AACE Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE DIAGNOSIS AND TREATMENT OF MENOPAUSE

AACE Menopause Guidelines Revision Task Force

American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health-care professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

AACE Menopause Guidelines Revision Task Force

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Abbreviations:
CAD = coronary artery disease; **CEE** = conjugated equine estrogen; **CI** = confidence interval; **DHEA** = dehydroepiandrosterone; **DHEAS** = dehydroepiandrosterone sulfate; **E+P** = combination of estrogen and a progestational agent; **FDA** = US Food and Drug Administration; **FSH** = follicle-stimulating hormone; **HDL** = high-density lipoprotein; **HERS** = Heart and Estrogen/Progestin Replacement Study; **HR** = hazard ratio; **HT** = hormone therapy; **LOE** = level of evidence; **MI** = myocardial infarction; **MPA** = medroxyprogesterone acetate; **RCTs** = randomized controlled trials; **RR** = relative risk; **VTE** = venous thromboembolic event; **WHI** = Women's Health Initiative

I. CURRENT ROLE OF HORMONE REPLACEMENT THERAPY FOR MANAGEMENT OF MENOPAUSE

Introduction

As a woman ages, her ovaries progressively fail to produce estrogen. This failure often begins in the late 30s, and most women experience near-complete loss of production of estrogen by their mid-50s. Currently in the United States, approximately 35 million women are beyond 50 years of age. Each day some 2,500 to 3,500 additional women have their 50th birthday. The transition from normal ovarian function to ovarian failure is described as the menopausal transition. Although for many women menopause is asymptomatic and associated with little disruption of normal life and well-being, many women experience symptoms—sometimes severe and disabling—that considerably affect their quality of life. Although some women may be asymptomatic, estrogen deficiency is associated with hot flashes, sweating, insomnia, and vaginal dryness and discomfort in up to 85% of menopausal women. Hormone therapy (HT) is the most effective intervention for management of these quality-of-life symptoms.

The goal of menopausal HT, defined as estrogen therapy alone or a combination of estrogen and a progestational agent (E+P), is to alleviate the quality-of-life symptoms. Most women with menopausal symptoms will experience spontaneous cessation of them within 5 years after onset; however, a substantial proportion of women continue to experience symptoms beyond 5 years, and in these cases, the long-term effects of use of HT must be considered. Investigators have proposed that the hypoestrogenic state associated with menopause can adversely affect the target tissues of estrogen action, including the brain, skeleton, integument, and urogenital and cardiovascular systems; nevertheless, the effectiveness of HT in the prevention of disease remains controversial.

The initial portion of this document will provide (*1*) guidelines for the use of HT for the relief of menopausal symptoms, (*2*) evidence for consideration of short-term and long-term risks associated with use of HT, including a venous thromboembolic event (VTE), endometrial cancer, breast cancer, and stroke, and (*3*) a discussion of the evidence that exists for primary prevention of disease that may result from a hypoestrogenic state (osteoporosis, dementia, or cardiovascular disease).

Methods

The purpose of these guidelines is to provide a consensus opinion about the appropriate management of menopause, with an emphasis on the hormonal therapies available to clinicians. The intended target audience is endocrinologists, nonendocrinologist physicians, and interested laypersons. Evidence presented in these guidelines was obtained through MEDLINE searches and available references developed by section heads and committee members. In addition, expert opinion was used to evaluate the available scientific literature, which was graded for treatment recommendations by evidence-based medicine guidelines and then presented in specific references in the appended reference list.

The available scientific studies cited in these guidelines have been reviewed and evaluated for strength of evidence on the basis of the definitions presented in Tables 1 and 2. These evidence-based guidelines are intended to identify which components of the decision-making process are objective and to facilitate the cohesive incorporation of traditional "standards" of care with scientific research paradigms. The "level of evidence" (LOE) structure, based on generally accepted evaluations of stan-

dards for evidence-based medicine, is presented in Table 1. References involving clinical evidence will have a denotation reflecting this evaluation in the reference list.

In addition to the LOE, a recommendation grade (1), as described in Table 2, may be cited with the reference number in the text. This format is intended to improve the ability of the readers to apply the information presented to clinical practice.

EXECUTIVE SUMMARY

Treatment of Symptomatic Women

In selected postmenopausal women, on the basis of an individually determined benefit-versus-risk profile, HT may be appropriate for the relief of severe menopausal symptoms (*LOE 1, grade A*). *Comment*: Strong evidence exists that HT is the most effective intervention for menopausal hot flashes as well as vaginal and urogenital atrophic symptoms. The recommendation to use estrogen in this setting is offset by the potential risks enumerated later in the text. Careful attention should be paid to absolute contraindications against use of estrogen, as described subsequently in the text. The US Food and Drug Administration (FDA) guidance should be followed in using HT at the lowest dose and for the shortest duration of time necessary to control such symptoms. The use of estrogen (in conjunction with a progestational agent in women with a uterus) should be thoroughly discussed by each woman with her physician.

- HT is prescribed during the perimenopause and early menopause for relief of menopausal symptoms and treatment of vulvovaginal atrophy (*LOE 1, grade A*).
- When used cyclically, a progestational agent should be administered in an adequate dose for 10 to 14 days each month (*LOE 1, grade A*).
- Amenorrhea may be achieved by using a low dose of a progestogen administered continuously (daily) in conjunction with estrogen (*LOE 1, grade A*).
- Long-cycle therapy with use of a progestogen for 14 days every 3 months has not been well validated for effectiveness, but it has been proposed to reduce breast exposure to progestogens (*grade B*).
- The dose may be reduced with advancing age (*grade C*).
- Estrogen in various forms may provide relief of vasomotor symptoms, and use of the transdermal or transvaginal route should be considered (*LOE 1, grade B*). *Comment:* Although it is reasonable to believe that the transdermal route of administration of estrogen avoids the hepatic first-pass effect and therefore may reduce thromboembolic risk, no randomized controlled trials (RCTs) to support this concept have been published. Likewise, local estrogen therapy may have vaginal and uterine benefits with less systemic absorption, but the same caveat applies.

Effect on Bone

- Data from multiple RCTs substantiate the efficacy of estrogens in preserving bone mass and, less consistently, preventing fractures (*LOE 1*). The Women's Health Initiative (WHI) was the first large clinical trial to show a significant reduction in osteoporosis-related fractures, including hip and vertebral fractures (2). Approximately 85% of osteoporotic fractures detected in the WHI trial were nonvertebral and nonhip fractures (*LOE*

Table 1
Definitions of Levels of Evidence in Evaluation of the Published Literature*

Level	Definition
1	Properly randomized controlled trial
2a	Well-designed controlled trial but without randomization
2b	Well-designed cohort or case-control analytic study, preferably from more than one center or research group
2c	Multiple time series with or without the intervention (cross-sectional and uncontrolled investigational studies); uncontrolled experiments with dramatic results could also be regarded as this type of evidence
3	Opinions of respected authorities that are based on clinical experience; descriptive studies and case reports; reports from expert committees

*Pertinent references have been evaluated for their levels of evidence.

Table 2
Criteria for Determining Recommendation Grades

Recommendation grade	Description
A	Homogeneous evidence from multiple well-designed randomized controlled trials with sufficient statistical power Homogeneous evidence from multiple well-designed cohort controlled trials with sufficient statistical power ≥1 conclusive level 1 publications demonstrating benefit >> risk
B	Evidence from at least one large well-designed clinical trial, cohort or case-controlled analytic study, or meta-analysis No conclusive level 1 publication; ≥1 conclusive level 2 publications demonstrating benefit >> risk
C	Evidence based on clinical experience, descriptive studies, or expert consensus opinion No conclusive level 1 or 2 publication; ≥1 conclusive level 3 publications demonstrating benefit >> risk No conclusive risk at all and no conclusive benefit demonstrated by evidence
D	Not rated No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk Conclusive level 1, 2, or 3 publication demonstrating risk >> benefit

From the American Association of Clinical Endocrinologists Ad Hoc Task Force for Standardized Production of Clinical Practice Guidelines (1).

1). The beneficial effects of HT on bone protection persist, even with doses of estrogen below those commonly used for relief of symptoms (*LOE 2c*). The decision to use estrogen for the prevention and treatment of osteoporosis should be made by the patient and her physician in the context of her age, symptoms, and other risk factors (*grade B*). *Comment*: Because other nonhormonal therapy is available for osteoporosis, use of estrogen should be considered with global risk-to-benefit potential in mind.

- Each patient should be appropriately monitored with use of dual-energy x-ray absorptiometry as well as known clinical factors of fracture risk to determine the adequacy of an administered dose of estrogen (*grade A*).

