, a case-control study in France to identify risk factors for DVT, cited an OR of 16.3 ($P<.001$) for orthopedic surgery, and an OR of 9.5 ($P<.001$) for general surgery procedures.³ Cancer is another well-known risk factor, with an OR of 2.3 ($P=.001$) in the Sirius study. Other risk factors identified in the study include a history of prior DVT or PE (OR, 15.6; $P<.001$), obesity (OR, 2.4; $P<.001$), and long-distance travel (OR, 2.4; $P<.001$).

Exposure to hormone therapy

Although it has long been understood that sex hormone exposure in the form of oral contraceptives imparts an increased risk of VTE, it was initially believed that the lower doses of estrogen associated with menopausal HT formulations did not carry this same risk.⁴ However, observational studies in the 1990s began to report a 2- to 4-fold risk of VTE with HT exposure,⁵⁻⁷ which was subsequently investigated by randomized trials.

The Heart and Estrogen/Progestin Replacement Study (HERS) was a prospective, randomized controlled trial of conjugated equine estrogens (CEE) with medroxyprogesterone acetate (MPA) in postmenopausal women with a history of coronary disease.⁸

The study was designed to evaluate secondary disease prevention in women with coronary disease, and enrolled 2763 women from 1993 to 1994 who were followed for an average of 4.1 years. A planned secondary outcome was to evaluate the risk of VTE with HT. In agreement with the more recent observational data, an increased risk of VTE was observed. During 10,985 woman-years of follow-up, there were 34 episodes of VTE in the hormone-treated group (6.2 per 1000 woman-years) compared with 13 in the placebo group (2.3 per 1000 woman-years), resulting in a relative hazard of 2.7 (95% CI, 1.4-5.0). In addition to the primary finding that HT did not prevent recurrent cardiac events, the study also revealed an excess risk of VTE of 3.9 cases per 1000 woman-years due to exposure to HT.

Reviewing the WHI

The Women's Health Initiative (WHI) was a subsequent prospective, randomized controlled trial designed to assess primary prevention of coronary heart disease (CHD) with CEE plus MPA in healthy postmenopausal women with a uterus and CEE alone in healthy postmenopausal women without a uterus.⁹ In addition to CHD, the study investigated VTE as part of a global risk/benefit index and observed 167 cases of VTE in women taking CEE plus MPA (3.5 per 1000 woman-years) and 76 cases in women taking placebo (1.7 per 1000 woman-years). This resulted in a hazard ratio of 2.1 (95% CI, 1.6-2.7) for exposure to CEE plus MPA.¹⁰ This risk increased with age, obesity, and the factor VLeiden heterozygote and homozygote genetic variants. In addition, the risk from HT was seen as early as the first year following exposure and continued to increase with duration of exposure.

Other investigations after WHI

To further investigate the impact of HT in menopausal women, a cohort from

TABLE 1 VTE risk factors

| RISK FACTOR FOR VTE | ESTIMATED RR* |
|--|----------------|
| Prior VTE event | 15.6 |
| Obesity (BMI>30 kg/m ²) | 2.4 |
| Long-distance travel | 2.4 |
| Surgery | |
| • Orthopedic surgery | 16.3 |
| • General surgery | 9.5 |
| Cancer | 2.3 |
| Heritable thrombophilias (mixed heterozygote and homozygote populations) | |
| • Factor V Leiden | 3.8 (2.2-6.4) |
| • Prothrombin G20210A mutation | 1.3 (0.8-2.2) |
| • Antithrombin deficiency | 3.2 (0.8-12.3) |
| • Protein C deficiency | 2.4 (1.2-5.1) |
| • Protein S deficiency | 5.3 (2.5-11.4) |

BMI, body mass index; VTE, venous thromboembolism.
*RR, relative risk, 95% confidence interval.

a United Kingdom primary care practice database, the General Practice Research Database (GPRD), was used to simulate the WHI.¹¹ The study included 37,730 unexposed women and 13,658 exposed women treated with CEE and norgestrel. Women aged 55 to 79 were included to match the average age of women in the WHI. During the 5 years of observation, the incidence rate of VTE was 4.2 per 1000 woman-years in the unexposed group and 5.8 per 1000 woman-years in the exposed group, resulting in an adjusted hazard ratio of 1.6 (95% CI, 1.4-1.8). This confirmed the previous findings of an increased risk of VTE with HT, although the degree seen in the GPRD was slightly less than that demonstrated in HERS or the WHI (TABLE 2). In addition, the baseline rate of VTE was notably higher in the unexposed GPRD population compared with the HERS and WHI placebo groups.

