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Hormone Therapy: Translating Recent Evidence Into Clinical Practice

With release of data from the Women's Health Initiative (WHI), management of menopause-related symptoms and associated conditions has become a topic of clinical debate and patient confusion. Some women are panicked about hormone therapy having learned of the data without the benefit of sound clinical perspectives. Many providers are uncertain how to interpret study results to make clinical decisions. They may not feel capable of providing definitive, accurate guidance for their patients regarding hormone therapy. Some may have stopped prescribing hormone therapy entirely.

The WHI provides key information about the safety and efficacy of one type of oral hormone therapy in a particular patient population. The study's investigators acknowledge that WHI results should not be generalized too quickly or too broadly. More data are needed on the safety and efficacy of other formulations of hormone therapy and the risk/benefit ratio in other patient groups—especially women who are newly postmenopausal and experiencing menopause-related symptoms, such as hot flashes. Bottom line: patients need us now, not later. The purpose of this monograph is to help providers understand the design, goals, and results of the study for the sake of their patients. We need to help interpret these data based on actual—rather than the perceived—risks associated with hormone therapy.

Many areas of uncertainty exist and may never be resolved due to the range of variables involved and the cost of conducting randomized controlled trials. ARHP's approach is to provide evidence-based guidelines where available, but not to shy away from practical recommendations where the data are incomplete. We relied on our expert faculty reviewers to fill in these areas of uncertainty based on their clinical experience.

The publication can help front-line providers—practitioners who are faced daily with the questions about hormone therapy. Its content was shaped during a roundtable discussion of clinicians, researchers, and women's health advocates. Our thanks go to these dedicated individuals for sharing their clinical acumen and practical knowledge about this contested and confusing topic.

Wayne C. Shields
ARHP President and CEO

LEARNING OBJECTIVES

After completing this *Clinical Proceedings*, participants will be able to:

1. Identify two physiological changes associated with menopause and three types of symptoms women commonly experience during perimenopause and menopause.
2. Discuss key findings from the Women's Health Initiative regarding coronary heart disease, breast cancer, venous thromboembolic events, stroke, and osteoporotic fractures and how these findings should be applied to the treatment of menopausal women.
3. Describe three effective menopausal therapy talking points that help patients make informed decisions about hormone therapy.
4. Discuss four basic differences between prescription hormone therapies and discuss the current data on herbal hormone products.
5. List four requisites for individualizing hormone therapy.

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THE PHYSIOLOGY OF MENOPAUSE

DEFINITIONS

Menopause, or the *climacteric*, is the cessation of menses, diagnosed retrospectively after 12 months have passed without menstruation. In the Western world, menopause occurs at 51.4 years, on average, with a range of 40 to 58 years.¹ The age at which menopause occurs is genetically determined, although cigarette smoking reduces the age of menopause by about two years.²

Perimenopause is the period that begins with the first signs and symptoms of endocrinologic change, during which the menstrual cycle becomes irregular, and ends one year after the final menstrual cycle.^{3,1} *Menopause transition*, a term sometimes used synonymously with perimenopause, also begins at the first signs and symptoms of endocrinologic change but ends with the final menstrual cycle.^{3,1} On average, perimenopause begins at about 47.5 years of age and lasts about four years, but it can span several years.¹ Anecdotally, many providers see women with menstrual changes that begin as early as age 35. About 10 percent of women do not experience perimenopause and have regular menses until menstruation ceases abruptly.^{2,1}

Menopause is a natural event that provokes divergent cultural and personal connotations. In societies in which youth is highly valued, menopause is often viewed as a period of loss and diminishment.⁴ In societies in which elders are valued, menopause is often viewed as providing enhanced status and greater respect.⁴ Women's personal beliefs about their fertility and identity can affect their view of menopause. Some women welcome the freedom from concerns about reproduction; others mourn the loss of fertility. Cultural and personal views about menopause may affect women's perceptions of menopause-related symptoms and their preferences for symptom management.

PHYSIOLOGICAL CHANGES

Two key physiological changes are associated with menopause: the loss of primary ovarian follicles and the resulting decrease in serum and tissue estradiol levels. The primary estrogen in premenopausal women is 17 beta-estradiol, which is produced in the ovary from the aromatization of testosterone.⁵ Commercial estradiol products are often referred to as containing "bioidentical" estrogen for this reason. Other sites, such as muscle and adipose tissue, produce smaller amounts of estrogen through the metabolism of androgens. After menopause,

these extragonadal sites become the primary source of estrogen, in the form of estrone and, to a lesser extent, estradiol.⁵

The physiological changes that eventually result in cessation of menses and the development of menopause-related symptoms begin long before menopause. From menarche on, the number of primary ovarian follicles decreases, with especially marked reductions after age 40.² The loss of primary ovarian follicles appears to be the key event that triggers perimenopause.⁴

In the past, researchers believed that menopause was caused solely by a lack of estrogen production by the ovary, resulting in higher levels of follicle-stimulating hormone (FSH) and cessation of menses. More recent evidence suggests that inhibin B, a glycoprotein synthesized by granulosa cells in the ovary, plays a major role in triggering the menopause transition.² FSH normally stimulates inhibin B synthesis, which then suppresses FSH via a negative feedback loop. After about age 45, however, inhibin B levels fall, perhaps due to the decreased number of ovarian follicles, causing a rise in FSH. The increased FSH levels can stimulate increased estradiol release from the remaining follicles and can also prompt them to release the estradiol more rapidly, resulting in shorter cycles. About six to twelve months before menopause, the number of follicles is even lower, and higher FSH levels fail to increase estradiol production. At this point, the reduced estradiol levels can result in menopause-related symptoms, such as hot flashes and vaginal dryness. During perimenopause, estrogen production by the ovary is erratic, such that estradiol levels are unpredictable and can fluctuate between normal, high, and low. For this reason, measurement of FSH and estradiol is not helpful for diagnosis during perimenopause; symptoms are a better marker of perimenopausal status.

MENOPAUSE-RELATED SYMPTOMS AND CONDITIONS

The reduction of endogenous estrogen at menopause leads to a constellation of symptoms directly related to lower estrogen levels or to estrogen withdrawal and increases the risk of several medical conditions. A majority of women (50 to 80 percent) report experiencing menopause-related symptoms around the time of menopause.⁶ As shown in Table 1, menopause-related symptoms can be divided into three categories: vasomotor, genitourinary, and other systemic symptoms.



Vasomotor symptoms are caused by estrogen withdrawal, whereas genitourinary symptoms are caused by a prolonged reduction in estrogen levels. Thus, women generally experience vasomotor symptoms in early menopause and genitourinary symptoms later, in the menopause transition.

TABLE 1. Menopause-related Symptoms

Vasomotor

- Headache
- Palpitations
- Night sweats
- Insomnia and sleep disturbances
- Hot flashes

Genito-urinary

- Vaginal dryness
- Dyspareunia
- Vaginal itching or burning
- Urinary frequency, dysuria, nocturia

Other systemic symptoms

- Fatigue
- Reduced sexual desire and arousal
- Anxiety, depression, irritability
- Cognitive difficulties
- Backache
- Stiffness

Source: See references 2 and 6

Hot flashes are described as an intense sensation of warmth in the upper body that lasts about four minutes and ends in a cold or sweating sensation. Of the women who develop vasomotor symptoms, most will experience symptoms for no more than two to three years, but some continue to have symptoms for several years.² When the symptoms occur at night, they can lead to irritability, chronic fatigue, and decreased memory.⁶ About one-third of women with vasomotor symptoms are bothered enough to seek medical attention.² Women who are obese are less likely to experience vasomotor symptoms, due to higher levels of circulating estrone produced by adipose tissue, which minimize the effects of estrogen withdrawal.⁶

The risk of several medical conditions is increased with menopause. The incidence of osteoporosis increases substantially after menopause. Estrogen reduction leads to increased rates of bone resorption, although the rate of bone formation remains unchanged. By age 60, 25 percent of white and Asian women without estrogen therapy will develop spinal compression fractures.²

By age 80, 20 percent of white women without estrogen therapy develop hip fractures, and 15 percent of these women will die within six months from the fracture or its complications. Annually, there are approximately 300,000 hip fractures and 500,000 other fractures in postmenopausal women in the United States.² It is not clear how menopausal changes increase the risk of osteoporosis, but it has been demonstrated that levels of serum calcium and phosphorus are increased, and the levels of parathyroid hormone and the active form of vitamin D are decreased.² It is possible that estrogen therapy blocks the actions of parathyroid hormone on bone, thus reducing bone resorption.

