

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

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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 but are in no way a substitute for a medical professional's independent judgment and should not be considered medical advice. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment of the authors 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, and not as a replacement for, 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.



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Abbreviations:

AACE = American Association of Clinical Endocrinologists; **BEL** = best evidence level; **CAD** = coronary artery disease; **CCS** = consecutive case series; **CEE** = conjugated equine estrogen; **CHD** = coronary heart disease; **CI**s = confidence intervals; **CSS** = cross-sectional study; **EL** = evidence level; **E+P** = combination of estrogen and a progestational agent; **ER** = estrogen receptor; **FDA** = US Food and Drug Administration; **FSH** = follicle-stimulating hormone; **HR** = hazard ratio; **MHT** = menopausal hormone therapy; **MNRCT** = meta-analysis of nonrandomized prospective or case-controlled trials; **MPA** = medroxyprogesterone acetate; **MRCT** = meta-analysis of randomized controlled trials; **MRI** = magnetic resonance imaging; **NE** = no evidence (theory, opinion, consensus, or review); **NRCT** = nonrandomized controlled trial; **OR** = odds ratio; **PCS** = prospective cohort study; **RCCS** = retrospective case-control study; **RCT**s = randomized controlled trials; **RR** = relative risk; **SCR** = single case report; **SS** = surveillance study (registries, surveys, epidemiologic study); **WHI** = Women's Health Initiative; **WHIMS** = Women's Health Initiative Memory Study

INTRODUCTION

Menopause is strictly defined as 1 year without menses. In fact, however, the 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. The transition from normal ovarian function to ovarian failure is described as the menopausal transition. The population affected by estrogen deficiency is substantial: there are approximately 70 million women in the United States beyond 50 years of age, with 2,500 to 3,500 women having their 50th birthdays each day (1). Although some of these 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. Most women with menopausal symptoms will experience spontaneous cessation of them within 5 years after onset; a substantial proportion of women, however, continue to experience symptoms beyond 5 years. Menopausal hormone therapy (MHT) is the most effective intervention for management of these symptoms that diminish the quality of life.

The goal of MHT, defined as estrogen therapy alone or a combination of estrogen and a progestational agent (E+P), is to alleviate the quality-of-life symptoms in menopausal and perimenopausal women. In addition, chronic disorders associated with both aging and the menopausal state affect the brain, skeleton, integument, and urogenital

and cardiovascular systems. The role of MHT in the prevention of such disorders remains controversial.

This consensus document will present recommendations for the use of MHT for the relief of menopausal symptoms. It will consider the possible role of MHT in the prevention of chronic disorders associated with estrogen deficiency. Moreover, it will assess the benefit-versus-risk profile of MHT, including our current understanding of the effects of MHT on multiple organ systems.

The target audience is endocrinologists, nonendocrinologist physicians, and interested laypersons. Evidence presented in these guidelines was obtained through MEDLINE searches and available references compiled by guideline chairs and task force members. In addition, expert opinion was used to evaluate the available scientific literature, which was graded for treatment recommendations by evidence-based medicine guidelines (2 [EL 4; NE]) and then presented in specific references in the appended reference list.

GUIDELINES FOR CLINICAL PRACTICE GUIDELINES

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 (3 [EL 4; NE]). 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. Evidence rating or the evidence level (EL) structure, based on generally accepted evaluations of standards for evidence-based medicine, is presented in Table 1 (3 [EL 4; NE]). References involving clinical evidence will have a denotation reflecting this evaluation in the reference list and the text.

A task force convened by the American Association of Clinical Endocrinologists (AACE) reviewed all available evidence from MEDLINE searches. Conference calls and online discussion were used to evaluate the strength of evidence. After the initial writing process, reviewers contributed their expertise to the document.

The task force followed the AACE Protocol for Standardized Production of Clinical Practice Guidelines (3 [EL 4; NE]). The current protocol includes rating of evidence on the basis of the strength of scientific studies, as outlined in Table 1, with the addition of a subjective factor impact that may modify the final recommendation grade (Table 2). Subjective factors may include physician preferences, costs, risks, and regional availability of specific technologies and expertise when there is no definite clinical evidence. Therefore, recommendation grades are based on the best evidence level (BEL) available, including strong BEL (Grade A; BEL 1), intermediate BEL (Grade B; BEL 2), weak BEL (Grade C; BEL 3), or subjective

Table 1
American Association of Clinical Endocrinologists
Evidence Rating Based on Reference Methodology^a

| Numerical descriptor (evidence level) | Semantic descriptor (reference method) |
|--|--|
| 1 | Meta-analysis of randomized controlled trials (MRCT) |
| 1 | Randomized controlled trial (RCT) |
| 2 | Meta-analysis of nonrandomized prospective or case-controlled trials (MNRCT) |
| 2 | Nonrandomized controlled trial (NRCT) |
| 2 | Prospective cohort study (PCS) |
| 2 | Retrospective case-control study (RCCS) |
| 3 | Cross-sectional study (CSS) |
| 3 | Surveillance study (registries, surveys, epidemiologic study) (SS) |
| 3 | Consecutive case series (CCS) |
| 3 | Single case report (SCR) |
| 4 | No evidence (theory, opinion, consensus, or review) (NE) |

^a 1 = strong evidence; 2 = intermediate evidence; 3 = weak evidence; and 4 = no evidence.
 From Mechanick et al (3).

factors when there is no clinical evidence, inconclusive clinical evidence, or contradictory clinical evidence (Grade D; BEL 4). When consensus statements are cited, even if based on a synthesis of evidence as in a published “evidence-based report,” EL 4 is assigned, in accordance with AACE protocol.

Of note, in this document, a Grade D recommendation is used when the BEL is 4, rather than when consensus cannot be reached, inasmuch as all recommendations were approved unanimously by the task force and reviewers. The correctness of the recommendation grades and ELs was subjected to review at several points during the preparation of these guidelines.

A recommendation grade is linked to the BEL available. In addition to the EL, a recommendation grade (3 [EL 4; NE]), 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 OF RECOMMENDATIONS

Each recommendation is labeled “R” in this summary.

All recommendation grades were determined by unanimous consensus of the primary writers and reviewers.

- **R1.** MHT may be appropriate for the relief of severe menopausal symptoms in selected postmenopausal women, on the basis of an individually determined benefit-versus-risk profile (**Grade A; BEL 1**).
- **R2.** MHT may be prescribed during the perimenopause and early menopause for relief of menopausal symptoms and treatment of vulvovaginal atrophy (**Grade A; BEL 1**).
- **R3.** The use of the transdermal route of estrogen administration should be considered in order to avoid the hepatic “first-pass effect,” which may theoretically reduce the risk of thromboembolic disease (**Grade B; BEL 3**).
- **R4.** The use of transvaginal estrogen may be considered to provide topical effects with less systemic absorption (**Grade B; BEL 3**).
- **R5.** The dose of MHT may be reduced with advancing age (**Grade C; BEL 3**).
- **R6.** Because of the increased risk of endometrial cancer, unopposed estrogen should not be used in women with an intact uterus (**Grade D; BEL 1**).
- **R7.** Progestational agents should be used for a minimum of 10 to 14 days per month in women treated with estrogen who have an intact uterus (**Grade A; BEL 1**).
- **R8.** Long-cycle therapy with use of a progestagen for 14 days every 3 months may be considered, in an effort to reduce breast exposure to progestagens, despite lack of definitive assessment of efficacy (**Grade B; BEL 2**).
- **R9.** Amenorrhea may be achieved by using a low dose of a progestagen administered continuously (daily) in conjunction with estrogen. Because recent studies suggest adverse breast outcomes with continuous progesterone exposure, this form of therapy is not recommended (**Grade D; BEL 2**).

