HORMONES AND HOT FLASHES:

SURVIVING MENOPAUSE IN THE ERA OF THE WOMEN'S HEALTH INITIATIVE

LU ANN BUNDRANT, M.D.

INTERNAL MEDICINE GRAND ROUNDS
MARCH 25, 2004

This is to acknowledge that Lu Ann Bundrant, M.D., has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Bundrant will be discussing off-label uses in her presentation.

Lu Ann Bundrant, M.D.
Assistant Professor of Internal Medicine
Division of General Internal Medicine
Areas of interest: Primary care internal medicine, women's health

Half of what we have taught you won't be true in 5 years. Unfortunately, we don't know which half.

(A Skeptic's Medical Dictionary)

INTRODUCTION

Since July 2002, women and their physicians have been inundated with new and sometimes confusing information about the use of hormone replacement therapy (HRT) after menopause. Although there were many important studies published prior to that date, the termination of the combined HRT arm of the Women's Health Initiative due to observed risks with therapy generated enormous publicity and concern among women. Medscape, a web-based search engine, ranked it number one among the top 10 medical-health stories of 2002.[1] Over the following two years multiple substudies have also been published; these include articles about the relationship of combined estrogen/ progesterone therapy to cardiovascular disease,[2] stroke,[3] breast cancer,[4] cognition,[5] osteoporosis,[6] and colon cancer.[7] In addition, the estrogen-only arm of the trial was discontinued earlier this month due to a higher rate of stroke seen in women taking estrogen.[8] Over the next few months, many more data will be forthcoming from the WHI about this arm of the trial.

Many women have gone to great lengths to stop taking HRT based on perceived risks from menopausal hormone treatment, resulting in a need for alternative treatments for those with more severe vasomotor symptoms. From herbal remedies to antidepressants to medications originally used for seizures, there are many options available. Some have evidence from randomized, controlled trials to support their use, and many do not. Estrogen remains the gold standard for treatment, and individual women's health profiles and preferences must be taken into account when making therapy decisions.

This presentation will summarize the findings of several important substudies of the WHI, with attention given to relevant background data as necessary. Also, the second portion of the article will focus on the supporting evidence (or lack thereof) for various nonhormonal therapies for common menopausal symptoms. A case example follows:

Mrs. Jones is a 65-year-old Caucasian lady with hypertension, breast cancer (treated with right lumpectomy and radiation) in 1988, and osteopenia (T-score at the femoral neck –1.64). She has not had a hysterectomy. She has been menopausal since age 51 and has persistent vasomotor symptoms, particularly at night. Her oncologist has told her not to take estrogen due to her history of breast cancer. The hot flashes contribute to chronic insomnia, for which she takes hypnotics frequently. She wishes to discuss nonhormonal treatments for her symptoms.

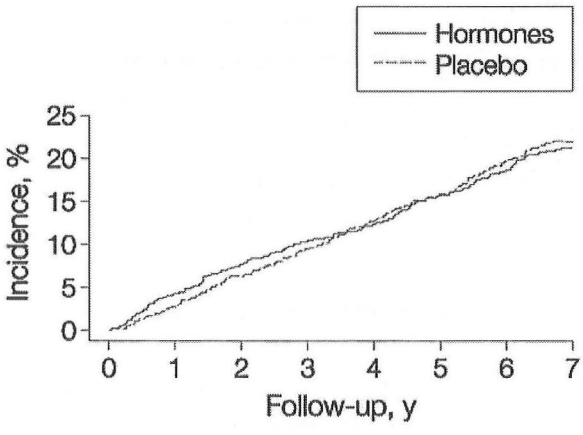
HRT AND CARDIOVASCULAR HEALTH

For years, women were told to take hormone replacement therapy to prevent heart disease. This was based on observational studies that suggested as much as a 40-50% decrease in risk for this condition with postmenopausal hormone therapy.[2] However, in the past several years, data from randomized, controlled trials have become available to better define the potential risks and benefits of HRT.[2,9,10,11,12,13] This information has resulted, in many cases, in an about-face from our previous recommendations to women regarding whether or not they should take hormones during the menopause, particularly for combination therapy with conjugated estrogens and progesterone. As with most advances in medical understanding, the new information on menopausal hormone replacement therapy raises as many questions as it answers.

Several randomized trials prior to the WHI began to challenge the conclusions from observational studies that HRT was beneficial for cardiovascular health, including the Heart and Estrogen/progestin Replacement Study (HERS)[9] which showed no benefit of therapy. Randomized trials looking at the progression of atherosclerosis in hormone users and nonusers included ERA (Estrogen Replacement and Atherosclerosis trial),[11] EPAT (Estrogen in the Prevention of Atherosclerosis Trial),[12] and WELL-HART (the Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial).[13] Following is a summary of major findings from these trials and a comparison with results from the WHI.

<u>The HERS Research Group: Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women[9]</u>

HERS found no reduction in the overall rate of cardiac events in 2763 menopausal women with established heart disease who took HRT for an average of 4.1 years.[9] Eligible patients were at least 55 years old, and established heart disease was defined as MI, CABG, PTCA, or 50% occlusion of 1 or more coronary arteries by angiography. Of note, the average age of these participants was about 67 years, and they were about 18 years from the onset of menopause. The HRT regimen used was oral conjugated equine estrogens, 0.625 mg, plus medroxyprogesterone acetate 2.5 mg, in one tablet daily. Primary outcome measures for HERS were nonfatal MI and coronary heart disease (CHD) death. Although the overall results showed no difference in cardiac events, subgroup analysis showed that women in the hormone group had more CHD events than the placebo group during the first year, but fewer by years 4 and 5. The HERS investigators postulated that the increase in CHD risk in year 1 might be due to "an immediate prothrombotic, proarrhythmic, or proischemic effect of treatment that is gradually outweighed by a beneficial effect on the underlying progression of atherosclerosis...". In their conclusions, they state that HRT should not be initiated for secondary CHD prevention, but that due to the possible decrease in events over time, it might be continued in women already taking hormone replacement.



HERS II[10] was a voluntary extension of HERS which followed the women previously enrolled, in non-blinded fashion, for a total of 6.8 years of observation (as opposed to 4.1 in HERS). The purpose of the study extension was to see if the possible beneficial effects of HRT seen in years 4 and 5 of HERS continued over longer-term follow-up. Women either continued with open-label hormones prescribed by their personal physician, or in the case of placebo-recipients, chose not to initiate HRT. 2321 patients, or 93% of the surviving enrollees in HERS, agreed to participate in HERS II. At the beginning of HERS, 81% of women reported compliance with the study hormone regimen, and this dropped to 45% during year 6. At the end of HERS II, no significant differences were found between hormone and placebo groups with regard to the defined CHD events. Thus, there were no beneficial effects seen with longer-term use of HRT. Subgroup analysis, including age, prior manifestations of CHD, cardiac risk factors, medication use, etc. failed to show any group that accounted for the early increased CHD risk seen in year 1.

Although the number of women who stopped HRT increased with time, the overall relative hazard (RH) was 0.97, with a 95% confidence interval of 0.82-1.14; thus it is statistically improbable that a true RH of less than 0.82 was missed.

Following are results from 3 large, randomized trials looking at progression of atherosclerosis, each with important distinguishing features.

ERA: Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis[11]

This randomized, placebo-controlled trial of 309 women with known coronary artery disease (based on prior angiography) showed no effect of HRT on the progression of coronary atherosclerosis over a 3 year period.[11] Subjects were menopausal women with at least 30% stenosis of one or more epicardial coronary arteries, and they were randomized to 0.625 mg conjugated equine estrogen either alone or with 2.5 mg medroxyprogesterone acetate, or to placebo tablets. The average age of these women was about 66 years, and they were about 23 years out from the onset of menopause. Subjects had baseline angiogram, either for clinical indication or for the study, and follow-up angiography was performed for 248 of these women an average of 3.2 years later. Compliance rates were 74% for women assigned to unopposed estrogen, and 84-86% for women assigned to combined therapy or placebo. No significant differences were found among treatment groups with regards to minimal coronary artery diameters, the primary outcome of this study. Individual segments of coronary arteries were also studied in order to see if more diseased arteries might have a different response to hormone treatment. A subgroup analysis showed no difference with treatment in segments with minimal versus more extensive disease. For example, analyses of the artery segments with 0-24% stenosis at baseline showed no significant changes with HRT, nor did segments with more severe involvement.

An important feature of this study was the inclusion of the unopposed estrogen group, which also failed to show improvement in disease with treatment. Previous hypotheses had suggested that progesterone might blunt the proposed beneficial effect of estrogen on progression of CAD, but in this study no differences were found between unopposed estrogen and combined therapy. As an explanation for their findings of no cardiac benefit from HRT, the authors proposed that estrogen might increase inflammatory proteins such as CRP, or that estrogen does not alter the progression of established CAD (as opposed to possible beneficial effects on early lesions).

EPAT: Estrogen in the Prevention of Atherosclerosis[12]

This study of 222 menopausal women who were not known to have existing CHD found a slower progression of atherosclerosis (as measured by rate of change in intima-media thickness in the distal common carotid artery) in women who took unopposed estrogen than in those who took placebo.[12] The investigators chose carotid ultrasound and wall-thickness as a measure of the early stages of atherosclerosis, which would pre-date the development of clinical CHD and be predictive of future vascular events. Lipid-lowering therapy is known to slow the progression of carotid artery wall thickening, so investigators looked at the effect of cholesterol treatment in a planned subgroup analysis as well.

The average age of these women was 62.2 years, and they were treated with unopposed micronized 17 β-estradiol, 1 mg, or placebo. The study followed women with carotid ultrasound at baseline and every 6 months for 2 years, and the primary end point was the rate of change in

intima-media thickness as above. There was over 90% compliance with study medications in both the treatment and placebo groups throughout the trial.

Results showed that intima-media thickness increased in the placebo group (0.0036 mm/y), and regressed in the estradiol group (-0.0017 mm/y). However, in women who received either treatment or placebo combined with lipid-lowering therapy, there was no difference in rate of progression of disease; also, there was no difference between women given placebo who also took cholesterol medication, and women only on estradiol. The authors felt that their data were consistent with the many observational studies suggesting a cardioprotective effect of unopposed estrogen given for primary prevention, as opposed to use in women with known CHD. In HERS[9] and ERA,[11] no benefit was shown for secondary prevention in women given conjugated equine estrogens; there were many differences between these 3 trials, as illustrated below.

	HERS[9]	ERA[11]	EPAT[12]
Subject age	67	65.8	62.2
Cardiovascular disease	Yes	Yes	No
Treatment	Conjugated equine estrogen or combined therapy	Conjugated equine estrogen or combined therapy	17 β-estradiol (unopposed)
End point	Cardiac events (MI, CHD death)	Coronary angiography	Carotid intima-media thickness

In summary, the two trials above which used conjugated estrogens for secondary prevention of heart disease failed to show any benefit with HRT, but the study using estradiol, the "natural" hormone, for primary prevention did suggest slower progression of atherosclerosis with treatment. Finally, WELL-HART,[13] which was submitted by the authors of EPAT about 2 years later, looked at secondary prevention in women taking estradiol, with or without a progestin.