These studies, in addition to other quality observational studies and randomized trials that have been conducted, provide very strong evidence for an increased risk of VTE associated with

TABLE 2 VTE risk with estrogen plus progestin hormonal therapy

| | BASELINE VTE RATE (PLACEBO OR CONTROL GROUP)* | VTE RATE WITH HORMONE THERAPY* | RR (95% CI) |
|-------------|---|--------------------------------------|---------------|
| HERS | 2.3 | 6.2 | 2.7 (1.4-5.0) |
| WHI | 1.7 | 3.5 | 2.1 (1.6-2.7) |
| GPRD | 4.2 | 5.8 | 1.6 (1.4-1.8) |

CI, confidence interval; GPRD, General Practice Research Database; HERS, Heart and Estrogen/Progestin Replacement Study; RR, relative risk. VTE, venous thromboembolism; WHI, Women's Health Initiative. *Per 1000 patient-years.

HT, which increases with duration of use and adds to the possibility of VTE posed by the many risk factors other than HT use.

What role does progestin play?

A second arm of the WHI provided important information regarding HT and VTE risk: What role does progestin play in this relationship? Data published from the CEE-only arm (women with a history of hysterectomy) in 2004 observed 101 VTE events in the CEE arm and 78 in the placebo arm, resulting in a hazard ratio of 1.3 (95% CI, 0.9-2.1), which did not reach statistical significance.¹² Similar to the effect seen in the CEE plus MPA WHI study group, the risk of VTE in the exposed group did increase with duration of use but was smaller in effect.

An observational study published by Smith et al in 2004 reported similar findings.¹³ In their case-control study of first VTE in perimenopausal and postmenopausal women using HT, they found an OR of 1.3 (95% CI, 0.9-1.9) in women using CEE alone and an OR of 2.2 (95% CI, 1.5-3.1) in women using CEE plus progestin. These 2 studies suggest that it is not only the estrogen component of HT that accounts for the increased risk of VTE, but that the progestin plays a significant role as well.

As there are different types of progestins, the Estrogen and Thromboembolism Risk (ESTHER) study was designed, in part, to assess the effect of different progestins on the risk of VTE.

The ESTHER trial is a multicenter, case-control study of VTE in postmenopausal women in France, which enrolled between the years 1999 and 2005.¹⁴ Women in the study were classified as oral or transdermal estrogen users and were also classified by progestin type: micronized progesterone, pregnane derivative (eg, MPA, medrogestone, cyproterone acetate), or norpregnane derivative (norgestrel acetate or promegestone).

The trial found an overall OR of 4.0 (95% CI, 1.6-10.1) for use of oral estrogen (estradiol; average daily dose, 1.5 mg) combined with any progesterone. This OR is notably higher than that found in other studies, potentially due to the restriction of cases to only idiopathic DVTs, underlying differences in the French population, the dose and type of estrogen used, and/or imprecision due to small sample size.

Interestingly, when stratified by progesterone type, this increased risk remained the same for use of norpregnane derivatives (OR, 4.0; 95% CI, 1.7-9.4), but was not seen with the use of either micronized progesterone (OR 0.9, 95% CI 0.4-2.2) or pregnane derivatives (OR 0.9; 95% CI, 0.4-2.2). This is not in agreement with the studies mentioned previously, in which MPA, a pregnane derivative, was found to increase the risk of VTE. Until the relationship between the different progestins and VTE is better understood, it is fair to conclude that they likely contribute to this risk, the degree to which may vary by compound.

Does estrogen type affect degree of risk?

It is also important to know if the type of estrogen affects the risk of VTE. As mentioned, it is unclear if the OR of 4.0 seen in the ESTHER study is higher than those of HERS or WHI due to the type of estrogen used (estradiol) or other differences between the 2 study populations.¹⁴ This question was also addressed in part by the study of Smith et al.¹³ The cohort for their study was the patient base of a large health maintenance organization (HMO) in Washington state. During the time period of the study, the type of estrogen on formulary was switched from esterified estrogens (EE) to CEE. The study found an increased risk of VTE with CEE use (OR, 1.65; 95% CI, 1.24-2.19), but not with use of EE (OR, 0.92; 95% CI, 0.69-1.22). With limited pharmacologic data on the differences between these compounds in vivo, the finding of this study that EE might be safer than CEE warrants further investigation.