Table 2
Grading of Recommendations:
How Different Evidence Levels Can Be Mapped to the Same Recommendation Grade^a

| Best evidence level | Subjective factor impact ^b | Two-thirds consensus | Mapping | Recommendation grade |
|---------------------|---------------------------------------|----------------------|-------------|----------------------|
| 1 | None | Yes | Direct | A |
| 2 | Positive | Yes | Adjust up | A |
| 2 | None | Yes | Direct | B |
| 1 | Negative | Yes | Adjust down | B |
| 3 | Positive | Yes | Adjust up | B |
| 3 | None | Yes | Direct | C |
| 2 | Negative | Yes | Adjust down | C |
| 4 | Positive | Yes | Adjust up | C |
| 4 | None | Yes | Direct | D |
| 3 | Negative | Yes | Adjust down | D |
| 1, 2, 3, 4 | Not applicable | No | Adjust down | D |

^a Starting with the left column, best evidence level, subjective factors, and consensus map to recommendation grades in the right column. When subjective factors have little or no impact (“none”), then the best evidence level is directly mapped to recommendation grades. When subjective factors have a strong impact, then recommendation grades may be adjusted up (“positive” impact) or down (“negative” impact). If a two-thirds consensus cannot be reached, then the recommendation grade is D. For not applicable (regardless of the presence or absence of strong subjective factors), the absence of a two-thirds consensus mandates a recommendation grade D.

^b See text for further information.

From Mechanick et al (3).

- **R10.** MHT should be used in the lowest dose and for the shortest period necessary to control menopausal symptoms (**Grade A; BEL 1**).
- **R11.** Therapeutic trials of nonhormonal prescription medications, including clonidine, antidepressants (selective serotonin reuptake inhibitors), and gabapentin, may be considered for the relief of menopausal symptoms in women with no specific contraindications (**Grade B; BEL 2**).
- **R12.** Over-the-counter supplements should be used with caution because they are not regulated by the US Food and Drug Administration (FDA) and have the potential for interactions with drugs and for causing harm (**Grade C; BEL 2**).
- **R13.** Phytoestrogens, including soy-derived isoflavonoids, result in inconsistent relief of symptoms. Because these compounds may have estrogenic effects, 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; BEL 1**).
- **R14.** Custom compounded “bioidentical hormone therapy” is not recommended (**Grade D; BEL 1**).
- **R15.** FDA-approved bioidentical hormone preparations may be considered, but evidence is lacking that they are safer or more effective than traditional forms of hormone therapy (**Grade C; BEL 2**).
- **R16.** MHT should be used for the prevention and treatment of osteoporosis within the context of the overall benefit-versus-risk analysis of each patient. Data from multiple randomized controlled trials (RCTs) substantiate the efficacy of estrogens in preserving bone mass and, less consistently, preventing fractures, but nonhormonal therapeutic options for bone health exist (**Grade A; BEL 1**).
- **R17.** Hormone therapy for the prevention or treatment (or both) of dementia is not recommended (**Grade D; BEL 1**).
- **R18.** MHT should be prescribed to women in conjunction with a thorough discussion of the possible relationship of MHT to breast cancer. Current evidence suggests that E+P regimens are associated with a possible higher risk of breast cancer than is therapy with estrogen alone (**Grade A; BEL 1**).
- **R19.** Concordant with current FDA warnings, we recommend that women who are at increased risk of

thromboembolic disease should not take estrogen-containing therapy (although there is evidence that transdermal estradiol may not increase this risk; see subsequent material) (**Grade D; BEL 1**).

- **R20.** Women should be advised that smoking increases the risk of cardiovascular and venous thromboembolic disease when taking estrogen, and aggressive smoking cessation programs should be advised (**Grade A; BEL 1**).
- **R21.** MHT is not recommended for primary or secondary prevention of cardiovascular disease (**Grade D; BEL 1**).
- **R22.** Lipid profiles, smoking history, and diabetes history as well as family history should be assessed to assist in the determination of individual cardiovascular risk (**Grade A; BEL 1**).
- **R23.** Women should be advised that cerebrovascular accidents occur with increased frequency in patients taking estrogen alone or E+P combination therapies in an age-dependent manner (**Grade A; BEL 1**).
- **R24.** Women should be advised that there may be an increase in ovarian epithelial tumors with the use of estrogen for more than 10 years (**Grade B; BEL 2**).
- **R25.** Women may be advised that several studies including the Women's Health Initiative (WHI) have demonstrated a lower risk of colon cancer in women treated with E+P combination (**Grade B; BEL 2**).

FDA APPROVAL

The FDA has approved the use of MHT 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 that have questioned 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 prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal preparations should be considered.
- Prevention of postmenopausal osteoporosis. When MHT is 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 drug-related risks.

FDA CONTRAINDICATIONS TO MHT

The FDA has recommended that MHT 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, myocardial infarction)
7. Untreated hypertension
8. Active liver disease
9. Known hypersensitivity to the active substances of MHT or to any of the excipients
10. Porphyria cutanea tarda (absolute contraindication) (**4**)

INDICATIONS FOR MHT

As previously noted, the FDA has approved the use of MHT for moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy.

Hot flashes are the most common complaint of perimenopausal and postmenopausal women. Hot flashes have been reported in up to 70% of women undergoing natural menopause and in almost all women who have undergone surgical menopause (**5 [EL 3; CCS]**). A prospective study of 436 women found that 31% experienced hot flashes during perimenopause, even before any changes occurred in menses (**6 [EL 2; PCS]**). 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 or several times per week. The physiologic mechanism whereby a hot flash occurs is thought to be an elevated body temperature leading to cutaneous vasodilation, which results in flushing and sweating in association with a subsequent decrease in temperature, chills, and potentially relief. 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 (**7 [EL 3; CCS]**). Proposed mediators of 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 the withdrawal of estrogen rather than simply low estrogen levels (**8 [EL 4; NE]**).

It has been postulated that the occurrence of hot flashes is related to the ability of the vasculature to undergo vasodilation, a function of the vascular endothelium. Therefore, the presence of hot flashes or flushing has also been considered a possible risk factor for cardiovascular disease or a predictor of the effect of MHT on coronary heart disease (CHD) outcomes (see subsequent material).

Modifiable and nonmodifiable risk factors for hot flashes should be evaluated. Modifiable factors that have been shown to increase the risk of occurrence of hot flashes include cigarette smoking (9 [EL 3; CSS], 10 [EL 3; CSS]), body mass index >30 kg/m² (9 [EL 3; CSS], 11 [EL 3; SS]), and lack of exercise (11 [EL 3; SS]). Nonmodifiable risk factors include maternal history, menopause at younger than 52 years of age, and abrupt menopause—induced by a surgical procedure (12 [EL 3; CCS]), chemotherapy, or irradiation. Approximately 65% of patients with a history of breast cancer have hot flashes (13 [EL 3; SS]), and adjuvant therapy with tamoxifen or tamoxifen plus chemotherapy is associated with substantial worsening of menopause-related symptoms (14 [EL 3; SS]).

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.

Numerous RCTs have proved the efficacy of estrogen in treating menopausal symptoms (15 [EL 1; RCT], 16 [EL 4; NE]). In addition, estrogen therapy may improve mood disorders (depression), cognitive disruption, and sexual dysfunction during early menopause (15 [EL 1; RCT], 16 [EL 4; NE]). It should be emphasized that not all mood disorders or cognitive disruption that coincides with menopause should be attributed to menopause per se without an evaluation of 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 the onset of menopause, approximately 3% of women report very frequent hot flashes, and 12% report moderate to severe hot flashes, 15 years after the onset of menopause (17 [EL 3; SS]). Therefore, in selected postmenopausal women, on the basis of an individually determined benefit-versus-risk profile, longer MHT might be appropriate (Grade C).

MHT: TREATMENT DETAILS

MHT is prescribed during the perimenopausal period and early menopause for relief of menopausal symptoms and for 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. Progestagens can be administered continuously or sequentially. When used cyclically, the progestagen should be given in an adequate dose for 10 to 14 days each month (16 [EL 4; NE]) (Grade A). Cyclic administration of the progestagen usually produces monthly menstrual periods. Because persistent menstrual bleeding seems to be the major reason for noncompliance with MHT, amenorrhea may be achieved by using a low dose of a progestagen administered continuously (daily) in conjunction with estrogen. When certain progestagens are used continuously, however, studies (discussed subsequently under “Breast Cancer”) have raised concerns about increased breast cancer risk. Many women given continuous combined E+P, however, will continue to experience episodes of breakthrough bleeding. Less frequent endometrial exposure to progestagens, so-called long-cycle therapy with use of a progestagen for 14 days every 3 months, has not been well validated for effectiveness, but it has been proposed to reduce breast exposure to progestagens (18 [EL 4; NE]) (Grade B). Abnormal vaginal bleeding, either between periods of exposure to progestagens 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 are associated with abnormal endometrial histologic findings.