<u>The WELL-HART Group: Hormone Therapy and the Progression of Coronary-Artery Atherosclerosis in Postmenopausal Women</u>[13]

This double-blind, placebo-controlled trial looked at progression of CAD as measured by follow-up angiography in 226 postmenopausal women.[13] Subjects had pre-existing coronary disease, defined as at least one lesion with ≥ 30% stenosis on prior angiogram, and repeat angiography was performed about 3 years after the baseline study. Treatment was 17β-estradiol with or without medroxyprogesterone (which was co-administered sequentially rather than daily). The average age of these women was 63.5 years, and they were a mean of 18.2 years from menopause.

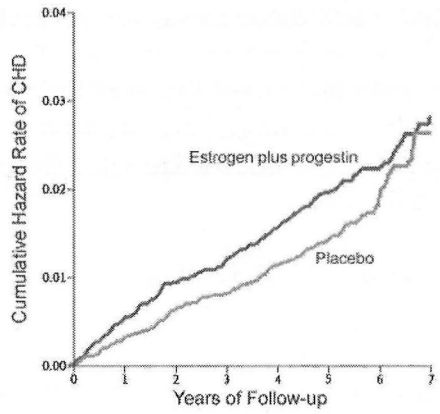
The primary endpoint of this study was the average change from base line in coronary stenosis as determined by angiography. This study found no difference in percent stenosis in women who took unopposed estrogen, estrogen with sequential progestin, or placebo. Of note, all of these women were given other treatments that were considered standard of care, such as lipid-lowering agents for persons with coronary artery disease; thus, estrogen showed no additional benefit over usual care for these women.

The authors compared and contrasted the opposing results of EPAT and WELL-HART: EPAT showed possible benefit with unopposed estradiol, while WELL-HART showed no difference with therapy. Since women in EPAT did not have a history of known CAD, the authors theorized that "the divergent outcomes of the two studies may be related to the timing of the intervention relative to the stage of atherosclerosis." Thus, women who initiate HRT soon after menopause may retain vascular responsiveness to estrogen; estrogen causes vasodilation in healthy coronary vessels, but not in those affected by atherosclerosis.

So is the timing of initiation of HRT the key issue involving benefit related to cardiovascular disease? The Women's Health Initiative addressed the question of primary prevention and began releasing initial results in July 2002, bringing controversies regarding menopausal hormone replacement therapy to national attention, for both physicians and their patients.

The Women's Health Initiative:Estrogen plus Progestin and the Risk of Coronary Heart Disease[2]

This pivotal study has changed the way physicians and patients think about prescribing or taking HRT after menopause. From 1993-1998, 161,809 women enrolled in this randomized, controlled, primary prevention study, which included, among others, 2 trials of postmenopausal hormone use. The estrogen + progestin arm was stopped early in July, 2002, due to evidence of increased risk for breast cancer in the treatment arm as compared to the placebo; there were also early adverse effects seen in the risk for cardiovascular disease.[2] The unopposed estrogen trial was halted on March 1, and preliminary results suggest that estrogen alone has no effect, beneficial or harmful, on CHD.[8] Further results from this arm of the trial are pending; results from the combination hormone therapy study (CHRT)[2] study are discussed below.



The primary outcomes for this trial were clinical, and included nonfatal MI and CHD death.[2] Invasive breast cancer was the primary adverse outcome. Expressed as hazard ratios, women treated with estrogen plus progestin were at higher risk of CHD events, HR 1.24 (CI 1.00-1.54). Expressing these results as absolute rates of CHD adds another perspective; there were 39 cases per 10,000 person-years for the treatment group, and 33 cases per 10,000 person-years in the placebo arm. As seen in HERS, the difference in CHD risk began to be noted during the first year of treatment, and there was a statistically significant trend toward less difference in relative risk over time.

Subjects included 16,608 menopausal women whose average age was 63.3 years, and 4.4% reported prior CHD or cerebral ischemia.[2] Baseline risk factors for heart disease were felt to be reflective of the general population, including 36% with HTN, 13% treated for elevated cholesterol, 4.4% with diabetes, and 10.5 % currently smoking. These women were treated with combined conjugated equine estrogen 0.625 mg, and medroxyprogesterone acetate, 2.5 mg (Prempro). There was a significant but similar dropout rate in each group: 42% of women in the treatment arm stopped taking the study drugs, and 38% in the placebo group discontinued. However, this was felt to compare favorably with the discontinuation rate of women taking HRT

in general. When data were analyzed on an as-treated basis, the hazard ratio was increased to 1.5 (95% CI 1.14-1.97), higher than that seen in the intention-to-treat analysis.

Subgroup analysis was also performed too see if there were risk factors which would identify women who were at increased risk for cardiovascular disease with use of hormone replacement therapy.[2] Characteristics such as lipid levels, inflammatory biomarkers such as CRP, demographics, and time since menopause were examined; of all the 36 comparisons made, only a higher baseline LDL was found to be associated with an increased hazard ratio for CHD with hormone therapy. Interestingly, a greater length of time since menopause (combined with hormone therapy) was associated with an increasing hazard ratio for CHD, but this association was not statistically significant. Nor were vasomotor symptoms predictive of CHD risk with hormone therapy, regardless of age. Other characteristics not found to be predictive were age, smoking status, HTN, DM, preexisting CHD, BMI, ASA use, and CRP levels. Thus, these variables would not be helpful in determining who should or should not use hormone replacement therapy.

The WHI investigators concluded that hormone therapy should not be offered to women for prophylaxis of heart disease. This study examined only the effect of a CEE regimen, not regimens using the human hormone, estradiol. Questions about type of estrogen replacement used, route of administration, and timing of HRT after menopause remain. Of note, given that the average age of these women was 63.3 years, many of them had been menopausal for several years at the onset of the study. The age of the women would also raise questions about whether or not the majority was truly free of cardiovascular disease, i.e. whether or not this was truly a primary prevention trial. These results may or may not be applicable to younger, healthy women at the onset of menopause. Although the WHI has greatly expanded the knowledge base from which we counsel our patients regarding HRT, many questions still remain.

If HRT causes increased risk of cardiovascular disease, is it due to increased levels of inflammatory markers such as CRP and IL-6?

The WHI also had an observational arm that looked at the effect of hormone replacement on CRP and IL-6.[14] They examined both whether HRT increased the levels of these markers, and whether such an increase would adversely affect cardiovascular risk in women taking menopausal hormone therapy. The observational study enrolled 93,724 women, over 75,000 of whom did not have known cardiovascular disease at baseline. Case subjects were women who developed a first MI during the course of the study, and they were matched with controls of similar age, smoking status, ethnicity, and follow-up time. On average, 36.5% were currently using HRT, with more users in the case group than in the controls. They found significantly higher baseline CRP and IL-6 levels in cases than in controls, and both of these markers were significantly associated with increased risk of CHD events (about a 2-fold increase). They found an association with HRT use and higher levels of CRP, but not with IL-6. Finally, they found that the baseline level of CRP or IL-6 was more important than whether or not HRT was used. Thus, women with similar baseline levels of either biomarker had similar odds ratios for CHD, regardless of whether or not they were taking HRT. The lack of impact of HRT on cardiovascular risk, as compared to the positive correlation with endogenous levels of CRP, led the authors to suggest that "diet, exercise, and smoking cessation are likely to remain the most important interventions for the primary prevention of vascular disease for some time to come."

Does route of estrogen replacement therapy make a difference?

Researchers at UT Southwestern found that transdermal estrogen therapy was not associated with the increase in CRP seen with oral ERT.[15] Twenty-one women were studied in a randomized, double-blind, crossover trial, in which they received each of 3 treatment regimens. The regimens included transdermal estrogen (a 0.1 mg Climara patch), oral conjugated equine estrogens (0.625 mg Premarin), or placebo, each for 8 weeks. They found the expected increase in CRP levels on oral estrogen, which was attributed to the first-pass effect on hepatic CRP production. However, when subjects were given the transdermal estrogen, there was no significant increase in CRP over baseline values. Although it is not known exactly how oral estrogen increases CRP levels (whether through a direct stimulatory effect on the liver or other indirect means), the increase in CRP was felt to be of potential clinical importance. CRP levels have been found to be an independent predictor of CHD in women even without a known history of heart disease, and researchers felt this might be partially responsible for the evidence of cardiovascular harm seen with oral HRT in previous studies.

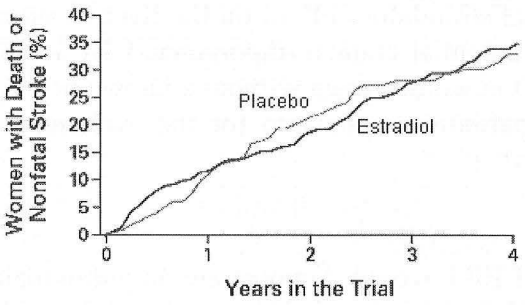
What about using lower doses of estrogen?

Wakatsuki, et al., theorized that lower doses of ERT would demonstrate an antioxidant effect with respect to LDL, an effect lost at higher doses due to an increase in triglyceride levels.[16] Since oxidation of LDL particles is an important step in atherosclerotic plaque development and instability, they looked at using lower doses of conjugated estrogens (0.3125 mg instead of the commonly used 0.625 mg) to avoid the possible increase in cardiovascular risk suggested with many of the previous studies. In a randomized trial, 51 women were treated with standard dose oral conjugated estrogens (0.625 mg), low-dose CEE (0.3125 mg), or no treatment. They found that while both doses lowered LDL cholesterol levels (reportedly due to stimulating hepatic synthesis of LDL receptors), only the higher estrogen dose raised triglyceride levels; an increase in TG was associated with reduced LDL particle size and increased LDL oxidation. Since the lower dose estrogen did not affect LDL particle size, they felt that "low-dose ERT can ameliorate the adverse effects of oral ERT on the size and oxidative susceptibility of LDL and could have a different effect on clinical outcome."[16] Obviously, more research would be needed to verify this hypothesis regarding different effects at different estrogen doses.

In summary, no beneficial effect of hormone replacement therapy on prevention of coronary heart disease has been demonstrated in the context of randomized, controlled trials, with the possible exception of EPAT. Several important questions have been raised regarding the significance of the use of CEE or estradiol, route of administration, dose utilized, and the timing of initiation of HRT with respect to the onset of menopause. The only potentially positive results with ERT involved the use of estradiol for primary prevention with a shorter duration of time after menopause, and this study looked at indirect outcome measures (carotid intima-media thickness), rather than clinical events. However, coronary heart disease is only one issue with regards to use of postmenopausal estrogen and vascular disease; the effect on stroke has also been evaluated.

