

Hormone Replacement Therapy: Current Concerns and Considerations

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AUDIENCE

This activity is designed for pharmacists and other healthcare professionals who evaluate and treat perimenopausal and postmenopausal women.

GOALS

To understand the benefits, risks, and adverse effects associated with estrogen replacement therapy (ERT) and hormone replacement therapy (HRT) and their influence on a postmenopausal woman's initiation, adherence, and satisfaction with therapy.

OBJECTIVES

1. Discuss menopause and its effects.
2. Identify ERT/HRT's potential benefits and risks.
3. Discuss ERT/HRT's adverse effects and management approaches.
4. Identify various administration routes for ERT/HRT.
5. Identify currently available ERT/HRT products.
6. Recognize potential reasons for lack of initiation and continuation as well as ways to improve adherence in patients.

The onset of menopause affects 1.8 million women in the United States each year. Women who are postmenopausal experience vasomotor instability as well as urogenital and vaginal atrophy due to estrogen deficiency. Postmenopausal women also are at increased risk for osteoporosis and heart disease.

Postmenopausal women taking estrogen replacement therapy (ERT) have less vasomotor instability and urogenital and vaginal atrophy. Estrogen replacement therapy decreases bone loss and the incidence of fractures in postmenopausal women. Despite these proven benefits, the use of ERT or hormone replacement therapy (HRT) in postmenopausal women with cardiovascular disease is controversial. Cardioprotective benefits reported in observational studies have not been found in randomized, controlled trials. Studies have demonstrated inconsistent benefits in preventing dementia, Alzheimer's disease, and colorectal cancer. Unopposed estrogen increases the risk of endometrial hyperplasia, which can develop into endometrial cancer. The risk of developing breast cancer is increased in women who utilize ERT or HRT compared with nonusers. The use of ERT also is associated with an increased incidence of venous thromboembolism and pulmonary embolism.

Adverse effects occur in women taking ERT/HRT, so women must be educated and involved in the decision to initiate and continue this therapy. This will enhance adherence and satisfaction with therapy.

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CONTINUING EDUCATION CREDIT



This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-999-02-207-H-01. This course expires on July 31, 2004.

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Postmenopausal women taking estrogen replacement therapy (ERT) have less vasomotor instability and urogenital and vaginal atrophy. Estrogen replacement therapy decreases bone loss and the incidence of fractures in postmenopausal women. Despite these proven benefits, the use of ERT and hormone replacement therapy (HRT) in postmenopausal women with cardiovascular disease (CVD) is controversial. At one time, ERT/HRT was assumed to be beneficial in protecting against CVD, preventing Alzheimer's disease, and preventing colorectal cancer in postmenopausal women, but the beneficial effects now are being questioned because of new data from published trials.

Are women getting relief of menopausal symptoms from ERT/HRT? What benefits and adverse

effects are associated with ERT/HRT use? What should be considered in choosing an ERT/HRT product and dose for a patient, and how do healthcare professionals select the best administration route for ERT/HRT delivery? What can healthcare professionals do to ensure patients adhere to their ERT/ HRT prescription?

... DEFINITION ...

The terms “ERT” and “HRT” are used interchangeably, but represent 2 distinctly different regimens. While ERT is defined as an estrogen-only regimen, HRT is defined as a regimen with estrogen and progestin. Both regimens may be used in women who are perimenopausal to postmenopausal.

... MENOPAUSE ...

The onset of menopause affects 1.8 million women in the United States each year.¹ “Perimenopausal” is the adjective used to define the time before menopause when estradiol levels are beginning to decline. Menopause is defined as the moment in time when the ovaries no longer produce eggs or estradiol and menstruation ceases. “Postmenopausal” is the adjective used to define the time after menopause occurs when women are estradiol deficient.² Most women experience menopause in their early to mid 50s. However, the time of onset for menopause varies. It may occur at an earlier age if a woman has had an oophorectomy, or it may occur in the late 50s, depending on the natural course of a woman’s body.

Women may experience numerous symptoms of menopause due to estrogen deficiency. Estrogen deficiency also is associated with an increase in the risk for osteoporosis and heart disease in postmenopausal women. There are 3 forms of endogenous estrogen: estradiol, estrone, and estriol. After menopause, estradiol, the primary premenopausal estrogen hormone, ceases to be produced by the ovaries. The body’s primary source for estrogen then becomes estrone, which comes from the peripheral tissues. Estrone is 4 times more abundant than estradiol, but has only one third the potency of estradiol. Estriol is produced from the metabolism of estradiol and estrone and exerts minimal physiologic effects because of its low potency.^{3,4}

Perimenopausal to postmenopausal women may seek help from healthcare providers in controlling the bothersome vasomotor symptoms associated with menopause. One of the biggest complaints from post-

menopausal women is hot flushes.* Other common complaints from postmenopausal women are vaginal dryness and itchiness, dysuria, increased urgency and frequency of urination, and pain with intercourse. All of these symptoms can be attributed to decreased estrogen with resultant urogenital and vaginal atrophy.

Osteoporosis is a major health problem for postmenopausal women. Eight million women in the United States have osteoporosis.⁵ Osteoporosis is a “disease characterized by low bone mass and structural deterioration of bone tissue leading to bone fragility and increased susceptibility to fractures of the spine, wrist and hip.”⁵ The rate of bone loss in postmenopausal women is 3% to 9% per year compared with the rate before menopause of 1% to 2% per year.⁶ Fifty percent of American women older than age 50 will have an osteoporosis-related fracture in their lifetime. National direct costs in 1995 for osteoporotic and associated fractures were \$13.8 billion, and the costs are expected to continue to rise.⁵

... POTENTIAL BENEFITS ...