The risk of atherosclerotic disease, including coronary heart disease and stroke, increases with age. Before age 50, the gender ratio for myocardial infarction is 1:3, with men having the greater incidence of disease.² However, after age 50, the rate of increase is greater in women than in men, so that by age 65, the ratio is 1:2, and by age 80 it is 1:1. Just as for men, cardiovascular disease is the leading cause of death of women.⁷ Investigators believe that total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels increase after menopause, whereas high-density lipoprotein (HDL) cholesterol levels decline, promoting atherosclerosis.²

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INFORMED DECISION-MAKING IN THE WAKE OF WHI AND HERS

The release of data from two large clinical trials—the Women’s Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS)—and the associated media attention have had an immense impact

on patient and provider opinion about hormone therapy. Several professional organizations have modified their treatment guidelines, based on WHI findings.¹ (See Weighing in on WHI: Professional Society Guidelines, page 10.)

Many patients are confused and fearful—in some cases, panicked—by the media hype. One clinician reviewer of this publication was approached by a healthy 30-year-old woman who wanted an oophorectomy because of fear about her own endogenous estrogen.²

A small, nationwide survey conducted in the fall of 2003, found that almost 70 percent of the women queried were confused about the safety of hormone therapy.³ In the days following the release of the first data from the WHI, many women contacted their providers, and some abruptly discontinued hormone therapy—on their own or at the advice of the provider—and experienced a predictable return of menopause-related symptoms over the following months. Many providers are uncertain how to handle patients’ concerns and how to counsel patients responsibly about hormone therapy. This monograph attempts to clarify the data from the WHI and HERS, describing the findings and the limitations.

Before beginning an examination of these studies, it is important to discuss terminology. Throughout this publication, we use some of the terms put forward by The North American Menopause Society (NAMS), which are listed in Table 2. We will avoid use of the term “hormone replacement therapy,” because some argue that menopause is a natural event, not a disease of hormone

absence requiring replenishment, and that the doses of hormone used during hormone therapy are lower than those produced premenopausally.⁴

TABLE 2. Hormone Therapy Terminology

Term	Abbreviation	Comments
Estrogen therapy	ET	
Combined estrogen-progestogen therapy	EPT	
Hormone therapy	HT	Term includes both ET and EPT.
Continuous-combined estrogen-progestogen therapy	CC-EPT	Term refers to the daily administration of both estrogen and progestogen.
Systemic estrogen or combined estrogen-progestogen therapy	Systemic ET/EPT	Term refers to preparations that have a systemic effect rather than solely a vaginal effect.
Local estrogen therapy	Local ET	Term refers to preparations that have a predominantly vaginal, rather than systemic, effect.
Progestogen	N/A	Term includes both progesterone and synthetic progestins.

Source: See reference 5

OVERVIEW OF WHI AND HERS

That hormone therapy is effective in relieving the vasomotor symptoms of menopause is well established.^{6,7} Less clear has been whether hormone therapy imparts other health benefits, such as cardioprotection or reduced risk of osteoporotic fractures, to a degree that outweighs the risk of clinically significant adverse events. Early studies that employed an observational design reported conflicting results: one found that HT users had half the risk of cardiovascular disease of women taking placebo; another found that HT users had twice the risk.^{8,9}

More recently, HERS, which was initiated in 1993, found no difference between the treatment and placebo groups in the occurrence of fatal or non-fatal myocardial infarctions.¹⁰ The study was a randomized, blinded, placebo-controlled secondary prevention trial in which 2,763 women with established coronary artery disease (defined as myocardial infarction, coronary artery bypass grafting surgery, percutaneous coronary



revascularization, or angiographic evidence of 50 percent or more occlusion of one or more major coronary arteries) were randomly assigned to receive either 0.625 mg of conjugated equine estrogen (CEE) with 2.5 mg of medroxyprogesterone acetate (MPA) or placebo. The women had a mean age of 66.7 years, were postmenopausal with an intact uterus, and were followed for an average of 4.1 years. Interestingly, although there was no net difference in myocardial infarction rate between the two groups, there was a significant time trend observed for the outcomes. There were more cardiovascular events in the hormone-treated group compared with the placebo group during Year 1 and fewer in Years 4 and 5 but no overall net benefit or detriment. Other findings included a statistically significant net decrease in LDL cholesterol and net increase in HDL cholesterol among hormone therapy users. There were also significantly more venous thromboembolic events (VTEs) and gallbladder disease in the active treatment group.

The estrogen-progestin (E-P) arm of the WHI was terminated in July 2002 after an average of 5.2 years of follow-up based on findings demonstrating an increase in breast cancer, an increase in coronary events, and an unfavorable global index, which indicated that the overall risk exceeded the documented benefits.^{11,12} The estrogen-only arm of the WHI was terminated in March 2004 because of an increase in stroke risk among women in the active treatment group. The investigators observed a decreased risk of hip fracture and no increased risk of coronary events or breast cancer among women in the estrogen treatment group.¹³ Additional results of the WHI will be discussed in the next section.

The complete results of the WHI estrogen and progestogen trial were published based on data obtained through April 30, 2002.¹¹ Subsequently, data on specific outcomes were published individually using follow-up information through the date at which women were asked to stop study treatment, amounting to approximately four months of additional data. Unlike HERS, the WHI was to be a primary prevention study. It had a randomized, double-blind, placebo-controlled design and had two arms: an estrogen-progestin arm, which included about 16,600 women, and an estrogen-only arm, which included about 11,000 patients. The study included predominantly healthy women aged 50 to 79 (average age 63) who were postmenopausal with an intact uterus (for the E-P arm) or postmenopausal and status-post hysterectomy (for the estrogen-only arm). Subjects were, on average, 12 years postmenopausal when the study was initiated. The study focused on older women because the rates of the primary outcomes studied (i.e., CHD events) are higher at older ages, and it limited the number of subjects *recently* postmenopausal out of concern about a

potentially high dropout rate among women in the placebo group who were experiencing menopausal symptoms. Women were randomized to receive 0.625 mg of CEE (with 2.5 mg of MPA for the E-P arm) or placebo daily. The primary outcome measure was the rate of non-fatal myocardial infarction (MI) or death due to MI.

UNDERSTANDING WHI RESULTS

A thorough understanding of the implications of the WHI results can help clinicians counsel patients about the relative risks and benefits associated with hormone therapy. The following sections delineate the specific findings of the WHI, the applicability of these findings, and the context in which the results can best be viewed.