Route of estrogen administration

Does the route of estrogen administration change the risk of VTE? The ESTHER study was designed to assess if the route of estrogen—oral vs transdermal—altered the risk of VTE. The study found no increased risk for woman exposed to transdermal estrogen (OR, 0.9; 95% CI, 0.4-2.1); however, there was an OR of 4.0 (95% CI, 1.6-10.1) for oral estrogen use.¹⁴ A recent systematic review and meta-analysis of HT and VTE pooled this result with other quality studies and found an OR of 1.2 (95% CI, 0.9-1.7) for transdermal estrogen, in comparison with the pooled OR of 2.5 (95% CI, 1.9-3.4) for oral estrogen.¹⁵

Some data exist to explain the differences seen. Transdermal administration avoids the first-pass metabolism of the liver and, in doing so, affects coagulant factors differently than do oral estrogens. A cross-sectional study of menopausal women, both users and

nonusers of HT, revealed an increase in factor IX, activated protein C (APC) resistance, and C-reactive protein with oral but not transdermal estrogen use.¹⁶ A randomized, placebo-controlled trial of oral and transdermal estrogen therapy also demonstrated a significant increase in resistance to APC with oral estrogen, and only a minimal increase with transdermal estrogen.¹⁷ At present, the small number of observational studies and existing biochemical data hold promise that the transdermal route may be a safer way to administer estrogen therapy.

Studying obesity or thrombophilic gene mutations

Sex hormone exposure is one of many risk factors for VTE and, in the Sirius study, more than 50% of the cases of VTE had 2 or more risk factors, whereas more than 80% of the control patients had 0 or 1 risk factor.³ In order to best risk stratify patients, the use of HT has been studied in women with obesity or thrombophilia to assess the risk of VTE in these individuals (TABLE 3).

The WHI investigators stratified the results of their CEE plus MPA group by body mass index (BMI) to assess the effects of HT use in women with obesity. In women not taking HT, they found an OR of 1.6 (95% CI, 0.8-3.2) for overweight individuals (BMI, 25-30) and an OR of 2.9 (95% CI, 1.5-5.4) for obese individuals (BMI, >30)¹⁰. With the addition of CEE and MPA, the risk increased to 1.8 (95% CI, 0.9-3.5), 3.8 (95% CI, 2.1-5.4), and 5.6 (95% CI, 3.1-10.1) for normal-weight, overweight, and obese individuals, respectively.

Similar findings were seen in the ESTHER study; with baseline risks of 2.7 (95% CI, 1.7-4.5) for nonexposed overweight individuals and 4.0 (95% CI, 2.1-7.8) for obese individuals. Oral estrogen use increased the ORs to 5.9 (95% CI, 3.0-11.7), 10.2 (95% CI, 3.5-30.2), and 20.6 (95% CI, 4.8-88.1) for

TABLE 3 Risk of hormone therapy in women with risk factors

| | RISK FACTOR ALONE (RR) | RISK FACTOR + ORAL HORMONE THERAPY (RR) |
|--------------------------------|------------------------|---|
| OVERWEIGHT/ OBESITY | | |
| WHI | | |
| Overweight (BMI 25-30) | 1.6 (0.8-3.2) | 3.8 (2.1-5.4) |
| Obese (BMI >30) | 2.9 (1.5-5.4) | 5.6 (3.1-10.1) |
| ESTHER | | |
| Overweight (BMI 25-30) | 2.7 (1.7-4.5) | 10.2 (3.5-30.2) |
| Obese (BMI >30) | 4.0 (2.1-7.8) | 20.6 (4.8-88.1) |
| THROMBOPHILIA | | |
| WHI | | |
| Factor V Leiden heterozygote | 1.0 ^a | 2.6 ^b (1.3-5.2) |
| Factor V Leiden homozygote | | 7.5 ^b (0.6-87.8) |
| TREATS | | |
| Factor V Leiden ^c | 3.6 (1.4-9.0) | 13.2 (4.3-40.5) |
| ESTHER | | |
| Factor V Leiden ^c | 2.6 (1.3-5.4) | 16.4 (4.3-62.2) |
| Prothrombin G20210A mutation | 6.4 (2.5-16.5) | — |

BMI, body mass index; RR, relative risk (95% confidence interval); ESTHER, Estrogen and Thromboembolism Risk study; TREATS, The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening; WHI, Women's Health Initiative.
^aReference value.
^bCompared to reference value.
^cMixed population of heterozygote and homozygote.

normal-weight, overweight, and obese individuals, respectively.¹⁸

In the ESTHER study, transdermal estrogen did not significantly increase the risk of VTE, irrespective of BMI, potentially making this a safer option in overweight and obese patients if the studies' results are confirmed.