Relief of Vasomotor Instability

One of the primary reasons women initiate ERT is for relief of vasomotor symptoms, commonly referred to as hot flushes. A hot flush is a sensation of intense warmth usually beginning in the head, neck, upper chest, or back, which can spread to the entire body. Hot flushes may last anywhere from 30 seconds to 5 minutes. These episodes may be caused by hypothalamic thermoregulatory center changes, although the exact cause is not precisely known. With decreasing estrogen levels, the change in the thermoregulatory center leads to heat dissipation through resultant vasodilation and perspiration; consequently, hot flushes may occur. Women may have hot flushes as frequently as several times per day or as infrequently as a few times per year. Hot flushes primarily occur at night and can be severe enough to awaken a woman from sleep. They can result in night sweats, sleep disturbances, and insomnia for some and can even result in fatigue, forgetfulness, irritability, depression, and inability to concentrate.⁶ Other symptoms experienced include diaphoresis, dizziness, headache, palpitations, nausea, and vom-

*The term “hot flush” refers to the physiologic condition, and the term “hot flash” refers to the woman’s feelings during the flushing episode.

iting. Up to 80% of women experience hot flushes within 3 months of menopause. Bilateral oophorectomy also induces hot flushes in approximately 50% of women. Eighty-five percent of women will have hot flushes for longer than 1 year, and 25% to 50% will have them for up to 5 years.⁶ Estrogen replacement therapy is the most effective therapy for relieving these vasomotor symptoms associated with menopause.⁷⁻⁹ Many women will only need ERT for an average of 5 years to assist with controlling vasomotor symptoms. Most women can gradually be tapered off estrogen as vasomotor symptoms decrease.

Nonpharmacologic options may offer some women relief. Women should be encouraged to wear absorbent cotton clothing in layers. It can be suggested that women lower the thermostats in their office, home, and car. Women should be advised to avoid spicy foods, caffeine, and hot beverages such as coffee and tea. Women should be encouraged to exercise regularly at least 3 hours before bedtime to prevent vasomotor exacerbations during sleep. Women also could be encouraged to learn and utilize relaxation techniques. Nonpharmacologic options will not prevent but rather help women cope with hot flushes.

Relief of Urogenital and Vaginal Atrophy

High estrogen levels during the premenopausal years help to maintain adequate glycogen levels in the vaginal epithelium, which helps to maintain healthy vaginal tissue. The vaginal epithelium's glycogen content is very important in establishing an environment that is rich in lactobacilli and thus acidic in nature with a low pH. At menopause, with the decrease in estrogen levels, the vaginal lining becomes thinner and more fragile, and the amount of glycogen in the cells of the vaginal epithelium also decreases. The vaginal pH increases and becomes more alkaline, causing an increased risk of vaginal infections such as bacterial vaginosis. There is decreased elasticity of the vaginal epithelium as well as decreased vaginal lubrication. These changes put postmenopausal women at risk for experiencing vaginal dryness and pain with intercourse. Estrogen replacement therapy has been shown to significantly relieve symptoms associated with vaginal atrophy. Estrogen replacement therapy decreases vaginal dryness, itchiness, and irritation.^{7,9,10} This therapy may be helpful in improving a woman's sexual function, but no clear effects on libido or sexual responsiveness have yet been proven. Estrogen replacement therapy also reduces urinary frequency in women, but has not demonstrated beneficial effects in women with urinary incontinence.^{7,10}

Nonpharmacologic methods may offer women some relief. Women may take warm baths to alleviate vaginal itching, making sure not to use bath soaps, gels, or salts that contain perfumes. Women should be encouraged to wear cotton underwear and to avoid pantyhose and tight clothing. Women should be advised not to use deodorized tampons and pads. Also, women should be encouraged to avoid petroleum-based products as they may promote vaginal infections. If a woman needs a lubricant for intercourse, her healthcare provider should suggest that she use small amounts of commercial vaginal lubricants and moisturizers such as Replens, KY Jelly, and Astroglide, which are available over the counter. Again, nonpharmacologic options will not eliminate the problems with urogenital and vaginal atrophy; rather, they enable the woman to better cope with the problems.

Prevention of Osteoporosis

The primary reason for women to use ERT long term is to prevent postmenopausal fractures and bone loss.¹¹⁻¹⁴ The rate of bone loss is 3% to 9% per year and is greatest in the first 5 years after menopause, after which it gradually begins to taper.⁵ Estrogen replacement therapy prevents the rapid bone loss that occurs after menopause and reduces the age-related loss to 0.5% per year.¹¹ If ERT is stopped, the rate of bone marrow density loss is similar to that seen in the first 5 years after menopause.¹¹ When ERT is initiated is as important as the duration. Estrogen replacement therapy should be started after an oophorectomy or "natural" menopause and continued throughout life to prevent bone loss and reduce fractures.^{11,12,14,15}

Observational studies report beneficial effects of estrogen with or without progestin for the prevention of bone loss and to decrease the number of fractures women may experience after menopause.^{11,12} Data from large, randomized, controlled trials comparing fracture rates of women on HRT versus women not on HRT are limited at this time. A recent randomized, controlled trial by Cauley et al showed no evidence of a reduction in the incidence of fractures.¹⁶ The results from this trial were not consistent with data from observational studies. A very important point is when HRT was initiated. Two thirds of the women in the trial were over the age of 65 years. Hormone replacement therapy was initiated on average 18 years after the onset of menopause. Bone loss had already occurred in the years prior, and HRT cannot replace bone once it is lost.¹⁶

In a meta-analysis, Torgerson et al reviewed all randomized, controlled trials published in the literature on HRT versus no HRT in postmenopausal women and nonvertebral fracture rates.¹⁴ The meta-analysis showed a 27% reduction in nonvertebral fractures in women on HRT. A greater reduction in fractures was found for women younger than age 60 compared with women older than age 60 (35% vs 12%). This analysis suggests the effects of HRT on fracture reduction may be attenuated with age.¹⁴ The trials included in the meta-analysis had different study designs with various ERT and HRT regimens and doses, as well as various times of initiation of ERT/HRT with regard to menopause and various durations of follow-up—all of which influenced the results reported in the meta-analysis.

