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Postmenopausal Hormone Replacement Therapy

Ongoing evaluation of benefits and risks

Summary

Postmenopausal hormone replacement therapy (HRT) is the most effective treatment for hot flashes.¹ Beyond this point of agreement, both consumer opinion and professional advice may differ about relative benefits and risks of therapy. New studies have cast doubt on cardiovascular benefits and have highlighted the association between hormone use and development of breast cancer.²⁻⁴ Over the last decade, women who may have accepted hormone replacement as a logical part of the menopausal transition now have harder questions to ask themselves and the health care professionals they consult. Even if widespread consensus has not coalesced, a review of past studies can provide a basis for evaluating how new studies affect our perceptions of risks and benefits for HRT users.

Introduction

Conjugated estrogens were first marketed in the United States in 1942 and for the next 40 years, were used chiefly for relief of menopausal symptoms on a short-term basis cyclically, usually for less than a year.^{5,6} In 1975, the causal relationship between endometrial cancer and unopposed estrogen was discovered.³ In addition, a warning appeared in the PDR about possible cardiovascular problems and prescribing decreased. Then, in 1981 when it was recognized that estrogen use reversed bone density loss in menopause, Premarin® was labeled as “possibly effective for estrogen-deficiency induced osteoporosis,” and the number of prescriptions began to increase again. During the decade, beneficial effects of postmenopausal estrogen on plasma lipid profiles were observed.⁷ Because unopposed estrogen use increases the risk of endometrial hyperplasia, a precursor of endometrial cancer, all women with a uterus require the addition of a progestin as well.¹ By the early 1990s, hormone replacement was routinely prescribed for menopausal women who had no contraindications to its use. Women were already living longer, but for those who might be disabled by coronary heart disease and by vertebral and hip fractures, HRT also extended the promise of living much better.

Many practitioners who would routinely have advised hormone replacement for women with no contraindications now must carefully balance risks and benefits in order to make recommendations for individual patients. Here, we will review risks, benefits and available dosage forms that may guide pharmacists to enable both health professionals and patients in making maximally informed choices.

Recent studies

Recently, McNagny has evaluated a number of studies on

the effects of HRT on conditions ranging from colon cancer to dementia.¹ The most difficult issue in judging the practical importance of these studies is how to determine how much evidential weight to assign to them. The problem is complicated by press reports which play on emotionally charged issues like increases in breast cancer incidence without discussion of how the new information fits in the context of all of the available scientific evidence. McNagny recently has summarized the benefits and risks of HRT by making two lists: 1) the strong evidence obtained from randomized controlled trials, and 2) the promising evidence from meta-analysis of epidemiological studies.¹ The epidemiological studies are more numerous, but the evidence is not as powerful because some are retrospective, and none are randomized. The observational studies include all the healthy, health-conscious women who chose HRT in addition to other recommended lifestyle choices like exercise, weight loss and smoking avoidance. If women who do not take HRT are less healthy as a group, not all the improved outcomes can or should be attributed to HRT alone.

Table 1 lists a summary of findings from these studies stratified in two evidential layers, adapted from McNagny.

Benefits of hormone replacement

Perimenopausal Symptoms

About 75% of menopausal American women experience hot flashes, with varying degrees of lifestyle interruption.⁸ When noticeable hot flashes occur at night, they can disrupt sleep five or six times or even more frequently during the night. Non-restorative sleep can contribute to depression which is not caused by menopause, but can be triggered at that time in women who are predisposed or who have experienced depression previously. Because urogenital tissues contain estrogen receptors, tissue atrophy can result in vaginal thinning and

Table 1

Health Effects Observed with Current HRT Use¹

Condition	Significant Outcome	Comment
Strong Evidence from Prospective, Randomized, Controlled Trials		
Hot flashes	↓70%	
Vertebral fractures	↓61%	1 year of transdermal estrogen
LDL cholesterol	↓10%	3 years of CE alone
HDL cholesterol	↑9%	3 years of CE alone
Triglycerides	↑14%	No effect with transdermal estrogen
Secondary prevention of CHD	No effect	CE + MPA
DVT or pulmonary embolism	↑3x	CE + MPA
Cholecystitis	↑40%	CE + MPA
Endometrial cancer	No effect	Estrogen + progestin
High blood pressure	No effect	
Weight	No increase	
Promising Evidence from Meta-analyses of Epidemiologic Studies		
Hip fracture	↓25%	11 studies
Primary prevention of CHD		
■ Estrogen alone	↓50%	16 studies
■ Estrogen + progestin	↓34%	7 studies
Risk for dementia	↓29%	10 studies
Colon cancer	↓31%	6 studies
Breast cancer		
■ < 5 years use	No effect	51 studies
■ ≥ 5 years use	↑35%	51 studies