Related Cancer

- Endometrial cancer has been shown to be increased with use of unopposed estrogen; thus, this treatment option should be avoided in women with an intact uterus (*LOE 1, grade A*).
- The overall hazard ratio (HR) of breast cancer in the E+P arm of the WHI trial was 1.26 (95% confidence interval [CI], 1.00 to 1.59) (*LOE 1*).
- In the WHI estrogen-only treatment arm, there was a lower relative risk (RR) of invasive breast cancer in the treatment group than in the placebo group (HR, 0.77; 95% CI, 0.59 to 1.01) (*LOE 1*).
- *Comment:* In the text of these guidelines, several studies (*LOE 2*) are cited with similar RR for breast cancer, noting that a difference may exist in the use of estrogen alone versus E+P. Therefore, the presence of a uterus and consequent need for the use of progesterone may temper the recommendation to use estrogen with regard to breast cancer risk.
- Several studies, including the E+P arm of the WHI trial, have demonstrated a decrease in colon cancer incidence (*LOE 1, 2a, 2b*).
- Patients may have an increase in ovarian epithelial tumors with use of estrogen for more than 10 years (*LOE 2*).

Vascular and Thromboembolic Disease

- Lipid profiles should be monitored to determine individual risk (*LOE 1, grade A*). Several progestational agents are available, which may have different biologic effects on lipid metabolism.
- In the WHI study (3), the incidence of venous thromboembolic disease and pulmonary embolism was 3.5 per 1,000 person-years in the E+P treatment group, in comparison with 1.7 in the placebo group (HR, 2.06). The incidence was greater with increasing age, obesity,

and factor V Leiden mutations (*LOE 1*). Women with a history of VTE should be advised about this risk when HT is being considered. Because smoking further increases risk, women should be counseled in smoking cessation (*grade A*).

- In both arms of the WHI trial, cerebrovascular accidents (strokes) were more common in the treated group than in the placebo group, a difference that was statistically significant at the nominal but not the adjusted levels (*LOE 1*).
- Observational studies such as the Nurses' Health Study (4) have shown an RR of 0.61 for myocardial infarction (MI) in women who took estrogen early in menopause (*LOE 2b*), but RCTs such as Estrogen Replacement and Atherosclerosis (5), the Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (6), and the Heart and Estrogen/Progestin Replacement Study (HERS) (7) did not show benefit from HT in older women with preexistent coronary artery disease (CAD) (*LOE 1*). The E+P arm of the WHI trial showed a small increase in coronary events during the early phase of the study, whereas later the incidence was equal to that in the placebo group. The estrogen-alone group showed no significant difference from the placebo group (*LOE 1*). HT is not recommended for primary or secondary cardiovascular protection (*grade D*), although young women in the menopause transitional years with severe symptoms should not be fearful of an increase in cardiovascular risk in this setting. In fact, on the basis of published studies and ongoing investigations, estrogen therapy during early menopause may later be shown to have benefit (*grade C*).

Dementia

- In several meta-analyses of observational studies, the risk of dementia has been reduced with long-term use of estrogen (*LOE 2*), whereas in the WHI trial, the HR for probable dementia was 2.05 (95% CI, 1.21 to 3.48) in women beyond age 65 years who were taking E+P (*LOE 1*). To date, use of HT for the prevention or treatment of dementia has not been recommended (*grade D*).

Nonhormonal Therapy

Prescription Medication

- Prescription drugs, including clonidine, antidepressants, and anticonvulsants, may have benefit for some menopausal women (on the basis of LOE 2 studies) and may be tried in individual patients who have no specific contraindications (*grade B*).

Over-the-Counter and Herbal Preparations

- Although they are not regulated by the FDA, supplements have the potential for interaction with other medications or medical conditions and the potential to cause harm.
- Studies have yielded inconsistent results in relief of symptoms with various preparations including black cohosh, phytoestrogens, and vitamin E (*LOE 2*). Women should be counseled that data regarding the estrogenic effects of soy are inconclusive. Therefore, women with a personal or strong family history of hormone-dependent cancers (breast, uterine, or ovarian), thromboembolic events, or cardiovascular events should not use soy-based therapies (*grade D*).

Androgen Therapy

- Normal postmenopausal women have a 50% reduction in the serum androstenedione concentration as a result of decreased adrenal production, with a consequent testosterone production from the peripheral conversion. The adrenal androgens dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) also decline with aging, independent of menopause; thus, by 40 to 50 years of age, their values are about half those for younger women (*LOE 2a*).
- Symptoms ascribed to androgen deficiency, such as low libido, decreased sexual response, decreased sense of well-being, poor concentration, and fatigue, may also be attributable to estrogen deficiency. Accordingly, symptoms ascribed to androgen deficiency may be a result of either androgen deficiency itself or a deficiency of estradiol (*LOE 3*).
- Conflicting data are available on the effects of androgen replacement therapy on sexual function in menopausal women. Administration of testosterone by various routes at supraphysiologic doses improves libido, sexual arousal, frequency of sexual fantasies, sexual function, body composition, muscle strength, and quality of life in comparison with administration of estrogen alone. Physiologic replacement testosterone therapy appears to have an inconclusive effect on sexual function (*LOE 2*).
- Numerous observations are compatible with androgen therapy yielding improved bone-related factors, particularly in doses that exceed the normal range (*LOE 2*).
- Adverse effects may occur with androgen replacement therapy at supraphysiologic levels. Acne, hirsutism, and a significant reduction in high-density lipoprotein (HDL) cholesterol levels have been described (*LOE 2b*).
- The FDA has not yet approved any use of androgens in women. Therefore, such therapy is considered an off-label intervention at this time (*grade C*).

INDICATIONS FOR HT

Various RCTs have proved the efficacy of estrogen in treating menopausal symptoms (*LOE 1*). In addition, estrogens can help diminish mood disorders (depression),

cognitive disruption, and sexual dysfunction during early menopause (*LOE 1*). It should be emphasized that not all mood disorders or cognitive disruption that coincides with menopause should be attributed to menopause without first evaluating psychosocial, medical, or other issues that may occur at the time of menopause. Even though only a small percentage of women continue to experience vasomotor symptoms 10 years after onset of menopause, approximately 3% of women report very frequent hot flashes, and 12% report moderate to severe hot flashes 15 years after onset of menopause (*LOE 2*). Therefore, in selected postmenopausal women, on the basis of an individually determined benefit-versus-risk profile, longer HT might be appropriate (*grade C*).

The FDA has approved the use of HT for the following applications:

- Treatment of moderate to severe vasomotor symptoms (such as hot flashes and night sweats) associated with menopause. This indication has not changed as a result of recently published studies questioning the safety of estrogen treatment of chronic conditions in postmenopausal women. Estrogen-containing products are the most effective approved therapies for these symptoms.
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (such as dryness, itching, and burning) associated with menopause. When estrogen is being prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal preparations should be considered.
- Prevention of postmenopausal osteoporosis. When these products are being prescribed solely for the prevention of postmenopausal osteoporosis, approved nonestrogen treatments should be carefully considered. Estrogens and combined E+P products should be considered only in women with substantial risk of osteoporosis that outweighs the potential risks of the drug.

CONTRAINDICATIONS TO HT

The FDA has recommended that HT should generally *not* be prescribed to women with the following conditions:

1. Current, past, or suspected breast cancer
2. Known or suspected estrogen-sensitive malignant conditions
3. Undiagnosed genital bleeding
4. Untreated endometrial hyperplasia
5. Previous idiopathic or current venous thromboembolism (deep vein thrombosis, pulmonary embolism)
6. Active or recent arterial thromboembolic disease (angina, MI)
7. Untreated hypertension
8. Active liver disease
9. Known hypersensitivity to the active substances of HT or to any of the excipients
10. Porphyria cutanea tarda (absolute contraindication)

HT: TREATMENT DETAILS

HT is prescribed during the perimenopause and early menopause for relief of menopausal symptoms and treatment of vulvovaginal atrophy (*grade A*). Estrogen alone is prescribed for women who have undergone a hysterectomy. In women with an intact uterus, a progestational agent should be added to the estrogen to protect the endometrium from the risk of unopposed estrogen causing development of hyperplasia and endometrial cancer. Progestogens can be administered continuously or sequentially. When used cyclically, the progestogen should be given in an adequate dose for 10 to 14 days each month (8) (*grade A*). Cyclic administration of the progestogen usually produces monthly menstrual periods. Because persistent menstrual bleeding seems to be the major reason for noncompliance with HT, amenorrhea may be achieved by using a low dose of a progestogen administered continuously (daily) in conjunction with estrogen (*LOE 1, grade A*). Many women given continuous combined E+P, however, will continue to experience episodes of breakthrough bleeding. Less frequent endometrial exposure to progestogens, so-called long-cycle therapy with use of a progestogen for 14 days every 3 months, has not been well validated for effectiveness, but it has been proposed to reduce breast exposure to progestogens (9) (*grade B*). Abnormal vaginal bleeding, either between periods of exposure to progestogens or simply unexpected during use of any regimen, necessitates careful monitoring of the endometrium with ultrasonography and endometrial biopsy. The clinician should have a low threshold for performance of endometrial sampling because no clear bleeding patterns that might not be associated with abnormal endometrium have been established.

Estrogens

The dose of estrogen should be the lowest amount necessary to provide relief from symptoms or bone protection, with consideration for the patient's age (that is, reducing the dose with advancing age) (*grade C*). Until clearly understood on the basis of scientific studies about the risk of any one product, each woman and her physician should choose the best HT for her individually.