Both studies also looked at the risk of VTE in women with known thrombophilic gene mutations. In the WHI CEE plus MPA study, a nested case-control study of 147 cases and 513 controls was performed, in which serum was tested for the factor V Leiden mutation, the prothrombin G20210A mutation, and other biomarkers. Only factor V Leiden was associated with an increased risk of VTE, with an OR of 2.6 (95% CI, 1.3-5.2) for heterozygotes on HT and 7.5 (95% CI, 0.6-87.8) for homozygotes on HT.¹⁰

These results were similar to those of a meta-analysis of 3 studies evaluating the use of HT in women with factor V Leiden. In this study, the baseline OR of 3.6 (95% CI, 1.4-9.0) in those with factor V Leiden (combined heterozygote and homozygote mutations) was increased to 13.2 (95% CI, 4.3-40.5) in those with the factor V Leiden who were receiving HT.²

In the ESTHER study, the investigators genotyped all study participants for 2 prothrombotic mutations: factor V Leiden and prothrombin G20210A. They found a baseline OR of 2.6 (95% CI, 1.3-5.4) for factor V Leiden (combined heterozygote and homozygote mutation carriers) and 6.4 (95% CI, 2.5-16.5) for the prothrombin gene mutation (also combined heterozygote and homozygote carriers), which increased to 16.4 (95% CI, 4.3-62.2) for factor

Risks of VTE unassociated with sex hormone exposure

Studies on the incidence of venous thromboembolic disease have helped to characterize the disease and identify risk factors. Population-based studies demonstrate that the incidence of both deep vein thrombosis (DVT) and pulmonary embolism (PE) increase with age, with an exponential increase in both males and females beginning at age 50. One study revealed a baseline annual incidence of VTE at 30 to 50 cases per 100,000 individuals under age 50. This annual rate increases to 300 cases per 100,000 for patients aged 65 to 69, and 800 cases per 100,000 for patients over age 85. The incidence rates were equal in men and women.¹ The rate of VTE also varies by ethnicity; a study of VTE and ethnicity within the Kaiser health plan in Northern California revealed rates of 2.1 and 2.2 cases per 10,000 person-years for Caucasian and African American populations, and 0.9 and 0.2 cases per 10,000 person-years for Hispanic and Asian populations.² This pattern of variation by ethnicity, in which lower risks are seen in Hispanic and Asian populations, has been confirmed in other studies.³

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V Leiden subjects receiving HT. No control both carried the prothrombin gene mutation and used oral estrogen, thus no OR could be calculated for this group.¹⁹ Again, transdermal estrogen use did not significantly raise the risk above the elevated baseline in those with thrombophilia, potentially making this a safer option for those patients.

Are SERMs and VTE safer alternatives?

Tamoxifen and raloxifene, both selective estrogen receptor modulators (SERMs), are not used for management of menopausal symptoms. They are used in postmenopausal women, however, for breast cancer prevention and treatment and, in the case of raloxifene, prevention and treatment of osteoporosis. Both have been shown to increase the risk of VTE. Tamoxifen was shown to be effective for breast cancer prevention in the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study. In this study, women receiving tamoxifen were found to have an increased risk of VTE, with an RR of 3.0 (95% CI, 1.2-9.3) for PE and an RR of 1.6 (95% CI, 0.9-2.9) for DVT.²⁰

Raloxifene was first studied for the treatment of osteoporosis, and data from these trials also showed an increased risk of VTE as a secondary outcome.²¹ A recent meta-analysis summarizes the risk of VTE in postmenopausal women using raloxifene from 9 clinical trials; the OR for VTE was 1.6 (95% CI, 1.2-2.1), not significantly different from the risk observed with HT.²² Thus, raloxifene is not a safer option than estrogen for prevention or treatment of osteoporosis with respect to VTE risk.