CHD = Coronary heart disease

CE = Conjugated estrogens

MPA = Medroxyprogesterone acetate

DVT = Deep vein thrombosis

dryness that can lead to painful intercourse. Urethral irritation can result in an increased number of urinary tract infections and incontinence. Estrogen therapy is effective for all symptoms due to loss of endogenous estrogen production. Depressed patients should be treated with antidepressants. Duration of menopausal symptoms is seldom longer than five years.

Osteoporosis

Up to six million women in the United States have osteoporosis. Progressive loss of bone mineral density leads to vertebral, wrist and hip fractures.⁸ Vertebral fractures, sometimes silent, sometimes acutely painful for prolonged periods, result in debilitating pain, muscular weakness and spinal deformity. In addition, a quarter million hip fractures per year result in enormous expense, frequent loss of independence and a 20% risk of death within a year. With long-term HRT use (three to ten years), the incidence of all types of osteoporotic fractures decreases by 30-50%. One early meta-analysis of 11 epidemiologic studies estimated that estrogen use reduces the risk of hip fracture by 25%.⁹ Use for ten years decreases the risk by 50%, but therapy discontinuation results in resumption of bone loss and an increase in fracture risk that returns to baseline in about six years.

Transdermal estrogen administration in women with pre-existing vertebral fractures has decreased the incidence of new fractures by 60%.¹⁰ One prospective, placebo-controlled study of 75 women used transdermal estradiol 100-mcg patches for cycle days 1-21 plus medroxyprogesterone 5-10 mg orally on days 11-21 for a year. Bone mineral density in the estrogen group increased in spine, femoral trochanter and mid-radius. The hormone-treated group developed less than half as many new vertebral fractures compared to the control group. The differences between treatment and placebo groups were seen in women over 65 years of age as well as in the younger women.

Coronary Heart Disease

A 50-year-old woman has a 46% lifetime probability of developing coronary heart disease.⁹ The probability of death from CHD for her is 31% at a mean age of 74 years. Evidence from 32 epidemiologic studies has showed a pooled reduction in risk for CHD of 35% overall for estrogen users. Concurrent improvements in lipid profiles include LDL decreases of 10-15% and HDL increases of 10-15%. Addition of a progestin attenuates these lipid changes somewhat, but the protective effects of the combination remain. Oral estrogens also increase triglyceride levels, but in women with hypertriglyceridemia, transdermal patches are a useful alternative because they do not affect triglyceride levels.

Although observational studies have shown a decrease of 35-50% in the incidence of CHD and overall mortality in HRT users, we do not have evidence available yet from prospective studies.¹¹ Two randomized clinical trials now in progress, the Women's Health Initiative and WISDOM, the Women's International Study of Long-Duration Oestrogen after Menopause, may yield results that confirm protective effects of hormone administration.

One recent prospective trial examined the possibility that estrogen plus progestin might decrease heart attacks in postmenopausal women with heart disease already present.² The

Heart and Estrogen/progestin Replacement Study (HERS) followed such a group for an average of 4.1 years while they were taking conjugated estrogen 0.625 mg and medroxyprogesterone 2.5 mg daily. There was no difference in number of heart attacks and fatal coronary heart disease deaths between the active and placebo groups. More CHD events occurred in the active treatment group during the first year of HRT, but there were fewer events in years four and five. The authors cautioned that there may be risks in starting a woman with CHD on hormone replacement, but if she already has been on HRT for some time, there is no reason for her to discontinue. Not only is there no added risk after the first year, but there are also the HRT-induced beneficial changes in lipid profiles.