The use of various forms of estrogen for relief of vasomotor symptoms has been extensively reviewed (8) (*LOE 1*). The forms and routes of delivery of estrogen and the corresponding daily doses most commonly used are as follows (8):

- Conjugated equine estrogens (0.3 to 0.625 mg)
- Micronized 17β-estradiol (0.5 to 1 mg)
- Transdermal estradiol (14 to 100 μg)

- Ethinyl estradiol (0.01 to 0.02 mg)
- Vaginal estrogenic preparations, including a vaginal estradiol ring

In addition, other available preparations, such as estrogen pellets, gels, creams, intranasal sprays, or injections (for example, Depo-Estradiol), can be prescribed. The major differences among these formulations are in the mode of absorption and the pharmacokinetics. Few, if any, clinically significant *qualitative* differences exist between free and conjugated estrogens.

The oral and transdermal routes are the most frequently used for administration of estrogen. Patient acceptance and prior experience are the major factors in determining the preferred route of delivery. The oral route is characterized by first-pass enterohepatic removal of a substantial fraction of the estrogen, followed by hepatic metabolism and conjugation to sulfates and glucuronides, which are then excreted through the bile back into the digestive tract. At this site, the sulfates are deconjugated to some extent and reabsorbed. All drugs subject to the first-pass effect show greater interindividual variability in the blood levels attained. This finding is true of the estrogens—a fact that may be of considerable clinical relevance. Furthermore, the high concentrations of estrogen delivered to the liver by the oral route (in comparison with transdermal absorption directly into the peripheral circulation) induce increased synthesis of triglycerides and certain proteins such as cortisol-binding globulin (transcortin), sex hormone-binding globulin, and angiotensinogen. Therefore, transdermal administration of estrogen is preferred in certain clinical situations, such as in women with hypertension, hypertriglyceridemia, and increased risk for cholelithiasis (*grade B*).

Vaginal administration of estrogen has been used for treatment of vaginal atrophy (*grade B*). Of note, this treatment can have systemic effects, depending on the dose and form (tablet, ring, cream) of the estrogen. Vaginally administered estrogens are readily absorbed through the vaginal mucosa and can result in appreciable blood levels of estrogen.

The desired effects of therapy manifest themselves slowly (for example, autonomic symptoms may begin to subside in a week or 2, whereas alleviation of dyspareunia may take months). In this situation, *one dose does not fit all*. Protection against bone mineral loss is somewhat dose-dependent, although very small doses of estrogen may be sufficient. Each patient should be appropriately monitored with dual-energy x-ray absorptiometry as well as by assessment of clinical variables indicative of fracture risk to determine the adequacy of an administered dose of estrogen (10) (*grade A*).

Measurement of serum follicle-stimulating hormone (FSH) levels cannot be used to monitor the adequacy of the estrogen doses the same way that thyrotropin levels are used to monitor the adequacy of doses of thyroid replacement therapy. Use of this determination is inappropriate because estrogen is not the only regulator of FSH secretion; inhibin also has a role. Serum FSH levels may remain increased despite adequate estrogen effect on the target tissues.

Progestogens

Common choices of orally administered progestational agents that have been shown to provide endometrial protection include the following (*LOE 1*):

- Medroxyprogesterone acetate (MPA) (2.5 mg daily or 5 mg for 10 to 12 days/mo)
- Micronized progesterone (11) (100 mg daily or 200 mg for 10 to 12 days/mo)
- Norethindrone (0.35 mg daily or 5 mg for 10 to 12 days/mo)
- Levonorgestrel (0.075 mg daily)

The side effects of progestational compounds are difficult to evaluate and will vary with the progestational agent administered (12). Some women experience premenstrual-tension-like symptoms, including mood swings, bloating, fluid retention, and sleep disturbance. Switching among various progestational agents may decrease these symptoms. Studies of the effect of progestational agents on lipids have reported conflicting results. Lipid profiles should be monitored to determine individual risk (*grade A*).

Some women will experience unacceptable side effects from all orally administered progestogens. Several transdermal patches are available that contain estradiol and a progestogen that can be used as an alternative (*grade B*). Moreover, transvaginally administered progesterone with improved absorption characteristics by means of a bioadhesive gel may achieve adequate endometrial management with fewer side effects. No published studies have as yet described the utility of this progesterone preparation in combination HT for menopausal patients, but it has proved effective in treating infertile women to maintain luteal phase endometrial integrity for embryo implantation. In addition to menopausal HT, a progestogen can be used for luteal phase supplementation in perimenopausal patients with irregular menstrual cycles. This treatment protects against endometrial hyperplasia and certain bleeding problems (*grade B*). Finally, a progestogen-releasing intrauterine system can effectively protect the endometrium, with little systemic absorption and reduced bleeding.

In terms of overall choice of HT, a comment from the initial WHI report bears consideration: “It remains possible that transdermal estradiol with [orally administered] progesterone, which more closely mimics the normal physiology and metabolism of endogenous sex hormones, may provide a different risk-benefit profile” (13).

REVIEW OF THE WHI

In the discussion in this section, reference will be made to the WHI study (13) (*LOE 1*), a planned 8.5-year randomized controlled primary prevention trial that enrolled postmenopausal women who were 50 to 79 years old. It involved the following study groups:

1. The E+P arm consisting of 16,608 women with an intact uterus, who received a daily tablet of conjugated equine estrogen (CEE) (0.625 mg) with MPA (2.5 mg) (N = 8,506) or placebo (N = 8,102)
2. The estrogen-only arm consisting of 10,379 women who had undergone hysterectomy, who received CEE (0.625 mg) or placebo alone

The primary outcome was CAD (nonfatal MI and CAD-related death), and the primary anticipated adverse outcome was invasive breast cancer. The E+P arm of the WHI trial was terminated near the end of the 5th year because of an apparent increase in the risk of breast cancer and an apparent adverse global index. The factors included in the global index, in addition to an increased risk of breast cancer, were CAD, stroke, and pulmonary embolism. An analysis by the WHI writing group of the complete 5-year period revealed that the increase in breast cancer was not statistically significant and the apparent increase in the cardiovascular hazard risk in year 5 had occurred because of a transient decline in the rates of CAD events in the placebo group, rather than an increase in the estrogen-progestin group (14). An unequivocal increased risk of VTE was noted in the treated group, which confirms the findings in previous studies of early postmenopausal HT use.

With respect to insights in the management of the menopause and associated symptoms, the major criticism of the results of the WHI trial is the age of the population of postmenopausal women who participated in the study. The mean age at enrollment in the WHI study was 63.3 years. These women were more than a decade older than the age at which most women begin HT. Only 10% of study participants were 50 to 54 years old, and only 16% of the women were less than 5 years after the onset of menopause. Of women randomly assigned in the WHI study, 36% had hypertension, 49% were current or past smokers, and 34% had a body mass index >30 kg/m^2. Therefore, the demographics of the WHI population were older postmenopausal women who had significantly increased risk factors for cardiovascular disease. In addition, these women did not have severe postmenopausal symptoms.

The results of the WHI study cannot be generalized to a population of women in early menopause because the WHI was designed to evaluate HT in an older population of aging postmenopausal women.

RISKS ASSOCIATED WITH SHORT-TERM AND LONG-TERM HT

Menopause is associated with the onset and progression of many chronic illnesses, including CAD, stroke, dementia, osteoporosis-related fractures, and cancer. Physicians who are responsible for the care of postmenopausal women must manage and attempt to prevent these health consequences of aging. Because the target tissues of estrogen action include the brain, skeleton, integument, and urogenital and cardiovascular systems and data from large observational studies have demonstrated that women who choose to take estrogen therapy experience fewer cardiovascular events and have lower overall mortality (4), it is useful to review the scientific data that support the benefits of estrogen in the prevention of disease. It should be emphasized that use of estrogen has been associated with disease prevention only when therapy has been initiated during early menopause. Many studies have shown that, except for prevention of fractures, estrogen therapy has little, if any, benefit when initiated after substantial progression of disease.

VTE and Endometrial Cancer

The risks of estrogen therapy are clearly established in regard to endometrial cancer and venous thromboembolic disease. Estrogen therapy has been associated with an increased risk of venous thromboembolic disease within 1 to 2 years after initiation of therapy. The increased RR is high, but the increased absolute risk is quite small. In the WHI study (3), the incidence of venous thromboembolic disease and pulmonary embolism was 3.5 per 1,000 person-years in the E+P treatment group, in comparison with 1.7 in the placebo group, with an HR of 2.06. The incidence was greater with increasing age, obesity, and factor V Leiden mutations (3) (*LOE 1*). Women with a history of VTE should be carefully advised about this risk when HT is being considered. Because smoking further increases the risk, women should be counseled in smoking cessation (*grade A*).

Breast Cancer

As of 2001, breast cancer was the leading cause of new malignant tumors in women (192,000 cases) and the second leading cause of cancer-related deaths (40,200 deaths). For the past several decades, observational studies have raised concerns about use of HT and an increased risk of breast cancer. A review of 45 studies published from 1975 to 2000 regarding use of HT and breast cancer risk revealed that 82% of these studies reported no significantly increased risk and 13% reported risk estimates greater than 1.0 but not greater than 2.0 (15) (*LOE 2a, 2b, 2c*).