Because both tamoxifen and raloxifene had shown efficacy in breast cancer prevention in postmenopausal women, the Study of Tamoxifen and Raloxifene (STAR) trial was designed to compare the relative effect and safety of these 2 drugs. When compared

head to head, the drugs were equally effective in preventing invasive breast cancer. But among other differences found, there were fewer VTE events in the raloxifene group. After 6 years of observation, the cumulative incidence of VTE events was 21 per 1000 in the tamoxifen group and 16 per 1000 in the raloxifene group, resulting in an RR of 0.7 (95% CI, 0.5-0.9).²³ Thus, both SERMs appear to carry a risk of VTE that is similar to HT, which may be slightly lower for raloxifene.

The role of phytoestrogens

Limited information exists to estimate the risk of VTE from phytoestrogens, which have mixed estrogen agonist and antagonist properties similar to SERMs. Although studies on the efficacy of phytoestrogens for vasomotor symptoms are mixed, soy and black cohosh are used by many women who prefer not to use synthetic estrogen. One trial has investigated the safety and efficacy of phytoestrogens. The Herbal Alternatives for Menopause (HALT) study was a randomized, controlled trial that compared black cohosh (160 mg daily), dietary soy (2 servings daily, ~12-20 g soy protein), a multibotanical, CEE (0.625 mg daily), and placebo.²⁴ The study did not show efficacy of black cohosh for treatment of vasomotor symptoms, nor did any of the herbal therapies show a change in estradiol level as seen with CEE treatment.²⁴ The HALT study did not comment on VTE specifically, nor did it reveal any significant health risk of taking phytoestrogens. However, when phytoestrogen therapy is effective, it is possible that it carries with it an increased risk of VTE as seen with estrogen and SERMs. Therefore, phytoestrogen therapy should not be presumed to be free of risk until further data are available.

Future research

While much has been learned about the efficacy and safety of postmenopausal

HT in the last few decades, there are many new questions to answer. Is transdermal estrogen really safer to use with respect to VTE? Which progestin can provide the needed endometrial protection without increasing risk? Can a better SERM be developed that would provide bone protection without increasing VTE risk? Advances in these areas will help guide us to better manage these medications in our menopausal patients.

One study to look forward to is the Kronos Early Estrogen Prevention Study (KEEPS), a multicenter trial comparing 0.45 mg of CEE, transdermal estradiol, and placebo (all used with cyclic micronized progesterone) to prevent cardiovascular disease.²⁵ The enrollment

period is from 2005 to 2010, with a 5-year follow-up. This study promises to provide new information in much-needed areas.

Conclusion

VTE is a common and serious condition, with the risk of acquiring it increasing with age and sex hormone exposure. This makes postmenopausal women particularly susceptible to VTE and requires health care providers to understand all possible risks and benefits to prescribe HT judiciously. Points to keep in mind as you counsel your patients on the decision of whether or not to use HT include the following:

- HT is effective when indicated for treatment of vasomotor symptoms.

- HT should be avoided in women at higher risk of VTE, such as those who have prior VTE or thrombogenic mutations, who are undergoing surgery, or who are subject to immobilization.
- Transdermal estrogen may be a safer alternative to oral estrogen with regard to VTE risk, especially for obese women.
- Estrogen and raloxifene are options for prevention and treatment of osteoporosis, especially for those women who cannot tolerate bisphosphonate therapy.
- Future studies may help to better define and minimize the risks of HT, thereby improving our ability to treat menopausal symptoms.

Disclosures

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Historical changes in hot flash treatment options

Race/ethnicity plays a role

► Laura T. Goldsmith, PhD, and Gerson Weiss, MD

Hot flashes and night sweats are the most commonly reported symptoms during menopause and the symptoms that most frequently cause women to seek medical care. Up to 80% of US women experience hot flashes at some time during perimenopause or postmenopause.

The prevalence of hot flashes varies with culture and ethnicity. Hot flashes occur more frequently and with greater severity, in African American women. In addition to having more frequent and more severe menopausal symptoms, African American women have an earlier onset of natural menopause than do Caucasian women (*see complete story on page S10*).

Menopause is defined as the permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy, or radiation. Natural menopause is recognized after 12 consecutive months without menstrual periods that are not associated with a physiologic (eg, lactation) or pathologic cause. The terminology used to describe the various stages that occur before and after the final menstrual period was defined by the Stages of Reproductive Aging Workshop (STRAW).¹ STRAW described 3 key

stages: the reproductive stage, menopausal transition, and postmenopause. The reproductive stage begins with the first menstrual period and ends with the beginning of the menopausal transition, when cycles become variable and circulating follicle-stimulating hormone (FSH) levels are increased. The postmenopause begins 12 months after the final menstrual period. The term perimenopause extends from the menopausal transition to the postmenopause.