HRT AND STROKE: WEST and the WHI

The Women's Estrogen for Stroke Trial was initiated in 1993 and recruited through 1998; it examined the effect of estradiol on risk for recurrent stroke.[17] This was a randomized, double-blind, placebo-controlled trial that enrolled 664 women, whose average age was 71 years, with a history of stroke or transient ischemic attack (TIA) within the previous 90 days. Subjects took either estradiol, 1mg daily, or placebo; progesterone was not given because it might interfere with potential vascular protection from the estradiol. These women were followed for 2.8 years, or until the occurrence of one of the trial endpoints (primary endpoints were death from any cause or nonfatal stroke, TIA or MI were secondary endpoints). Researchers found no beneficial effect with ERT on the primary or secondary endpoints, and women taking estradiol were more likely to have vaginal bleeding or to require a hysterectomy. Although the incidence of stroke was not significantly different, women taking estradiol were more likely to die from a stroke than those in the placebo group. Also, in similar fashion as HERS, there was an increase in stroke risk seen during the first 6 months of the trial which diminished over time. Thus, taking estradiol for the secondary prevention of stroke was not recommended.



WHI: Effect of Estrogen Plus Progestin on Stroke in Postmenopausal Women[3]

In the Women's Health Initiative, women who took combination estrogen plus progestin had a higher incidence of ischemic stroke than those who took placebo.[3] Also, in the recently halted estrogen-only arm of the trial, an increase in stroke risk similar to that with CHRT was found and was an important reason the trial was stopped. [8] Further details will be published soon. Of the 8506 women taking combination HRT, 151 (1.8%) experienced a stroke, and 80% of these were classified as ischemic (as opposed to hemorrhagic).[3] In the placebo group, 107 of 8102 women had a stroke, 75.7% of which were ischemic. The hazard ratio for ischemic stroke with treatment was found to be 1.44 (95% CI, 1.09-1.90). There were no differences between treatment groups for other types of strokes. Simplifying the numbers, researchers stated that for every 10,000 women who took estrogen plus progesterone for 1 year, 31 strokes could be expected, as compared to 24 strokes in women on placebo. This calculated to be a 31% increase in the risk of stroke due to combination HRT. This risk was apparent by the second year of the study, as opposed to being more pronounced during the first few months. They did not find any difference in stroke risk in women with less time from menopause or who were still having hot flashes. Of interest, prior use of oral contraceptives was not related to stroke risk. Finally, they did not identify a subgroup of women who could safely use HRT; there were no differences in characteristics such as age, presence of vasomotor symptoms, time since menopause, or inflammatory biomarkers between groups. Their conclusion, as above, was that HRT should not be administered for the prevention of cardiovascular disease.

HRT AND VENOUS THROMBOEMBOLISM

The increase in risk for venous thromboembolism (VTE) seen with postmenopausal estrogen replacement therapy is well-documented and widely accepted. The U.S. Preventive Services Task Force performed a systematic review and meta-analysis of 12 estrogen studies in an attempt to estimate the risk of VTE with postmenopausal estrogen therapy.[18] Three of these twelve studies were randomized, controlled trials, including HERS, PEPI, and ERA. This meta-analysis was published before the initial reports from the Women's Health Initiative. Pooled data from these studies indicated that women currently taking estrogen replacement therapy had a relative risk for VTE of 2.14 (95% CI, 1.64-2.81). This translates to an absolute rate increase of 1.5 events per 10,000 women per year. Results from other trials have shown a similar increase in the risk of venous thromboembolic events.

HRT AND BREAST CANCER

An association between use of menopausal hormone replacement therapy and breast cancer has long been suspected, and there have been numerous studies looking at this relationship. Most of these trials have been observational, including cohort and case-control studies; the WHI has added data from a randomized, controlled trial to our understanding of this important issue. Questions about the nature of the interaction between HRT and breast cancer are similar to those raised with heart disease: is it estrogen, progesterone, or both; how does length of therapy impact risk; does sequential vs. continuous therapy make a difference; and what types of breast cancers are most impacted by the use of menopausal hormones. Below is a discussion of four recent studies, including data from the Women's Health Initiative, regarding HRT and breast cancer risk.

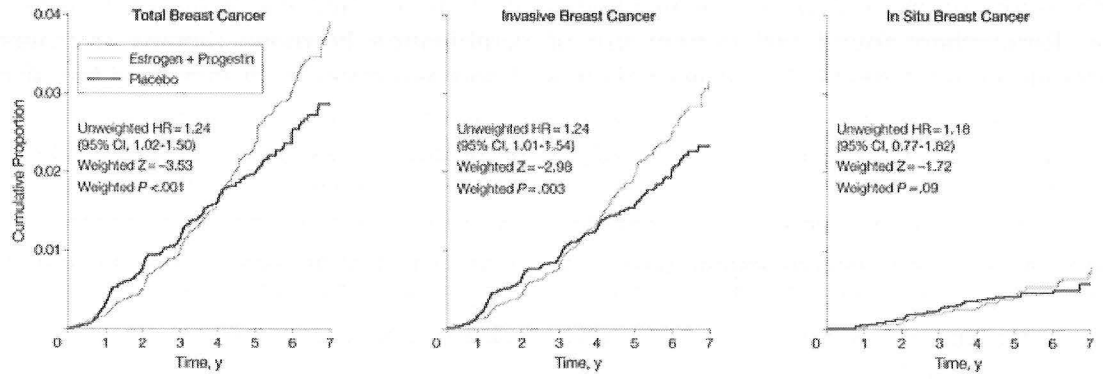
In the Breast Cancer Screening Program (BCSP),[19] a nested, case-control study of 705 women in the Seattle area, women newly diagnosed with a primary invasive breast cancer during the period between 1990-1995 were matched with controls of similar age. Outcome measures were the incidence and type of breast cancer as related to the duration and type of HRT use. Subjects were similar, but women with breast cancer more often had a family history of the disease. Researchers found that current use of combination hormone therapy (estrogen and progesterone in use 1 year before cancer diagnosis) was associated with increased breast cancer risk; past use (women who had discontinued) was not. Also, women who used HRT for most of the five-year period ending 1 year before diagnosis (defined as women with longer duration of HRT) had a higher risk of breast cancer as compared to non-users. This risk was regardless of type of HRT, estrogen alone or in combination with progesterone, and whether or not progesterone was administered sequentially or continuously. The increase in risk as compared to controls was more evident in lobular carcinoma than in ductal, although the absolute numbers of ductal carcinomas were significantly higher. The risk for lobular cancers was almost four times higher in current HRT users, and three times higher in women with longer duration of HRT ($\geq$ 57 months of use). The increase in risk for ductal carcinoma was about 50%.

Another observational study, published in JAMA concurrently with the breast cancer data from the Women's Health Initiative, examined long-term use of HRT in menopausal women,

and how this related to various histological types and receptor profiles of breast cancer.[20] As above, this was a case-control study; cases were 975 women age 65-79 who were diagnosed with invasive breast cancer over a 2-year period in 1997-1999. Differences among cases and controls included cases having a higher likelihood of a family history of breast cancer, higher levels of alcohol consumption (which increases endogenous estrogen levels),[21] and cases being more likely to be white. Interestingly, they found that women with exclusive use of estrogen-only therapy, even for as long as 25 years, had a breast cancer risk similar to that of women who never took HRT, regardless of tumor type.[21] Women who took combined HRT (CHRT) had increased risk of both invasive lobular and ductal carcinomas (ILC and IDC). As in the first study, the increase was more pronounced in the risk for ILC than for IDC, with odds ratios of 2.7 and 1.5 respectively. When examining results based on ER/PR status, ERT was not associated with increase in risk for any receptor profile, and CHRT was associated with greater risk for ER+/PR+ tumor only. The increase in risk patterns noted with CHRT was similar for both continuous and sequential therapy. The authors note that lobular carcinoma is more likely to be ER+ and PR+ than is ductal. The increase in breast cancer risk became greater with longer duration of use.

These results differ from those of the study first discussed in that in the latter, ERT as well as combined therapy was associated with an increase in breast cancer risk. However, in the JAMA study, women were placed in the CHRT group if they had ever used CHRT for even 6 months; thus, the criteria for the ERT group were more strict. It may be that the former study included a subgroup of women who had used CHRT for some length of time in their ERT group; this could have affected the level of risk that they documented.[20]

In the Women's Health Initiative, CHRT was associated with a 24 % increase in incidence of breast cancer;[4] preliminary results from the ERT trial show no increase in breast cancer risk during the time period of the study.[8] In the combined therapy study,[4] women were treated with CEE and medroxyprogesterone in continuous fashion, and there were over 8000 women in each study group (treatment and placebo). In the hormone group, there were 245 total cases of breast cancers diagnosed, and 185 in the placebo arm. Tumors in the treatment group were larger and at a more advanced stage at diagnosis, and there was increase in both receptor-



positive and receptor-negative tumors. Initially these breast cancers were diagnosed at a somewhat lower rate than those in the placebo group, but this rate increased with time. To the authors, this pattern combined with the more advanced stage at diagnosis suggested a delay in

diagnosis due to HRT, possibly due to differences in mammographic result interpretation. However, the overall diagnosis of breast cancer in the estrogen + progesterone group was relatively earlier than expected based on prior observational studies. The increase in risk began to be seen in the WHI after only the third to fourth years.

Another very important finding in this trial was an increase in the treatment group of abnormal mammographic findings requiring further work-up. This difference emerged after only the first year of therapy; 31.5% of the hormone group had abnormal mammography, as compared to 21.2% in the placebo group. This might be due to an increase in breast density with combined HRT, and an ancillary study in the WHI formally evaluating this possibility is ongoing. The implications of a significant increase in the need for follow-up breast imaging are enormous, both in terms of health care cost and the impact of such results on the patients themselves.

An editorial published in the same issue of JAMA as the previous two studies summarized the importance of the findings regarding breast cancer in the WHI:

> "The expanded report from the WHI trial is significant because it strongly suggests that breast cancers related to estrogen plus progestin use are not "good" ones, that they occur earlier than expected based on some previous studies, that there are no easily identified subgroups at higher risk, and that, to top it off, women using estrogen plus progestin experience a much higher rate of mammographic abnormalities leading to anxiety and further costly workups." [22]

Criticisms of this study included the age of the patients in the trial (average age 63.2), and the fact that over 25 % of the women had used hormones prior to the trial.

Finally, a study published in March 2003 in *Cancer*[23] also found that hormone regimens containing progesterone were associated with increased breast cancer risk, while estrogen-only regimens were not. This was an observational, prospective, cohort study, which followed over 29,000 Swedish women for about 10 years. The increase in risk appeared after ≥48 months. The authors felt that estrogen-only therapy demonstrated little risk for breast carcinoma, and recommended that women with an intact uterus who required a progestin use a more androgenic therapy, such as tibolone. This drug is not available in the United States, but will be briefly discussed later.