It is important to realize that the Food and Drug Administration has removed the treatment indication for ERT/HRT in osteoporosis. The ERT/HRT prevention indication has remained, and it is considered first-line therapy for osteoporosis prevention because estrogen has definitely been shown to increase spine and hip bone marrow density T-scores.¹³

Prevention of Cardiovascular Disease

Based on observational data, HRT was once accepted and commonly recommended for secondary prevention of CVD. Currently, the American Heart Association recommends that ERT/HRT should not be initiated for secondary prevention of CVD. The decision to initiate and continue ERT/HRT in patients without confirmed CVD should be based on the established noncoronary benefits and risks of ERT/HRT as well as patient preference.¹⁷ This change is based on data from recent randomized, controlled trials that have contradicted what earlier observational studies had previously reported.

The Heart Estrogen Replacement Study (HERS), a randomized, double-blind 5-year trial of 2763 postmenopausal women, demonstrated there was “no overall cardiovascular benefit” despite a decrease in low-density lipoprotein cholesterol (LDL-C) and an increase in high-density lipoprotein cholesterol (HDL-C) for patients on HRT. There was a pattern of increased risk of coronary artery disease events occurring in the first year compared with a decreased number of events in years 4 and 5. Based on these results, the American College of Cardiology no longer recommends HRT initiation for the prevention of postmenopausal osteoporosis for patients with preexisting CVD. However, given the favorable pattern in women on HRT for sever-

al years, women may continue if they have been on it.¹⁸

A trial conducted by Herrington et al looked at ERT and HRT and their impact on women’s mean arterial diameter. Despite a decrease in LDL-C and an increase in HDL-C levels, 30% of women on ERT, 20% of women on HRT, and 33% of women on placebo developed 1 or more new lesions. Neither treatment altered the progression of coronary atherosclerosis in women with established coronary artery disease. The authors concluded that women should not use ERT/HRT with an expectation of cardiac benefits from them.¹⁹

The Postmenopausal Estrogen/Progestin Intervention (PEPI) trial evaluated 875 postmenopausal women and compared hip and spine bone marrow density T-scores at baseline and at 12 and 36 months after therapy. A secondary outcome studied was the effect of treatment on LDL-C and HDL-C levels. Effects on LDL-C and HDL-C observed in the PEPI trial were similar to those observed in the HERS trial. However, clinical outcomes data were not studied in the trial.²⁰ At present, no data support the use of ERT/HRT to prevent the development of CVD. Ongoing studies are currently addressing this issue.

Effects on Cognitive Function/Alzheimer’s Disease

Although observational data have suggested a relationship between lifelong endogenous estrogen exposure and a beneficial effect on cognition, randomized, controlled trials have not consistently demonstrated this same benefit. Meta-analyses, including randomized, controlled trials, cohort studies, and case-control studies conducted in women taking ERT/HRT, have failed to demonstrate a clear protective effect of estrogen on cognitive function and onset of dementia.^{21,22} This may be due to major methodologic limitations in the various studies conducted to date. Estrogen replacement therapy also failed to improve cognitive or functional outcomes in patients with mild to moderate Alzheimer’s disease.²³ Therefore, these findings should be taken into account when recommending ERT/HRT use solely for the prevention or treatment of dementia or Alzheimer’s disease until future studies demonstrate a clear benefit.²¹⁻²³

Prevention of Colorectal Cancer

Epidemiologic data suggested that ERT use in postmenopausal women may decrease the risk of developing colon or colorectal cancer.²⁴⁻²⁶ This risk reduction tends to be greatest in women who are current users of estrogen.^{24,25} The protective effects

are attenuated shortly after ERT discontinuation and disappear completely after 5 years.²⁵ Studies have also demonstrated that ERT use has no effect on the risk of colorectal cancer, and a few studies have demonstrated an increased risk associated with ERT use.²⁶ At present, ERT should not be used to prevent colon or colorectal cancer.

... POTENTIAL RISKS ...

Endometrial Cancer

Exogenous estrogen without progestin use in women with an intact uterus will increase the development of endometrial hyperplasia, therefore increasing the risk of endometrial cancer. This risk increases with increasing doses and duration of estrogen therapy.^{10,27,28} The PEPI trial reported an increased incidence of endometrial hyperplasia in women on estrogen alone compared with placebo, but the incidence was equivalent to that with placebo in women treated with estrogen and progestin.²⁹ Progestin use at sufficient doses and duration with estrogen in women who have a uterus reduces the risk of endometrial hyperplasia and cancer to that of baseline.^{9,30} The American College of Obstetricians and Gynecologists recommends medroxyprogesterone acetate doses of 5 to 10 mg for 12 to 14 days of the cycle, with estrogen given daily. An alternative regimen is 2.5 mg of medroxyprogesterone acetate per day given continuously with estrogen. Both regimens reduce the incidence of hyperplasia. The American College of Obstetricians and Gynecologists also suggests micronized progesterone at a dose of 200 mg per day for 12 days per month to protect against hyperplasia as well. Norethindrone 1 mg per day protects against endometrial hyperplasia.^{9,30,31} Norgestimate 90 µg per day for 3 days followed by 3 days without norgestimate, continuously alternating, also is protective against hyperplasia.³²

Breast Cancer

The overall risk of a woman developing breast cancer in her lifetime is 1 in 8 (12.8%). The risk of developing breast cancer increases with age. A woman in her 50s with no prior history of breast cancer has between a 2.5% (for a black woman) to 2.8% (for a white woman) risk of developing breast cancer by age 60.³³ Observational studies have demonstrated that women currently taking ERT/HRT have an increased risk of developing breast cancer compared with nonusers.³⁴⁻³⁶ This risk increases with a duration of use longer than 5

years. The greatest risk is in women who use ERT/HRT for more than 15 years.³⁷ The risk is even greater in women of increased age, with increased duration of use.^{34,35} However, once ERT/HRT is stopped, the elevation in breast cancer risk decreases and almost completely disappears within 5 years.^{35,36}