What WHI results tell us

The data obtained from the WHI inform us about the risks and benefits of the use of oral systemic HT (specifically CEE with or without MPA) for the prevention of coronary heart disease in predominantly healthy women who are, on average, 12 years postmenopausal. The data showed that CEE with or without MPA does not reduce CHD risk in older women who are relatively far from their last menstrual period when they start HT. Specific data were as follows:

Coronary heart disease. Women treated with E-P had a risk of CHD that was 24 percent higher than women in the placebo group (hazard ratio 1.24).¹⁴ This figure was not statistically significant, however, as evidenced by a confidence interval (CI) that included 1.00, meaning that active treatment neither promoted nor protected against CHD. The absolute rate of CHD events was 39 cases per 10,000 person-years for the HT group and 30 cases per 10,000 person-years for the placebo group. The investigators also observed a time trend. There was an increased risk of CHD apparent at Year 1 and a longitudinal trend toward benefit overall ($p = 0.02$). The estrogen-only arm also demonstrated no increased or decreased risk of CHD in women treated with HT (hazard ratio 0.91; adjusted 95 percent CI 0.72–1.15).¹³ In comparison with HERS and the E-P arm of the WHI, in the estrogen-only arm, there was no increase in CHD risk in the first year of the study. Although the study had inadequate statistical power to draw definitive conclusions about subgroups, there was a suggestion of differential effects by age in the estrogen-only arm with a potentially reduced rate of CHD in women aged 50 to 59. The cumulative effect of these data suggests a possible small benefit with longer-term use.¹³ The discrepancy between the data for the estrogen-only arm and those for the E-P arm suggests that progestogen may be an important mediator of risk.



A case-control observational study of a subgroup of women in the WHI who did not want to be randomized found that the risk of CHD was lower among current HT users than non-users, with a relative risk of about 0.5 among those at the lowest tertile for baseline cardiovascular risk markers.¹⁵ The explanation for these findings is not entirely clear; further study regarding CHD risk is needed.

Breast cancer. In the definitive outcome-specific paper for the E-P arm of the WHI, there were more invasive breast cancers (unweighted hazard ratio 1.24; unweighted 95 percent CI 1.01–1.54; weighted $p = 0.003$) and more total breast cancers (unweighted hazard ratio 1.24; unweighted 95 percent CI 1.02–1.50; weighted $p < 0.001$) in treated women than in the women receiving placebo.¹⁶ There was no significant difference between the groups in rate of in situ breast carcinoma. In addition, the invasive breast cancers were larger and more advanced at diagnosis in the active treatment arm ($p = 0.04$ for both comparisons). In the estrogen-only arm, there was an opposite trend with a non-significant reduction in risk of breast cancer among women treated with HT (hazard ratio 0.77; adjusted 95 percent CI 0.57–1.06).¹³ This finding suggests that progestogen may make an important contribution to breast cancer risk.

Venous thromboembolic events. The risk of VTE was increased among women in the E-P group of the WHI compared with the placebo group.¹¹ The hazard ratio for pulmonary embolism was 2.13 (95 percent CI 1.39–3.25); the absolute risk attributable to treatment with E-P was eight additional cases of pulmonary embolism (PE) per 10,000 person-years. In the estrogen-only arm, the incidence of VTE, including both deep vein thrombosis (DVT) and pulmonary embolism, was increased in women treated with estrogen compared with women who received placebo (28 versus 21 per 20,000 person-years), but only the rate for DVT reached statistical significance.¹³

Stroke. The E-P arm showed an increased rate of ischemic (i.e. thrombotic) stroke among women treated with HT compared with those who received placebo.¹⁷ The hazard ratio for ischemic stroke was 1.44 (95 percent CI 1.09–1.90); there was no increased risk of hemorrhagic stroke. The increased risk was observed in all age groups and was regardless of baseline stroke risk. There was a slight increased risk of stroke, equivalent to approximately 12 additional events per 10,000 person-years (44 versus 32 per 10,000 person-years), among treated women in the estrogen-only arm of the WHI compared with women who received placebo.¹³

Osteoporotic fractures. In the E-P arm of the WHI, there was a statistically significant lower risk of experiencing an osteoporotic fracture among the women treated with HT than among those who received placebo (hazard ratio

0.76; 95 percent CI 0.69–0.83).¹⁸ There was also a decreased risk of hip fractures among women in the active treatment group compared with those in the placebo group in the estrogen-only arm of the WHI (hazard ratio 0.61; adjusted 95 percent CI 0.33–1.11; 11 events versus 17, $p = 0.01$).¹³

Colorectal cancer. In the E-P arm of the WHI there was a statistically significant reduction in the risk of colorectal cancer among the women treated with HT compared with the women who received placebo (hazard ratio 0.61; 95 percent CI 0.42–0.87).¹⁶ There was no overall reduction in colorectal cancer with estrogen alone, although this effect also varied by age, with women aged 50 to 59 demonstrating a markedly lower rate than older participants. The treatment by age interaction was statistically significant ($p = 0.048$).¹³

Quality of life. Quality of life (QoL) measures were assessed at baseline and Year 1 in all women and in Year 3 in a subgroup of about 1,500 women who participated in the WHI.²⁰ Among the entire cohort, 88% of whom were asymptomatic for menopausal symptoms at entry into the study, there were no significant differences between the groups in most QoL measures. Among a small group (574) of symptomatic women aged 50 to 54, hormone therapy was associated with a significant improvement in vasomotor symptoms and an increase in QoL in the domain of sleep disturbance but not in the other QoL dimensions. Data on QoL are not yet available for the estrogen-only arm of the WHI.

Gynecological cancer. The rates of invasive ovarian cancer and endometrial cancer were low in the WHI, and the rates were similar among women treated with E-P and those who received placebo.²¹ Data from the estrogen-only arm of the WHI are not yet available.

Dementia. In a subgroup of women from the WHI who were at least 65 years of age, there was no evidence of a protective cognitive effect with HT.²² More women in the treatment group experienced a clinically significant decline in Mini Mental Status Exam scores than in the placebo group (6.7 percent versus 4.8 percent; $p = 0.008$). When the data from the WHI were segmented by five-year age groups, the only active treatment group with an increased risk of dementia was the one including women who were 75 to 80 years of age.²³ In the estrogen-only arm of the WHI, there was a nonsignificant trend toward an increased risk of dementia and mild cognitive impairment in women treated with HT compared with women who received placebo.²⁴ Data are not yet available on the risk of dementia by age group in the estrogen-only arm.

What WHI results do not tell us

Because only one-third of women were younger than 60 years old, only 13 percent were 50 to 54 years old, and,



most importantly, only 16 percent were within five years of their final menstrual period, the WHI does not provide strong evidence about younger postmenopausal women who are closer to menopause—the women who are most likely to initiate HT for treatment of menopausal symptoms. Evaluating the subgroup of women in the WHI who were 50 to 54 years of age is risky, because the study was not designed to provide reliable data on these women. Thus, the WHI does not provide information on the benefits and risks of beginning HT at the time of menopause or for the treatment of menopausal symptoms. The data from the estrogen-only arm, in which treatment more closely mirrored the early observational literature, suggest, but are not adequate to prove, that associations between HT and coronary events may depend on the age at which treatment is started. The WHI also has a limited ability to evaluate the effects of HT on the quality of life of women with menopausal symptoms, although the WHI does report on QoL in a small number of women with moderate to severe hot flashes. In addition, the WHI does not provide information about the use of other doses, formulations, regimens, durations, and routes of administration of HT. Finally, the WHI does not provide information on the events that follow cessation in the women who decided to stop HT, although the investigators are following participants to gather and subsequently publish this information.

Putting WHI into context

The WHI was a well-designed randomized clinical trial that evaluated the impact of a specific oral HT in mostly asymptomatic women relatively distant from menopause. Its focus was coronary heart disease outcomes. The study was not designed to assess the risks and benefits of HT in the population most likely to use it: symptomatic women within a few years of their final menstrual period. The study investigators themselves note that the subgroup findings, such as results among women 50 to 59 years old, need to be interpreted with caution because of the limited numbers of subjects (and thus the limited statistical power) in these smaller groups.¹⁴

In the media frenzy that accompanied the cessation of the combined E-P arm of the WHI in 2002, the study results were generalized to other patient populations and to the use of other formulations of HT. The WHI findings *may* apply to other patient populations and to other formulations, but this is not yet known—a fact that has been overlooked by many. In addition, there is some preliminary evidence that the risks and benefits of HT may be different in younger versus older women. In a recent analysis of first-year data, the time frame in which early harm was seen in HERS and WHI, from two randomized clinical trials that included more than 4,000 women with a mean age of 53.6 years (who were an average of 4.9 years from the final menstrual period),

there were no CHD-related deaths and no myocardial infarctions diagnosed in the women who received HT. The overall incidence rate of CHD and vascular events combined was 1.96 events per 1,000 person-years in the active treatment group compared with 3.01 events per 1,000 person-years in the placebo group.²⁵ Perhaps older women who are further from menopause have already developed coronary atherosclerotic lesions that can be destabilized by estrogen, whereas younger women have not yet developed the lesions, the synthesis of which may be retarded by estrogen. Overgeneralizing the data from the WHI may inadvertently obscure a beneficial effect in a particular subgroup of patients. However, more data are clearly needed to delineate the benefits and risks of HT in younger postmenopausal women.