HRT AND COGNITION

The potential effects of hormone replacement therapy on cognition and possible development of Alzheimer disease have been widely reported. Findings vary from a beneficial effect on cognitive processes[24] to no effect at all,[25] and more recently, possible harm from menopausal hormone therapy.[5] Also, trials have shown no benefit for treatment of established dementia. The issues of duration of treatment and timing of initiation of hormone therapy related to onset of menopause continue to be important in interpreting study results. A few important studies published in the past three years include a large meta-analysis, the Cache County Study, the cognition arm of HERS, and the WHI.

Hormone Replacement Therapy and Cognition: Systematic Review and Meta-analysis[26]

Researchers reviewed 29 studies, including 9 randomized controlled trials and several cohort and case-control studies, to evaluate the effect of HRT on cognition and risk of dementia in menopausal women.[26] They broke down effects on cognition into several processes, such as memory, attention, motor speed, verbal function, and others; they found no consistent effects in any of these categories. They did state however, that the changes that were found were more likely to occur in women experiencing vasomotor symptoms as opposed to asymptomatic women. Perhaps women who experienced relief from hot flashes with treatment had improved sleep or well-being which affected their performance on test measures. Most of the studies they examined used unopposed estrogen. In looking at the risk for dementia, they examined 2 cohort studies and 10 case-control studies; there were no randomized trials at that time. Although these combined studies indicated a risk reduction for Alzheimer disease (AD) of 34%, overall many of these studies were found to have significant methodological flaws that limited their usefulness. These included the possibility of healthy user bias, self-reported data with proxy for dementia cases, different assessment tests that were used, and potential confounders.

Hormone Replacement Therapy and Incidence of Alzheimer Disease in Older Women; The Cache County Study[24]

This prospective, observational, cohort study found that prior use of HRT for at least 10 years reduced the risk of AD, but shorter-term use did not.[24] Researchers followed 1889 women over age 65 (a group of men was followed as well) for an average of 3 years from 1995-1997 through 1998-2000, and 88 women (4.7%) had a diagnosis of AD during this time. Of these women, 58 were taking placebo, and 26 were using HRT. Women had a higher risk of AD compared to men, with a hazard ratio of 2.11; this difference disappeared in women who had used HRT for more than 10 years. The HR for hormone users compared to nonusers was 0.41 (95% CI, 0.17-0.8). Another interesting finding in the Cache County study was that HRT may be effective during a specific window of time, but not within the short period prior to the onset of AD. The authors state that "potentially neuroprotective agents may be useful only in the latent pathogenetic stages of AD, before there is extensive damage to the integrity of the brain." Also, since no benefit from HRT was found with short-term use, the authors point out that the potential benefits may take years to develop. They specifically advocated caution in interpreting other trials with early results showing no benefit.

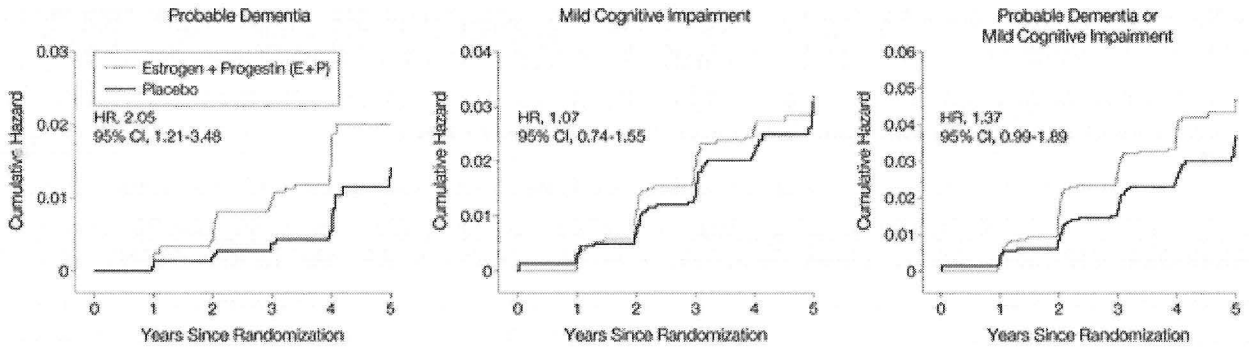
Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study[25]

A subgroup in HERS, 517 women in the hormone group and 546 in the placebo group (out of a total of 2763 women), underwent cognitive evaluation with six standardized tests at the end of the 4-year study.[25] Of note, these women had not undergone cognitive evaluation at baseline. They found no differences in cognitive function test scores between these groups, other than a small improvement in Verbal Fluency in the placebo group. At the time of testing, these women had an average age of 71 ± 6 years, and as define earlier, all participants had pre-existing coronary artery disease. These results may or may not apply to younger women or women without a previous history of vascular disease; researchers did feel that cognitive function among these subjects was comparable to other populations of elderly women. Also, this trial only tested combination HRT, so these results cannot be generalized to an estrogen-only regimen.

Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women; The Women's Health Initiative Memory Study: A Randomized Controlled Trial[5]

The Women's Health Initiative Memory Study (WHIMS) is an ancillary study in the WHI which has examined the effect of CHRT or estrogen-alone on dementia from all causes in women over age 65.[5] Secondary outcomes included mild cognitive impairment (MCI), and global cognitive functioning (as measured with the Modified Mini-Mental State Examination [3MSE]). Women completed the 3MSE at baseline and annually, and scores below a preset cutoff triggered a more extensive battery of cognitive testing (designated as phases 2 and 3 of the study protocol). After this neuropsychiatric testing, subjects were diagnosed as having no dementia, MCI, or probable dementia. For example, MCI patients scored below the 10th percentile in at least 1 area of testing and had evidence of some functional impairment (although not in a basic activity of daily living). Women in the treatment and placebo groups were similar except for a slightly lower history of stroke and slightly higher rate of statin use in the treatment arm as compared to the placebo arm.

Results of the CHRT trial demonstrated that the number of women diagnosed with dementia in the treatment group was twice that of the placebo group. Also, women in the estrogen-only trial showed a trend toward increased risk of probable dementia or mild cognitive impairment; details are forthcoming. Of 4532 women enrolled in the combined therapy arm of the WHIMS, 61 were diagnosed with probable dementia, 40 from the hormone group and 21 taking placebo. The difference in risk for dementia could be seen 1 year after the trial began, and was persistent during the 5 years of follow-up (HR, 2.05; 95% CI, 1.21-3.48). Expressed another way, 22 women per 10,000 were at risk of dementia on placebo, and 45 women per 10,000 in the combination therapy group. The most common cause of dementia in the study was Alzheimer disease. Researchers looked at several subgroups of women to see if there were risk factors that might cause a group of women to be at higher risk of dementia when taking HRT; these characteristics included age, educational level, prior stroke or diabetes, previous use of hormones, statins, or aspirin, and baseline 3MSE score. None of these factors was significantly different between treatment and placebo groups; thus, the authors could not identify women more likely to have adverse results in terms of dementia with HRT prior to treatment. No



difference was found in the risk for MCI in women given CHRT vs. placebo. MCI is a less precise diagnosis, with more potential etiologies, which may make it harder to establish a causal relationship with any one particular factor. Finally, a separate analysis found no beneficial

effects of CHRT on global cognitive function as compared with placebo.[27] Global cognitive function was measured with the 3MSE, which was administered to all participants annually. Since it is a screening test, it may be less sensitive to specific cognitive changes than is more detailed testing.

A possible explanation for the increase in dementia cases with CHRT is the increased risk of stroke seen in these women, including small events that might not be detected during the course of the trial.[5] The WHIMS did not specifically examine women during the perimenopausal period (recall that all patients in this substudy were over age 65), and thus cannot say whether HRT taken during this window of time might have a different effect on the risk of dementia. Finally, detailed results from the estrogen-only arm of the trial will be published soon, and they appear to be similar to the CHRT study. In a statement from the NIH, "Preliminary data suggest that for the WHIMS participants who were on estrogen alone when compared to the women who were taking the placebo, there was a trend toward increased risk of probable dementia and/or mild cognitive impairment." [8]

HRT: QUALITY OF LIFE AND DEPRESSIVE SYMPTOMS

About 20% of menopausal women will seek assistance from their physician for symptoms related to the climacteric (WHI). Vasomotor symptoms, sleep difficulty, mood swings, and even depression are all frequently reported by these women. The possible benefit of HRT for improvement in quality of life and depressive symptoms in menopausal women has been studied extensively, with a wide spectrum of results. Some studies have suggested a beneficial effect for treatment of depression, while others have shown no significant benefit and possible harm related to other effects of the medication.

Several of the large, randomized trials have examined the effects of HRT on depression and quality of life (QOL). The PEPI Trial (Postmenopausal Estrogen/Progestin Interventions), in a study published in 1998, did not find any significant effect of hormone replacement therapy on cognitive or affective symptoms.[28] This was despite a significant reduction in vasomotor symptoms in study patients. In HERS, effects of HRT on these measures were variable and depended on whether or not a woman was experiencing vasomotor symptoms.[29] Researchers assessed physical activity, energy/fatigue, mental health, and depression using standardized indices. Those who were having hot flashes had improvement in emotional health, and those without vasomotor symptoms had comparatively lower scores on physical measures. Women who had hot flashes had lower scores on all of the above indices throughout the trial, despite the improvement in mental health and depressive symptoms with HRT.

In the WHI, six quality-of-life-related variables were identified and measured in trial participants.[30] These included QOL and functional status (Rand 36-Item Health Survey), depression (Burnam scale), sleep disturbance (scale validated for use in the WHI), sexual functioning (a single item with a four-point response scale), cognitive functioning (3MSE), and a checklist of menopausal symptoms. The focus in the WHI was to identify clinically relevant effects, not just those that were statistically significant, i.e. to find a "minimal clinically meaningful difference" that could help guide therapeutic decision-making. In year one they found small, statistically significant effects of CHRT benefit for physical functioning, pain, and sleep disturbance. However, these differences were so small as to be deemed not of clinical

importance (i.e. 0.8 point improvement on a 100-point scale). By year 3 of the trial, no significant differences were found at all.

Interestingly, when results were limited to women who were age 50-59, and therefore closer to menopause, there were still no significant improvements in quality-of-life measures. Also, women who had reported moderate-to-severe hot flashes at baseline experienced relief of their vasomotor symptoms, and some improvement in sleep disturbance, but no other effects on health-related quality of life.

Overall, the WHI found no significant effects of CHRT on QOL or depression, although these results may not apply to women with the most severe vasomotor symptoms. These women may have declined to participate in a trial in which they could be randomized to a placebo. As in previous studies, researchers concluded that the risks of estrogen-progestin therapy outweighed the benefits.