Although progestin use in combination with estrogen once was thought to offer some protection against breast cancer, 2 studies refute this protective effect. Progestin use may increase the risk of breast cancer development.^{37,38} Schairer et al found that the likelihood of developing breast cancer increased 3% per year in women using estrogen versus 12% per year in women using estrogen plus progestin.³⁷ The relative risk of developing breast cancer was 30% in women using estrogen and progestin and 10% in women using estrogen alone.³⁷ Therefore, if a woman has a 2.8% chance of developing breast cancer by age 60, her risk would increase to 3.08% on ERT alone and 3.64% on HRT. Because many women will not use ERT or HRT because they fear breast cancer, it is very important that healthcare professionals assess their individual patients' risks, listen to patient concerns, and assist them with the decision to utilize ERT/HRT.

Venous Thromboembolism and Pulmonary Embolism

Oral contraceptive use increases the risk of developing a venous thromboembolism (VTE) and pulmonary embolism (PE).³⁹ Previously, it was not known whether this same risk would apply to women utilizing ERT/HRT, because the potency of the estrogens used in HRT/ERT is one fourth to one fifth the potency of the estrogens used in oral contraceptives.⁴⁰

Recent observational data suggest a two- to fourfold increase in the risk of VTE and PE for women who use ERT/HRT, with the greatest risk for women in the first few years of treatment; however, this risk returns to baseline once ERT/HRT use ceases.^{41,42} The HERS trial reported an increased incidence of VTE and PE and confirmed the risk reported in observational studies. The risk of VTE was 3 times greater in women using HRT than in nonusers. Increased risk was noted in patients who had a lower extremity fracture, cancer, or a recent myocardial infarction, or who were 90 days postoperative.⁴⁰ Therefore, the risks and the benefits of ERT/HRT must be weighed before initiating this therapy in women at high risk for VTE and PE. In women who are already on

ERT/HRT and experience a lower extremity fracture, are hospitalized, have surgery, or are otherwise nonambulatory, ERT/HRT should be discontinued at least for the time the patient is at increased risk, or the patient should be placed on VTE prophylaxis.

... ADVERSE EFFECTS ...

Estrogen

The most frequent adverse effects associated with estrogen use are bloating, nausea, and breast tenderness.^{9,10,43} Only 10% of women experience persistent adverse effects associated with estrogen.⁴³ Most adverse effects resolve spontaneously with continued use.¹⁰ Women respond differently to different products and different doses of estrogen. Therefore, changing the dose or the product may be helpful in decreasing adverse effects that have failed to resolve with time.

Nausea is one of the primary adverse effects women experience when taking estrogen. It typically occurs with the initiation of estrogen and resolves with continued therapy.¹⁰ Taking estrogen with food or taking it before bedtime may decrease nausea.

Estrogen can cause water retention in women, which may result in increased bloating and breast tenderness. This adverse effect is most noticeable with the initiation of estrogen therapy and should decrease with continued use. Headaches associated with estrogen use may be dose or product related. Decreasing the estrogen dose or changing to another product may be very beneficial in women experiencing headaches due to estrogen. Women with histories of migraine headaches may experience more frequent and/or more severe migraines while on estrogen therapy.^{9,10}

Cholelithiasis is a result of the saturation of the bile due to changes in hepatic excretory function, thus predisposing patients to increased gallstone formation. High estrogen doses (more than 2.5 mg per day of conjugated equine estrogen, esterified estrogen, or estropipate and more than 2 mg per day of estradiol) increase the risk of cholelithiasis to twice that of a woman not taking estrogen.^{10,44}

Progestin

Many bothersome adverse effects are associated with the use of progestin. The most commonly reported adverse effects are irritability, depression, headaches, breast tenderness, and irregular vaginal bleeding.^{9,43,44} Irritability, depression, headaches, and breast tenderness should resolve with contin-

ued use of HRT therapy. If adverse effects do not resolve, changing to another progestin product may be beneficial. Micronized progesterone may produce less irritability and depression compared with medroxyprogesterone acetate.^{9,43}

It is very important that women are aware of irregular vaginal bleeding, probably the most bothersome adverse effect associated with progestin. The method of progestin administration will influence the bleeding pattern women experience. Progestins are administered in 1 of 3 ways: cyclical, also known as sequential; continuous; or pulsatile.^{43,45,46} All are equally protective of the endometrium, with the main difference being the bleeding pattern induced. Cyclical progestins are given for 10 to 14 days depending on the progestin used in HRT. The 10 to 14 days of progestin therapy may be at the beginning or the end of the cycle. Women may find it easier to remember to take the progestin if it is always taken on days 1 through 14 of each month, which may help with adherence. Women who utilize cyclical progestins will have withdrawal bleeding after finishing the 10- to 14-day course of progestin therapy. This bleeding is similar to that experienced with oral contraceptives, with a lighter bleeding pattern than normal menses. Withdrawal bleeding may continue for several years. Continuous progestin is given daily with estrogen throughout the cycle, but at lower daily doses than those used in sequential therapy. Bleeding is unpredictable during the first 6 to 12 months of continuous progestin use. Bleeding may be only spotting or could be heavy at times. This unpredictable vaginal bleeding should gradually resolve in 1 to 2 years with the atrophy of the endometrium.⁴³ The longer the use of continuous progestins, the less likely unexpected vaginal bleeding will be.⁴⁵ Pulsatile progestin administration has been approved only for norgestimate administration. Ninety micrograms of norgestimate is given daily for 3 days, followed by 3 days free of norgestimate; this cycle is repeated continuously. Bleeding is unpredictable in the first 12 months of pulsatile progestin use. Bleeding may be only spotting or could be heavy at times. The unpredictable vaginal bleeding should gradually resolve in 1 to 2 years.⁴⁷

Progestin is used in women with an intact uterus along with estrogen therapy. However, some women may need progestin for reasons other than endometrial protection (eg, for treatment of endometriosis). Progestin use is not for every woman, and it is important to ensure that women are qualified candidates for its use. **Table 1** shows the contraindications and precautions associated with ERT/HRT use.