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) (16 [EL 4; NE]). Until the risk of any one product is clearly understood on the basis of scientific studies, each woman and her physician should choose the best MHT for her individually.

The use of various forms of estrogen for relief of vasomotor symptoms has been extensively reviewed (16 [EL 4; NE]). The forms and routes of delivery of estrogen and the corresponding daily doses most commonly used are as follows (16 [EL 4; NE]):

- Conjugated equine or synthesized conjugated estrogens (0.3 to 0.625 mg)
- Micronized 17 β -estradiol for oral administration (0.5 to 1 mg) or injection
- Transdermal estradiol (25 to 100 μ g)
- Ethinyl estradiol (0.01 to 0.02 mg)
- Topically applied estradiol emulsion, gel, and spray
- Vaginal estrogenic preparations, including a vaginal estradiol ring and creams of conjugated equine estrogen (CEE) and estradiol

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 main 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 subjected to the first-pass effect show greater interindividual variability in the attained blood levels. 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**) and possibly to reduce the risk of thromboembolic disease (see subsequent material). Although currently most authorities believe there is an absolute contraindication to the use of estrogen in women with a previous history of thromboembolic disease or in women with thrombogenic mutations, recent evidence suggests that transdermal administration of estrogen may be safe in those situations. Further study of this issue is warranted (**19 [EL 3; SS], 20 [EL 3; PCS]**).

Likewise, local estrogen therapy may have vaginal and uterine benefits with less systemic absorption, but the same caveat applies. 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, or cream) of the estrogen. Vaginally administered estrogens are readily absorbed through the vaginal mucosa and can result in appreciable blood levels of estrogen (**21 [EL 3; CSS]**).

The desired effects of estrogen therapy manifest 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 (**22 [EL 4; NE]**) (**Grade A**).

Measurement of serum follicle-stimulating hormone (FSH) levels cannot be used to monitor the adequacy of the estrogen doses in 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 (**23 [EL 4; NE]**). Serum FSH levels may remain increased despite adequate estrogen effect on the target tissues.

Progestagens

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

- Medroxyprogesterone acetate (MPA) (2.5 mg daily or 5 mg for 10 to 12 days/mo)
- Micronized progesterone (**24 [EL 1; RCT]**) (100 mg daily or 200 mg for 10 to 12 days/mo)
- Norethindrone acetate (0.35 mg daily or 5 mg for 10 to 12 days/mo)
- Drospirenone (3 mg daily)
- Levonorgestrel (0.075 mg daily)

Products that combine estradiol with a progestagen for combined-continuous therapy include the following:

Oral:

- Estradiol-drospirenone
- CEE-MPA
- Ethinyl estradiol-norethindrone acetate
- Estradiol-norgestimate

Transdermal:

- Estradiol-levonorgestrel
- Estradiol-norethindrone acetate

The side effects of progestational compounds are difficult to evaluate and vary with the progestational agent administered (**15 [EL 1; RCT]**). 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.

Differences in lipid effects (**25 [EL 1; RCT]**), androgenic potency, glucocorticoid and antimineralocorticoid activity (**26 [EL 4; NE]**), procoagulant activity, and fibrinogen levels (**27 [EL 1; RCT]**) have been described among various progestational compounds. Potentially, these differences may have clinical significance in affecting insulin sensitivity, glucose tolerance, fluid retention, blood pressure, and vascular dilation (**26 [EL 4; NE]**). In primate studies, the protective effect of estrogen (CEE)

in preventing early atherosclerosis was not antagonized by the coadministration of MPA in vivo (28 [EL 4; NE]). Lipid profiles as well as other variables of cardiovascular risk should be monitored to determine individual risk (Grade A).

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

Because studies have suggested a difference in the risk of breast cancer in patients treated with estrogen alone, in comparison with E+P therapy, it has been suggested that systemic estrogen with local (endometrial) progesterone might provide the benefit of protection from endometrial hyperplasia without the risk to breast tissue. Thus far, only one study has addressed this issue and suggests that there is not a statistically significant difference. The use of a levonorgestrel-releasing intrauterine system was associated with a higher risk of breast cancer in comparison with that in nonusers. The odds ratio (OR) in 154 women using it alone was 1.45, whereas its use as a complement to estradiol in 137 women was associated with an OR of 2.15 (29 [EL 2; RCCS]).

In terms of overall choice of MHT, 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" (30 [EL 1; RCT]).

Bioidentical Hormone Therapy

The term "bioidentical hormone therapy," as used in the popular press, refers to the compounding of plant-derived hormones by pharmacists which are purported to be "identical in structure" to human endogenous hormones, a claim that is not biochemically substantiated in many cases. Phytoestrogens are not detected by assays for estrone, estradiol, or estriol. In fact, compounded preparations for the treatment of menopause may contain estradiol, estrone, estriol, progesterone, testosterone, and dehydroepiandrosterone, which are not found naturally in plants

but are synthesized from botanical precursor sterols. These preparations are compounded by pharmacists—as pills, gels, creams, suppositories, or injectable solutions (31 [EL 4; NE], 32 [EL 4; NE]). In contrast to commercially produced pharmaceutical agents, compounded medications are not subjected to FDA oversight. Currently, there are commercially produced hormones, including estrogen and progesterone, that are, indeed, molecularly identical to human endogenous hormones and are under the purview of the FDA. The benefits of progesterone, dehydroepiandrosterone, and testosterone for the treatment of menopause have not been adequately substantiated by scientific studies.

Compounded mixtures of estrogens, including estradiol, estrone, and estriol, are purported to mimic physiologic ratios that occur in young women with intact ovaries. The hormonal ratios found in these compounds, however, are not based on the estrogenic potency or individual bioavailability of each agent. Estrone is minimally produced by ovarian secretion. Most of it is produced by peripheral conversion from adrenal and ovarian androstenedione, mainly in adipose tissue (33 [EL 3; CSS]). Nevertheless, estrone, as estrone sulfate (a commercially available product), can provide adequate hormonal therapy. Estriol is the peripheral metabolite of estrone and estradiol—not a secretory product of the ovary (34 [EL 4; NE]). Estriol is produced in substantial amounts by the placenta during pregnancy. Therefore, concentrations of this hormone are very low in healthy nonpregnant young female subjects. In nonpregnant female subjects, the formation of estriol is considered an example of metabolic detoxification—that is, conversion of biologically active material to a less active form (34 [EL 4; NE]). Each woman uniquely produces estriol on the basis of individual tissue estrogen metabolism. The enthusiasm about the potential role of estriol in MHT may be traced back to past reports that this estrogen limited the growth of breast tumors in the rat model (35 [EL 4; NE]). Subsequent research, however, did not confirm those initial observations (36 [EL 4; NE], 37 [EL 2; RCCS]).

Some topical formulations of bioidentical hormones may contain progesterone. Progesterone cream is classified as a supplement; therefore, it can be purchased without a prescription, and 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 (38) 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. The usefulness of progesterone and progestagens in the treatment of menopausal symptoms is discussed later (see page 19).

Salivary hormone level testing is recommended by many bioidentical hormone proponents as a means of

providing patients with “individualized” therapy. Yet these methods are not approved by either the FDA or the Clinical Laboratory Improvement Amendments (the US Health and Human Services agency regulating laboratory standards). Accurate studies have revealed large intrasubject variability in salivary sex hormone concentrations (31 [EL 4; NE], 39 [EL 4; NE]), which fluctuate depending on numerous variables, including diet, hydration, and circadian rhythm. These conditions are difficult to standardize (31 [EL 4; NE]). Standardized blood tests, which are available for sex steroids, are well established but have limited clinical value in evaluating MHT.