So is there any good news for women taking hormone replacement therapy (or the physicians who have been recommending it)? Although the overall recommendations of the WHI have been that the risks of HRT outweigh the benefits, combination hormone therapy has been shown to decrease osteoporotic fractures, reduce the risk of developing colon cancer, and to be an effective treatment for vasomotor symptoms. These issues will be discussed below, as well as the impact the WHI findings have had on women's use of HRT.

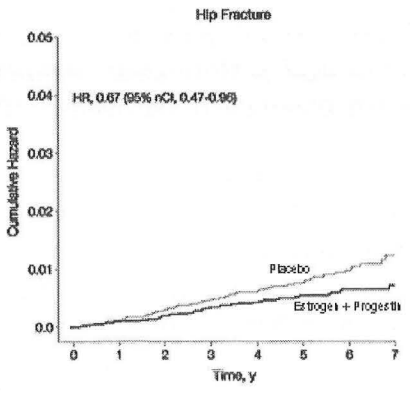
HRT AND OSTEOPOROSIS

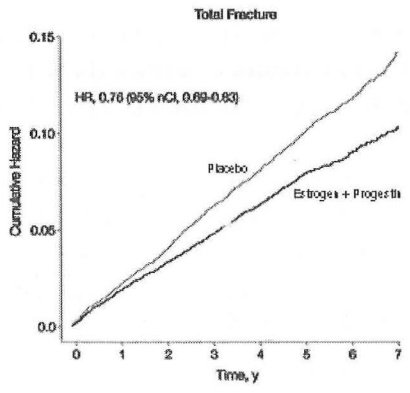
Estrogen has long been used clinically for prevention and even treatment of osteoporosis, although it was originally FDA-approved only for prevention due to lack of fracture data from randomized, controlled trials. The WHI has strengthened the data significantly regarding the ability of HRT to prevent fracture, but many issues remain, including concerns about the overall impact of HRT on women's health (not just bone health). Other recent studies have examined issues such as whether or not elderly women increase their bone density in response to estrogen therapy, and identifying the lowest dose of HRT that is effective for increasing BMD.

Villareal, et al., studied the effect of HRT on BMD in frail, elderly women.[31] Subjects were 67 women who were older than 75 who had at least 2 markers of physical frailty. Markers included low peak aerobic power, need for assistance with 2 instrumental activities of daily living (ADL) or 1 basic ADL, and reduced scores on a test of physical performance. Women were treated for 9 months with cyclic, combined HRT (0.625 mg conjugated estrogens with medroxyprogesterone acetate (MPA), 5 mg for 13 days every third month), unopposed estrogens (women without a uterus), or placebo. All women were given supplemental vitamin D and calcium. BMD and markers of bone turnover, such as serum bone-specific alkaline phosphatase and urinary cross-linked N-telopeptide, were measured and followed. At baseline, 91% of women in the placebo group and 93% in the HRT group had bone loss consistent with osteopenia or osteoporosis at the femoral neck. They found that the treatment group had significantly larger increases in BMD in the lumbar spine (4.3% vs. 0.4%) and total hip (1.7% vs. –0.1%) than did the placebo group, and significant decreases in bone turnover markers. The trial did not have enough subjects or long enough duration to find any decrease in fracture rate. Also, as the authors pointed out, fractures in elderly women are usually multifactorial, related to cognitive status, medication use, other physical ailments, and environmental factors; thus BMD is not the only determining factor.

Regarding the dose of estrogen necessary to prevent osteoporosis, two recent studies, published in JAMA in 2002 and 2003, indicated that doses lower than those historically used can increase BMD and reduce bone turnover. The first study, by Lindsay et al., used conjugated equine estrogens at doses of 0.625 mg, 0.45 mg, and 0.3 mg (with MPA for women with a uterus).[32] This study was part of the Women's HOPE trial (Health, Osteoporosis, Progestin, Estrogen), which also looked at the effects of low-dose CEE/MPA regimens on vasomotor symptoms, lipids, and endometrial thickness. Subjects in this randomized, double-blind, placebo-controlled trial were 822 healthy menopausal women who were within 4 years of their last menstrual period. All women were given supplemental calcium. At all the hormone doses given, women in the treatment group experienced a significant increase in BMD. This increase was dose-related at the spine, but not at the hip, which has a slower bone turnover rate. MPA added additional improvement only when used with the 0.625 mg dose of CEE, and only at the spine. As noted above, these women were relatively young so the fracture rate was too low to measure; thus, this trial looked at BMD rather than fracture outcomes. Another study by Prestwood, et al., published in August 2003 in JAMA,[33] examined the effect of ultralow-dose 17β-estradiol (0.25mg/day) on BMD and bone turnover in women who were over age 65. They found that women in the treatment group had significantly increased BMD at all sites compared with placebo; this increase was similar in women with a uterus who had also received cyclic progesterone. The authors stated, however, that the increase in bone density was smaller than has been reported with other agents, such as bisphosphonates (femoral neck, 2%, total femur 4%, and lumbar spine, 3%), and again, the study was not powered to look for differences in fractures. With this low dose of estrogen, no difference in adverse effects (including breast tenderness, fluid retention, bloating, headache, number of abnormal mammogram results, or endometrial hyperplasia) was found.

The WHI was the first randomized, controlled trial to demonstrate that HRT reduces fracture in menopausal women.[6] In the combined HRT arm, 16, 608 women received either Prempro or placebo, as noted previously. In this group, 733 women (8.6%) in the HRT group, and 896 (11.1%) in the placebo group had fractures during a total of 5.6 years of follow-up. Expressed differently, for 10,000 women taking HRT per year, 152 experienced a fracture, as compared to 199 in the placebo group. Hip fracture, specifically, was reduced by 33% (HR 0.67, 95% CI 0.47-0.96) overall, but by 60% in women who consumed at least 1200mg /day of calcium. The beneficial effects of HRT on fracture were similar in women with different fracture risk profiles, including age, smoking status, presence of a family history of fracture, or personal history of fracture. The ERT study also found a decreased risk of hip fracture, with specifics to be published soon. In addition, the WHI analysis created a "global index" to examine the overall risk-benefit ratio in terms of CHD, breast cancer, stroke, pulmonary embolism,

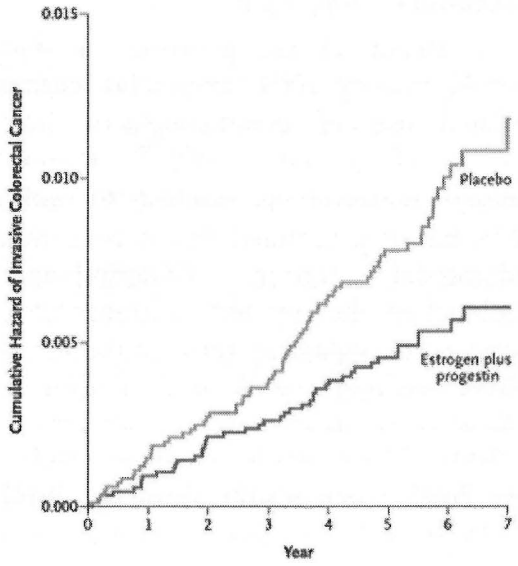




endometrial cancer, colon cancer, hip fracture, or death from other causes. This index did not show any overall benefit with HRT, even in the women who were at the greatest risk of fracture. The WHI authors stated that estrogen plus progestin treatment should not be recommended to women without vasomotor symptoms for osteoporosis prevention, since there are other effective alternatives available, and women should be informed of the potential adverse effects on health before starting the medication.

HRT AND COLON CANCER

The Women's Health Initiative was also the first randomized trial to document a decreased incidence of colon cancer in women who took CHRT.[7] In HERS, the decrease in colon cancer risk was non-significant. In the combined HRT arm of the WHI, there were 43 invasive colorectal cancers in the treatment group, and 72 in the placebo group (out of a total of 16,608 women), with a hazard ratio of 0.56, 95% CI 0.38-0.81. This risk reduction, however, occurred primarily in small, local cancers; the percentage of cancers with positive nodes or metastases was actually higher in the hormone group. Nine women died of colon cancer in the treatment group, and eight in the control group. More women in the placebo group had first-degree relatives with colon cancer, but re-analyzing the data after adjusting for this did not increase the hazard ratio for the hormone group. The authors note that possible mechanisms for a decrease in risk for colon cancer with HRT include effects of estrogen on bile acids, estrogen receptors on intestinal epithelium, or a reduction in fasting glucose and insulin levels (high levels may also increase risk for colon cancer). In summary, women taking Prempro had a decreased risk of colon cancer, but the tumors that were diagnosed were found at a later stage with more advanced disease.



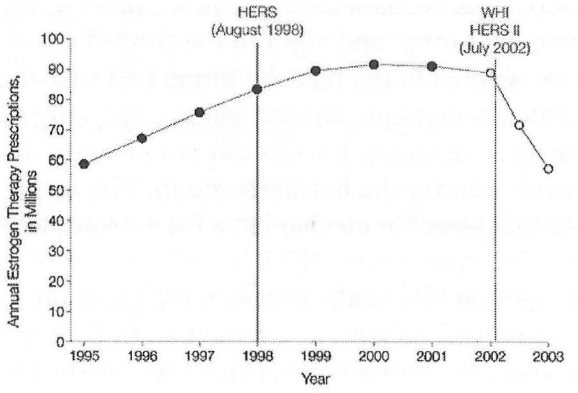
SO WHAT HAPPENED AFTER THE WHI?

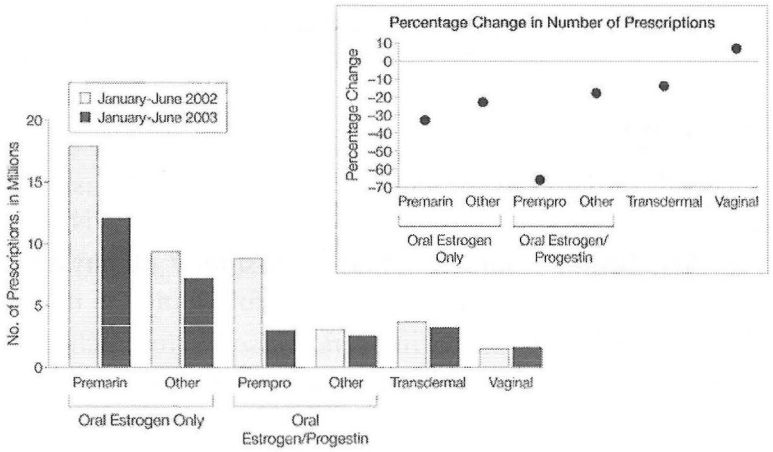
The results from the Women's Health Initiative were widely published and discussed in the media, and as many as 93% of women heard about the findings, either through television or print sources, their physicians, or even their health insurance plans.[34] A survey of physician attitudes to the prescribing of HRT reflected several changes in the months following the release of the WHI information in July 2002.[1] The study, published in *Menopause* by researchers in Chile, found that over 97% of gynecologists were aware of the findings of the WHI, and 65% changed their approach to prescribing for patients. Different modifications made by these physicians included a more stringent risk/benefit assessment for individual women, lower hormone dosage prescribed, decrease in prescription of combined HRT, shortened duration of

therapy, and use of alternative prescriptions including transdermal estrogen or non-hormonal agents.