... PRODUCT DELIVERY SELECTION ...

Administration of ERT and HRT is by 1 of 3 routes: oral, transdermal, or intravaginal. The beneficial outcomes desired, the adverse effects to be avoided, and patient preferences will assist patients and healthcare providers in deciding which administration route is most appropriate.

The oral route is the most commonly utilized route for ERT/HRT. Oral estrogens are efficacious in relieving postmenopausal vasomotor instability and urogenital and vaginal atrophy, as well as in preventing osteoporosis. The bioavailability of oral estrogen is 2% to 10% as a result of first-pass hepatic metabolism. Many of the adverse effects of ERT are associated with this first-pass effect, such as an increase in bile concentrations, alteration in the production of clotting factors, and alteration in lipoprotein metabolism.^{45,48,49}

Table 1. Contraindications and Precautions for Use of ERT and HRT

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| <p>Contraindications</p> <ul style="list-style-type: none"> • Active thrombophlebitis or thromboembolic disorder • Acute or chronic liver disease • Breast or genital cancer • Endometrial hyperplasia • Estrogen-dependent neoplasia • Known hypersensitivity to any product • Pregnancy • Undiagnosed abnormal vaginal bleeding <p>Precautions</p> <ul style="list-style-type: none"> • Depression • Endometriosis • Familial hyperlipoproteinemia • Family history of breast cancer • Fibrocystic breast disease • Fluid retention • History of gall bladder disease • History of hypercoagulable state or thromboembolism • Impaired liver function • Migraine headaches • Preexisting hypertension • Uterine fibroids • Smoking |
|---|

ERT = estrogen replacement therapy, HRT = hormone replacement therapy.

Adapted from reference 44.

Transdermal ERT/HRT is an alternative to oral administration. Transdermal estrogen is as efficacious as oral estrogen in both relieving postmenopausal symptoms and preventing osteoporosis.⁵⁰ Women may be less likely to experience nausea and headache while on transdermal estrogen.⁹ However, skin irritation has been associated with transdermal patch use.

Estrogen and progestin are well absorbed when given transdermally. Avoiding the first-pass metabolism in the liver can decrease the alteration in bile production and clotting factors seen with oral estrogens, as well as decrease the incidence of gallstones, VTEs and PEs.⁴⁹ When given orally, estrogen concentrations are lower in women who smoke compared with nonsmokers. Smoking can increase estrogen's metabolism through the first-pass effect in the liver. If estrogen is given transdermally to women who continue to smoke, concentrations are generally higher than those with the oral route. Higher estrogen concentrations may be more beneficial in achieving the goals of estrogen therapy. Transdermal estrogen is associated with less elevation of serum triglycerides than oral preparations because of the lack of first-pass metabolism. Transdermal estrogens provide more consistent steady-state concentrations and often are better tolerated in women with migraine headaches exacerbated by estrogen use.⁴⁹ Transdermal ERT/HRT can be used in women who are unwilling or unable to take oral estrogen. Good candidates for transdermal ERT/HRT are women with gastrointestinal side effects, elevated triglycerides, increased risk for VTE, or increased risk for gallstones; migraineurs; or smokers.^{43,49}

Estrogen also can be administered intravaginally via tablet, gel, cream, or ring. Intravaginal estrogen is well absorbed through vaginal membranes and avoids first-pass metabolism. Despite it being well absorbed, concentrations are insufficient for relief of menopausal symptoms or prevention of osteoporosis.⁴³ Intravaginal estrogen is helpful in relieving vaginal and urogenital atrophy symptoms.⁹

... PRODUCTS AND DOSING ...

The choice of a product as well as the dose and duration depends on both the woman's and the healthcare professional's preferences and treatment goals. Symptom relief and adverse effects will determine any future alterations to therapy. As a general rule, the earlier a woman experiences menopause or

Table 2. Estrogen-Only Products

| Generic Name | Brand Name and Availability | Dose for Vaginal Atrophy | Dose for Vasomotor Symptoms | Dose for Osteoporosis Prevention | Average Monthly Cost (\$)* |
|------------------------------|--|---|--|---|----------------------------|
| Oral conjugated estrogens | Premarin 0.3, 0.625, 0.9, 1.25, 2.5 mg | 0.3-1.25 mg/d | 0.625-1.25 mg/d | 0.625 mg/d 0.3 mg/d may be adequate for women with adequate calcium intake | 17.00-24.00 |
| | Cenestin 0.625, 0.9, 1.25 mg | 0.3-1.25 mg/d | 0.625-1.25 mg/d | | 16.00-19.00 |
| Vaginal conjugated estrogens | Premarin | 2-4 g of cream per day for 3 weeks each month (1.25- 2.5 mg of conjugated estrogen) | | | 47.00 |
| Oral esterified estrogen | Estratab 0.3, 0.625, 2.5 mg | 0.3-1.25 mg/d | 0.3-1.25 mg/d | 0.3 mg/d | 12.00-34.00 |
| | Menest 0.3, 0.625, 1.25, 2.5 mg | 0.3-1.25 mg/d | 0.3-1.25 mg/d | 0.3-1.25 mg/d | 5.00-13.00 |
| Oral estropipate | Ogen 0.625, 1.25, 2.5 mg | 0.625-5 mg/d | 0.625-5 mg/d | 0.625-5 mg/d | 21.00-30.00 |
| | OrthoEst 0.625, 1.25 mg | 0.625-5 mg/d | 0.625-5 mg/d | 0.625-5 mg/d | 12.00-17.00 |
| Vaginal estropipate | Ogen | 2-4 g of cream per day for 3 weeks each month (3-6 mg of estropipate) | | | 48.00 |
| Oral estradiol | Estrace (micronized) 0.5, 1, 2 mg | 0.5-2 mg/d | 0.5-2 mg/d | 0.5 mg/d | 11.00-13.00 |
| | Estinyl (ethinyl) 0.02, 0.05 mg | 0.02-0.05 mg/d | 0.02-0.05 mg/d | | 12.00-19.00 |
| Transdermal estradiol | Climara 0.025, 0.05, 0.075, 0.1 mg | 0.025-0.1 mg/d; applied to the abdomen or buttocks once per week | 0.025-0.1 mg/d; applied to the abdomen or buttocks once per week | 0.025-0.1 mg/d; applied to the abdomen or buttocks once per week | 25.00-27.00 |
| | Estraderm 0.05, 0.1 mg | 0.05-0.1 mg/d; applied to the abdomen or buttocks twice per week | 0.05-0.1 mg/d; applied to the abdomen or buttocks twice per week | 0.05-0.1 mg/d; applied to the abdomen or buttocks twice per week | 26.00 |