Because it is expected that postmenopausal women will have low levels of all sex steroids, any measure of these hormones in postmenopausal women has no predictive value of what the “normal” or “individualized” therapeutic levels of sex hormones should be. Moreover, such a measurement cannot be used for achieving these goals through administration of various proportions of sex hormones and routes of delivery.

Claims that treatment with compounded bioidentical hormones is safer, more effective, and free of side effects in comparison with pharmacologically produced agents are not substantiated by a systematic review of current scientific literature. Peer-reviewed, carefully scrutinized, well-designed studies are needed.

A major concern regarding these unregulated compounds is the finding of variable potency in many samples evaluated by FDA surveys (40-42 [EL 4; NE]), with either higher or lower levels of the active ingredient than stated, leading to potential risk of either overdose or lack of therapeutic benefit. Concerns have also been raised about possible cross-contamination of compounded preparations and the regulation of sterility in the preparation of compounds for parenteral use (40-43 [EL 4; NE]).

AACE, The Endocrine Society, and the American Society for Reproductive Medicine have introduced a resolution through the American Medical Association urging the FDA to increase regulation and oversight of bioidentical hormones (44 [EL 4; NE]). Specifically, the American Medical Association asked the FDA to do the following:

- Conduct surveys for purity and dosage accuracy of all compounded bioidentical hormone formulations
- Require mandatory reporting by drug manufacturers, including compounding pharmacies, of adverse events related to the use of bioidentical hormones
- Create a registry of adverse events related to the use of bioidentical hormones
- Require inclusion of uniform patient information (warnings and precautions) in packaging of compounded bioidentical hormones

This current AACE guideline reiterates those recommendations.

BENEFIT-VERSUS-RISK ANALYSIS OF MHT

Menopause and aging are associated with the onset and progression of many chronic illnesses, including CHD, stroke, osteoporosis, dementia, and cancer. Physicians who are responsible for the care of women must consider the potential benefit and risk of therapy for both treating symptoms and potentially preventing disease with MHT. The timing of therapy may be critical because it has been shown that disease prevention may be possible only if therapy is initiated early in menopause, whereas the same treatment may prove more deleterious later.

Endometrial Cancer

The use of unopposed estrogen in menopausal women with an intact uterus has been associated with development of endometrial cancer. The use of progestational agents in this group of women to prevent development of endometrial hyperplasia and cancer has been addressed in the earlier section “MHT: Treatment Details.”

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 relative risk (RR) is high, but the increased absolute risk is quite small. In a WHI study (45 [EL 1; RCT]), 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 a hazard ratio (HR) of 2.06. The incidence was greater with increasing age, obesity, and factor V Leiden mutations (45 [EL 1; RCT]). Women with a history of venous thromboembolic disease should be carefully advised about this risk when MHT is being considered. Because smoking further increases the risk, women should be counseled about smoking cessation (**Grade A**). Although currently most authorities believe that there is an absolute contraindication to the use of estrogen in women with a previous history of thromboembolic disease or in women with thrombogenic mutations, recent evidence suggests that transdermal estrogen may be safe in those situations. Further study of this issue is warranted (19 [EL 3; SS], 20 [EL 3; PCS], 46 [EL 3; SS]).

Breast Cancer

The weight of evidence from years of basic research indicates that exposure to estrogen is an important determinant of the risk of breast cancer. The proposed mechanism of estrogen-induced carcinogenesis is the transformation of estrogen into genotoxic, mutagenic metabolites that initiate and promote the development of breast cancer cells (47 [EL 4; NE]). To date, however, no clinical studies have definitively demonstrated that estrogen metabolites contribute to human breast cancer.

It has been stated that “hormones can influence tumor growth, but it is questionable whether hormones induce malignant tumors *de novo*. The long developmental process of tumors is in apparent contradiction to results of some epidemiological studies that describe an increased cancer risk, implying primary initiation in MHT users within observation periods of 1 to 6 years. The mechanisms of initiation versus promotion of hormone-sensitive cancers, particularly breast cancer, are only partly understood” (48 [EL 4; NE]).

Most studies examining the risk of MHT and breast cancer have been observational, with the inherent bias and confounding associated with use of this method. The controversy centers on the accuracy of statistical analysis to provide a clear definition of risk, comparing RR (HRs) versus absolute risk. The RR can be misleading when the actual increases (absolute risk) are very small and may be insignificant. Some scientists consider such small absolute risks statistically insignificant and suggest that the use of HRs exaggerate the risk. Many investigators support the concept that unless the HR is 3.0 or higher, it is of no consequence (49 [EL 4; NE]).

For the past several decades, observational studies have raised concerns about the association of postmenopausal estrogen and combined E+P therapy with an increased risk of breast cancer. A review of 45 studies published from 1975 to 2000 regarding the use of MHT 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 (50 [EL 4; NE]). Since 2000, several epidemiologic studies have distinguished breast cancer risk by comparing estrogen alone versus E+P therapy (51 [EL 2; RCCS], 52 [EL 3; SS], 53 [EL 2; RCCS], 54 [EL 2; PCS], 55 [EL 2; RCCS]). These recent observational cohort and case-control studies reported no significant increase in breast cancer risk with the use of estrogen alone but a significantly increased risk with the use of continuous combined E+P. 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 of breast cancer with E+P therapy (54 [EL 2; PCS]).

On reanalysis of worldwide observational data, the Collaborative Group on Hormonal Factors in Breast Cancer (56 [EL 4; NE]) reported that, for current users of MHT 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 MHT, the RR was 1.6 (95% CI, 1.25 to 2.05). There was a significant reduction in nodal spread, and nodal and distant metastatic lesions were reported less frequently, in MHT users versus never-users, with the following findings: (1) localized to the breast (RR 1.00), (2) spread to axillary lymph nodes only (RR 0.82), and (3) metastatic involvement beyond

breast and lymph nodes (RR 0.54). This study, however, is confounded by a subgroup analysis of women who had discontinued the use of MHT 5 years or more before their breast cancer was diagnosed, which demonstrated no increased risk of breast cancer in comparison with the nonusers, despite prior use of MHT for 5 years or more.

This same potential bias was noted in the Million Women Study (57 [EL 4; NE]), an observational study of a breast screening program in the United Kingdom that reported an increase in breast cancer risk within 2½ years of observation with the use of all types of MHT regimens, beginning with the first year of therapy. As in the aforementioned Collaborative Group Study (56 [EL 4; NE]), the risk disappeared from 1 to 5 years after the withdrawal of MHT. The appearance of significant breast cancer risk during the first year of MHT strongly suggests that the surplus of cases of breast cancer arose from preexistent disease, before the onset of the observational period, as observational bias (58 [EL 4; NE]). In women taking combined E+P MHT for 10 or more years (the group at highest risk for developing breast cancer), in absolute terms, the excess risk was still confined to approximately 0.75%.

In contrast, the French MISSION Study (Menopause: Risk of Breast Cancer, Morbidity and Prevalence) (59 [EL 2; PCS]) was a historical-prospective observational study, which collected data from 4,949 patients: 2,693 in the MHT group (using estrogen alone, E+P, or selective progestagen combinations, excluding medroxyprogesterone) and 2,256 in the unexposed group. The MHT group had a mean duration of use of 8.3 years, with 31% being exposed for ≥10 years. The incidence of new breast cancer cases was 0.64% in the MHT-exposed group and 0.70% in the unexposed group, with an RR of 0.914 (CI, 0.449 to 1.858). No evidence was found for an increased risk of breast cancer in the women exposed to MHT in comparison with the nonexposed women (the CI included 1).

A family history of breast cancer increases an individual's risk of developing breast cancer. Data from the Iowa Women's Health Study (60 [EL 2; PCS]), however, did not support a further increased risk caused by the use of MHT in a patient with a family history of breast cancer (RR, 1.13; 95% CI, 0.82 to 1.57).