Observational studies that have evaluated the effects of estrogen use on strokes in women have not produced consistent outcomes, although there is a decreased risk of death from stroke in estrogen users.⁹

Dementia

Observational studies have noted that ever-users of HRT are 30% less likely to develop Alzheimer's Disease.¹² Positive outcomes in small studies suggest that Alzheimer's can be prevented or delayed by the use of HRT, but there is not enough information to recommend specific doses or duration of treatment. McNagny has commented succinctly that "current information is incomplete, uncontrolled and conflicting."¹¹ One small prospective study of daily estrogen administration in women with established Alzheimer's Disease did not produce measurable improvement in dementia symptoms or cognitive performance.¹³

Colon Cancer

The weight of epidemiologic evidence supports the existence of a protective effect against colorectal cancer, but studies have reported inconsistent results.

Risks of Hormone Replacement

Breast Cancer

Fear of cancer is the most frequently mentioned reason why women refuse to begin HRT.¹⁴ Recent studies have presented evidence that the addition of progestins to estrogen does not protect against breast cancer, but may actually increase risk with increasing duration of HRT use.³ One large observational study of over 5,000 women found that unopposed estrogen use did not increase breast cancer risk until 15 or more years on therapy. In contrast, breast cancer risk increased about 10% per 5 years of HRT use. The risk appeared higher with sequential rather than combined regimens of progestin use, but conclusions are limited by the smaller number of women who have extended experience with combined therapy. It is logical to expect that the smaller progestin doses used with continuous therapy may have fewer adverse effects.

There is good news when the histology of breast tumors in HRT users is compared to those in controls.¹⁵ Estrogen use may lead to a less malignant type of cancer. A small population-based case-control study of 537 women in the state of Washington, aged 50-64 years with breast cancer revealed a preponderance of lobular rather than ductal carcinoma. Overall, 80-85% of breast cancers are of ductal origin. More important, lobular cancer is more hormonally dependent and has a better prognosis. Estrogen replacement carries a relative risk of 1.4 for lobular disease, but only of 0.6 for ductal disease. Similarly, relative risks for HRT users are 2.1 and 0.7 respectively, so that there is actually a lower risk of developing ductal cancer.

One constantly recurring question is whether HRT is a reasonable option for breast cancer survivors. One recent study in a practice that followed HRT users with previous breast cancer for up to 32 years of hormone replacement shows no excess mortality in these women.¹⁶ The authors reflect current practitioner opinion in recommending that HRT be offered to such patients after a complete discussion of risks and benefits. They acknowledge that safety cannot be adequately predicted in the absence of a randomized, placebo-controlled study.

Now that long-term hormone replacement is considered for the prevention of chronic diseases like osteoporosis and heart disease, its long-term safety should be more carefully assessed. It is unquestionable that HRT increases the risk of breast cancer in proportion to duration of use.⁴ On the other hand, studies have documented decreased mortality in HRT users. The extent of the breast cancer risk is an increase of 2% per year of use and, once discontinued, no increased risk after five years. When risk is translated to numbers of women affected, 15 years of HRT will lead to 12 additional cases of breast cancer per 1,000 women. After age 70, heart disease kills more American women than cancer and a long-term strategy to prevent heart disease is reasonable. Fortunately, there are many modifiable factors in addition to hormone replacement to improve outcomes for those at risk for CHD. For osteoporosis, other treatment modalities to increase bone mineral density may supplant HRT after the first few years of treatment. For those who continue, a very small increased number will develop breast cancer. One of the most difficult aspects of patient counseling is the paradox that statistical risk cannot be applied to an individual case. Neither the given individual who will become the lottery winner nor the HRT user who will develop breast cancer can be predicted. Even a small risk may be unacceptable for an individual who becomes the statistical designee. Overall, because most people benefit, long-term hormone use is still beneficial from a public health point of view.