(Continued on next page)

*Average wholesale price.

Adapted from references 44 and 51-53.

Table 2. Estrogen-Only Products (*Continued*)

| Generic Name | Brand Name and Availability | Dose for Vaginal Atrophy | Dose for Vasomotor Symptoms | Dose for Osteoporosis Prevention | Average Monthly Cost (\$)* |
|---|---|---|---|---|----------------------------|
| Transdermal estradiol (<i>Continued</i>) | Vivelle 0.025, 0.0375, 0.05, 0.075, 0.1 mg | 0.025-0.1 mg/d; applied to the abdomen or buttocks twice per week | 0.025-0.1 mg/d; applied to the abdomen or buttocks twice per week | 0.025-0.1 mg/d; applied to the abdomen or buttocks twice per week | 25.00 |
| | Vivelle Dot 0.035, 0.05, 0.075, 0.1 mg | 0.035-0.1 mg/d; applied to the abdomen or buttocks twice per week | 0.035-0.1 mg/d; applied to the abdomen or buttocks twice per week | 0.035-0.1 mg/d; applied to the abdomen or buttocks twice per week | 26.00 |
| | Alora 0.05, 0.075, 0.1 mg | 0.05-0.1 mg/d; applied to the abdomen or buttocks twice per week | 0.05-0.1 mg/d; applied to the abdomen or buttocks twice per week | 0.05-0.1 mg/d; applied to the abdomen or buttocks twice per week | 22.00 |
| Vaginal estradiol | Estrace cream | 2-4 g of cream per day for 3 weeks each month (200-400 mg of estradiol) | | | 39.00 |
| | Estring | 7.5 µg/d, the ring is placed in the upper one third of the vaginal vault and replaced every 90 days | | | 75.00 |
| | Vagifem | 25-µg tablet per day inserted in the vagina daily for 2 weeks; mainten- ance dose is 1 tablet (25 µg) inserted 2 times per week | | | 5.00-10.00 |

*Average wholesale price.
Adapted from references 44 and 51-53.

the more abrupt the onset of menopausal symptoms, the higher the dose of estrogen that will be required to control the vasomotor symptoms. As women age, the doses required to control vasomotor symptoms and urogenital and vaginal atrophy should decrease.⁴³ Attempts should be made on a regular basis to decrease the estrogen dose to the lowest possible to maintain symptom control.

Numerous ERT/HRT products are available on the market today. **Table 2**, **Table 3**, and **Table 4** list some of the estrogen-only, progestin-only, and

combination products available and their average wholesale price.

... ADHERENCE TO ESTROGEN AND HORMONE REPLACEMENT THERAPY ...

It has been estimated that only 10% to 20% of postmenopausal women in the United States use ERT/HRT.^{50,54} Thirty percent of women who receive a prescription for ERT/HRT never have the pre-

Table 3. Progestin-Only Products

| Generic Name | Brand Name | Cyclical (Sequential) Dose | Continuous Dose | Average Monthly Cost (\$)* |
|----------------------------------|--------------------------|--|-----------------|----------------------------|
| Oral medroxyprogesterone acetate | Provera 2.5, 5, 10 mg | 5-10 mg/d given for 10-14 days per cycle | 2.5 mg/d | 12.00-15.00 |
| Oral norethindrone | Micronor 0.35 mg | | 1 mg/d | 100.00 |
| Oral micronized progesterone | Prometrium 100 mg | 200 mg/d for 12 days per cycle | | 18.00 |

*Average wholesale price.
Adapted from references 44 and 51-53.

scription filled.⁵⁵ Of women who do have the prescription filled and initiate ERT/HRT, 20% to 40% discontinue use within 1 year.^{10,56,57} Reasons why women are not filling the initial prescription and are discontinuing ERT/HRT within 1 year of starting therapy should be addressed to try to enhance adherence.