Since 2000, several epidemiologic studies have distinguished breast cancer risk comparing estrogen-alone

and E+P therapy (16-20) (*LOE 2b*). These recent observational cohort and case-control analytic studies reported no significant increase in breast cancer risk with use of estrogen alone but a significantly increased risk with use of continuous combined E+P therapy. Most of these studies, however, have not shown or have barely attained statistical significance, with CIs including 1 or <1.1. Only long-term exposures of 15 years or more have demonstrated a statistically significant increased risk with E+P therapy (18).

On reanalysis of worldwide observational data, the Collaborative Group on Hormonal Factors in Breast Cancer (21) (*LOE 2b, 2c*) reported that, for current users of HT for 5 years or longer, the RR was 1.35 (95% CI, 1.21 to 1.49), and with more than 15 years of use of HT, the RR was 1.6 (95% CI, 1.25 to 2.05). There was a significant reduction in nodal spread and distant metastatic lesions in HT users versus never-users. This study, however, is confounded by a subgroup analysis of women who had discontinued the use of HT 5 years or more before their breast cancer was diagnosed, which demonstrated no increased risk in comparison with the nonusers, despite prior use of HT for 5 years or more. This finding prompts the following question: If estrogen induces breast cancer, why would the risk disappear shortly after HT is discontinued?

This same potential bias was noted in the Million Women Study (22) (*LOE 2b*), an observational study of a breast screening program in the United Kingdom that reported an increase in breast cancer risk with use of all types of HT regimens, beginning with the 1st year of use. As in the aforementioned Collaborative Group Study (21), the risk disappeared from 1 to 5 years after the withdrawal of HT. The appearance of significant risk during the first year strongly suggests that the surplus of cases of breast cancer arose from observational bias and was not induced by the treatment (23).

A family history of breast cancer increases an individual's risk of developing breast cancer. Epidemiologic data from the Iowa Women's Health Study (24), however, did not support a further increased risk caused by use of HT in a patient with a family history of breast cancer (RR, 1.13; 95% CI, 0.82 to 1.57).

The E+P arm of the WHI trial examined breast cancer risk as an adverse outcome (25) (*LOE 1*). The overall HR was 1.26 (95% CI, 1.00 to 1.59), demonstrating that there was no statistically significant increase in breast cancer risk. Adjustment of the WHI data for prior exposure to HT showed no increased breast cancer risk in women without previous exposure to HT (Table 3).

Results of the WHI estrogen-only treatment arm surprisingly demonstrated that invasive breast cancer was diagnosed at a 23% lower RR in the group taking CEE than in the placebo group (HR, 0.77; 95% CI, 0.59 to 1.01). This difference just missed statistical significance (26) (*LOE 1*).

Table 3
Breast Cancer Risk in WHI Study Participants* Stratified by Duration of Previous Use of Hormone Therapy†

Prior use of HT (yr)	Hazard ratio	95% CI
0	1.06	0.81-1.38
<5	2.13	1.15-3.94
5-10	4.61	1.01-21.02
>10	1.81	0.60-5.43

*The estrogen + progestin treatment arm.
†CI = confidence interval; HT = hormone therapy; WHI = Women's Health Initiative.

In summary of the information gleaned from the studies of breast cancer and HT, breast cancer risk is influenced by the duration of exposure to estrogen and progestogens. Progestogens can have an adverse influence on breast cancer detection through proliferation of estrogen-dependent mammary tissue and increasing breast density; these changes make early breast cancer detection by mammography more difficult. On the basis of epidemiologic and RCT evidence, there does not appear to be an increased frequency of breast cancer diagnosed through 5 to 7 years of use of HT. This translates into about 4 or fewer cases per 1,000 women after 5 years of exposure to HT, with the assumption that the controversy of the statistical significance of these studies can be validated. Of note, the increased breast cancer risk attributed to HT is less than that associated with obesity and smoking.

If the risk of breast cancer is increased with use of HT, it seems to be a small increase and possibly isolated to susceptible women, especially older women with longer estrogen exposures. Because the increased risk appears to become null within 5 years or less after discontinuation of HT, the pathogenesis of the effect of estrogen on the breast to increase detection but then reverse after discontinuation of HT is unclear. Investigators have proposed that surveillance bias might contribute to this observation because women taking estrogen are likely to have mammograms more frequently than those not taking estrogen (27).

This low risk is further substantiated by the reduced mortality associated with breast cancer diagnosed in HT users in comparison with nonusers (28). No scientific evidence indicates that estrogen causes normal breast tissue to undergo malignant transformation. On the basis of the observation that cancer has usually been in the breast for 7 to 8 years or longer before it is diagnosed by mammography, an explanation for the observations of HT and breast

cancer risk would be that HT causes breast cancer to grow faster and thus leads to an earlier mammographic diagnosis. The reduced mortality rate is compatible with the observation that HT-associated breast cancers are smaller, better differentiated, and associated with lower proliferation rates than those tumors in nonusers of HT (29) (*LOE 2b*) (*grade B*). Analysis of breast cancer data from the WHI (25), however, revealed that invasive breast cancers, although of similar histologic features and grade, were somewhat larger in the E+P group and manifested at a more advanced stage than those in the placebo group.

Other Cancers

In regard to the relationship of other cancers to estrogen use, several studies including the E+P arm of the WHI trial have demonstrated a decrease in incidence and mortality of colon cancer (13,25,30) (*LOE 1, 2a, 2b*). Reported effects of estrogen and E+P therapy on the occurrence of ovarian cancer have been inconsistent. The data suggest a possible increase in ovarian epithelial tumors with >10 years' use of estrogen only (25,31) (*LOE 2*).

Stroke

In both treatment arms of the WHI study, cerebrovascular accidents (strokes) were more common in the treated group than in the placebo group, a difference that was statistically significant at the nominal but not at the adjusted levels (32) (*LOE 1*). There was no increase in fatal strokes, but an increase was noted in the nonfatal category (nominal but not adjusted). The clinical criteria for stroke events (what imaging studies were performed and how many patients were classified as having a nonfatal stroke but had no imaging studies performed), however, have not been published as adjudicated data; thus, questions are raised about the statistical significance of this diagnosis in this older population.

In the Nurses' Health Study (4), the risk for ischemic or hemorrhagic stroke was modestly but statistically significantly increased among women taking 0.625 mg or more of CEE: RR of 1.35 (95% CI, 1.08 to 1.68) for 0.625 mg/day and 1.63 (95% CI, 1.18 to 2.26) for women taking 1.25 mg/day or more. Women who took 0.3 mg/day of CEE had a decrease in stroke risk: RR of 0.54 (95% CI, 0.28 to 1.06), although this finding was not statistically significant *(LOE 2b*). This dose-dependent increase in cerebrovascular risk might explain the observed increased risk of stroke noted in the WHI study, in which older women were exposed to a relatively high daily dose of 0.625 mg of CEE.

USE OF HT TO PREVENT DISEASE

Prevention of the consequences of aging and menopause by use of estrogen has been evaluated in many studies, including observational, case-controlled, and interventional trials.

Osteoporosis

Postmenopausal osteoporosis leading to spine and hip fractures is associated with considerable morbidity and mortality. Scientific data from RCTs (2) substantiate the efficacy of estrogens in preserving bone mass and, less consistently, preventing fractures (*LOE 1*). The WHI was the first large clinical trial to show a significant reduction in osteoporosis-associated fractures, including hip and vertebral fractures. Approximately 85% of osteoporosis-related fractures noted in the WHI trial were nonvertebral and nonhip fractures (*LOE 1*). Dual-energy x-ray absorptiometry scans and spinal radiography were not performed in the overall population at entry into the study or during treatment. Hence, the reduction in clinically evident (that is, painful) vertebral fractures likely underestimates the true effect because approximately 60% of these fractures are reportedly silent. The number of hip fractures was significantly reduced by 50% (5 per 10,000 less in the E+P group) or stated as an HR of 0.66 (95% CI, 0.45 to 0.98).

The beneficial effects of HT on bone protection (33) persist even with doses of estrogen below those commonly used for relief of symptoms (34) (*LOE 2c*), although the benefit may decrease with lower doses of estrogen. In some women, the skeleton may not respond to conventional doses, and a lower dosage may be effective. The duration of use of HT for prevention of osteoporosis is a decision that can be made only on an individual basis in consultation with the patient's physician; the patient's risk-to-benefit profile and alternative preventive therapies with bisphosphonates and selective estrogen receptor modulators should also be considered (*grade B*). Lifestyle measures including regular weight-bearing exercise, adequate calcium and vitamin D intake, smoking cessation, and prevention of falls should be encouraged for preservation of bone mass and prevention of fractures (*grade C*).

Dementia

After age 80 years, women have an increased risk of Alzheimer's disease in comparison with men (possibly attributable to postmenopausal depletion of endogenous estrogen). The prospective, longitudinal Cache County (Utah) Study (35) investigated the prevalence and incidence of Alzheimer's disease in a cohort of 5,677 elderly adults. Study results showed that the risk of this disorder varied with the duration of self-selected use of HT. Longer duration of HT use was associated with greater reduction in the risk of Alzheimer's disease. Prior HT use was associated with a decreased risk in comparison with nonusers, and women's higher risk versus men was virtually eliminated after more than 10 years of exposure to HT. In addition, there was no apparent benefit with current use of HT unless that use exceeded 10 years (35) (*LOE 2c*).