For postmenopausal women who are relatively young and in need of treatment for menopause-related symptoms, the WHI data provide little new information that would change decision making about HT—with the exception of better quantifying the breast cancer risk (lower than previously estimated at 0.8 additional cases per 1,000 women years after five years of E-P). The increased risk of VTE with oral estrogen, for example, was known before the study. Management of menopause-related symptoms and conditions must be individualized; this was also true before the WHI but was perhaps undervalued. A “one size fits all” philosophy of hormone therapy was not the most advantageous approach before the WHI, and that remains true today. Individualization of treatment, including assessment of the risks and benefits for each woman, is critical, especially in light of the attention, confusion, and misinformation that currently surround HT.

TRANSLATING WHI RESULTS INTO CLINICAL PRACTICE

What should providers do with the information from the WHI? What guidelines do the studies provide for clinical decision making? How should providers counsel their patients about HT?

Two specific conclusions can be drawn from the WHI and HERS data:

- On the basis of WHI data, women who are relatively distant from menopause should not take oral HT for cardioprotection.
- On the basis of HERS data, oral HT should not be used to treat cardiovascular disease.

Because the WHI and HERS studied only oral HT, no firm conclusions can be drawn from these studies about HT administered by other routes. Because these studies evaluated mostly older postmenopausal women, firm conclusions cannot be drawn about HT that is initiated closer to the final menstrual period.



Weighing in on the WHI: Professional Society Guidelines

In response to the discontinuation of the E-P arm of the WHI in 2002, professional societies and governmental agencies released opinion statements or revised practices guidelines for HT. A summary of the current stance of these organizations follows:

American College of Obstetricians and Gynecologists (ACOG; note that ACOG plans to release revised guidelines in the near future.)²⁶

- Women using HT for prevention of cardiac disease or osteoporosis, should discontinue use.
- HT may be appropriate to treat menopause-related symptoms depending on an individual woman's risks and benefits.
- If HT is used for menopause-related symptoms, it should be used for the shortest possible duration in the smallest effective dose.

National Association of Nurse Practitioners in Women's Health²⁷

- The best candidate for HT is the woman whose quality of life is affected by menopause-related symptoms.
- If HT is prescribed, the lowest dose for the shortest duration should be used; patient preference about type of delivery system should guide prescription.
- If urogenital concerns are the primary problem, local hormone therapy or the vaginal ring should be considered.
- If HT is prescribed for menopause-related symptoms, a woman's choice about duration of use should be respected.

The North American Menopause Society⁵

- Systemic HT is FDA approved for the treatment of moderate to severe menopause symptoms.
- If HT is prescribed solely for symptoms of vaginal and vulvar atrophy, local therapy should generally be used.
- HT should not be used for primary or secondary prevention of CHD or stroke.
- In women at high risk for osteoporosis, for whom preventing this condition is the sole reason for use of HT, alternatives to HT should be considered.
- Initiating EPT after age 65 for the sole purpose of primary prevention of dementia is not recommended.
- Data from the WHI and HERS should not be extrapolated to women who initiate HT to treat premature menopause.
- Use of HT should be limited to the shortest possible duration, taking into account treatment goals, individual risks and benefits, and symptoms that affect quality of life.
- Doses lower than standard should be considered, although data on outcomes with such doses are not yet available.
- Under strict clinical supervision and after patients are fully informed of the risks, extended use of HT is acceptable for:
 - Women who believe relief of their menopause-related symptoms outweighs the risks of use.
 - Women with moderate to severe menopause-related symptoms who are at high risk of osteoporosis.
 - Women at high risk for osteoporosis for whom alternative therapies are not appropriate.

U.S. Food and Drug Administration²⁸

- HT products are effective in treating moderate to severe vasomotor symptoms, moderate to severe vaginal dryness, and preventing osteoporosis associated with menopause.
- If HT is prescribed solely for vaginal dryness, topical hormone therapies should be considered instead.
- If HT is prescribed solely for prevention of osteoporosis, other treatments should be considered first and the severity of risk should be significant.
- If HT is prescribed, it should be used at the lowest effective dose and for the shortest possible duration to reach treatment goals.

All four guidelines recommend that the lowest dose and shortest duration of HT be used; however, there are no randomized, controlled clinical data showing that lower dose and shorter duration are as effective or safer. In fact, the WHI and HERS showed a greater risk of CHD in Year 1 and then improvement of CHD risk over time. As mentioned previously, the WHI and HERS data apply to the use of one formulation of oral HT at one dosage in generally older postmenopausal women.



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COUNSELING PATIENTS ABOUT HORMONE THERAPY

More research on the benefits and risks associated with hormone therapy is clearly needed. In the interim period, women need accurate information about what is currently known about HT and are looking for guidance from their health care providers about this subject. They may even ask providers what course of action they themselves or their spouses have taken regarding HT. Patients often want more than just information about HT, they want advice from their providers to help them make an informed choice. With this in mind, it is important for providers not to allow the risks delineated for a particular population to prevent them from recommending HT to women who do not appear to be at increased risk and who may benefit from its therapeutic effects. In general, there are three talking points that providers can discuss to help patients make informed decisions about hormone therapy: each woman must weigh the risks and benefits of HT in light of her personal circumstances; putting the risks associated with HT into perspective is critical for making a fully informed decision; and a woman must clarify her purpose or expectations for using HT.

According to package labeling, women with absolute contraindications to estrogen should not be prescribed systemic HT, including women who are pregnant or with current or past:

- Venous thromboembolic event
- Breast cancer
- Estrogen-sensitive cancer
- Liver disease
- Hypertriglyceridemia

WEIGHING THE RISKS AND BENEFITS IN LIGHT OF PERSONAL CIRCUMSTANCES

Health care providers need to provide accurate information that is individualized to a woman's particular circumstances, allowing her to weigh the risks and benefits of HT for herself. Women should be encouraged to approach the question from their own perspective, asking, "What are the potential risks and benefits of hormone therapy for me?"¹ Initial factors to take into account include the woman's age, time since final menstrual period, and desire to use HT. It is important for providers to query women who voice concerns or fears about HT. It may be helpful to ask, "Do you have any concerns about HT from what you've read and heard?"

Providers should listen and validate women's concerns, then correct any misinformation and provide accurate data. When providing data, it is important to give patients credit for their ability to understand properly explained scientific information.

It is also important to discuss lifestyle changes that may reduce the risk of chronic diseases and help reduce menopause-related symptoms. Healthy dietary choices, regular exercise, and stress management can reduce women's risks of chronic degenerative diseases and may be helpful in reducing symptoms associated with menopause. Lifestyle changes, such as reducing caffeinated and alcoholic beverages, can also reduce vasomotor instability and associated symptoms.

PUTTING RISKS IN PERSPECTIVE IS CRITICAL FOR INFORMED DECISION MAKING

It is important for providers to put the risks delineated in the WHI in perspective, remembering that the risks enumerated by the WHI should not automatically be generalized to all postmenopausal women. A meta-analysis of 51 epidemiological studies assessed the risk of breast cancer in women taking HT.² The analysis found that a woman's risk increased by a factor of 1.023 for each year of HT use. This rate is similar to the increased risk associated with later menopause: for each additional year of age at menopause, a woman's risk of breast cancer increases by a factor of 1.028. (See Table 5.)