Many misconceptions and concerns about ERT/HRT influence therapy initiation and continuation. Common misconceptions include that ERT/HRT is not “natural”; that it causes cancer, heavy periods, or weight gain; that it restores fertility; and that it is needed only when menopausal symptoms are unbearable.^{54,55,58,59} Common concerns are fear of breast cancer, fear of endometrial cancer, and return of withdrawal or irregular bleeding.^{52,59,60} These misconceptions and patient concerns must be addressed. Women initiate and continue ERT/HRT based not only on the actual but also on the perceived benefits, risks, and adverse effects. A woman’s decision to initiate and continue therapy is influenced not only by her opinion, but also by the opinions of her family, friends, and healthcare providers.^{54,61} Education on these actual and perceived benefits, risks, and adverse effects of ERT/HRT and involvement in discussions about therapy issues will assist women in the decision to initiate ERT/HRT.⁵⁸

Many women will discontinue therapy due to lack of a perceived benefit, irregular or withdrawal bleeding, alterations in mood, breast tenderness, or an alarming news report.^{10,54,56,58,59} It is important that the appropriate dose is selected to maximize the benefits of ERT/HRT and to mini-

mize adverse effects as much as possible. Too low a dose will not improve the vasomotor, vaginal, or urogenital symptoms and complaints. Too high a dose may result in adverse effects that women are not willing to tolerate. Women who experience menopause at an earlier age or undergo surgical menopause by an oophorectomy require higher doses of estrogen than older women to control the vasomotor symptoms as well as the urogenital and vaginal symptoms.⁴³ Thin women

are more likely to require higher doses of ERT than obese women because the endogenous production of estrogen is less in thin women.⁵⁹ The dose of ERT should gradually be decreased as metabolism slows with increased age. The lowest effective estrogen dose should be used to minimize the occurrence of adverse effects.

Women need to understand that they will experience adverse effects. Preparing patients for the inevitability of adverse effects and explaining ways to minimize these effects can be very helpful. Offering women different methods or plans to deal with adverse effects before they occur could help them adhere to therapy. Encourage women to ask for additional options in case the method they are using does not control intolerable adverse effects.

Patients should be encouraged to bring in any articles that may have caused alarm about therapy issues.⁵⁴ Discussing any concerns with healthcare professionals will enhance a woman’s understanding of her actual benefits and risks and minimize the influence of perceived benefits and risks. Addressing these issues will help women in maintaining long-term treatment adherence (Table 5).

... CONCLUSION ...

There is much we do not understand about the benefits and the risks of ERT and HRT. Ongoing studies should increase our knowledge and understanding of these benefits and risks. The Women’s

Table 4. Combination Products

| Generic Name | Brand Name | Cyclical Dose | Continuous Dose | Average Monthly Cost(\$)* |
|-----------------------------|--|--|--|---------------------------|
| Oral CEE + MPA | Premphase CEE 0.625 mg + MPA 5 mg | 0.625 mg of CEE per day for 14 days only, followed by 0.625 mg of CEE + 5 mg of MPA per day for 14 days | | 22.00 |
| Oral CEE + MPA | Prempro CEE 0.625 mg + MPA 2.5 mg or CEE 0.625 mg + MPA 5 mg | | 0.625 mg of CEE + 2.5 mg of MPA per day or 0.625 mg of CEE + 5 mg of MPA per day | 24.00 |
| Oral estradiol + NG | OrthoPrefest estradiol 1 mg and estradiol 1 mg + NG 0.09 mg | 1 mg of estradiol per day for 3 days followed by 1 mg of estradiol + 0.09 mg of NG per day for 3 days; regimen is repeated continuously | | 27.00 |
| Oral estradiol + NE | Activella estradiol 1 mg + NE 0.5 mg | | 1 mg of estradiol + 0.5 mg of NE per day | 30.00 |
| Oral ethinyl estradiol + NE | FemHRT ethinyl estradiol 5 µg + NE 1 mg | | 5 µg of ethinyl estradiol + 1 mg of NE per day | 31.00 |
| Transdermal estradiol + NE | CombiPatch estradiol 0.05 mg + NE 0.14 mg and estradiol 0.05 mg + NE 0.25 mg | Apply estrogen-only patch for days 1-14, then apply CombiPatch twice weekly for days 14-28; 0.05 mg of estradiol + 0.25 mg of NE applied to the abdomen (keep refrigerated before use) | Apply CombiPatch twice weekly; 0.05 mg of estradiol + 0.14 mg of NE or 0.25 mg of NE applied to the abdomen (keep refrigerated before use) | 30.00 |

CEE = conjugated estrogen; MPA = medroxyprogesterone acetate; NE = norethindrone; NG = norgestimate.

*Average wholesale price.

Adapted from references 44 and 51-53.

Table 5. Tips to Enhance Adherence to Estrogen and Hormone Replacement Therapy

| |
|---|
| <p>Provide patient education.</p> <ul style="list-style-type: none"> • Discuss up-to-date information on menopause, the benefits of estrogen and hormone replacement therapy, risks, and adverse effects with healthcare providers. • Provide written material patients can read at home. • Encourage patients to ask questions and voice concerns at any time during therapy. <p>Schedule frequent follow-up visits in the first year of therapy to address issues such as adverse effects, questions, concerns, and adherence.</p> <p>Select the optimal dose, route, and product to maximize benefits and minimize adverse effects.</p> |
|---|

Adapted from references 54 and 55.

Health Initiative is a large, multicenter, randomized, controlled trial that should provide answers to many of the questions regarding ERT/HRT use.⁶²

Until those results are available, the known benefits and risks must be evaluated for each woman because ERT/HRT is not appropriate for every postmenopausal woman. Only then can the healthcare provider and the patient determine whether ERT/HRT is appropriate. Healthcare providers and women will have different preferences, goals, needs, and risks. Including a woman in the decision to initiate ERT/HRT will enhance therapy initiation, continuation, and satisfaction.

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CONTINUING PHARMACY EDUCATION



This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-999-02-207-H-01. This course expires July 31, 2004.

Instructions

After reading the article "Hormone Replacement Therapy: Current Concerns and Considerations," select the best answer to each of the following questions.