Women also took matters into their own hands. A Kaiser Permanente study in California found that a majority of women, 56%, attempted to stop taking HRT in the months after the preliminary WHI results, despite not having a reliable understanding of the trial itself.[34] In a survey designed to assess women's knowledge of the study, researchers found that 64% did not know what the findings of the WHI were, 13% were unsure or had misconceptions about the study, and about 23% had correct information. Only 30% of those surveyed could correctly answer at least 4 out of 5 true/false questions about the trial. Women who were better informed were more likely to try to stop HRT, however about ¼ of women with correct information about trial results elected to continue hormone therapy regardless of the new study information. This implies that there is a subgroup of women for whom the benefits of treatment outweigh the risks, presumably with regard to treatment of vasomotor symptoms or other quality of life issues. This group may be underrepresented in trials of hormone therapy due to reluctance to give up their medications. Women who started HRT for preventive health reasons were more likely to be successful in stopping it.

Hersh, et al., published a study in JAMA, January 2004, examining changes in national use of postmenopausal hormone therapy since July 2002.[35] Historically, estrogen prescriptions reached 30 million in 1975, but then declined due to concern about endometrial cancer. Prescriptions for combination therapy with estrogen/progestin increased in popularity through the 1980s and 1990s, reaching a peak of 91 million (up to 42% of menopausal women from ages 50-74) in 2001. These levels remained stable until July 2002, when results from the WHI and HERS II were published, initiating a significant decline in hormone therapy prescriptions.





Between July 2002 and July 2003, overall hormone prescriptions fell by 38%, with a 74% decline for Prempro alone. The authors note that the mass media was very effective in disseminating the idea that HRT may be harmful, and that physicians more quickly change practice habits when there is evidence that a therapy causes harm.

TREATMENT OF VASOMOTOR SYMPTOMS

LIFESTYLE MODIFICATION

Studies have shown potentially modifiable risk factors for menopausal symptoms including smoking and higher body mass index (BMI). Women with a higher BMI reported more hot flashes in a cross-sectional survey of menopausal women.[36] This could be due to earlier ovarian insufficiency in obese women, or due to a physical insulation effect of body fat on core body temperature, predisposing menopausal women to hot flashes. Smokers also reported more frequent and more severe vasomotor symptoms, possibly due to lower estrogen levels. It is not known if weight loss or smoking cessation prospectively improves menopausal symptoms, but there are certainly other health benefits to be obtained with these measures.[37]

Other potentially helpful measures often recommended (although not well studied) include lowering ambient air temperatures, exercise, and relaxation techniques.[37] Women may be able to lower their core body temperature, and decrease risk for hot flashes, by using a fan, dressing in layers, and consuming cold beverages. Some women routinely avoid spicy foods or alcoholic drinks. Exercise may actually trigger hot flashes by raising core body temperature, however women who are more physically fit report less hot flashes than sedentary women. Finally, relaxation techniques such as paced respiration (slow, controlled diaphragmatic breathing) may have efficacy in treating hot flashes. Paced respirations are initiated at the start of a hot flash, and have been helpful in some studies. Behavioral relaxation techniques may also have benefit.

ESTROGEN, PROGESTERONE, AND COMBINATION HRT

Both estrogen replacement and combination therapy are known to be effective for treatment of vasomotor symptoms. This was documented in the PEPI trial, among others, which looked at treatment with estrogen with or without a progestin on various outcomes, including hot flashes and other menopausal symptoms.[38] This was a 3-year, randomized, controlled trial which assigned 875 menopausal women to placebo, ERT, or HRT with 1 of 3 different progesterone regimens (cyclical MPA, daily MPA, or cyclical micronized progesterone). The average age of study participants was 56.1, and the most common symptoms they experienced at baseline were vasomotor, musculoskeletal, weight gain, and cognitive-affective problems. Results showed that women in any of the treatment groups had significantly lower vasomotor symptoms (odds ratio range 0.17-0.28 at year one). The difference between the HRT groups and placebo diminished with time, although HRT was still effective, with OR 0.26-0.53. There were no significant differences in cognitive-affective or musculoskeletal symptoms with HRT, and women assigned to one of the progesterone groups were more likely to have mastalgia (breast discomfort).

A Cochrane review of 21 randomized, double-blind trials comparing the effect of oral HRT to placebo found a 77% reduction in hot flash frequency with treatment; residual symptoms were less severe.[39] They also found a 50.8% improvement in symptoms with placebo. Withdrawal from therapy due to adverse effects such as mastalgia, edema, or psychological symptoms was not different in either group.

Many different regimens, preparations, routes of administration, and doses of HRT have been found to be effective for relief of vasomotor symptoms. All oral and transdermal

preparations of estrogen are FDA approved for hot flashes, and one vaginal ring is approved (delivering 0.05 or 0.1 mg/day of estradiol acetate over a 3 month span).[37] Oral CEE and estradiol (orally and transdermally) are all comparable for treatment of menopausal symptoms. Regimens with a constant estrogen and intermittent progestin therapy (1 mg micronized 17β-estradiol daily plus 90 μg norgestimate in a 3 days on, 3 days off) are effective;[40] patches with doses as low as 0.025 mg daily also relieve vasomotor symptoms.[41] Of course, all women with an intact uterus require a progestogen to prevent endometrial hyperplasia.

Progesterone. Several progestogens have been effective for treatment of menopausal symptoms. The term "progesterone" refers to the human hormone, and "progestin" to the synthetic preparations. Oral administration of "natural" human progesterone (identical to that which is produced by the ovaries and the placenta) results in metabolism by the gut and liver, leading to irregular effects and serum levels. Synthetic progesterones are typically used in oral HRT products to avoid this problem.[42] The most common side effect with systemic progestogens is uterine bleeding, and it has not been established whether or not these agents are safe in women with a history of breast cancer. The recent WHI data would suggest that progesterone plays an important role in breast cancer risk.

Progesterone creams have become popular remedies for vasomotor symptoms, and they are available over-the-counter; the FDA treats them as dietary supplements rather than drugs.[37] Studies of transdermal creams have not shown consistent results in terms of symptom relief. Leonetti et al found that vasomotor symptoms were significantly improved in women using a progesterone cream in a base of mixed tocopherol, although there were no effects on lipid profiles, women's moods, or bone density.[43] Wren et al gave subjects 32 mg of progesterone daily in a cream, Pro-Feme, and followed 72 women for 12 weeks.[42] No differences were found in lipid levels, bone turnover markers, or QOL measures such as vasomotor symptoms, mood, or sexual symptoms. They noted that serum levels of progesterone rose from 0.11 ng/mL to 0.31 ng/mL after the 12 weeks; this level is significantly below that which would cause endometrial changes (typical post-ovulation progesterone levels are between 4.7 and 15.7 ng/mL). It is not known if progesterone creams have any effect on hormone-receptor positive tumors. Finally, wild yam cream is also marketed as a "natural progesterone"; it contains a progesterone precursor, diosgenin, in amounts which vary widely from product to product. Humans cannot convert diosgenin to the active progesterone, and there is no evidence that wild yam cream is effective for hot flashes.[44]

Medroxyprogesterone acetate has been shown to be effective with both oral and intramuscular administration.[37] Studies have shown that IM doses of 50, 100, and 150mg monthly reduce hot flashes dramatically compared to placebo (75%, 90%, and 100% respectively). When compared directly with CEE, there was no difference in treatment efficacy. Oral MPA at a dose of 20mg/day also significantly reduces hot flashes compared to placebo.

Finally, megestrol acetate used at relatively low doses, 20 mg twice daily (160-800mg daily doses are used for increasing appetite) was shown to reduce hot flashes by 85% in women with a history of breast cancer.[37] As with depot MPA, effects may take 3-4 weeks to be fully realized. In addition to uterine bleeding, increased appetite and possible worsening of diabetic control are potential side effects.

Other hormonal agents. Oral contraceptives are often used for hot flashes in women who are younger and may still need contraception.[37] Low dose preparations can be used; Loestrin 1/20 (0.02 mg ethinyl estradiol and 1 mg norethindrone acetate) has been studied, as have low-dose triphasic OCPs. Also, many women who do not obtain adequate symptomatic relief with estrogen use a combination esterified estrogen/methyltestosterone preparation (0.625 or .125 mg estrogen with 1.25 or 2.5 mg androgen), although it has not been well studied for efficacy. Concerns about androgen side effects, including worsening lipid profile, atherosclerosis, or masculinization, have also been raised, although observable effects such as acne or hirsutism are rarely seen with available hormone doses.

Tibolone (brand name Livial) is a synthetic steroid which has been used in Europe for many years for relief of vasomotor symptoms, as well as osteoporosis prevention.[45] It has estrogenic, progestagenic, and androgenic properties. Its activities are entirely mediated by its metabolites on its target tissues. Tibolone is effective in reducing hot flashes compared to placebo, and is comparable in efficacy to HRT. It also increases BMD, primarily in the lumbar spine, and decreases markers of bone turnover. There is no fracture data. Endometrial effects include an increase in vaginal bleeding, although its activity is progestagenic rather than estrogenic in this tissue. Bleeding is increased compared to placebo, but only about half that seen with HRT. In breast tissue, it slows the proliferation rate and increases differentiation and apoptosis, and did not increase mammographic breast density, but there is no direct data on breast cancer risk. In summary, it reduces hot flashes and has beneficial effects on lumbar BMD, but many of its other systemic effects are not yet well-documented.

NONHORMONAL PRESCRIPTION TREATMENTS

Antidepressants

Several selective serotonin-reuptake inhibitors (SSRIs) have been studied for treatment of vasomotor symptoms. Interactions between estrogens and neurotransmitter systems such as dopamine, norepinephrine, or serotonin have been documented.[46] Also, women with more severe menopausal symptoms have been shown to have lower serum serotonin levels compared to women with milder symptoms (36.2 ng/mL vs. 97.7 ng/mL).[47] The effectiveness of SSRIs may be due to changes in central serotonin or norepinephrine concentrations. Depression treatment may also be a factor in their effectiveness, however these medications were equally effective for women who were not depressed at baseline, and the reduction in hot flashes typically occurred after only 1 week, sooner than is required for an antidepressant effect. Some of the trials excluded women with depression in order to avoid this potentially confounding variable. SSRIs are contraindicated for use with MAO inhibitors.