Causes of hot flashes remain an enigma

Hot flashes often severely limit daily function and may be responsible for sleep disorders in many women. Their physiology and etiology are poorly understood. The precise trigger of a hot flash is not known. Using estrogen to treat hot flashes is based on the increase in symptoms when estrogen levels decline and the effectiveness of estrogen therapy. However, there is not always a correlation between levels of estrogen and symptom occurrence. Furthermore, symptoms occur when levels of estradiol are not declining, indicating that declining estrogen alone may be an insufficient explanation for occurrence of symptoms. For example, premenopausal symptomatic women may have estrogen secretion that is similar in quantity or higher than the estrogen secretion of younger women.^{2,3} Thus, it is clear that they are not hypoestrogenic (ie, having lower than normal levels of estrogen). Years after menopause,

most women are asymptomatic, even with strikingly low levels of circulating estrogen. These data strongly suggest that estrogen deficiency alone cannot explain vasomotor symptoms.

Aging vs estrogen deficiency?

Available data suggest that vasomotor symptoms result from hypothalamic changes, which are caused by the aging process rather than estrogen deficiency.⁴ Thermoregulation studies in animals indicate a role of the hypothalamus and other central nervous system components in the etiology of vasomotor symptoms that occur with reproductive aging.⁵ The hypothalamus controls thermoregulation. In perimenopausal and postmenopausal states, the hypothalamus seems to destabilize thermoregulation. Estrogen or other agents may stabilize hypothalamic thermoregulation. Currently, understanding of the causes of hot flashes is inadequate to enable therapy directed toward any specific etiology. However, in view of current knowledge, an approach directed at the central nervous system seems warranted.

In addition to commonly occurring in older women, hot flashes also occur in women with chemotherapy-induced ovarian failure or in those being treated for endometriosis or infertility with GnRH agonists/antagonists; in younger women with idiopathic premature ovarian failure or oophorectomy; and in men being treated for prostate cancer with androgen deprivation therapy (ADT). Thus, while hot flashes affect millions of women, they are also a major quality-of-life issue for a significant proportion of men receiving ADT. It is estimated that more than 150,000 men in the United States have hot flashes associated with ADT therapy.

Hormone therapy was preferred treatment

Hormone therapy (HT)—either estrogen alone or estrogen plus progestins—

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has been the preferred treatment for menopausal vasomotor symptoms because of its high efficacy. Estrogen treatment markedly improves the frequency and severity of hot flashes, reducing frequency by 80% to 95%—an effectiveness that has been demonstrated repeatedly in randomized, placebo-controlled trials. Hormonal preparations have been found to be 2 to 5 times more effective than placebos, reducing self-reported hot flashes by 50% to 100% in women and 80% in men given transdermal estradiol.

However, since the publication in 2002 of the results of the Women's Health Initiative (WHI),⁶ there has been a substantial decline in hormone use for treatment of menopausal symptoms. Findings from the WHI failed to confirm previous expectations about the net benefits of menopausal hormone therapy and have resulted in reduced use of these medications.

Additional non-estrogen therapies introduced

Since publication of the WHI findings, attempts to find effective non-estrogen therapies have increased. Various alternative therapies, including herbs, soy products, and black cohosh, have been tried in order to alleviate hot flashes, with many showing no effect.⁷ A number of centrally acting drugs have been tested in published clinical trials, including the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), alpha-adrenergic agonists, monoamine oxidase (MAO) inhibitors, antidopaminergics, beta-blockers, and gabapentin. Several in-depth comprehensive reviews of clinical studies on the effects on various nonhormonal treatments have been published.⁸⁻¹¹

As noted in these reports, and in the 2004 National Institutes of Health report, *Assessing and Improving Measures of Hot Flashes*, most are studies of a small number of subjects, and some

were carried out for only a short time period.¹² Time of study is important, since it is not clear if any benefits seen at 4 weeks will be maintained at later time periods. For example, the combination belladonna-ergotamine tartrate-phenobarbital has been shown to have significant benefits over placebo in the treatment of hot flashes after 4 weeks, but is no longer efficacious after 8 weeks of treatment.¹³ The US Food and Drug Administration (FDA) recommends at least 12 weeks of double-blind therapy for clinical trials of estrogen-based therapies for hot flashes. Only a few large (>50 subjects) randomized, double-blind, placebo-controlled trials of several of these agents have been performed, and only gabapentin has been tested in comparison to estrogen.