1. Hot flushes most frequently occur:

- a) during the night
b) in the morning
c) with exercise
d) after a shower

2. Menopause involves the following:

- a) the ovaries no longer produce eggs
b) menstruation ceases
c) estrone becomes the dominant physiologic estrogen
d) all of the above

3. What percentage of American women over age 50 will have an osteoporotic fracture in their lifetime?

- a) 80%
b) 50%
c) 30%
d) 10%

4. The most effective therapy for relieving vasomotor symptoms is:

- a) loose clothing
b) avoiding spicy foods
c) ERT
d) regular exercise

5. To prevent bone loss over the long term, ERT must be taken for:

- a) 5 years
b) 1 year
c) 10 years
d) for the rest of the patient's life

6. According to the American Heart Association, which of the following statements is true?

- a) ERT/HRT should not be initiated for secondary prevention
b) The decision to continue ERT/HRT in women with CVD should not be based on noncoronary benefits and risks and patient preferences
c) If a patient is immobilized, ERT/HRT should not be stopped, nor should VTE prophylaxis be initiated
d) If a patient has an acute CVD event, HRT should not be stopped, nor should VTE prophylaxis be initiated

(CPE questions continued on following page)

Hormone Replacement Therapy: Current Concerns and Considerations

ACPE Program Number: 064-999-02-207-H-01

(PLEASE PRINT CLEARLY)

Name

Home Address

City

State/ZIP

Daytime Phone #

States in Which CE Credit is Desired

Please circle your answers:

- 1. a b c d 6. a b c d 11. a b c d 16. a b c d
2. a b c d 7. a b c d 12. a b c d 17. a b c d
3. a b c d 8. a b c d 13. a b c d 18. a b c d
4. a b c d 9. a b c d 14. a b c d 19. a b c d
5. a b c d 10. a b c d 15. a b c d 20. a b c d

Please complete the Program Evaluation on following page, and send with \$15 fee, payable to University of Tennessee, to:

Glen E. Farr, PharmD
University of Tennessee College of Pharmacy
600 Henley Street, Suite 213
Knoxville, TN 37902

...CPE QUIZ...

7. ERT/HRT has not demonstrated a benefit in preventing:

- a) colon cancer, Alzheimer's disease, dementia
- b) osteoporosis, Alzheimer's disease, dementia
- c) osteoporosis, colon cancer, dementia
- d) osteoporosis, Alzheimer's disease, colon cancer

8. Estrogen should be used with progestin to:

- a) prevent bone loss
- b) prevent breast cancer
- c) prevent endometrial hyperplasia
- d) prevent CVD

9. HRT therapy will:

- a) decrease HDL and increase LDL
- b) increase HDL and decrease LDL
- c) have no effect on HDL and lower LDL
- d) increase HDL and have no effect on LDL

10. ERT and HRT may be administered by all of the following routes:

- a) intravenously, orally, transdermally
- b) orally, transdermally, intravaginally
- c) intravaginally, intravenously, orally
- d) intravenously, transdermally, intravaginally

11. To prevent endometrial hyperplasia, the medroxyprogesterone dose should be:

- a) 5 to 10 mg/day for 10 to 14 days per cycle
- b) 2.5 mg/day every day
- c) the dose doesn't matter as long as it is given 20 days per cycle
- d) a or b

12. ERT and HRT increase the risk for breast cancer in women who are:

- a) currently using ERT or HRT
- b) have used ERT or HRT for more than 5 years
- c) are older
- d) all of the above

13. The risk of VTE or PE in women on HRT is increased by:

- a) having a lower extremity fracture
- b) having an MI
- c) none of the above
- d) a and b

14. Adverse effects associated with ERT will usually resolve when:

- a) the ERT dose is changed
- b) ERT is given continuously for several months
- c) the ERT product is changed
- d) all of the above

15. The potency of estrogens used in ERT and HRT is _____ the potency of the estrogens used in oral contraceptives.

- a) one fourth to one fifth
- b) one third to one half
- c) one half to three fourths
- d) twice

(CPE questions continued on following page)

CPE PROGRAM EVALUATION (064-999-02-207-H-01)

The University of Tennessee College of Pharmacy would like to have your opinion. Please fill out the questionnaire below, tear off along the dotted line, and mail along with your CPE test form. We thank you for your evaluation, which is most helpful.

Please circle your answers:

| | | | | |
|--|----------------|--------------|-----------------|-------------------|
| My pharmacy practice setting is: | Independent | Chain | Hospital | Consultant |
| The objectives of the lesson were achieved: | Yes | No | | |
| The quality of presentation of the material was: | Excellent | Good | Fair | Poor |
| The information presented will be useful to me in my practice. | Strongly agree | Mildly agree | Mildly disagree | Strongly disagree |

How long did it take you to read the material and respond to the Continuing Education questions: (Please specify the number of hours.)

Please send this evaluation, along with your answer sheet and \$15 check payable to University of Tennessee, to:

Glen E. Farr, PharmD
University of Tennessee College of Pharmacy
600 Henley Street, Suite 213
Knoxville, TN 37902

...CPE QUIZ...

16. All of the following adverse effects are associated with ERT:

- a) cholelithiasis, headaches, withdrawal bleeding
- b) withdrawal bleeding, headaches, water retention
- c) headaches, water retention, cholelithiasis
- d) water retention, cholelithiasis, withdrawal bleeding

17. HRT therapy:

- a) restores fertility
- b) causes weight gain
- c) makes facial hair grow
- d) none of the above

18. Transdermal ERT or HRT may be used in women who:

- a) experience nausea and vomiting with oral therapy
- b) smoke
- c) are at increased risk for clots
- d) all of the above

19. Women who take progestins continuously may:

- a) have unpredictable vaginal bleeding initially, then gradually develop amenorrhea
- b) have withdrawal bleeding
- c) be more irritable
- d) have more water retention

20. Cyclical progestins are:

- a) not protective of the endometrium
- b) given for 10 to 14 days each month
- c) given for 15 to 20 days each month
- d) given to women without an intact uterus

Please fill out the University of Tennessee College of Pharmacy program evaluation that accompanies this quiz (page 677).