The 2002 report by the WHI, an RCT, was intended to settle the controversy (30 [EL 1; RCT]). This study noted a significantly increased risk (HR) of breast cancer associated with the use of E+P (specifically, CEE-medroxyprogesterone) combination therapy by postmenopausal women (61 [EL 1; RCT]). The overall HR was 1.26 (95% CI, 1.00 to 1.59) and did not reach statistical significance, with the CI including 1. The final HR of 1.26 had an adjusted 95% CI of 0.83 to 1.92, and the absolute risk increase was 0.08% or 8 per 10,000 person-years. Such a broad CI that includes 1.0 indicates there is no significant increase in risks attributable to hormone use.

Adjustment of the WHI data for prior exposure to MHT showed no increased breast cancer risk in women without previous exposure to MHT (Table 3) (61 [EL 1; RCT]).

Since the publication of the WHI study, this value of a 26% increased RR of invasive breast cancer in the combined hormone group has been cited by many in the scientific community and the media as proof of the estrogen-breast cancer relationship. Yet the WHI authors themselves have acknowledged that it “almost reached nominal statistical significance,” validating the lack of statistical significance. In the estrogen-only arm of the WHI study, fewer cases of invasive breast cancer were reported in estrogen-treated women in comparison with placebo, with the HR of 0.77 (95% CI, 0.59 to 1.01) just missing statistical significance for a reduced risk (63 [EL 1; RCT], 64 [EL 1; RCT]).

After the publication of the initial WHI study in 2002, the use of MHT declined by about 38% by 2003. Using data from the Surveillance, Epidemiology and End Results Program of the National Cancer Institute, Ravdin et al (65 [EL 3; SS]) reported that between 2002 and 2003 there was a 6.7% decrease in the incidence of breast cancer in the United States, implying that the decrease during this time was due to the decline in the number of women taking MHT. Although this finding might suggest a cause-and-effect relationship between hormone treatment and breast cancer, careful evaluation of the Surveillance, Epidemiology and End Results data did not support this hypothesis. The incidence of estrogen receptor (ER)-positive breast cancer appeared to peak in 1999, and a downward trend appeared to begin in 2000—not in 2002—before the decrease in MHT use (66 [EL 3; SS]). Additionally, the 7% decrease is probably an overestimate because the number of women undergoing mammography during this time decreased, with fewer breast cancers being detected.

In a follow-up study from the WHI (67 [EL 1; RCT]), participants from the RCT and observational groups were examined for breast cancer incidence after discontinuation of MHT. The increased risk of breast cancer previously reported by the WHI associated with E+P combination therapy declined substantially soon after discontinuation of the therapy and was unrelated to a change in the use of mammography. The rapid decrease in breast cancers during the period after intervention might be interpreted as suggesting that withdrawal of E+P therapy leads to a regression of pre-clinical cancers, again supporting the view that hormone therapy does not initiate breast cancer development.

The role of progestagen choice for MHT has been investigated to clarify the absence of increased breast cancer risk in the estrogen-only users (68 [EL 2; PCS]). Most studies have evaluated estrogen associated with MPA or 19-nortestosterone derivatives. With use of data from the French E3N cohort study, comparison of MHT never-users with ever-users of E+P (RR, 1.00; 95% CI, 0.83 to 1.22) showed no significantly increased risk of any breast cancer subtype. Nevertheless, estrogen combined with other

Table 3
Breast Cancer Risk in Women’s
Health Initiative Study Participants,^a
Stratified by Duration of Previous Use
of Hormone Therapy

| Prior use of MHT (y) | Hazard ratio | 95% confidence interval |
|----------------------------|-----------------|-------------------------------|
| 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 |

Abbreviation: MHT = menopausal hormone therapy.

^a The estrogen + progestin treatment arm.

From Cobin et al (62).

progestagens was associated with significant increases in risk of ductal and lobular carcinomas (RR, 1.69; 95% CI, 1.50 to 1.91).

A recent report from the California Teachers Study (69 [EL 2; PCS]) evaluated the breast cancer risk in women using estrogen therapy and various combinations of E+P products. There was an increasing risk of invasive breast cancer with longer duration of progestin exposure and specifically for women with more than 15 years of use. This study was limited because the data were collected by questionnaire, with attendant recall bias and confounding.

Conflicting data have been presented regarding the initial clinical manifestations and prognostic features of breast cancer diagnosed in women taking MHT in comparison with nonusers. If the risk of breast cancer is increased with the use of MHT, it seems to be a small increase and possibly isolated to susceptible women, especially older women with longer exposures to estrogen.

This low risk is further substantiated by the reduced mortality associated with breast cancer diagnosed in MHT users in comparison with nonusers (70 [EL 2; PCS]). No clinical 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 MHT and breast cancer risk would be that MHT causes breast cancer to grow faster and thus leads to an earlier mammographic diagnosis. In addition, the adverse effects of MHT on increasing mammographic breast density may also contribute to delay in diagnosis of breast cancer, which becomes evident after MHT has been discontinued.

The reduced mortality rate is compatible with the observation that MHT-associated breast cancers are smaller,

better differentiated, and associated with lower proliferation rates than those tumors in nonusers of MHT (71 [EL 4; NE]). Analysis of breast cancer data from the WHI (61 [EL 1; RCT]), 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.

A recent publication from the WHI reported mortality rates in postmenopausal women diagnosed with breast cancer from the E+P group in comparison with nonusers of MHT (66 [EL 3; SS]). Breast cancers in the E+P group were similar in histologic features and grade to breast cancers in the placebo group but were more likely to be node-positive (81 [23.7%] versus 43 [16.2%], respectively; HR, 1.78; 95% CI, 1.23 to 2.58). Nevertheless, deaths directly attributed to breast cancer (25 deaths [0.03% per year] versus 12 deaths [0.01% per year]; HR, 1.96; 95% CI, 1.00 to 4.04) did not meet statistical significance, inasmuch as the CI included 1.

As noted previously in this section, the choice of progestational agent may be the most important factor in observations of breast cancer risk. Recent studies suggest that the use of micronized progesterone in comparison with medroxyprogesterone and the avoidance of combined continuous therapy may be associated with a lower risk of breast cancer in MHT users (68 [EL 2; PCS], 72 [EL 2; PCS]).

Other Cancers

Colon Cancer

Several studies, including the E+P arm of the WHI trial, have demonstrated a decrease in incidence of and mortality related to colon cancer (30 [EL 1; RCT], 61 [EL 1; RCT], 73 [EL 2; PCS]).

Ovarian Cancer

Reported effects of estrogen and E+P therapy on the occurrence of ovarian cancer have been inconsistent. Available data suggest a possible increase in ovarian epithelial tumors with >10 years of estrogen use only (61 [EL 1; RCT], 74 [EL 4; NE]).

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 (75 [EL 1; RCT]). 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 have been raised about the statistical significance of this diagnosis in this older population.

In the Nurses' Health Study (76 [EL 2; PCS]), 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 daily and 1.63 (95% CI, 1.18 to 2.26) for women taking 1.25 mg daily or more. Women who took 0.3 mg daily 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. 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.

A follow-up magnetic resonance imaging (MRI) study from the Women's Health Initiative Memory Study (WHIMS) evaluated ischemic brain lesions in women with no previously documented strokes. Total ischemic lesion volume was determined by post-study brain MRI, comparing WHI participants in the MHT groups versus the placebo group. There were no differences in total ischemic lesion volumes; therefore, no concrete measurements were available to support the increased stroke risk noted in the WHI (77 [EL 3; CSS]).

EFFECT OF MHT ON NONREPRODUCTIVE ORGAN SYSTEMS

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

Osteoporosis

Postmenopausal osteoporosis causing spine and hip fractures is associated with considerable morbidity and mortality. Data from RCTs (78 [EL 1; RCT]) substantiate the efficacy of estrogens in preserving bone mass and, less consistently, preventing fractures. The WHI was the first large clinical trial to show a significant reduction in osteoporosis-associated fractures, including hip and vertebral fractures, with use of MHT. Approximately 85% of osteoporosis-related fractures noted in the WHI trial were nonvertebral and nonhip fractures. 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 person-years 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 MHT on bone protection (79 [EL 1; RCT]) persist even with doses of estrogen below those commonly used for relief of symptoms (80 [EL 1; RCT]), 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 MHT 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 benefit-versus-risk 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 disease in comparison with men (possibly attributable to postmenopausal depletion of endogenous estrogen). The prospective, longitudinal Cache County [Utah] Study (81 [EL 3; CSS]) investigated the prevalence and incidence of Alzheimer 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 MHT. A longer duration of MHT use was associated with a greater reduction in the risk of Alzheimer disease. Prior MHT use was associated with a decreased risk in comparison with nonusers, and women's higher risk in comparison with men was virtually eliminated after more than 10 years of exposure to MHT. In addition, there was no apparent benefit with current use of MHT unless that use exceeded 10 years (81 [EL 3; CSS]).