Cholecystitis

From epidemiologic studies, the relative risk of gallbladder disease in postmenopausal women using HRT varies from

Table 2

Selected Dosage Forms Available in the U.S. for Postmenopausal Hormone Replacement

Trade Name	Generic Name	Dosage Strength	Dose	FDA Approval for Osteoporosis	30-Day Cost (AWP)
Oral Preparations					
Estrace	Estradiol, micronized	0.5, 1, 2 mg tabs	1-2 mg/day	✓	\$11.76 - 22.88 brand \$4.46 - 7.62 generic
Ortho-Prefest	Estradiol/Estradiol+ norgestimate	1mg/1mg + 90 mcg	1 tab/day Alternate Q 3 days	✓	\$25.43
Activella	Estradiol + norethindrone acetate	1mg + 500 mcg	1 tablet daily	✓	\$27.95
Premarin	Conjugated estrogens	0.3, 0.625, 0.9, 1.25, 2.5 mg	0.625 mg daily	✓	<u>\$18.13</u> (\$13.82 - 44.75)
Prempro	Conjugated estrogens + MPA	0.625 mg + 2.5 or 5 mg MPA	1 tablet daily	✓	<u>\$28.68</u>
Premphase	Conjugated estrogens/ Conjugated estrogens + MPA	0/6.25 mg/0.625 mg + 5 mg MPA	CE 1 tab daily x 14 days, then combo x 14 days	✓	<u>\$26.29</u>
Ogen Ortho-Est	Estropipate	0.625, 1.25, 2.5, 5 mg SES	0.625 mg daily for osteoporosis; up to 5 mg daily cyclically [#] for Sx relief	✓	<u>\$22.68</u> - 55.14 <u>\$12.02</u> - 16.47
Estratab Menest	Esterified estrogens	0.3, 0.625, 1.25*, 2.5 mg	1 tablet daily; may give cyclically [#] for menopausal Sx	✓	(\$17.94) \$13.76 - 44.44 (\$9.65) \$6.79 - 13.46
Estratest	Esterified estrogens + methyltestosterone	1.25 mg + 2.5 mg MT	1 tab daily; for short-term cyclical use		\$39.86
Estratest H.S.	Esterified estrogens + MT	0.625 mg + 1.25 mg MT	1 tab daily; for short-term use		<u>\$32.18</u>
Cenestin	Conjugated estrogens, plant-derive	0.625, 0.9, 1.25 mg	1 tablet daily; 1.25 mg d is usual dose for Sx relief		\$14.05 - <u>18.83</u>
Estinyl	Ethinyl estradiol	20, 50, 500 mcg	1 tablet daily; for short-term cyclical use		\$11.81 - 19.89
femhrt	Ethinyl estradiol + norethindrone acetate	5 mcg + 1 mg	1 tablet daily	✓	\$22.18

Transdermal Systems**Release Rate (mcg/24 hrs)**

Alora	Estradiol	50, 75, 100	Apply twice weekly		\$20.64 - 22.81
Climara	Estradiol	25, 50, 75, 100	Apply weekly	✓	\$26.44 - 28.69
Esclim	Estradiol	25, 37.5, 50, 75, 100	Apply twice weekly		\$24.50
Estraderm	Estradiol	50, 100	Apply twice weekly	✓	\$25.56 - 27.89
Vivelle/Vivelle-Dot	Estradiol	25, 37.5, 50, 75, 100	Apply twice weekly	✓	\$25.68 - 27.28
Combipatch	Estradiol + norethindrone acetate	50 + 140 50 + 250	Apply twice weekly	✓	\$31.19

MPA = medroxyprogesterone acetate

MT = methyltestosterone

Sx = symptoms

Underlined prices are for 0.625-mg dosage forms

[#] Cyclically is three weeks on and one week off

* Menest® only

SES = sodium estrone sulfate

Table 3

Other Drugs Used for Treatment and Prevention of Osteoporosis

Trade Name	Generic Name	Dosage Strength	Dose		30-Day Cost (AWP)
			Prevention	Treatment	
Fosamax	Alendronate	5,10,35, 70 mg tabs	5 mg QD or 35 mg weekly	10 mg QD or 70 mg weekly	5,10 mg, \$66.15 70 mg \$49.39 direct
Actonel	Risedronate	5 mg tabs	5 mg QD		\$54.80
Generic* Calcimar Miacalcin	Calcitonin salmon	2-ml vials 200IU/ml		100 IU SC/IM QD	\$292.50 \$400.50 \$280.65
Miacalcin Nasal Spray	Calcitonin salmon	2-ml metered-dose btl		200IU (one activation) QD	\$43.45
Evista	Raloxifene	60 mg tabs	60 mg QD		\$63.38

* Astra Zeneca

1.02 to 3.72 compared to non-users.¹⁷ Estrogen administration increases the saturation of bile with cholesterol and the consequent probability that crystals of cholesterol will precipitate as gallstones. About 80% of gallstones are composed of cholesterol. In the HERS Study, the relative risk of gallbladder disease was 1.4 in the HRT group.² Most of these episodes were treated with gallbladder surgery.