When counseling patients, it is also important to help them to understand not only the relative risk but also the absolute risk. The relative risk helps investigators identify potential causes for a condition, but the absolute risk may be more helpful in assessing the impact on a particular population or individual.³ For example, the WHI reported a 26 percent increase in breast cancer for women treated with E-P.^{4,5} Some patients may mistakenly believe this means they have a 26 percent chance of developing breast cancer if they use this treatment. Instead, the 26 percent reflects the difference in absolute breast cancer rates between the placebo and E-P treatment groups (3.0 and 3.8 per 1,000 person-years, respectively). The increased risk translates into a rate of 0.8 per 1,000 women per year, or less than one additional breast cancer case per 1,000 women per year.⁴ Table 3 shows the absolute risk of a number of outcomes, as quantified by the WHI data. It also can be helpful to compare the risks



associated with HT with other known risks. To put these risks and benefits in perspective, the chance of flipping a coin 13 consecutive times and having it land heads up every time is about 1 in 10,000; the chance of dying from pneumonia is about 3.2 per 10,000 per year and from breast cancer, is 1.6 per 10,000 per year.³

Many women fear that they will develop breast cancer, and it may be especially helpful to put the risk of breast cancer associated with HT in perspective. Tables 4 and 5 put the risk associated with HT into context with other health behaviors.

CLARIFY THE GOAL FOR USING HT

In weighing potential benefits, women should consider their purpose or goal in using HT. Women need to understand that the risk/benefit ratio will vary based on

the goal for use of HT. When a woman's goal is disease prevention, a lower risk of adverse events is essential. When the goal is treatment of moderate to severe symptoms, a higher risk may be tolerable. It may be helpful for providers to ask, "What is most important among your menopause-related health concerns?" or "Why do you want to start/continue hormone therapy?" Clarifying her goals for treatment will help a woman understand the potential benefits to her and make an informed decision about whether or not to use HT.

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Table 3. Absolute Risk for Use of Estrogen Plus Progestin in the WHI (per 10,000 Women per Year)

Outcome	Absolute risk or benefit associated with E-P Tx*
Myocardial infarction	7 more
Stroke	8 more
Breast cancer	8 more
VTE	18 more
Colorectal cancer	6 fewer
Hip fractures	5 fewer

*If 10,000 women were treated with HT, over the course of one year, this number of additional (or fewer) women in the treatment group would develop the outcome compared with the placebo group.

Source: WHI June 2002 HRT Update.

Table 5. Relative Risk of Breast Cancer, by Risk Factor

Risk factor	Relative risk of breast cancer
First pregnancy after age 30	1.48
Body mass index more than 29.68 kg/m ²	1.48
College graduate	1.36
Alcohol use more than 5 g/day	1.16
Menopause five years or more past average	1.14
HT use for five years	1.12

Source: See reference 10

Table 4. Risk of Breast Cancer, by Risk Factor or Behavior

Risk factor or behavior	Risk of breast cancer (per 1,000 women aged 50 to 70)	Extra breast cancers
Baseline risk	45	—
HT for 5 years	47	2
HT for 10 years	51	6
HT for 15 years	57	12
Menopause occurring after age 54	58	13
Body mass index more than 31 kg/m ² (compared with less than 20 kg/m ²)	59	14
Lifetime alcohol excess	72	27
Lack of exercise	72	27

Source: See references 5, 6, 7, 8



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INDIVIDUALIZING HORMONE THERAPY

If there is one aspect of menopausal care that the results of the WHI have highlighted, it is the fact that hormone therapy must be individualized to best suit a woman's personal goals, needs, and risk factors. Individualization of HT requires familiarity with the types of products that are available and an understanding of how to help each woman who has decided to use HT find the product and regimen best suited for her.

TYPES OF HORMONE THERAPY

The various types of prescription hormone therapy differ in four basic ways: estrogen component, progestogen component, route of administration, and regimen.

Estrogen component

The estrogens used for management of menopause-related symptoms can be divided into three groups:

- 17 beta-estradiol
- Conjugated equine estrogen
- Estrone derivatives—including synthetic conjugated estrogens, esterified estrogens, and other estrogen derivatives

Several estrogen products are touted as being the most "natural": 17-beta estradiol because it is the estrogen made in abundance by the ovaries before menopause, estrone because it is the estrogen most abundant after menopause, and CEE because it is manufactured from a natural source—horse urine. However, 17 beta-estradiol given orally is metabolized by the liver to estrone, so the

distinction from estrone products is moot once the product has been taken by mouth.

Progestogen component

In women with an intact uterus, the addition of progestogen to estrogen is necessary to prevent endometrial hyperplasia and carcinoma. The relative risk of endometrial cancer after 10 years of unopposed estrogen therapy is 8.0.¹ There are two types of progestogens: progesterone, which is produced by the ovary after ovulation and the placenta during pregnancy, and the progestins, which are synthetic progestogens. Progestins are not identical to progesterone, but they have progesterone-like activity. An important distinction between the two is that micronized progesterone does not interfere with lipid benefits associated with oral estrogen, whereas the synthetic progestogens block a large proportion of the estrogen-related benefit.²⁻⁵ The synthetic progestogens can be divided into two groups:

- Those structurally related to progesterone—including MPA
- Those related to testosterone—including norethindrone, norethindrone acetate norgestrel, and levonorgestrel.

The most important clinical distinction between the progestogens is their relative potency, or the degree to which they downregulate the estrogen receptors in the endometrium and elsewhere in the body. MPA is the most potent progestogen available, strongly downregulating estrogen receptors in the uterus but also leading to more



frequent adverse effects, such as breast tenderness and swelling, than other progestogens.⁶ Progesterone (given in micronized form to enhance gastrointestinal absorption) is about 50 times less potent than MPA, based on analysis of endometrial changes in estrogen-primed postmenopausal women; levonorgestrel and norethindrone are more potent than MPA.⁷ Nevertheless, micronized progesterone is as effective as MPA in protecting against estrogen-induced endometrial hyperplasia.⁸ Because of its glucocorticoid-like activity, swelling and breast pain may be more common with MPA than with other progestogens.⁶ Androgen-related effects, such as acne and hirsutism, are more common with levonorgestrel and norethindrone.⁶ High-dose progesterone is associated with dizziness and fatigue, but these symptoms are generally mild at recommended doses.⁶ Norethindrone acetate, levonorgestrel, and norgestimate have potencies between those of MPA and progesterone.⁹ Both the WHI and HERS used oral estrogen (0.625 mg of CEE) with continuous progestogen (2.5 mg of MPA). These studies used the progestogen with the strongest potency—a distinction that may be important in applying the study results to populations that use other, less-potent, progestogens.

Progestogens vary in their metabolic effects. For example, MPA thwarts most of the increase in HDL cholesterol seen with concomitant oral estrogen use and does little to blunt the increase in triglycerides seen with oral estrogen. In contrast, norethindrone acetate decreases HDL cholesterol levels and reduces the elevated triglyceride levels associated with oral estrogen intake.¹⁰ Micronized progesterone has an essentially neutral effect on lipids, preserving estrogen effects including the rise in HDL cholesterol, decrease in LDL cholesterol, and increase in triglycerides.⁸ Unlike MPA, micronized progesterone does not attenuate the estrogen-associated protection against coronary vasospasm seen in non-human primates.³

In terms of clinical differences between the progestogens, one study documented that significantly fewer women on continuous combined HT experienced vaginal bleeding with ethinyl estradiol and norethindrone acetate than with CEE and MPA.¹¹ Another study of the same regimens found that more women in the ethinyl estradiol/norethindrone acetate group attained amenorrhea compared with the CEE/MPA group.¹² A clinical trial of CEE plus continuous MPA, CEE plus cyclical MPA, and CEE plus cyclical micronized progesterone found nine times as many days of unexpected bleeding with CEE plus continuous MPA than with CEE plus cyclical micronized progesterone. CEE plus cyclical MPA was associated with twice as many days of unexpected bleeding compared with CEE plus cyclical micronized progesterone.¹³

Monotherapy with synthetic progestogens can reduce hot flashes and may be used for women who are unable to take systemic estrogen. For example, in a prospective observational study, megestrol acetate reduced vasomotor symptoms, had equivocal effects on cardiovascular risk markers, and did not increase bone density.¹⁴ Some providers have used progesterone creams to treat vasomotor symptoms, but there are no randomized, controlled studies supporting the safety and efficacy of progesterone cream alone for the treatment of these symptoms.