Several meta-analyses have examined the use of MHT 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 (OR, 0.66; 95% CI, 0.53 to 0.82) with use of MHT (82 [EL 2; MNRCT]).

In a WHIMS report (83 [EL 1; RCT]), 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.

The WHIMS-MRI Study (84 [EL 3; CSS]) measured total brain, ventricular, hippocampal, and frontal lobe volumes in a subgroup of WHI participants, comparing the MHT groups with the placebo group, to assess correlation with dementia and cognitive dysfunction. There was

a slightly significant decrease in volume in 2 brain areas in this subset of MHT users (women with a mean age of 78.5 years and a mean duration of 28.7 years after menopause) who entered the WHI with the largest vascular lesion burdens—that is, already compromised brains, both in reduced cognitive function and increased vascular damage. The findings in this study are in contradiction to several earlier reports demonstrating *increased* brain volumes with MHT in younger women, who started hormone therapy within 10 years after menopause (85 [EL 3; CSS], 86 [EL 3; PCS]).

The methods used to evaluate the effects of MHT 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 WHIMS trial (83 [EL 1; RCT]), cases of probable dementia were noted during the first year of intervention in both the E+P and the placebo groups; this finding supports the considerable incidence of cognitive dysfunction at baseline in both groups.

Cardiovascular Disease

Because coronary artery disease (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 (87 [EL 2; PCS]). Counseling about prevention of CAD should include discussions of lifestyle modifications, including weight reduction, exercise, and cessation of smoking (Grade A). Medical interventions for at-risk postmenopausal women include antihypertensive agents and lipid-lowering treatments.

Both basic science and clinical investigations enhance our current understanding of the use of MHT and the risk of cardiovascular disease. The effects of estrogen and progesterone on vascular tissue appear to be dependent on age, the time from menopause, and preexistent cardiovascular disease. Moreover, it is clear that different chemical formulations of both estrogenic and progestational agents interact differently with their receptors and activate different signaling pathways. Therefore, extrapolation of data from studies that use a particular hormone to other compounds within the same treatment group may be inappropriate. With these caveats in mind, current treatment guidelines seek to improve the quality of life while optimizing cardiovascular benefits.

Basic Science Studies

Estrogen acts on nuclear receptors ER alpha and beta to produce genomic effects. These receptors have been found in cardiac myocytes as well as vascular endothelial cells and vascular smooth muscle cells (88 [EL 4; NE]). Estrogen compounds exert a substantial effect on

cardiovascular risk indirectly by affecting lipid concentrations, inflammatory markers, thrombotic and fibrinolytic factors, antioxidant effects, and carbohydrate metabolism as well as by direct effects on vascular and myocardial cells (89 [EL 4; NE]). Recently described extranuclear ERs mediate multiple nongenomic rapidly active effects, including cell membrane ion channels, G-protein-coupled regulation, and tyrosine kinase effects. In vascular endothelial cells, vasodilation caused by estrogen has been shown to be mediated by an increase in nitrous oxide activation of endothelial nitrous oxide synthase by means of the PI3K/Akt pathway as well as by sSrc/ERK1/2, heat shock protein, and G-protein pathways (90 [EL 4; NE], 91 [EL 4; NE]). In vascular smooth muscle cells, including those in coronary arteries, estrogen activates nitrous oxide synthase as well as creating ion fluxes that favor vasodilation (91 [EL 4; NE]). The antiinflammatory effects of estrogen have been attributed to both nuclear and extranuclear receptor-mediated processes (90 [EL 4; NE]).

It has been proposed that estrogen may cause more harmful effects in aging vasculature because in this setting there may be diminished ER amount or expression, a change in promoter methylation, diminished ER integrity, inactive ER subtypes, or unfavorable ER cellular distribution (92 [EL 2; PCS]).

Progestational agents may affect the vascular effects of estrogen. This is highly dependent on the structure and functional characteristics of the progestational agent used. Progestational agents have differing influences in antagonizing the vasodilatory/nitrous oxide synthase effect of estrogen. Those that have androgenic activity may adversely affect lipid profile, insulin sensitivity, and carbohydrate tolerance, whereas the use of antimineralocorticoid progestational compounds may be useful in causing natriuresis and potentially improving blood pressure (26 [EL 4; NE]). Glucocorticoidlike effects may be deleterious. In primate studies, estrogen inhibits plaque formation early in life, and this effect is partly antagonized by MPA, but not by progesterone or a 19-norprogesterone derivative nomegestrol acetate. Lipid effects in human subjects in clinical trials vary significantly depending on the agent used, with MPA worse than nomegestrol acetate and micronized progesterone or nestorone (93 [EL 4; NE]). Less androgenic progestagens have less pronounced procoagulant effects.

Primate Studies

In primate studies, MHT is effective in inhibiting progression of early-stage (fatty streak) atherosclerosis. In contrast, it is much less effective in inhibiting progression of more advanced (established plaque) atherosclerosis (94 [EL 4; NE]).

Clinical Practice Guidelines

In clinical practice guidelines, recommendations must be formulated on the basis of the outcomes of well-designed

and adequately powered clinical trials. Therefore, although there is still considerable uncertainty about cardiovascular risk versus benefit of MHT, depending on age, time from menopause, and the specific agents used, current guidelines are derived from studies already performed. It is anticipated that future trials will modify these recommendations.

Clinical Trials

In the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, low-density lipoprotein cholesterol and Lp(a) levels decreased, high-density lipoprotein cholesterol levels increased, while fibrinogen and triglycerides were increased in hormone users in comparison with control subjects (25 [EL 1; RCT]). In the prospective observational Nurses' Health Study, women using estrogen therapy had an OR of 0.6 for major cardiovascular events in comparison with nonusers (87 [EL 2; PCS]). In contrast, in the Heart and Estrogen/Progestin Replacement Study (HERS) trial, older women with preexisting CAD did not experience a reduction in risk, despite lower levels of low-density lipoprotein cholesterol and Lp(a) and higher levels of high-density lipoprotein cholesterol. Once corrected for other cardiovascular risk factors and the use of statins, there were more heart attacks and deaths during the first year and fewer during the later years; however, at final analysis at 6.8 years, ORs of 1 were seen (95 [EL 1; RCT]). In 226 women with established CAD who underwent angiography, the use of 17 β -estradiol did not affect the progression of atherosclerotic lesions in comparison with that in nonusers (96 [EL 1; RCT]). In the WHI, estrogen-only users had RRs for cardiovascular disease of 1.12 and for CHD of 0.91 (63 [EL 1; RCT]), while the HR for CHD in the combined CEE-MPA group was 1.24 (97 [EL 1; RCT]).