Venlafaxine. In a randomized, placebo-controlled trial published in *The Lancet* in 2000, venlafaxine reduced hot flash scores by 37-61% at doses of 37.5 mg and 75/150 mg respectively (no difference in the two higher doses).[48] The placebo group had a reduction of 27%, typical for a placebo effect on hot flashes. Doses above 75 mg were no more effective and were associated with more side effects, including mouth dryness, decreased appetite, nausea, and constipation. No effects were seen on blood pressure at the doses used. The authors recommended a starting dose of 37.5 mg, and if further treatment is needed, increasing after a week to 75 mg.

Paroxetine. The SSRI paroxetine (Paxil) has also been found to be effective in treating vasomotor symptoms. A randomized, controlled trial published in JAMA, January 2003, evaluated 165 menopausal women who were experiencing at least 2-3 hot flashes on daily basis.[49] Women were treated with Paxil CR, 12.5 mg or 25 mg for 6 weeks; at the end of the trial both groups and significant reductions in the hot flash composite score, 62-64% (no difference between dosages). This compared to a 37.8% reduction with placebo. The most common side effects with paroxetine were headache, nausea, and insomnia, and the lower dose was better tolerated. The authors suggested starting with the 12.5 mg dose given the similar efficacy of the two treatments.

Fluoxetine. Efficacy for vasomotor symptoms has also been demonstrated with fluoxetine, although to a lesser degree than with paroxetine or venlafaxine.[50] Women who either had a history of breast cancer or were at high risk took 20mg daily for 4 weeks in this randomized, cross-over trial. Hot flash scores decreased by 50% in the treatment group and by 36% in the placebo group.

Gabapentin

Gabapentin is a γ-aminobutyric acid analogue which has been used for seizures since 1994, but is also used for many other conditions, including neuropathic pain and chronic pain syndromes. In a randomized, controlled trial, menopausal women were treated with 12 weeks of gabapentin, 300 mg three times a day, or placebo.[51] Dosage was titrated upward slowly, beginning with 300mg nightly, then 300mg twice daily, and then 300mg three times a day. Researchers found a 54% decrease in the mean hot flash score in the treatment group compared to 31% in the placebo, with the difference emerging after the first week of treatment. An open-label extension of the study allowed women to up-titrate their gabapentin dose to a maximum of 2700mg (increasing by 300mg every 4 days) on an as-needed basis. Women taking higher doses had greater reductions in hot flash scores, around 61-67%. Adverse effects with gabapentin included somnolence in 20%, dizziness in 13%, rash, and peripheral edema. In order to minimize these problems, the authors recommended a slow dosage titration and taking the medication with meals. They speculated that the mechanism of action of gabapentin involved modulation of calcium currents, possibly with effects on tachykinin activity in the hypothalamus.

Clonidine

Clonidine has been used for treatment of hot flashes for many years, both orally and in patch form. There have been several trials showing efficacy in women with and without breast cancer. Overall, however, the magnitude of the effect on vasomotor symptom relief is less than that seen with the SSRIs, and the side effects are more bothersome. In one of the more recent clonidine studies involving 194 breast cancer patients who were taking tamoxifen, women were treated with oral clonidine, 0.1 mg/d, or placebo for 8 weeks.[52] Women in the treatment group experienced a 38% decline in hot flash symptoms, compared to 24% in the placebo group. The main side effect at this low dose was sleep difficulty. Studies using higher doses (i.e. 0.4 mg/d) have shown greater efficacy but also demonstrate greater adverse effects and a higher dropout rate. These unwanted effects included nausea, fatigue, headaches, dizziness, and dry mouth. Contraindications to clonidine administration include cardiac sinus node dysfunction, and the drug lowers blood pressure and heart rate.

Methyldopa

This antihypertensive medication has been shown to be effective in decreasing menopausal symptoms at doses of 500 to 1,000 mg daily.[37] However, its effect is not as robust as that achieved with newer, safer medications (such as SSRIs), and its use is fraught with adverse effects. Liver disorders, hemolytic anemia, sedation, and edema can all occur, and it is rarely used.

Bellergal

This is a combination of a low dose of phenobarbital, ergotamine, and belladonna alkaloids. Its efficacy in hot flash treatment is variable in different studies, with some reporting no significant effects.[37] It should not be used in patients with cardiovascular or liver disease, and adverse effects include somnolence, dizziness, dry mouth and even flushing. It has several drug interactions, including anticoagulants and oral contraceptives. Also, phenobarbital has the potential for dependency. It is not recommended for long-term use.

NON-PRESCRIPTION TREATMENTS

Black Cohosh

The substances collectively termed "black cohosh" are derived from the rhizomes of *Cimicifuga racemosa*, and were used originally by Native Americans and in traditional Chinese medicine for menstrual and other conditions.[53] It is approved by the German government for treatment of menopausal symptoms. The active ingredients appear to be triterpene glycosides, which include actein, 27-deoxyactein, and cimifugoside.[37] Different products have different formulations and dosages; Remifemin (made by GlaxoSmithKline) is the best-studied. There have been several RCTs, most of which used Remifemin, and conflicting reports have emerged. A study with breast cancer patients, most of whom were on tamoxifen, found improvement with black cohosh on hot flashes, but it was not different from placebo.[53] Other studies have found that Remifemin was more effective than CEE or placebo for symptom relief. There have been no serious adverse events with black cohosh, but it is thought to be mildly estrogenic, and thus may not be safe for use in patients with breast or endometrial cancer. Also, black cohosh may contain a small amount of salicylic acid, which could account for some of its pain-relieving effects but may cause adverse reactions in persons sensitive to salicylates.

Isoflavones

Isoflavones, sometimes referred to as phytoestrogens, are diphenolic compounds commonly derived from soy or red clover.[37] They bind to estrogen receptors, $\beta > \alpha$, and they act as partial agonists in some tissues and have antagonist properties in others. Some of the individual isoflavones include genistein, daidzein, formononetin, and others. As many as 30-50% of women convert daidzein to equol, a nonsteroidal estrogen with estrogenic effects.[37] It was previously hypothesized that "equol producers" might have a more pronounced response to treatment with isoflavones, but a recent RCT found no difference in treatment effect for women with high or low equol levels.[54]

A randomized trial of soy-derived isoflavones in menopausal women found a relatively mild effect of treatment on hot flash symptoms.[55] In the 12-week trial, women taking soy had a

45% reduction in daily vasomotor symptoms, as compared to a 30% reduction with placebo. Gastrointestinal symptoms, including constipation, were the most common side effects, and a significant number of women dropped out of the trial. Another study examined the effects of tablets containing 114mg of isoflavones vs. placebo in a crossover trial of 62 women with a history of breast cancer.[54] Each treatment was for 3 months, with a 2-month washout period between. This dose, which significantly elevated serum levels of the isoflavones in the tablet, did not relieve hot flashes or other menopausal symptoms. The treatment was well-tolerated, but data regarding estrogenic effects are reported to be inconclusive.

Finally, the ICE (Isoflavone Clover Extract) Study investigated the effects of Promensil and Rimostil, both isoflavones compounds derived from red clover, on hot flashes and menopausal QOL.[56] This randomized, placebo-controlled, double-blinded trial studied 252 postmenopausal women for 12 weeks. Study tablets were independently verified by an outside lab for contents. They found that the reduction in hot flash counts were similar in all three groups, including both treatments and placebo (ranging from a 34-41% reduction). At the end of the 12-week trial, women in all 3 groups were still experiencing at least 5 hot flashes per day. Thus, the authors found no significant benefit with treatment; there were also minimal adverse effects. The long-term effects of red clover isoflavones are not known.

Vitamin E

A randomized, crossover trial of vitamin E given as 400 IU twice daily showed minimal benefit for hot flash symptoms with treatment.[57] Patients were menopausal women with a history of breast cancer, and they were treated for 4 weeks each with placebo and vitamin E in blinded fashion. Although the difference in treatment and placebo did reach statistical significance, it translated in to one less hot flash per day. No toxicities were seen with vitamin E, including no bleeding risk, however researchers were unimpressed with the magnitude of benefit seen in the trial.

Other therapies

Other herbal preparations, including dong quai and evening primrose oil, have been at times recommended for the treatment of menopausal vasomotor symptoms. However, neither has been found to have any benefit over placebo in randomized trials.[37] Women using warfarin should not take dong quai, and evening primrose oil may cause nausea or diarrhea. Finally, ginseng has also been found to have no benefit over placebo in a RCT, and it has several drug interactions, including anticoagulants and MAO inhibitors. Its estrogenicity is not known.

TREATMENTS FOR UROGENITAL SYMPTOMS

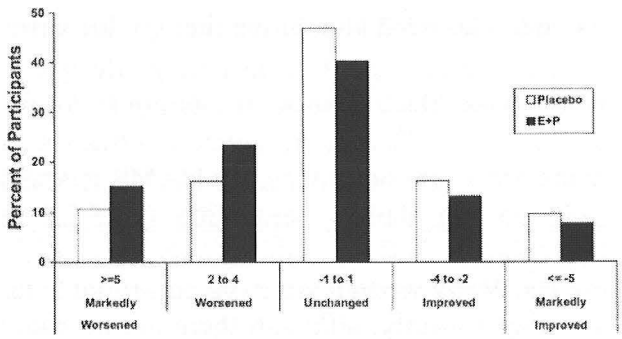
Urogenital complaints, including those typically related to atrophy (dryness, itching, dyspareunia), incontinence, and frequent urinary tract infections (UTIs), are commonly reported by menopausal women. Discomfort related to vaginal atrophy is reported in 45% of women in some studies, making this a frequently seen complaint in many physicians' offices.[58] Urinary incontinence occurs in 15-50% of postmenopausal women,[59] and UTI is a problem for 9% of women over age 50 (the peak incidence is actually in younger, sexually active women).[60] Hormone replacement therapy has been postulated to be an effective therapy for all of these conditions.

Vaginal atrophy

Although oral estrogens can alleviate symptoms of vaginal atrophy, many women find topical, locally applied preparations to be particularly helpful. This is especially true for women who wish to avoid systemic estrogens for various reasons. Estrogen receptors have been identified in squamous epithelium in the urethra, vagina, and the trigone of the bladder, although not in urothelial (transitional cell) tissue.[61] A review article found that all vaginal treatments tested were effective in reducing symptoms of dryness, itching, and dyspareunia.[58] They examined the effects of the estradiol ring, CEE cream, estriol cream, estradiol vaginal tablets, and estriol pessaries; all were similarly effective for atrophy as well as dyspareunia. For itching, however, the estradiol ring was more effective than the cream, and many women preferred a ring to the perceived messiness and inconvenience of a cream. Some of the specific regimens found to be effective included Estring (2mg estradiol ring placed intravaginally for 12 weeks), CEE cream (1 gram every night for 3 weeks, followed by a treatment free week OR 1gram three times in the first week, twice in the second week, and once weekly for 6 weeks), estriol cream (0.5 mg/day for 2 weeks, then thrice weekly), and Vagifem tablets (25 μg estradiol tablets used once daily for 2 weeks, then twice weekly).