Route of administration

Three routes are used for delivery of hormone therapy to treat menopause-related symptoms and conditions: oral, transdermal, and vaginal. Oral HT undergoes first-pass metabolism in the liver and thus requires a higher dose to achieve the same bioavailability as other routes of administration.¹⁵ For example, the systemic availability of estradiol after oral administration is 20 times lower than after transdermal administration.¹ Indeed, estrone is the predominant estrogen in the circulation after oral administration because of hepatic metabolism and first-pass effects. Products administered via the vagina include those that are used for their local effects only (creams, vaginal tablets, and the Estring vaginal ring) and one that is used for both local and systemic effects (the Femring[®] vaginal ring).

The risks and benefits associated with HT vary based on the route of administration. The choice should depend on the woman's preference, bearing in mind the need to support adherence, and the particular clinical scenario. Administration via the oral, transdermal, and systemic vaginal (e.g., Femring) routes consistently leads to systemic effects, but local vaginal administration at routine doses generally does not. However, local vaginal HT, when given in high doses, can result in serum concentrations that are as high as, or higher than, those seen with oral administration.¹⁰

Transdermal HT provides more consistent and even blood hormone levels, which translates into prevention of withdrawal symptoms. In addition to effectiveness at lower doses compared with oral administration, products administered in low doses by the non-oral route avoid first-pass hepatic effects. Oral estrogen is associated with prothrombotic changes in hemostatic factors and an increase in inflammatory markers, such as C-reactive protein, that are seen only minimally with transdermal estrogen.^{16, 17} The difference in C-reactive protein level may be due to the first-pass effect associated with oral drugs and a resultant stimulation of C-reactive protein synthesis in the liver.



The risk of VTE is associated with oral but not with transdermal estrogen use.¹⁸ The Estrogen and ThromboEmbolic Risk (ESTHER) Study documented a 3.5-fold greater risk in women using oral estrogen compared with the placebo group (95 percent CI 1.8–6.8) and, more important, no significant difference in VTE rates between the transdermal group and the placebo group.¹⁸ Vaginal systemic therapy with Femring was not associated with an increased risk of VTE in the clinical studies supporting its FDA approval.¹⁹ However, oral estrogen improves lipid values, such as LDL cholesterol, more than transdermal estrogen does.²⁰ Limited data are available comparing oral estrogen with vaginal creams, gels, or rings. A 2002 pilot study of eight women using 17 beta-estradiol-releasing vaginal rings found no statistically significant alterations in the levels of a number of hemostatic factors.²¹

Local estrogen therapy is administered vaginally via creams, rings, and tablets. Until recently, vaginal estrogen was used for local therapy only. A vaginal ring—Femring—is now available to treat systemic symptoms such as hot flashes.¹⁹ Although progestogen is not needed for local vaginal therapy, it is needed for systemic vaginal therapy, including with Femring. Vaginal tablets or rings may provide more reliable dosing than vaginal creams or gels, because the administered dose is not affected by patient technique with the former products.¹⁰ Local vaginal therapy can be used in combination with systemic HT products to treat vaginal atrophy symptoms. Estrogen creams can be used in combination with other HT products to treat external vaginal symptoms, such as atrophy at the vaginal introitus. Vaginally applied progesterone could be useful for menopausal women, but there are limited data about the ability of such products to provide adequate protection for the endometrium.¹

Differences of dosage strength and frequency of administration in the various HT products allow treatment to be tailored to the severity of a woman's symptoms. For example, transdermal patches are available in five different dosages. Some are administered twice weekly, and others are used once a week. Women with more severe symptoms may benefit from a higher-dose patch. Women who desire added convenience might opt for a once-weekly patch, whereas women who develop estrogen withdrawal symptoms toward the end of the dosing week with a once-weekly patch might have steadier symptom relief with a twice-weekly patch.

Regimen

When added to estrogen for endometrial protection, progestogens can be administered in a variety of regimens, which are listed in Table 6. There are conflicting data about the effectiveness and safety of the long-cycle regimen; more research is needed to clarify

Hormone Therapy and Compounding Pharmacies

Compounding pharmacies offer patients “custom-made” combination hormone therapy, such as Bi-Est, which contains estrone and estradiol, and Tri-Est, which contains estrone, estradiol, and estriol. Part of the allure of these pharmacies may be the claim of more precise individualization of HT, which appeals to many women's desire for “special for me” therapy to treat menopause-related symptoms. The allure may also be due to the pharmacies' promotion of “bio-identical” hormones, or those biochemically similar to the ones that occur naturally in the body. The pharmacist may use serum estradiol and FSH levels to diagnose menopause and to follow therapeutic interventions.²² Based on salivary testing or, less commonly, serum testing, the pharmacist mixes varying amounts of progesterone, estradiol, estrone, estriol, and testosterone.²³ During follow-up, the pharmacist adjusts the dose of hormones to a tenth of a milligram based on a particular woman's symptoms or serum hormone levels.

There is no evidence to support the notion that minute alterations in the concentration of hormones administered correlate with better therapeutic outcomes, nor is there evidence to support frequent dosage adjustment based on regular serum testing as an effective method for HT management. Rather, the endpoints for HT therapy should be based on the woman's symptoms, goals, and risk/benefit profile. The fact that the normal range of estradiol for a premenopausal woman is wide (40 to 500 pg/mL) calls into question the concept that a health care professional can find a “normal” value for a particular woman.²⁴ All prescription non-oral estrogen products, such as patches, creams, and rings, are bio-identical in that they contain 17 beta-estradiol. The popularity of compounding pharmacies, however, highlights women's preference for individualized therapy. Providers need to respond to this preference within the realm of their own clinical practice.



Table 6. HT Regimens

Regimen	Estrogen dosing frequency	Progestogen dosing frequency
Cyclic	Daily	Last 10–14 days of HT cycle
Old cyclic	Days 1–25	Days 16–25
Continuous combined	Daily	Daily
Long cycle	Daily	10–14 days every three to six months, depending on the progestogen used and the bleeding response
Cyclic combined	Daily	Days 1–25

Table 7. Selective List of HT Products

Route of administration		
Product	Estrogen component	Progestogen component
Oral		
Cenestin	Synthetic conjugated estrogens	—
Estrace	Estradiol	—
Menest	Esterified estrogens	—
Ogen	Estropipate	—
Premarin	CEE	—
Prometrium	—	Micronized progesterone
Provera	—	MPA
Activella	Estradiol	Norethindrone acetate
Femhrt	Ethinyl estradiol	Norethindrone acetate
Prefest	Estradiol	Norgestimate (pulsed regimen: 3 days off then 3 days on, and repeated)
Premphase	CEE	MPA (Days 15–28)
Prempro	CEE	MPA
Transdermal patch and gel		
Alora	Estradiol	—
Climara	Estradiol	—
Climara/Pro	Estradiol	Levonorgestrel
Estraderm	Estradiol	—
Vivelle	Estradiol	—
Combipatch	Estradiol	Norethindrone acetate
EstroGel (gel)	Estradiol	—
Vaginal creams and tablets		
Premarin (cream)	CEE	—
Estrace (cream)	Estradiol	—
Vagifem (tablet)	Estradiol hemihydrate	—
Crinone (gel)*	—	Micronized progesterone
Prochieve (gel)*	—	Micronized progesterone
Vaginal ring		
Estring (for local use)	Estradiol	—
Femring (for local and systemic use)	Estradiol	—
Intrauterine system (IUS)		
Mirena*	—	Levonorgestrel

*Not labeled by the FDA for menopause-related symptoms
Sources: see references 10, 37, 30



these issues.⁶ If the long-cycle regimen is chosen, a potent progestogen should be used to ensure sufficient endometrial shedding. The cyclic combined regimen may be helpful, after appropriate evaluation of the endometrium, for women who experience bleeding on the continuous combined regimen. The old cyclic regimen of discontinuing both hormones for a number of days each month has fallen out of use, because many women experience menopause-related symptoms on a monthly basis with this regimen.