The SSRIs have been the most extensively evaluated agents in these trials. Generally, results from small-scale, short-duration trials showed that SSRIs such as sertraline may be effective in reducing frequency and severity of hot flashes. However, larger, longer studies have shown mixed results. For example, a 1997 study of 15 postmenopausal women found that sertraline may be effective in reducing the frequency and severity of hot flashes.¹⁴ Other studies have shown either no effect of sertraline in women with breast cancer, or no effect or minimal effectiveness in menopausal women.

Other SSRIs that have been studied for treatment of hot flashes show either no benefit over placebo or mixed results. Study of citalopram indicated no benefit over placebo.¹⁵ Results of studies of fluoxetine have shown mixed results; one study showed no benefit over placebo in a group of 150 postmenopausal women, and a modest improvement in women with breast cancer.^{15,16} A prospective, randomized, 6-week trial reported reduced severity and frequency of hot flashes in breast cancer patients treated with paroxetine.¹⁷

In addition to the inconsistent results of these drugs, as many as 30% of women treated with SSRIs report sexual dysfunction,¹⁸ and treatment with SSRIs is associated with weight gain.¹⁹ Also, certain reports indicate increased hot flashes with SSRI treatment.²⁰ Thus, these drugs may be limited in their usefulness.

Studies show mixed results

Studies of the SNRIs have also reported mixed results. One randomized, controlled trial reported reduced hot flash severity and frequency in women with breast cancer treated with venlafaxine for 4 weeks,²¹ whereas another randomized, controlled trial reported no effect of venlafaxine on hot flash frequency or severity in postmenopausal women.²² In contrast, a trial of desvenlafaxine significantly reduced symptoms in postmenopausal women. Enthusiasm for use of these drugs is compromised due to associated sexual dysfunction, gastrointestinal intolerance and the rare appearance of hypertension.²³

Clonidine, an alpha-adrenergic agonist developed for treatment of hypertension, has been tested as a treatment for hot flashes. Studies have shown reduced hot flash frequency at 4 weeks in menopausal and breast cancer patients and at 8 weeks in naturally menopausal women and in women with breast cancer. In contrast, in an earlier study of 100 women, Lindsay and Hart (1978) saw no effect of clonidine, with a 50% dropout rate.²⁴ The tolerability of this drug was considered poor due to various adverse events, particularly postural hypotension. Since clonidine is a potent antihypertensive and is poorly tolerated, it is rarely viewed as an appropriate therapy for hot flashes. In the 1980s, 3 trials of methyl dopa were reported, which have been viewed as inconclusive due to either low numbers of subjects who completed the study or inadequate analysis of the data.⁸ Thus,

Prevalence of hot flashes varies among African Americans and Caucasians

The prevalence of hot flashes varies with culture and ethnicity.¹⁻⁵ Hot flashes occur more frequently, and with greater severity, in African American women. This has been demonstrated in 2 independent, population-based studies: the Penn Ovarian Aging Study, which longitudinally assessed subjects for 9 years, and the Study of Women's Health Across the Nation (SWAN), a multiethnic, community-based natural history cohort study of women at 7 US sites who are followed annually as they approach and traverse menopause.

In the Penn Ovarian Aging Study, 436 women (218 African American and 218 Caucasian) between the ages of 35 and 48 were categorized as ever (n=356) or never (n=257) experiencing hot flashes. Data showed that African American women (53%) were significantly more likely than Caucasian women (29%) to have experienced hot flashes ($P < .001$). The difference remained after adjustment for body mass index (BMI), education, menstrual cycle characteristics, and gynecologic and medical history.² This is important since BMI may be an independent risk factor for hot flashes. More recent reports from the Penn Ovarian Aging Study confirm these earlier findings. African Americans were significantly more likely to report symptoms (46% vs 30%; $P < .001$) and rated their hot flashes as more severe ($P < .008$) than Caucasian women.³

In a 2004 analysis of SWAN data, significantly more African American women (46.5%, n=750) reported vasomotor symptoms compared with

Caucasian women (36.6%, n=1418; $P < .0001$).⁴ More recent analyses of the SWAN data demonstrate that, although BMI was a significant risk factor for increased hot flash reporting in Caucasian women, the higher hot flash occurrence in African-American women was independent of BMI.⁵

In addition to having more frequent and more severe menopausal symptoms, African American women have an earlier onset of natural menopause than do Caucasian women. Menopause occurs at a median age of 51.3 years in American women. In African-American women, the onset of natural menopause was reported to occur at a median age of 48 by one study while another study found a median age of 49.3 years.^{6,7} Thus, African American women may experience more frequent and severe symptoms for a longer period of time than other women, although these data may be confounded by a higher hysterectomy rate among African American women.