Several meta-analyses have examined the use of HT and the incidence of dementia in older postmenopausal women. One meta-analysis, which included 2 cohort studies and 10 case-control studies, showed a 34% reduction in

the risk of dementia (odds ratio, 0.66; 95% CI, 0.53 to 0.82) with use of HT (36) (*LOE 2b*).

In the Women's Health Initiative Memory Study (37), E+P was associated with an increased risk of dementia among women 65 years of age or older, and therapy did not prevent mild cognitive impairment. In comparison with placebo, the HR for probable dementia was 2.05 (95% CI, 1.21 to 3.48) in women who received E+P (*LOE 1*).

The methods used to evaluate the effects of HT on memory and cognition among asymptomatic women are insensitive and cannot accurately distinguish early dementia from cerebrovascular disease. Therefore, these older women (age >65 years) with abnormal results on tests of cognition and memory were designated as having probable dementia. In the Women's Health Initiative Memory Study (37), cases of probable dementia appeared during the first year of intervention in both the E+P and the placebo groups; this finding supports the significant incidence of cognitive dysfunction at baseline in both groups.

Cardiovascular Disease

Because CAD is the leading cause of death in postmenopausal women, counseling women during the menopausal transition regarding primary prevention of CAD is a chief concern (38). Counseling about prevention of CAD should include discussions of lifestyle modifications, including weight reduction, exercise, and cessation of smoking (*grade B*). Medical interventions for at-risk postmenopausal women include antihypertensive agents and lipid-lowering treatments.

Scientific studies have demonstrated that estrogen has direct antiatherogenic effects in the coronary arteries at a molecular level and prevents the formation of atheromatous plaques in the oophorectomized primate model and in humans (39). Results of the Estrogen in the Prevention of Atherosclerosis Trial (40), a randomized, double-blind, placebo-controlled trial of the direct protective effect of estrogen on carotid intimal thickening, were consistent with estrogen's potential for primary prevention of atherosclerosis (*LOE 1*).

Observational studies of HT have consistently shown that the risk of CAD is 35% to 50% lower in self-selected HT users, even after adjusting for other risk factors (38). The Nurses' Health Study (4) has consistently shown a reduced risk of nonfatal MI or CAD mortality in self-selected HT users versus never-users, results that support the primary prevention of CAD in postmenopausal women (41) (*LOE 2b*). In the latest reanalysis of this population, the RR was 0.61 (95% CI, 0.52 to 0.71), after adjustment for cardiovascular risk factors (14). It should be emphasized that estrogen users in the Nurses' Health Study (4) began HT predominantly during the early menopause, distinguishing this study population from the older-age women in the WHI trial. Specifically, age at initiation of HT may be critical for determining whether this therapy can prevent CAD. The younger the patient when HT is started (that is, perimenopausal and early menopausal), the less likely that significant preexistent atherosclerosis would be present. In this setting, the primary prevention of CAD may be possible. If HT is initiated after significant atherosclerotic plaque has formed, estrogen therapy may cause disruption and rupture of the plaque, leading to an acute myocardial event (42).

One large, multicenter observational study demonstrated that prior exposure to HT resulted in a significant reduction in CAD mortality in women admitted to a hospital with their first documented MI (odds ratio, 0.41; 95% CI, 0.36 to 0.43) (43) (*LOE 2b*).

Two RCTs have examined the direct effect of estrogen on preexistent atherosclerosis. The Estrogen Replacement and Atherosclerosis trial (5) (*LOE 1*) used angiographic end points to evaluate progression of atherosclerosis in postmenopausal women with CAD. Neither estrogen alone nor E+P in comparison with placebo prevented the progression of CAD during 3.2 years of follow-up. The Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (6) (*grade A*) assessed the progression of carotid intimal thickening in postmenopausal women with established CAD and failed to show a protective effect of estradiol or estradiol in conjunction with MPA (*LOE 1*).

Most clinical studies of HT in postmenopausal women with preexistent CAD (history of angina pectoris or MI) have failed to show a cardioprotective effect. The HERS secondary prevention trial (7) (*grade A*) involved 2,763 postmenopausal women, 55 to 80 years old (mean age, 66.7 years), with CAD. The treated group received the same HT as the women in the WHI study (13) (0.625 mg of CEE plus 2.5 mg of MPA daily) and underwent follow-up for 4.1 years. Overall, E+P treatment had no effect on MI or CAD death (relative hazard, 0.99; 95% CI, 0.80 to 1.22), but there was a significant increase in CAD events with E+P early in the study (*LOE 1*). In the WHI study (13), the primary CAD outcome was nonfatal MI and CAD death (*LOE 1*). The final analysis of the E+P arm of the WHI study demonstrated a nonsignificant risk of CAD, with HR of 1.24 (95% CI, 1.00 to 1.54) (14) (*grade A*). The absolute risk was 7 more CAD events per 10,000 woman-years in the E+P group in comparison with the placebo group. The higher risk with E+P use was due principally to the 28% higher rate of nonfatal MI, which was significantly higher only during the first year of the study. The rate of CAD death was not significantly increased. Nonsignificant CAD event differences were noted during years 2 through 5. Increased CAD rates in the placebo group during year 6 and later resulted in an apparent risk reduction in the E+P treatment group. When the WHI data are reanalyzed by time since onset of menopause when treatment was initiated, the CAD risk associated with E+P use shows a small, nonsignificant trend for a decrease in coronary events in treated women who were within 10 years after onset of menopause. CAD risk was significantly increased by use of E+P among

women who were 20 or more years after the onset of menopause. In the HT arm of the WHI trial and in HERS, it has been subsequently demonstrated that women receiving both HT and one of the statin class of drugs for lowering the serum cholesterol level were at no greater risk for CAD than those not taking HT.

In the WHI estrogen-only treatment arm (26), there was no benefit or risk of estrogen therapy relative to CAD, with an overall HR of 0.91 (95% CI, 0.75 to 1.12) (*grade A*). A preliminary subgroup analysis by age at enrollment in the study revealed that the estimated HRs for treated women for several monitored CAD outcomes were lower for women 50 to 59 years of age than for others, although these differences across age-groups were not statistically significant. Therefore, this WHI trial demonstrated that estrogen alone does not significantly affect the primary outcome—CAD incidence—in postmenopausal women with prior hysterectomy.

Finally, recent randomized studies of HT in a younger population of menopausal women (50 to 60 years of age) found no increased risk of CAD or stroke (44) (*LOE 1*).

CONCLUSIONS FOR HT IN PREVENTION OF CARDIOVASCULAR DISEASE

1. Epidemiologic and observational studies suggest that cardioprotection is provided by use of HT—especially for estrogen alone (without a progestin)—when it is prescribed for women early during the menopausal transition (*LOE 2b, 2c*).
2. RCTs that have demonstrated no cardioprotective benefit of HT were studies of postmenopausal women more than 10 years beyond the menopausal transition (mean age of mid-60s—an older patient population that would be expected to have a higher incidence of subclinical CAD at initiation of HT) (*LOE 1*).
3. RCTs used a fixed-dose, single-form, combined HT. Therefore, these results cannot be applied to other HT regimens.
4. There is no evidence of increased CAD risk, nor are there RCTs that support a primary cardioprotective benefit, when HT is initiated during the menopausal transition for symptomatic women.
5. HT should not be initiated for the secondary prevention of CAD (*grade D*).

CONCLUSIONS FOR HT USE IN MANAGEMENT OF MENOPAUSAL SYMPTOMS AND PREVENTION OF DISEASE IN WOMEN

1. Each postmenopausal woman should be provided with individualized evaluation regarding the benefits and risks of HT, in consultation with her treating physician. The "one size fits all" approach to education, counseling, and treatment is inappropriate (*grade C*).
2. The short-term use (5 years or less) of estrogen and progestin does not seem to be associated with significant risks (*grade B*).
3. The long-term primary protection benefits provided by estrogen therapy regarding CAD and dementia remain controversial. There is no support for the initiation of HT in older postmenopausal women to treat these medical conditions as secondary prevention. In younger postmenopausal women who initiate HT within 5 years after the onset of menopausal symptoms, however, the primary prevention benefit issues should be considered as relevant. These women might consider continued use of HT until the controversy is resolved (*grade C*).
4. The choice of HT sex steroids should emphasize the use of estradiol as the first-line estrogen, either orally or transdermally (*grade C*). The choice of progestogen should favor intermittent use of progesterone or norethindrone rather than MPA (*grades B, C*).

II. NONHORMONAL THERAPY FOR MENOPAUSE

Alternative Therapies for Management of Vasomotor Symptoms in Menopause

History

Menopause is defined as the absence of menses for 12 consecutive months. Perimenopause is the transitional period between normal menses and menopause. Hot flashes have been reported in up to 70% of women undergoing natural menopause and in almost all women undergoing surgical menopause (45). A prospective study of 436 women found that 31% experienced hot flashes during perimenopause, even before any changes occurred in menses (46).