A meta-analysis of the relative risk of endometrial cancer with HT found no difference between continuous and intermittent regimens.²⁵ In the Postmenopausal Estrogen/Progestin Interventions (PEPI) study, the risk of endometrial hyperplasia was lower among women who received progestogens than those who took estrogen alone, whether these were administered in a continuous or sequential frequency.⁵

Table 7 lists some HT products available in the United States.

HERBAL AND NUTRITIONAL PRODUCTS

A number of herbal and nutritional products are marketed for treating menopause-related symptoms or preventing menopause-related conditions. These products are generally categorized as nutritional supplements, and as such, are neither controlled nor screened by the FDA. In addition, the manufacture of nutritional and herbal products is not controlled with the rigor used for prescription products; thus, the contents and potency of a therapy can vary considerable from product to product and from vial to vial of the same product.

Some small studies have suggested that soy proteins improve vasomotor symptoms, but a controlled study of 241 women with vasomotor symptoms found that treatment with soy protein had no effect.^{26,27} A number of small, unblinded studies have suggested that black cohosh (*Cimicifuga racemosa*) extracts may be helpful in reducing menopause-related symptoms.²⁶ A 2003 meta-analysis also noted promising evidence for black cohosh, but the studies evaluated were limited by poor methodology.²⁸ Overall, the meta-analysis concluded that there is as yet no convincing evidence of the effectiveness of any herbal products for the treatment of menopause-related symptoms. Another review noted that no herbal products for vasomotor symptoms have randomized, controlled data that support their efficacy and safety and that the products that have been tested do not show statistically significant improvement in symptoms compared with placebo.¹⁰ Yam cream without additives has been shown to be ineffective for the treatment of menopause-related symptoms. In an attempt to improve effectiveness, some manufacturers have begun adding progesterone to these creams, a fact that may disturb women who have chosen these products thinking they are “hormone free.”

Avlimil® is an herbal product that has been heavily advertised for treatment of sexual dysfunction in the wake of the WHI results. It is a combination herbal product that is available in tablet form without prescription. In an unpublished study on the product Web site, there was a statistically significant improvement in sexual function, as assessed by a number of questions, in the active-treatment group compared with the placebo group.²⁹ There are no published clinical trials. In addition to the concern about the lack of reliable data supporting the efficacy of this product, there is reason to be concerned about its safety. A primary component of Avlimil is sage leaf, prolonged use of which can result in neurotoxicity from the toxin thujone. The exact dose of thujone in Avlimil is unknown.³⁰ As with other herbal products, Avlimil has not been evaluated by the FDA.

ANDROGENS

In addition to estrogens and progestogens, one other hormone has been used to treat menopause-related symptoms: testosterone. Testosterone is important in women: prior to menopause, ovarian estradiol is produced by the aromatization of testosterone, and after ovarian production of estradiol is reduced with menopause, estrone is produced by the aromatization of androgens in the peripheral tissues. Two products are currently approved by the FDA for the treatment of menopause-related symptoms: Estratest® and Estratest® HS. These products, which are indicated for treatment of vasomotor symptoms in women who do not have improvement from estrogens alone, are combinations of esterified estrogens and methyltestosterone.^{31,32} The two products are available in tablet form and differ only by dosage. The availability of these products is under consideration by the FDA, however.³³ The agency is currently re-evaluating the net benefits of estrogen/androgen products in women for whom estrogen alone is ineffective in relieving vasomotor symptoms.

Testosterone has been administered to postmenopausal women to improve sexual function, although it is not FDA approved for this use. In one study, postmenopausal women with low sexual desire had significantly improved sexual functioning after treatment with a combination of oral methyltestosterone and esterified estrogen compared with women who received estrogen alone.³⁴ In another study, women aged 31 to 56 years old who had undergone hysterectomy with oophorectomy had improved sexual functioning and higher well-being scores after treatment with transdermal testosterone in combination with oral CEE compared with women who received estrogen alone.³⁵ (For more information on the use of androgens, see the ARHP monograph, *Perimenopause Update: Women and Libido—Is There a Role for Testosterone?* Available at: <http://www.arhp.org/perimenopauseupdate>.)



SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)

Selective estrogen receptor modulators (SERMs) are a group of drugs that mediate their effects through binding to estrogen receptors, resulting in activation of certain estrogenic pathways and blockade of others.³⁶ One SERM, raloxifene (Evista), is FDA approved for the treatment and prevention of osteoporosis in postmenopausal women.³⁶ It appears to lack estrogen-like effects on the uterus and breast tissue but can cause hot flashes as a result of estrogen receptor blockade.³⁶

INDIVIDUALIZING CARE

Women want care that is personalized for them. In general, they do not want to receive “cookie cutter” management of their menopause-related symptoms. Individualized care requires gathering specific health-related information, providing information about HT that is accurate and specific to the patient’s particular circumstances, supporting informed decision making, and addressing ongoing health needs specific to each patient.

Gathering information

The process of individualizing care for women who decide to use HT must begin with gathering information. The provider needs to know the patient’s age, the date of her last menstrual period, her medical history, and her family history. The provider needs to spend time talking with the woman, gathering information on risk factors, signs, symptoms, family history, lifestyle, lipid profile, and nutritional status. This information will help ascertain any contraindications to HT. It is critically important that the provider ask about any current or past therapies used for menopause-related symptoms, including HT, other prescription drugs, over-the-counter (OTC) medications, or alternative therapies. The provider also should ask the woman what she knows or has heard about HT and about any fears or concerns she may have about it. Finally, the provider should conduct a physical examination with laboratory testing as needed for preventive care; hormonal testing is generally not necessary to diagnose menopause.

Providing information

For a woman to make a truly informed decision about HT, she must have accurate information about the risks and benefits specific to her situation. Clinicians should provide women with this information perhaps by maintaining a file of various HT-related handouts—or direct them to resources that have accurate, reliable information. (See the Appendix for a list of books and resources for patients.)

Supporting informed decision making

In addition to providing sound information about HT, the provider should help the woman understand the difference between absolute and relative risk, thus allowing her to place the risks and benefits of HT in perspective. Women need complete and balanced information to be able to make an informed decision—information that comes from a health care professional rather than an attention-grabbing headline or sound bite.

Addressing ongoing health needs

Individualized HT requires frequent reassessment (at least annually) of a woman’s symptoms, continuing need for therapy, and personal risk/benefit ratio, as well as a review of any side effects associated with treatment. Some women will decide to continue HT for a short period of time; others will decide to continue it longer. In addition, women in the postmenopausal age range are at risk for a number of health conditions, including CHD, diabetes, hypertension, and breast cancer. Providers must ensure that women are receiving comprehensive preventive care to screen for and address these health issues.