African American women may have additional reasons to require non-estrogen-based therapy. Recent studies have shown ethnic diversity in drug efficacy for various conditions. For example, the responses to beta-blockers and angiotensin converting enzyme (ACE) inhibitors appear to be less robust in African Americans.⁸ Biological differences, including increased levels of TGF beta in African Americans, have been detected and may be responsible for differences in drug efficacy.⁹ Preliminary data from the Women's Health Initiative (WHI) study suggest decreased efficacy of estrogen

to date, none of these agents have been proven to be a consistently effective, useful therapy for hot flashes.

What provides better efficacy?

Studies of the gamma-aminobutyric acid (GABA) analog gabapentin, which is FDA-approved for treatment of seizures and neuropathic pain, have shown better efficacy. After menopausal

patients who were taking gabapentin for migraine prophylaxis reported pronounced relief of hot flashes to their neurologists,²⁵ it has been tested for its efficacy in treatment of hot flashes in women with natural menopause and in women with cancer.²⁵ In a randomized, double-blind, placebo-controlled trial of breast cancer patients, a significant decrease in hot flash severity score (15%

for placebo, 46% for gabapentin, with frequency and severity combined into one score) was observed between baseline and 8 weeks.²⁶ Another randomized, double-blind, placebo-controlled trial in naturally postmenopausal women found that hot flash frequency and composite score at week 12 in the gabapentin-treated women was significantly below those of placebo controls.²⁷

for hot flash therapy in African American women, compared with Caucasian women. Thus, it should no longer be assumed that the efficacy of estrogen for hot flashes is equivalent for African American women and Caucasian women. African American women may require higher doses of estrogen for equivalent relief, placing them at greater risk of the negative effects of estrogen than users of a lower dose.

Although African American women may have a greater need for therapy for hot flashes, they may be worse candidates for estrogen than Caucasian women. Data on the breast cancer burden of American women have documented paradoxical rates of incidence and mortality for African Americans compared with Caucasians over the past 30 years.¹⁰ Despite the substantial heterogeneity of ethnic ancestry that exists within many African American families, a disproportionate risk of breast cancer mortality has been consistently demonstrated for women who identify themselves as African

American. African American women have a lower lifetime risk of being diagnosed with breast cancer, accounting for approximately 8% of all estimated new cases in the United States. In contrast, they account for approximately 13% of all breast cancer deaths.¹⁰

Summary

The severity of hot flashes seriously limits function and increases the need for medical attention.

Gabapentin has been shown to be equivalently effective as estrogen in decreasing the frequency and severity of hot flashes in Caucasian women. African American women suffer from increased frequency and severity of hot flashes, but are poor candidates for hormone therapy, since estrogen appears to be less effective for them and they are at higher risk for aggressive breast cancer. Additional studies are clearly needed to identify effective, non-hormonal therapy for treatment of hot flashes.

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Gabapentin has also been tested for its effects on hot flashes. Another randomized, placebo-controlled trial compared the effects of gabapentin to estrogen. In another trial of menopausal women, gabapentin was found to be as effective as estrogen in inhibiting hot flash composite score.²⁸ In this study, both gabapentin and estrogen significantly decreased hot flash com-

posite scores compared with the placebo effect at all weekly time points from 1 to 12 weeks. The effects of gabapentin on the frequency and severity of hot flashes were similar to those of estrogen.²⁸ The potential usefulness of gabapentin—which appears thus far to be more efficacious than either antidepressants or clonidine—is a promising non-estrogen therapy for hot flashes.²⁹

The mechanism by which gabapentin relieves hot flashes has not yet been precisely defined. However, it is known that hot flashes are due to a lowering of the hypothalamic thermoregulatory set point, which results in a sudden perception of heat; and gabapentin binds with high affinity to voltage-gated calcium channels of the hypothalamus, thought to mediate temperature regulation.³⁰

Disclosures

Dr Goldsmith has no commercial or financial interests to report. Dr Weiss reports the following potential conflict of interest: He is a member of the speakers' bureau of Wyeth Pharmaceuticals.

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