Hot Flashes

Hot flashes are the number one complaint of perimenopausal and postmenopausal women. A hot flash can be described as a warm sensation that begins at the top of the head and progresses toward the feet, frequently followed by chills. A hot flash may last for a few seconds or for several minutes and may occur as frequently as every hour to several times per week.

Risk Factors.—Modifiable and nonmodifiable risk factors for hot flashes should be evaluated. Modifiable factors that have been shown to increase the risk of hot flashes include cigarette smoking (47,48), body mass index >30 kg/m^2 (48,49), and lack of exercise (49) (*LOE 2c*). Nonmodifiable risk factors include maternal history, menopause younger than 52 years of age, and abrupt menopause—induced by a surgical procedure (50), chemotherapy, or irradiation. Approximately 65% of patients with a history of breast cancer have hot flashes

(51), and adjuvant therapy with tamoxifen or tamoxifen plus chemotherapy is associated with substantial worsening of menopause-related symptoms (52).

Differential Diagnosis.—It is important to exclude other causes of hot flashes, as clinically indicated. The differential diagnosis may include hyperthyroidism, pheochromocytoma, carcinoid, panic disorder, diabetes, and side effects to medications such as antiestrogens or selective estrogen receptor modulators.

Pathophysiologic Factors.—The physiologic mechanism whereby a hot flash occurs is thought to be a result of elevated body temperature leading to cutaneous vasodilatation, which results in flushing and sweating in association with a subsequent decrease in temperature, chills, and potentially relief. One belief is that within the hypothalamic thermoregulatory zone there is an interthreshold zone, defined as the threshold between sweating and shivering. Available evidence indicates that, after menopause, this interthreshold zone becomes narrowed (53). Proposed triggers for this change in interthreshold zone include serotonin (5-hydroxytryptamine), norepinephrine, and estrogen deprivation. The estrogen effect on hot flashes is thought to be attributable to withdrawal of estrogen rather than decreased estrogen levels (54).

Therapeutic Options

Because of the prevalence of hot flashes during the perimenopausal and postmenopausal period and the risks, controversies, and fears surrounding the use of estrogen therapy, various alternative therapies for managing these symptoms have been sought. An important fact to know is that, in most studies, interventions for menopausal symptoms have a 20% to 30% placebo response rate within 4 weeks after initiation of treatment, with some randomized trials having more than a 50% placebo response rate (55). In most women, treatment of hot flashes can be discontinued within 1 year, but about a third of the menopausal women have symptoms for up to 5 years (10% of whom have symptoms for up to 15 years). In light of the high placebo response rate and the natural regression of symptoms over time in most women, double-blind RCTs are needed to evaluate the efficacy of each therapeutic option appropriately. Additionally, because of the varied duration of time these treatments are used, both the short-term and long-term effects must be properly evaluated. Of note, other than estrogen, no therapy has been approved by the FDA for the treatment of hot flashes in women. Estrogen remains the most studied and most effective therapy for vasomotor symptoms attributable to menopause. No RCTs comparing estrogen and other pharmacologic agents have been published. The level of evidence for each therapeutic intervention is presented in the subsequent material.

Lifestyle Alterations

Lifestyle changes designed to maintain a cool environment and aid heat dissipation may help with mild to moderate symptoms. The use of fans, air conditioning, and light cotton clothing may be helpful. Relaxation therapy may also be beneficial in some patients, although RCTs are needed for accurate assessment (*LOE 3*).

Prescription Medications

A summary of the various agents and the related published studies (56-78) is presented in Table 4. As previously mentioned, no therapy other than estrogen has been approved by the FDA for treatment of vasomotor symptoms.

Antidepressants

The most studied medications in the antidepressant class include venlafaxine, paroxetine, and fluoxetine. Venlafaxine is both a serotonin and a norepinephrine reuptake inhibitor. There have been 3 published RCTs in which these medications were used (57-59) (*LOE 2*). Side effects of these agents may include nausea, dry mouth, insomnia, fatigue, sexual dysfunction, and gastrointestinal disturbances.

Clonidine

Clonidine is a central α_2-adrenergic agonist and can be given orally or transdermally. A summary of results of trials that used clonidine preparations is shown in Table 4 (60-62,73) (*LOE 2*). Side effects, including dry mouth, postural hypotension, fatigue, and constipation, often limit the use of this medication.

Gabapentin

Gabapentin is an analogue of γ-aminobutyric acid and has an unknown mechanism of action. It is approved by the FDA for treatment of seizure disorders but has also been used to treat neuropathic pain. A small RCT (64) has demonstrated significant reductions in hot flashes (Table 4), but larger trials are needed to study long-term efficacy and safety (*LOE 2*). Side effects may include fatigue, dizziness, and peripheral edema.

Progesterone and Progestins

Oral, intramuscular, and topical formulations of progestins have been used in the treatment of hot flashes. There have been 3 RCTs of orally administered progesterone (56,68,69) and 1 RCT of oral versus intramuscular administration of progesterone (70) (Table 4) (*LOE 2*). Although these studies showed effectiveness in reducing hot flashes, the associated side effects, including withdrawal bleeding and weight gain, often limit the use of this medication.

Progesterone cream is classified as a supplement; therefore, it can be purchased without a prescription, and

Table 4
Alternatives to Estrogen for Management of Vasomotor Symptoms Studied in Randomized Controlled Trials*

- Placebo
  - Reductions of 20-50% (56-67)
- Lifestyle modifications
- Selective serotonin reuptake inhibitors
  - Fluoxetine, 20 mg orally daily
    - Reduction of 50% compared with 36% for placebo (59)
  - Paroxetine, 12.5-25 mg orally daily
    - Reduction of 62-65% compared with 38% for placebo (58)
  - Venlafaxine, 75 mg orally daily
    - Reduction of 61% compared with 27% for placebo (57)
- Progestins
  - Megestrol, 20 mg orally twice a day
    - Reduction of 85% compared with 21% for placebo (56)
  - Medroxyprogesterone acetate, 20 mg orally daily
    - Reduction of 73.9% compared with 25.9% for placebo; after crossover, treatment group had immediate return of symptoms and placebo group had additional reduction of 34.5% (68)
  - Medroxyprogesterone acetate, 100 mg orally twice a day
    - Reduction of 86% compared with 33% for placebo (69)
  - Depot medroxyprogesterone, 500 mg intramuscularly every 2 weeks
    - Reduction of 86%, with no difference from 40 mg of megestrol (70)
  - Transdermal progesterone, 20 mg daily
    - Reduction of 83% compared with 19% for placebo (71)
  - Transdermal progesterone, 32 mg daily
    - No significant effect (72)
- Centrally acting α-adrenergic blocking agents
  - Clonidine, 0.1 mg orally daily
    - Reduction of 38-78% compared with 24-50% for placebo (60,61)
  - Transdermal clonidine (equivalent of 0.1 mg daily) given as weekly patch
    - Reduction of 20-80% compared with 36% for placebo (62,73)
- Dopamine antagonists
  - Veralipride (not available in the United States)
    - Response in 63-80% (63)
- Other
  - Gabapentin, 900 mg daily in divided doses
    - Reduction of 45% compared with 29% for placebo (64)
- Phytoestrogens
  - Soy
    - Reduction of 30% with soy compared with 40% for placebo (no significant difference in response) (65)
    - No significant difference at 12 weeks, although minor improvement at 6 weeks (66)
    - No significant difference (67)
    - Reduction of 45% with soy compared with 30% for placebo (74)
    - Reduction of 27% with soy compared with 1% for placebo (75)
  - Black cohosh, 40 mg orally daily
    - Equipotent to conjugated estrogen, 0.6 mg orally daily, both > placebo (76)
    - No significant difference at 60 days (77)
- Vitamin E, 400 IU orally twice a day
  - Minimal decrease of 1 hot flash per day compared with placebo (78)

*Note that no therapy other than estrogen has been approved for this indication by the US Food and Drug Administration.

its contents are neither standardized nor regulated. Progesterone cream is derived from a plant precursor sterol, which in its unaltered or "natural" form is unable to be converted to progesterone by the human body. Commercial preparations of progesterone creams vary widely and may contain an unaltered, unusable form of progesterone or a variant that has been derived from plant sterols but modified in the laboratory to a form that can be utilized by the body.

Two RCTs of transdermal progesterone have been reported in the literature (71,72), and these studies yielded conflicting results (Table 4) (*LOE 2c*). Because of the paucity of data and the variability of these preparations, in addition to possible systemic effects, progesterone creams should not be recommended for the treatment of hot flashes.

Over-the-Counter Preparations

In 1994, the US Congress passed the Dietary Supplement Health and Education Act that defined dietary supplements as a separate regulatory category and outlined ways in which information about supplements could be advertised. It is important to be aware that this act does not require scientific evidence demonstrating safety or efficacy of supplements, and it does not regulate or require standardization of the manufacturing of supplements. Moreover, demonstration of harm from a supplement must be reported before the FDA will intervene or regulate that supplement. Despite these loose regulations and the intended benefits, supplements have the potential for interaction with other medications and medical conditions as well as the potential to cause harm.