Subsequent analysis of both the Nurses' Health Study and the WHI has revealed that the risk of both heart attack and stroke are related to age (as expected), with the effect of MHT being related to both age and time from last menses. In the Nurses' Health Study, women beginning MHT near menopause had a significantly reduced risk of CHD—RR, 0.66 (95% CI, 0.54 to 0.80) for estrogen alone and RR, 0.72 (95% CI, 0.56 to 0.92) for the E+P combination therapy. In the subgroup of women demographically similar to those in the WHI, no significant relationship between MHT and CHD was found among women who initiated therapy at least 10 years after menopause—RR, 0.87 (95% CI, 0.69 to 1.10) for estrogen alone and RR, 0.90 (95% CI, 0.62 to 1.29) for E+P. Among women who began taking hormones at older ages, there was no relationship between current use of estrogen alone and CHD (for women aged 60+ years: RR, 1.07; 95% CI, 0.65 to 1.78), although there was a suggestion of a possibly reduced risk for CHD with use of combined MHT (RR, 0.65; 95% CI, 0.31 to 1.38) (92 [EL 2; PCS]). Likewise, in a reanalysis of data from the WHI, age and time from last menses were significantly predictive of the occurrence of cardiovascular events and

death. In the estrogen-only arm of the study, the OR was 0.5 for women 50 to 59 years old, 0.9 for those 60 to 69 years old, and 1.1 for those 70 to 79 years old (**98 [EL 1; RCT]**), and in the combined E+P arm, the OR for CHD was directly related to the time since menopause, with the OR for CHD in the hormone-treated versus placebo groups of 0.9 for <10 years, 1.2 for 10 to 19 years, and 1.7 for ≥20 years (**97 [EL 1; RCT]**). Overall in the WHI, women younger than 60 years had a lower OR for CHD with therapy in comparison with control subjects, whereas older women experienced more events both relative to control subjects and as absolute numbers (**99 [EL 1; RCT]**) (Table 4).

A meta-analysis of 23 trials of MHT that compared results in younger women (<60 years old or <10 years since menopause) versus older women found that MHT significantly reduced CHD events in the former but not in the latter. The ORs for CHD in hormone-treated women were 0.68 (95% CI, 0.48 to 0.96) for younger women and 1.03 (95% CI, 0.91 to 1.16) for older women (**100 [EL 1; MRCT]**).

Three years after intervention ended in the WHI study, the health outcomes of 15,730 women treated with estrogen alone, estrogen + MPA, or placebo were compared. There was no significant difference in the rate of cardiovascular

events (1.97 per year versus 1.91 per year in the treated versus control groups) (**101 [EL 1; RCT]**). Indeed, coronary artery calcification scores have been shown to be lower in estrogen-treated women in comparison with control subjects, with an OR of 0.39 (95% CI, 0.21 to 0.73) ($P<.004$) for the highest coronary artery calcification scores (**102 [EL 1; RCT]**).

Hot Flashes and Cardiovascular Risk

Of note in the WHI, few women with severe hot flashes were included in the study in order to avoid affecting the blinding of subjects, in comparison with previous observational studies in which such women were highly represented and not excluded. Although the correlation of vasomotor symptoms with cardiac outcome itself, as well as such symptoms serving as a predictor of the vascular effect of hormone therapy, remains controversial, it is clear that the WHI population, based on both age and symptoms, differs from the general population of menopausal women. Thus, concern exists about the generalizability of conclusions regarding the effect of MHT on cardiovascular disease. In the Rancho Bernardo Study, reported night sweats were associated with a reduced risk of death during the subsequent 20 years, independent of multiple risk factors including past or current use of postmenopausal estrogen

Table 4
Data Reanalysis in 10,739 Postmenopausal Women
in the Women's Health Initiative Study:
Hormone Treatment Group (396 Cases of Coronary Heart Disease)
Versus Placebo Group (370 Cases of Coronary Heart Disease)^a

| Factor | Hazard ratio | | Absolute excess of coronary heart disease events per 10,000 person-years |
|--------------------------|------------------------|-------|--|
| | Coronary heart disease | Death | |
| By years since menopause | | | |
| <10 | 0.76 | ... | −6 |
| 10-19 | 1.1 | ... | 4 |
| ≥20 | 1.28 | ... | 17 |
| By age (y) | | | |
| 50-59 | 0.93 | 0.70 | −2 |
| 60-69 | 0.98 | 1.05 | 1 |
| 70-79 | 1.26 | 1.14 | 20 |

^a Cerebrovascular accident: hazard ratio 1.3 for both study arms; not age or time related.
Estrogen only versus estrogen plus progestational agent: hazard ratio similar in older age; lower (but not significant) in younger age.
Vasomotor symptoms: lower risk in younger patients; higher risk in older patients.
Adapted from Rossouw et al (99).

therapy (**103 [EL 2; PCS]**). When women in early menopause were classified into those described as having either intolerable or tolerable hot flashes, the latter group had a less favorable response to orally administered estrogen, as assessed by the ventricular ejection response and endothelial response to nitroglycerin. Overall, hot flashes did not affect the changes in arterial or aortic stiffness or endothelial function in response to orally or transdermally administered estrogen, with or without progesterone (**104 [EL 1; RCT]**).

In the Kronos Early Estrogen Prevention Study (KEEPS) population of recently menopausal women, menopausal symptoms including hot flashes at the onset of the study were not correlated with coronary artery calcification (**105 [EL 4; NE]**). It has been suggested that peripheral blood flow-mediated reactive hyperemia, a marker of endothelial function, might provide information about early vascular disease (in addition to traditional surrogate markers such as coronary artery calcification and carotid intima-media thickness) and perhaps might yield better identification of a subpopulation of women for whom hormonal therapy may be beneficial (**106 [EL 3; CSS]**). In the Study of Women's Health Across the Nation (SWAN), hot flashes were associated with increased coronary artery calcification and aortic calcification as well as lower flow-mediated dilation, with the latter 2 associations persisting in models adjusted for risk of cardiovascular disease and estradiol use (**107 [EL 3; CSS]**). Further studies of this important issue may provide tools in the future for better stratification of a woman's risk of cardiovascular disease during estrogen therapy, along with consideration of her age, years after menopause, and traditional cardiovascular risk factors.

Conclusions Regarding Cardiovascular

Aspects of MHT Use

1. Epidemiologic and observational studies suggest that cardioprotection *may* be provided by the use of MHT—especially estrogen therapy alone (without a progestin)—when it is prescribed for women early during the menopausal transition.
2. RCTs that have demonstrated no cardioprotective benefit of MHT 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 MHT).
3. RCTs used a fixed-dose, single-form, combined MHT. Therefore, these results cannot be applied to use of other MHT regimens.
4. There is no evidence of increased CAD-related risk, nor are there RCTs that support a primary cardioprotective benefit, when MHT is initiated during the menopausal transition for symptomatic women.

5. MHT should not be initiated for the primary or secondary prevention of CAD (**Grade D**).

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

1. Each postmenopausal woman should be provided with an individualized evaluation regarding the benefits and risks of MHT, 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 MHT in older postmenopausal women for treatment or for secondary prevention of these medical conditions. In younger postmenopausal women in whom MHT is initiated within 5 years after the onset of menopausal symptoms, however, the primary prevention benefit issues should be considered relevant. These women might consider continued use of MHT until the controversy is resolved (**Grade C**).
4. The choice of MHT sex steroids should emphasize the use of estradiol as the first-line estrogen, administered either orally or transdermally (**Grade C**). The choice of progestagen should favor intermittent use of progesterone or norethindrone rather than MPA (**Grades B and C**).

NONHORMONAL ALTERNATIVE THERAPIES FOR MANAGEMENT OF VASOMOTOR SYMPTOMS IN MENOPAUSE

Lifestyle Alterations

Lifestyle changes designed to maintain a cool environment and aid heat dissipation may help with mild to moderate vasomotor 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 (**9 [EL 3; CSS]**, **10 [EL 3; CSS]**, **11 [EL 3; SS]**, **108 [EL 3; NRCT]**, **109 [EL 3; CSS]**, **110 [EL 1; RCT]**, **111 [EL 3; NRCT]**, **112 [EL 4; NE]**).

Prescription Medications

A summary of the various agents and the related published studies (**113-135 [EL 1; RCT]**) is presented in Table 5. As previously mentioned, no therapy other than estrogen has been approved by the FDA for treatment of menopause-related vasomotor symptoms.