Deep Vein Thrombosis/Pulmonary Embolism

In healthy women, the incidence of deep venous thrombosis is very low in HRT users, about 1 in 5,000 women per year.¹ In the women of the HERS trial who had established coronary disease, the relative risk in users was 2.9 compared to the placebo group.² The problem is an infrequent complication, affecting only small numbers of women.

Administration

In the last ten years, continuous rather than cyclic regimens of HRT administration have become much more frequently used. One recent review stated that there is "no advantage to the commonly used regimen in which estrogen is given for 25 days out of the month."¹⁸ For women with an intact uterus, the usual progestin added to the estrogen has been medroxyprogesterone 2.5 mg daily, or 5-10 mg in previous cyclic regimens for 10-14 days of the cycle. Less frequently used progestins have been progesterone 100 mg daily or 200 mg cyclically and megestrol acetate, 10 mg daily continuously or 20 mg daily for part of the cycle. The esthetic disadvantage of continuous regimens is that many women have intermittent vaginal bleeding for the first six to twelve months. The long-term advantage is that eventually vaginal bleeding should cease entirely.

Discussing benefits and risks with patients

The approach to patient counseling should be tailored to the profile, including patient preferences, of the individual prospective HRT user.

- First, those with absolute contraindications should be screened out in the patient's consultation with the physi-

cian.¹ These contraindications include pregnancy, unexplained vaginal bleeding, active or chronic liver disease, a history of breast or endometrial cancer or recent vascular thrombosis. Informed patient refusal is an absolute contraindication as well.

- Relative contraindications should be assessed by the physician and discussed with the patient. These include a family history of breast cancer, migraines, gallbladder disease, elevated plasma triglycerides, history of thromboembolic disease, uterine leiomyoma, or seizure disorders.
- The physician must determine if the patient's history is consistent with menopause, and should rule out the possibility of late pregnancy. Examinations should include blood pressure, breast and pelvic examinations, mammography and Pap smears.
- Pharmacists can be helpful in discussing risks and benefits of HRT. The benefits of short-term therapy for symptom relief are self-evident.
- A variety of oral and transdermal dosage forms are now available for increased user convenience. (See Table 2). Oral combinations of estrogen and progestin include Prempro®, Premphase®, Ortho-Prefest®, Activella®, and fmhrt®. Transdermal systems are preferable in patients with elevated triglyceride levels, liver disease or a history of gallbladder disease.¹⁹ The incidence of patch reactions is about 10% for alcohol-based reservoir products like Estraderm® and about 5% for the estrogen-in-adhesive matrixes like Vivelle®.
- Longer-term therapy to prevent osteoporosis may be advisable for anyone with a long life expectancy, considering that a 50-year-old white woman has a 15% lifetime probability of sustaining a hip fracture at the median age of 79 years.⁹ In addition, calcium supplements should be taken to ensure a daily intake of at least 1500 mg of elemental calcium from dietary and supplemental sources. Vitamin D 400 IU daily should be included to optimize calcium absorption. There are, of course, alternative medications to

maintain or increase bone mineral density in patients who cannot or do not wish to take hormones. Current dosage forms are listed in Table 3.

- Patients looking for cardiovascular benefits should be encouraged to evaluate their individual risk for coronary disease, based on lipid profiles, blood pressure, lifestyle, and family history. Those at higher risk may prevent disease before it develops, but HRT has not so far been useful in secondary prevention of heart attacks in people with existing coronary disease.
- To assess how the latest information or most recent studies will affect ongoing risk and benefit assessment, it is helpful to subscribe to Web sites like www.medscape.com which can provide the consensus of clinical guidelines as well as e-mailed weekly updates in the therapeutic areas of your choice. ■

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