In 1998, alternative medicine visits by patients outnumbered visits to conventional primary physicians. Seventy percent of these visits were never discussed with the primary physician. In 44% of such visits, the patients were 50 to 64 years old (79). In one study, predictive factors for use of alternative care included higher education and chronic medical problems (80). Some third-party carriers have begun providing coverage for alternative therapies (albeit at a premium). One survey of 100 postmenopausal women at a San Francisco health conference found that women who used dietary supplements for relief of menopausal symptoms had the highest perceived quality of life, felt most in control of their symptoms, and had a sense of empowerment (81). In general, women are now living a third of their lives after menopause, and in light of the trend of increasing use of alternative medical therapies, the use of supplements for the management of hot flashes is likely to increase.

Phytoestrogens

Phytoestrogens, which can be subclassified as shown in Figure 1, are sterol molecules produced by plants with weak estrogenic activity. They are similar in structure to human estrogens and have been shown to interact and have estrogenlike activity with the estrogen receptor (greater activity at the beta receptor) (82). Plant sterols are used as a precursor for biosynthetic production of mass manufactured pharmaceutical-grade sterols.

Isoflavones, a type of phytoestrogen, have been investigated in the treatment of hot flashes because women in Asia, whose diets characteristically contain 40 to 80 mg of isoflavones daily (in comparison with a typical American diet that contains <3 mg daily), have low rates of hot flashes (83). Consumption of 1 g of soy yields between 1.2 and 1.7 mg of isoflavones. Because of the large amount of soy that must be consumed to achieve an intake of isoflavones that is typical of an Asian diet, a market for isoflavone concentrates (a nutraceutical) has developed.

Multiple RCTs examining the effects of soy or isoflavone consumption on the reduction of hot flashes have yielded inconsistent results (65-67,74,75) (Table 4) (*LOE 2*).

Some studies of the effects of soy on hot flashes have examined raw soy consumption, whereas others have

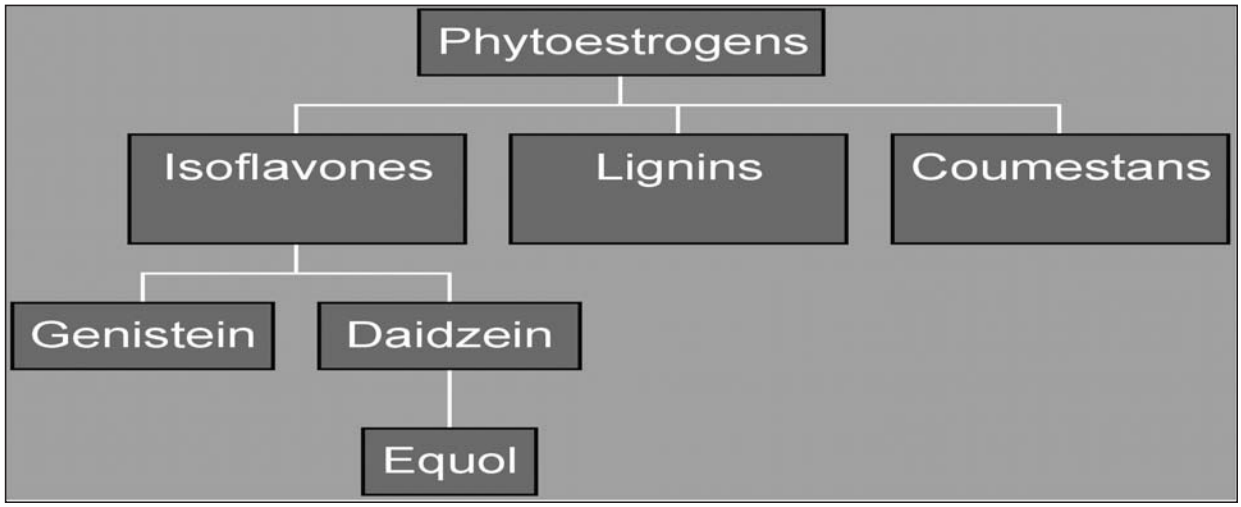

Fig. 1. Subclassification of phytoestrogens, plant sources of weak estrogenic activity.

examined the effects of consumption of isoflavones. In addition, different amounts and formulations of these products were used in the various studies; thus, comparisons between studies are difficult. Isoflavones can be broken down to form daidzein, which can be further metabolized by intestinal bacteria into equol—a stable compound with estrogenic activity (84,85). Only 30% to 50% of adults are able to excrete equol after a soy food challenge (86), and differences in the ability to metabolize soy may explain variations in the response to soy treatment.

If women are interested in using soy, the average amount of isoflavones studied has been 40 to 80 mg daily for up to 6 months. It may take several weeks for any effect to occur, and women should be encouraged to use whole food sources, rather than supplements, because of the risk of overdosage and the lack of known long-term effects with use of isoflavone supplements. Women should be counseled that data regarding estrogenic effects of soy have been inconclusive; therefore, women with a personal or strong family history of hormone-dependent cancers (breast, uterine, or ovarian) or thromboembolic or cardiovascular events should not use soy-based therapies (*grade D*). Some evidence has indicated that soy can stimulate estrogen-dependent breast cancer cells in vitro (86). Of note, a recent double-blind RCT of use of soy protein in older postmenopausal women did not yield differences in cognitive function, bone mineral density, or plasma lipids (87). Long-term randomized controlled safety and efficacy studies in postmenopausal women with vasomotor symptoms are needed.

Black Cohosh

In Germany, black cohosh has been used for many years in the treatment of hot flashes. Most studies of black cohosh have used a commercial preparation, "Remifemin," which is reported to contain 1 mg of triterpene glycoside, calculated as 27-deoxyactein in each 20-mg tablet.

There are 3 published randomized, placebo-controlled trials of black cohosh—2 in the English-language literature (76,77) (*LOE 2*) and 1 in German (88)—which yielded inconsistent results. Although this therapy is thought to be generally safe, there have been rare case reports of hepatitis associated with preparations containing black cohosh (89). Of importance, no safety trials of black cohosh have been conducted for longer than 6 months. Package labeling generally recommends use for no more than a 6-month period.

Vitamin E

The use of vitamin E for reduction of hot flashes in patients with a history of breast cancer has been reported in one randomized, placebo-controlled trial (78) (Table 4) (*LOE 2*). At the conclusion of that study, there was no difference in results between vitamin E and placebo.

Vitamin E is considered relatively safe. In a review of studies of vitamin E, no adverse effects had been reported with dosages of 800 IU of vitamin E daily and even higher doses in some studies (90,91). Evaluation of data from the WHI study indicated that 600 IU of natural-source vitamin E taken every other day provided no overall benefit for major cardiovascular events or cancer, did not affect total mortality, and decreased cardiovascular mortality in healthy women (92). According to the investigators, "these data do not support recommending vitamin E supplementation for cardiovascular disease or cancer prevention among healthy women" (*grade D*).

Recommendations

For women who cannot or do not wish to use estrogen for control of severe vasomotor symptoms, lifestyle changes should be implemented first. If pharmacologic therapy is needed, the most effective nonestrogen class of agents is the antidepressants. Venlafaxine is probably the most beneficial in this class. If antidepressants are not tolerated or cannot be used, then clonidine or megestrol may be considered, although side effects may occur more frequently with these agents. Gabapentin can be considered as a promising new therapeutic option, although both long-term efficacy and safety remain to be substantiated. Data on most nutritional supplements are limited by the lack of placebo-controlled trials and by existing trials that have generally shown no differences between therapy and placebo. Because soy may have some estrogen agonist properties, long-term safety issues, especially in patients with breast cancer, remain of concern for high-dose therapy. A healthful diet that incorporates some soy protein seems reasonable (*grade C*).

III. ANDROGEN DEFICIENCY IN POSTMENOPAUSAL WOMEN

Background and Diagnosis

Androgen therapy has been proposed as a component of treatment for postmenopausal women. In this section, the rationale and evidence for this proposal will be reviewed and evaluated.

All women produce some androgens, which may contribute to the maintenance of normal ovarian function, bone metabolism, cognition, and sexual behavior. Testosterone has direct effects by the stimulation of androgen receptors and also serves as a prohormone in its conversion to estradiol. The adrenal androgens— androstenedione, DHEA, and DHEAS—are very weak androgens but may be converted to testosterone and estrogen. Moreover, symptoms ascribed to androgen deficiency, such as low libido, decreased sexual response, decreased sense of well-being, poor concentration, and fatigue, may also be symptoms of estrogen deficiency. Therefore, it is possible that symptoms ascribed to androgen deficiency may be a result of either androgen deficiency itself or a deficiency of estradiol.

The following questions may be asked: Does an androgen deficiency state exist in postmenopausal

women? In fact, does an androgen deficiency state exist in premenopausal women? In premenopausal women, the only therapy directed at androgens is intervention to reduce rather than increase androgen levels.