Table 5
Alternatives to Estrogen for Management of Vasomotor Symptoms
Studied in Randomized Controlled Trials^a

| |
|---|
| Placebo |
| Reductions of 20%-50% (113-124) |
| Lifestyle modifications |
| Selective serotonin reuptake inhibitors |
| Fluoxetine, 20 mg orally daily |
| Reduction of 50% compared with 36% for placebo (117) |
| Paroxetine, 12.5-25 mg orally daily |
| Reduction of 62%-65% compared with 38% for placebo (121) |
| Venlafaxine, 75 mg orally daily |
| Reduction of 61% compared with 27% for placebo (115) |
| Progestins |
| Megestrol, 20 mg orally twice a day |
| Reduction of 85% compared with 21% for placebo (116) |
| 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% (125) |
| Medroxyprogesterone acetate, 100 mg orally twice a day |
| Reduction of 86% compared with 33% for placebo (126) |
| Depot medroxyprogesterone, 500 mg intramuscularly every 2 weeks |
| Reduction of 86%, with no difference from 40 mg of megestrol (127) |
| Transdermal progesterone, 20 mg daily |
| Reduction of 83% compared with 19% for placebo (128) |
| Transdermal progesterone, 32 mg daily |
| No significant effect (129) |
| Centrally acting α -adrenergic blocking agents |
| Clonidine, 0.1 mg orally daily |
| Reduction of 38%-78% compared with 24%-50% for placebo (113,119) |
| Transdermal clonidine (equivalent of 0.1 mg daily) given as weekly patch |
| Reduction of 20%-80% compared with 36% for placebo (118,130) |
| Dopamine antagonists |
| Verapride (not available in the United States) |
| Response in 63%-80% (124) |
| Other |
| Gabapentin, 900 mg daily in divided doses |
| Reduction of 45% compared with 29% for placebo (114) |
| Phytoestrogens |
| Soy |
| Reduction of 30% with soy compared with 40% for placebo (no significant difference in response) (123) |
| No significant difference at 12 weeks, although minor improvement at 6 weeks (122) |
| No significant difference (120) |
| Reduction of 45% with soy compared with 30% for placebo (131) |
| Reduction of 27% with soy compared with 1% for placebo (132) |
| Black cohosh, 40 mg orally daily |
| Equipotent to conjugated estrogen, 0.6 mg orally daily, both >placebo (133) |
| No significant difference at 60 days (134) |
| Vitamin E, 400 IU orally twice a day |
| Minimal decrease of 1 hot flash per day compared with placebo (135) |

^a Note that no therapy other than estrogen has been approved for this indication by the US Food and Drug Administration.
 From Cobin et al (62).

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 (**115 [EL 1; RCT]**, **117 [EL 1; RCT]**, **121 [EL 1; RCT]**). 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 for management of menopausal symptoms is shown in Table 5 (**113 [EL 1; RCT]**, **118 [EL 1; RCT]**, **119 [EL 1; RCT]**, **130 [EL 1; RCT]**). 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 has been approved by the FDA for treatment of seizure disorders but has also been used to treat neuropathic pain. A small RCT (**114 [EL 1; RCT]**) has demonstrated significant reductions in hot flashes with use of gabapentin in postmenopausal women (Table 5), but larger trials are needed to study the long-term efficacy and safety. 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 (**116 [EL 1; RCT]**, **125 [EL 1; RCT]**, **126 [EL 1; RCT]**) and 1 RCT of oral versus intramuscular administration of progesterone (**127 [EL 1; RCT]**) (Table 5). 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.

Two RCTs of transdermal progesterone have been reported in the literature (**128 [EL 1; RCT]**, **129 [EL 1; RCT]**), and these studies yielded conflicting results (Table 5). 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 use of 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 consultations with 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 (**136 [EL 3; SS]**). In one study, predictive factors for use of alternative care included higher education and chronic medical problems (**137 [EL 3; SS]**). 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 (**138 [EL 3; SS]**). 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 (**62 [EL 4; NE]**). They are similar in structure to human estrogens and have been shown to interact and have estrogenlike activity with the ER (with greater activity at the beta receptor) (**139 [EL 4; NE]**). 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 (**140 [EL 3; SS]**). 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 (**120 [EL 1; RCT]**, **122 [EL 1; RCT]**, **123 [EL 1; RCT]**, **131 [EL 1; RCT]**, **132 [EL 1; RCT]**) (Table 5).

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

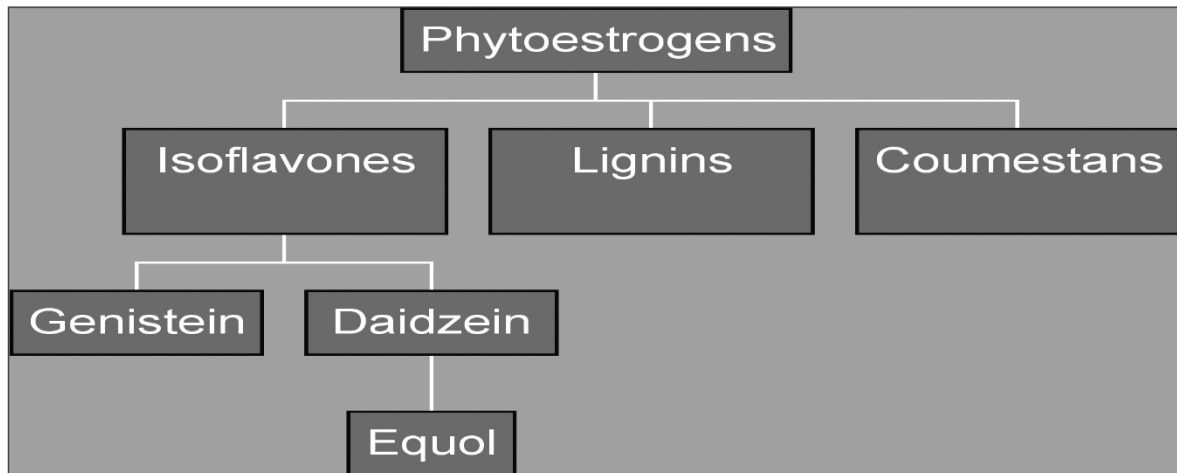


Fig. 1. Subclassification of phytoestrogens, plant sources of weak estrogenic activity. From Cobin et al (62).

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 (141 [EL 1; RCT], 142 [EL 4; NE]). Only 30% to 50% of adults are able to excrete equol after a soy food challenge (143 [EL 4; NE]), 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 the 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 of 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 (143 [EL 4; NE]). Of note, a recent double-blind RCT of the use of soy protein in older postmenopausal women did not yield differences in cognitive function, bone mineral density, or plasma lipids (144 [EL 1; RCT]). Long-term randomized controlled safety and efficacy studies of soy in postmenopausal women with vasomotor symptoms are needed.

Black Cohosh

Black cohosh has been used to control symptoms of menopause including hot flashes. In one placebo-controlled

RCT, the use of a symptom scale demonstrated relief of hot flashes with black cohosh extract comparable to the results with MHT, with no difference in tolerability, laboratory findings, or clinical adverse events in comparison with placebo (145 [EL 1; RCT]). Concerns regarding the possible estrogenicity of this preparation seem to be allayed by the absence of ER binding, upregulation of estrogen-dependent genes, and lack of stimulation of growth of estrogen-dependent tumors in animal models (146 [EL 4; NE]). Of importance, no safety trials of black cohosh have been conducted for longer than 6 months. There have been isolated case reports of uncertain significance of hepatitis (147 [EL 3; CCS]) and myopathy (148 [EL 3; SCR]) with the use of this agent. Package labeling generally recommends use for no more than a 6-month period.

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 in results between such 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**).

DISCLOSURE

Cochairpersons

Dr. Neil F. Goodman reports that he has received speaker honoraria from Bayer AG and consulting fees from Noven Pharmaceuticals, Inc. and Pfizer Inc.

Dr. Rhoda H. Cobin reports that she does not have any relevant financial relationships with any commercial interests.

Task Force Members

Dr. Samara B. Ginzburg reports that she does not have any relevant financial relationships with any commercial interests.

Dr. Ira A. Katz reports that he does not have any relevant financial relationships with any commercial interests.

Dr. Dwain E. Woode reports that he does not have any relevant financial relationships with any commercial interests.

Reviewers

Dr. Pauline M. Camacho reports that she has received research grant support for her role as principal investigator from Eli Lilly and Company and Procter & Gamble and speaker honoraria from Warner Chilcott.

Dr. JoAnn E. Manson reports that she does not have any relevant financial relationships with any commercial interests.

Dr. Steven M. Petak reports that he does not have any relevant financial relationships with any commercial interests.

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