Financial Concerns

In addition to clinical issues, providers must consider and discuss with patients the financial barriers and concerns that may hinder individualization of care. In a managed care setting, the choice of drugs on formulary is generally limited. The CEE/MPA combination may be the only oral HT available, which may limit individualization of therapy. In addition, there may be an incentive for both providers and patients to choose combination products, because separate prescriptions for the estrogen and progestogen components generally translate into an additional co-payment for the patient. Providers should be aware of the financial issues related to the use of HT and discuss them with patients, recognizing that financial barriers may affect a patient’s ability to adhere to a *specific* treatment regimen. Providers should not allow managed care decisions about the placement of drugs on formulary to hinder appropriate clinical decision making. Instead, providers should advocate for women, querying the formulary choices of managed care organizations when necessary to realize a range of HT options.



CASES

The following cases, which are based on the clinical experience and acumen of the faculty reviewers, illustrate individualizing care for women using HT.

Case 1: Mary S. had her final menstrual period 18 months ago, at the age of 49. She is otherwise healthy and has no risk factors for CHD. She has tried herbal remedies for the hot flashes she experiences daily, but these are not helping. She is “terrified of those hormone drugs.”

Suggestion for management: Mary is a candidate for HT. She has no contraindications and is significantly affected by the vasomotor symptoms she is experiencing. In deciding between oral or non-oral HT, it is important to consider Mary’s preference for the route of administration, her medical history, and other factors, such as hypertriglyceridemia, to find the best choice for Mary. For example, if she has a low HDL cholesterol level, oral HT might be a good choice. If she has hypertriglyceridemia, oral HT would not be as good a choice. If she has low libido, transdermal HT or estrogen combined with an androgen might be a good choice, to avoid increasing production of sex hormone-binding globulin (SHBG) and the resultant reduction in bioavailable estrogen and testosterone. (See Case 6 for more information on SHBG.) Providers should weigh factors such as these in making a recommendation about the optimal choice for patients like Mary. Local vaginal therapy would not be indicated for Mary, because she has systemic symptoms. If oral, transdermal, or systemic vaginal therapy (Femring) is chosen, a progestogen should be added. It may be helpful to remind Mary that HT could be used for a relatively short time to address her vasomotor symptoms and then gradually reduced over time to avoid estrogen withdrawal symptoms.

Case 2: Zelda K. is 60 years old, eight years postmenopausal, and has never taken HT. She has developed severe dyspareunia and urinary urgency and frequency over the past year. She has a friend who developed a deep vein thrombosis on estrogen and for this reason does not want to take oral estrogen herself.

Suggestion for management: Zelda has severe vaginal and urinary symptoms but no vasomotor symptoms. For this reason and by her preference, she is a candidate for vaginal estrogen, either in the form of cream, tablet, or locally acting ring. She also may be a candidate for systemic HT use to manage any systemic symptoms, if appropriate. However, to avoid increased risk of VTE, non-oral systemic therapy would be a better option than oral therapy.

Case 3: Ann P. is 56 years old. She had been taking oral HT to manage severe vasomotor symptoms when her internist called her and told her to stop the HT immediately because of recent study results. She has been off HT for several months. She no longer has vasomotor symptoms but wants to restart HT to improve her sexual function. She has low sexual desire, which was not a problem while she was taking HT. She does not have vaginal dryness. She has no contraindications to systemic HT.

Suggestion for management: If Ann’s sexual dysfunction had been solely related to vaginal dryness, a lubricant might be effective. However, low sexual desire may be related to diminished androgen levels. After appropriate consultation about her sexual function, relationship, stress, and after pharmacological causes have been ruled out, she may be a candidate for restarting HT with the possible addition of an androgen. (For more information on the use of androgens, see the ARHP monograph, *Perimenopause Update: Women and Libido—Is There a Role for Testosterone?* Available at: <http://www.arhp.org/perimenopauseupdate>.)

Case 4: Terri O. is 48 years old and perimenopausal, with menses that are generally regular. She comes to your office complaining of hot flashes, mood swings, and fatigue and requests HT. During questioning, she tells you that she developed a deep vein thrombosis while on oral contraceptives at age 35. She has no other medical problems and is taking no prescription, OTC, or herbal products.

Suggestion for management: During perimenopause, the ovaries continue to produce estradiol but at levels that are highly variable. Use of HT does not suppress the erratic function of the ovary and thus can compound problems such as vaginal bleeding, breast tenderness, and bloating. If education and lifestyle changes are not successful, the “gold standard” for treatment of symptoms during perimenopause is a low-dose oral contraceptive. This type of product will suppress the ovarian function and even out irregular estrogen levels. However, with a history of VTE, Terri has an absolute contraindication to oral contraceptives. There are as yet no data about the safety of the contraceptive patch or contraceptive ring among women with a history of VTE. Some providers believe patients such as Terri are candidates for *non-oral* estrogen augmentation therapy, however, and would treat her with an estrogen patch. During periods of higher ovarian estradiol production, when she experienced breast tenderness, for example, she could remove the patch. She does not need a progestogen added to the estrogen patch, because she is still menstruating somewhat regularly, but she should be given a progestogen challenge if she does not bleed at least every three months. If she were having heavy



bleeding, the levonorgestrel intrauterine system could be considered in addition to estrogen augmentation. Before any form of HT is started, the possibility of pregnancy should be investigated, as appropriate.

Case 5: Katherine W. is a 54-year-old woman who had a hysterectomy (without oophorectomy) for dysfunctional uterine bleeding four years ago. She presents to her provider's office complaining of recent severe vasomotor symptoms and mild cognitive symptoms, such as forgetfulness during business meetings. She is "afraid" of HT because her family physician told her that recent studies have shown that it "causes breast cancer." She is healthy and has no contraindications to use of HT.

Suggestion for management: Katherine is a candidate for either oral or non-oral estrogen. Because there is no need to worry about endometrial hyperplasia, she does not need a progestogen. Data from the estrogen-only arm of the WHI should be applied with caution to Katherine's situation, because of her relatively young age. However, the WHI estrogen-only arm found no increased risk of breast cancer overall, with lower risk estimates for women aged 50 to 59 and 60 to 69 compared with those aged 70 to 79. In discussing the fear of breast cancer from estrogen, it may be helpful to differentiate between factors that promote breast cancer and those that initiate it; estrogen may stimulate the growth of cancerous cells that are already present rather than stimulate the transformation into cancerous cells. It is important to help Katherine put the risk of breast cancer in perspective. (See Tables 4 and 5 for details.) HT could be used for a relatively short time to treat vasomotor symptoms and then gradually reduced to avoid estrogen withdrawal symptoms.

Case 6: Debra R. is 58 years old and has been taking oral HT for the past four years. The vasomotor symptoms and vaginal dryness, which had been completely relieved, have returned over the past three months.

Suggestion for management: If adherence to HT is not an issue, the relapse of Debra's symptoms is likely caused by an increase in sex hormone-binding globulin, which can occur with oral estrogen. The increased SHBG not only lowers bio-available testosterone but also can lower bio-available estrogen, thus triggering estrogen-withdrawal or -deficiency symptoms. Increasing the dose of the oral estrogen will only temporarily rectify the problem until the SHBG increases even more, necessitating further dose increases. In contrast, androgens reduce SHBG. Options include adding an androgen to the oral HT or changing to non-oral formulations of HT. More detailed questioning about the frequency and pattern of symptoms can alert providers to this common and important phenomenon.

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RECOMMENDATIONS FOR FURTHER STUDY

RESEARCH NEEDS

Recent studies, such as the WHI and HERS, have shed light on the use of oral HT in particular patient populations. However, many questions remain unanswered about hormone therapy. There are limited data about the relative risks and benefits of HT using other routes of administration, hormone components, and regimens. It would be very helpful to better understand the differences among various progestogens, for example. Data allowing the comparison of “bio-identical” products also would be very helpful, as would data on the use of androgens alone or in combination with HT. Data are also limited on factors that affect patient adherence to HT, on how patients make decisions about the use of HT, and on optimal regimens for discontinuing HT. Further study, in the form of well-designed, controlled trials, is needed to assess the potential risks and benefits of hormone therapy in these areas.



APPENDIX: BOOKS AND RESOURCES FOR PATIENTS

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