The addition of androgen supplements to hormone replacement therapy in the menopausal woman dates from the 1940s. The efficacy of such therapy continues to be debated at this time. Two recent publications have summarized much of what is known or has been speculated about the future of androgen therapy for menopausal women. A 2001 Princeton consensus conference (93) proposed a conservative definition of androgen deficiency in menopausal women (*LOE 3*). Three components were necessary for this diagnosis:

1. Clinical symptoms of androgen insufficiency must be present. Symptoms of androgen deficiency include loss of libido and decreased sexual motivation, arousal, fantasy, and enjoyment. Other nonsexual symptoms include loss of motivation, insomnia, depression, headache, loss of sense of well-being, fatigue, poor concentration, and decreased lean body mass in conjunction with osteopenia or osteoporosis (94).
2. Androgen deficiency should be diagnosed only in women with adequate estrogen status.
3. Free testosterone levels should be at or below the lowest quartile of the reference range found in reproductive-age women (20 to 40 years old).

Further discussion of androgen therapy for postmenopausal women was provided in a 2004 *Mayo Clinic Proceedings* supplement (95). This publication emphasized that the FDA has never approved any use of androgens in women and that any such therapy must be considered an off-label application. At this time, the FDA has postponed approval of a testosterone skin patch for use in menopausal women. Most investigators recommend that androgen therapy should be offered only when the patient continues to have problems while receiving adequate estrogen replacement therapy.

A diagnosis of androgen deficiency in postmenopausal women is challenging, not only in the definition of androgen-deficiency symptoms but also because of technical difficulty in the laboratory measurement of testosterone and unrealistic "normal ranges" for postmenopausal women. Many commercial laboratories list normal serum testosterone levels up to 70 to 80 ng/dL; however, research publications have found levels between 30 and 40 ng/dL in premenopausal (96) and between 20 and 30 ng/dL in postmenopausal (97-99) normal female subjects. In women, high-performance liquid chromatography/tandem mass spectrometry is a more accurate method for measurement of serum testosterone levels (100,101). An even greater variation exists in the normal ranges for DHEA, DHEAS, and androstenedione.

Some investigators have suggested that it is more accurate to measure free testosterone or to calculate a free androgen index through measurement of total testosterone and sex hormone-binding globulin. Even these measurements provide considerable variation in what can be considered normal (102).

Androgen Production in Postmenopausal Women

In normal postmenopausal women, the ovarian production of androstenedione declines, the adrenal gland becomes the primary source of this precursor, and an overall 50% reduction occurs in the serum androstenedione concentration. Consequently, there is a decrease in the rate of production of testosterone from the peripheral conversion of androstenedione to testosterone (96-98,103,104). Ovarian production of testosterone remains relatively stable; in fact, the relative contribution of the ovarian testosterone to total testosterone increases, as evidenced by a testosterone decline of about 40% to 50% after oophorectomy in postmenopausal women (98,103). The adrenal androgens DHEA and DHEAS also decline with aging, independent of menopause; accordingly, by 40 to 50 years of age, their values are about half those in younger women (94,105). The decline of serum testosterone concentrations is small after menopause despite the decrease in adrenal androgens (94,104), an indication that DHEA is a minor source of androstenedione and testosterone in older women (106). In contrast to the sharp decline in production of estrogen at menopause, the modest decline in ovarian production of testosterone is maintained with gonadotropins (96,97,105).

Androgen Replacement Therapy in Postmenopausal Women

Loss of sexual function, diminished libido, decreased bone mass, decreased muscle mass, increased fat mass, and depression have all been ascribed, at least in part, to deficiency of androgen in postmenopausal women (102). Clinical trials have been conducted to assess the efficacy of androgen replacement therapy in addressing these problems and its safety in this setting.

Cameron and Braunstein (107), after a MEDLINE search, reviewed 14 reports of double-blind, randomized, placebo- or estrogen-controlled evaluations of androgen therapy in menopausal women with low libido. In 8 of the 14 studies, serum testosterone levels increased as much as 5 times above baseline levels, resulting in hyperandrogenemia. Androgen levels were not measured in 4 studies, and in the remaining 2 studies, one reported a physiologic level of free testosterone and the other described a physiologic level of total testosterone but a supraphysiologic free androgen index. These data suggest that, to be effective, androgen levels must be increased above normal (*LOE 2a*).

Estrogen therapy in postmenopausal women does not affect the serum pharmacokinetics of transdermally

administered physiologic testosterone (108). It is interesting that no published clinical trials have included a third group treated with estrogen plus estrogen to compare with the estrogen only and estrogen plus testosterone groups. If one considers that testosterone serves as a prohormone to be converted to estradiol, it is possible that some seemingly androgen-induced effects could actually be estrogen effects. Most, if not all, symptoms of androgen deficiency might also be considered symptoms of estrogen deficiency. Consequently, it might be informative for each study of androgen therapy in menopausal women to include a group given a higher dose of estrogen that could be compared with groups receiving estrogen only and those receiving the same dose of estrogen plus an androgen.

Sexual Function

Reports of the effects of androgen replacement therapy on sexual function in menopausal women are conflicting. Administration of testosterone by injections (109), pellet implants (93,102,110), or methyltestosterone orally (111,112) at supraphysiologic doses improves libido, sexual arousal, frequency of sexual fantasies, sexual function, body composition, muscle strength, and quality of life in comparison with administration of estrogen alone. Physiologic replacement testosterone therapy seems to have an inconclusive effect on sexual function (113). Adverse effects, however, were also reported when the androgen replacement therapy resulted in supraphysiologic levels. Acne, hirsutism, and a significant reduction in serum HDL cholesterol levels have been described (102) (*LOE 2b*).

Bone Metabolism

A direct correlation between bone density and serum androgens has been noted in postmenopausal women (114). The effect of androgen therapy on bone in postmenopausal women has been examined in studies of androgen alone and of androgen in combination with estrogen. Numerous observations are compatible with androgen-induced improvement in bone variables, particularly with use of androgen doses that exceed the normal range (93,115-119). Biochemical markers of bone reabsorption and formation in women receiving estrogen or estrogen plus androgen showed evidence of increased bone formation, whereas bone reabsorption decreased only in women receiving estrogen alone (115). In another report (116), androgen monotherapy in postmenopausal women with osteoporosis reduced markers of bone turnover (serum alkaline phosphatase concentrations and urinary calcium excretion) to the same extent as did estrogen (*LOE 2c*).

Adrenal Androgen Replacements

Serum concentrations of DHEA and DHEAS decline with aging in both men and women. DHEA replacement therapy for aging men and women has been proposed to boost immune function and alleviate postmenopausal and perimenopausal symptoms (for example, hot flashes, insomnia, irritability, loss of libido), improve memory, and promote a sense of well-being (98,120) (*LOE 3*). A dose of 50 mg of DHEA daily in comparison with placebo in 60 perimenopausal women significantly increased serum DHEAS and testosterone concentrations (121). Symptomatic improvement was not documented. Thus, although DHEA can improve testosterone levels in women, it does not appear to offer relief of symptoms or improvement in cognitive function (119,122).

The use of androgens other than testosterone (such as DHEA, DHEAS, or androstenedione) cannot be recommended. These substances are available as over-the-counter drugs and are not controlled relative to the amount of medication that is actually present in each tablet. A recent report evaluating amounts of DHEA in over-the-counter tablets found that three brands had no DHEA at all, one had 149% of the labeled amount, and most had 59% to 82% of the labeled amount (121) (*grade D*).

At the current time, the following preparations might be *considered* for androgen therapy in menopausal women (*grade C*):

- *For oral administration*: Methyltestosterone
- *For injection*: Testosterone enanthate, testosterone cypionate
- *For topical application*: Androderm, AndoGel, Testim
- *Not available in the United States*: Testosterone undecanoate, testosterone pellets

All these preparations except methyltestosterone are designed for use in men with testosterone deficiencies and would not be appropriate in women. Other therapeutic options are being investigated. A testosterone skin patch is undergoing clinical trials. Over-the-counter preparations cannot be recommended until their consistent quality can be documented. Therapeutically, caution must be exercised if the most common androgen, methyltestosterone, is used. This weak androgen cross-reacts with the measurement of serum testosterone in most laboratory kits. Consequently, one might see a considerable elevation of the serum testosterone level that is a result of cross-reactivity of this weak androgen. In fact, when testosterone levels are measured after chromatographic separation from methyltestosterone, the administration of methyltestosterone results in a reduction in the serum testosterone concentration (123). The potential side effects of androgen replacement therapy in women are dependent on the dose and include acne, hirsutism, deepening of the voice, and clitorimegaly. Lowering of the HDL cholesterol level is a concern, and long-term studies are needed to assess the cardiovascular benefits or risks of androgen therapy (93-109). A recent study by Sturgeon et al (124) suggested that higher serum concentrations of testosterone or estradiol are risk factors for breast cancer in premenopausal women.

Conclusion

Overall, in selected, symptomatic, postmenopausal women, or women who have undergone bilateral oophorectomy, estrogen replacement alone may not be adequate therapy but should be implemented first (*grade C*). Combined estrogen-androgen therapy may be used in those patients who continue to have symptoms of androgen deficiency while receiving estrogen therapy (*grade C*). Because endogenous androgen production declines after spontaneous menopause as well as after oophorectomy, symptomatic women may benefit from androgen therapy in conjunction with estrogen therapy. The data on androgen therapy in postmenopausal women are suggestive of benefits, but further long-term safety studies are needed. Our recommendations are against the general use of androgen therapy at menopause, except in women with continuing symptoms during adequate estrogen therapy (*grade C*).

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