Incontinence

Stress and urge incontinence have also been theorized to be related to estrogen deficiency. If the bladder pressure exceeds urethral pressure, stress incontinence can occur.[62] Urethral tissues tend to thin and atrophy without estrogen, which may cause improper closure. Bladder contractions during the filling phase can cause urinary urge incontinence. HERS examined a subgroup of women, 1525 out of 2763, who reported at least one weekly episode of incontinence at baseline.[59] They then asked women to quantify symptoms such as nocturia, daytime urinary frequency, stress incontinent episodes, and urge incontinent episodes. They actually found that incontinence symptoms worsened in women assigned to HRT as compared to placebo, and thus did not recommend systemic estrogen for incontinence symptoms.



A review article in *Urology* found that oral estrogen was not an effective treatment for stress incontinence, but theorized it might work well in combination with an α-agonist.[61] Data are conflicting for urge incontinence; Vagifem tablets may help with urgency, as may Estring. Improvement in symptoms may be due to a positive effect on vaginal atrophy however.

Recurrent UTI

Several factors are thought to contribute to increased susceptibility to UTI in menopausal women. The vaginal pH rises after menopause, leading to a decrease in the normal lactobacillus colonization and a rise in uropathogens such as *Escherichia coli.*[60] The HERS investigators also looked at incidence of UTI in study participants (who were on oral CHRT).[60] They found no

benefit with oral therapy on the incidence of UTI. UTI risk factors they identified included diabetes, urge incontinence, and vaginal dryness and itching. Vaginal estrogen therapy, on the other hand, has been shown to prevent UTI in menopausal women with recurrent infections, including Estring[63] and estriol cream.[60]

Endometrial safety

There are no long-term data on endometrial hyperplasia with vaginal estrogen preparations. Some studies did routine endometrial biopsies in all subjects, while others only did them if clinically indicated, i.e. abnormal bleeding. The longest trials were for up to a year, and the risk of hyperplasia was found to be very low.[58] There is some evidence of systemic absorption; the estradiol ring can affect serum hormone levels, lipids, and BMD. Researchers recommended discussing this with patients when initiating long-term therapy.[58]

CONCLUSION

Many women will be asking their physicians for advice regarding menopausal hormone replacement therapy. Some will want assistance treating bothersome vasomotor symptoms, and others may want to discontinue HRT due to concerns about adverse effects. The FDA recommends that estrogen and/or progestins be limited to use for treatment of moderate to severe vasomotor symptoms, moderate to severe symptoms of vulvar and vaginal atrophy (with consideration given to topical products), and prevention of postmenopausal osteoporosis (advising women that non-hormonal medications should also be considered). In addition, HRT should be prescribed at the lowest effective doses for the shortest duration of time possible. For women who need alternative therapy for vasomotor symptoms, the North American Menopause Society[37] recommends considering lifestyle changes with or without herbal remedies such as isoflavones, black cohosh, or vitamin E, for mild symptoms due to their safety. HRT may still be necessary to relieve more severe hot flashes and menopausal symptoms. If the decision has been made not to use hormones, the NAMS recommends starting with the antidepressants venlafaxine (37.5-75 mg daily), paroxetine (12.5-25 mg/day), or fluoxetine (20mg/day). Gabapentin, beginning at 300mg nightly, may also be used. Clonidine may be useful but has many side effects. Many women are more comfortable tapering off HRT over a period of weeks rather than stopping abruptly, although there are no data that one method is more successful than another. There are questions about HRT that remain unanswered, and many physicians believe that use of HRT in younger, perimenopausal women is relatively safe. Further research will be needed to address these important issues.

Resolution of case:

Mrs. Jones was started on Paxil 10mg daily for her persistent hot flashes and insomnia. This medication was chosen based on the data for SSRIs and vasomotor symptoms. Also, Paxil is felt by many psychiatrists to be less activating than other SSRIs, which may be helpful in patients with insomnia. Mrs. Jones reported significant improvement in her vasomotor symptoms within 1-2 weeks of starting the drug, and she was able to sleep without waking for 5-6 hours nightly. She did obtain further improvement with an increase in dose to 20mg. For her osteopenia, she was treated with calcium and vitamin D supplementation. She has been telling all of her menopausal friends about Paxil.

REFERENCES

1. Blümel JE, Castelo-Blanco C, Chedraui PA, *et al.* Patients' and clinicians' attitudes after the Women's Health Initiative study. Menopause 2004;11(1):57-61.
2. Manson JE, Hsia J, Johnson KC, *et al.* Estrogen plus progestin and the risk of coronary heart disease. New England Journal of Medicine 2003; 349(6):523-34.
3. Wassertheil-Smoller S, Hendrix S, Limacher M, *et al.* Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. JAMA 2003; 289(20): 2763-2684.
4. Chlebowski RT, Hendrix SL, Langer RD, *et al.* Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. JAMA 2003;289(24):3243-3253.
5. Shumaker SA, Legault C, Rapp SR, *et al.* Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289(20):2651-62
6. Cauley JA, Robbins J, Chen Z, *et al.* Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003;290(13):1729-38.
7. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, *et al.* Estrogen plus progestin and colorectal cancer in postmenopausal women. New England Journal of Medicine 2004;350(10): 991-1004.
8. NHLBI advisory for physicians on the WHI trial of conjugated equine estrogens versus placebo. (Internet) www.nhlbi.nih.gov/whi/e-a_advisory.htm
9. Hulley S, Grady D, Bush T, *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280(7):605-13.
10. Grady D, Herrington D, Bittner V, *et al.* Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). JAMA 2002;288(1):49-57.
11. Herrington DM, Reboussin DM, Brosnihan KB, *et al.* Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. New England Journal of Medicine 2000;343(8):522-9.
12. Hodis HH, Mack WJ, Lobo RA, *et al.* Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled trial. Annals of Internal Medicine 2001;135(11):939-53.
13. Hodis HN, Mack WJ, Azen SP, *et al.* Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. New England Journal of Medicine 2003;349(6):535-45.
14. Pradhan AD, Manson JE, Rossouw JE, *et al.* Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. JAMA 2002; 288(8):980-7.
15. Vongpatanasin W, Tuncel M, Wang Z, *et al.* Differential effects of oral versus transdermal estrogen replacement therapy on C-reactive protein in postmenopausal women. Journal of the American College of Cardiology 2003;41(8):1358-63.
16. Wakatsuki A, Okatani Y, Ikenoue N, *et al.* Effect of lower dose of oral conjugated equine estrogen on size and oxidative susceptibility of low-density lipoprotein particles in postmenopausal women. Circulation 2003;108:808-13.
17. Viscoli CM, Brass LM, Kernan WN, *et al.* A clinical trial of estrogen-replacement therapy after ischemic stroke. New England Journal of Medicine 2001;345:1243-9.
18. Miller J, Chan BKS, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. Annals of Internal Medicine 2002;136(9):680-90.
19. Chen CL, Weiss NS, Newcomb P, *et al.* Hormone replacement therapy in relation to breast cancer. JAMA 2002;287(6):734-41.
20. Li CI, Malone KE, Porter PL, *et al.* Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. JAMA 2003; 289(24): 3254-3263.
21. Chen WY, Colditz GA, Rosner B, *et al.* Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. Annals of Internal Medicine 2002;137:798-804.
22. Gann PH, Morrow M. Combined hormone therapy and breast cancer; a single-edged sword. JAMA 2003; 289(24):3304-3306.
23. Olsson HL, Ingvar C, Bladström A. Hormone replacement therapy containing progestins and given continuously increases breast carcinoma risk in Sweden. Cancer 2003;97(6):1387-92.
24. Zandi PP, Carlson MC, Plassman BL, *et al.* Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. JAMA 2002;288(17):2123-9.
25. Grady D, Yaffe K, Kristof M, *et al.* Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestins Replacement Study. American Journal of Medicine 2002; 113(7):543-548.
26. LeBlanc ES, Janowsky J, Chan BK, *et al.* Hormone replacement therapy and cognition: systematic review and meta-analysis. JAMA 2001;285(11):1489-99.
27. Rapp SR, Espeland MA, Shumaker SA, *et al.* Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289(20):2663-72.
28. Greendale GA, Reboussin BA, Hogan P, *et al.* Symptom relief and side effects of postmenopausal hormones. Obstetrics & Gynecology 1998; 92;982-988.
29. Hlatky MA, Boothroyd D, Vittinghoff E, *et al.* Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. JAMA 2002;287(5):591-7.
30. Hays J, Ockene JK, Brunner RL, *et al.* Effects of estrogen plus progestin on health-related quality of life. New England Journal of Medicine 2003;348(19):1839-54.

31. Villareal DT, Binder, EF, Williams DB, *et al.* Bone mineral density response to estrogen replacement in frail elderly women: a randomized controlled trial. JAMA 2001;286(7):815-20.
32. Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. JAMA 2002;287(20):2668-76.
33. Prestwood KM, Kenny AM, Kleppinger A, Kulldorff M. Ultralow-dose micronized 17B-estradiol and bone density and bone metabolism in older women: a randomized controlled trial. JAMA 2003;290(8):1042-48.
34. Ettinger B, Grady D, Tosteson AN, *et al.* Effect of the Women's Health Initiative on women's decisions to discontinue postmenopausal hormone therapy. Obstetrics & Gynecology 2003;102(6):1225-32.
35. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA 2004;291(1):47-53.
36. Whiteman MK, Staropoli CA, Langenberg PW, *et al.* Smoking, body mass, and hot flashes in midlife women. Obstetrics & Gynecology 2003;101(2):264-72.
37. The Board of Trustees of The North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: position statement of the North American Menopause Society. Menopause 2004; 11(1);11-33.
38. Greendale GA, Reboussin BA, Hogan P, *et al.* Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. Obstetrics & Gynecology 1998;92(6):982-8.
39. MacLennan A, Lester S, Moore V. Oral oestrogen replacement therapy versus placebo for hot flushes (Cochrane Review). Cochrane Database of Systematic Reviews. 2001;1:CD002978.
40. Gelfand MM, Moreau M, Ayotte NJ, *et al.* Clinical assessment and quality of life of postmenopausal women treated with a new intermittent progestogen combination hormone replacement therapy: a placebo-controlled study. Menopause 2003; 10(1); 29-36.
41. Utian WH, Burry KA, Archer DF, *et al.* Efficacy and safety of low, standard, and high dosages of an estradiol transdermal system (Esclim) compared with placebo on vasomotor symptoms in highly symptomatic menopausal patients. The Esclim Study Group. American Journal of Obstetrics & Gynecology 1999;181:71-9.
42. Wren BG, Champion SM, Manga RZ, Eden JA. Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women. Menopause 2003; 10(1): 13-18.
43. Leonetti HB, Longo S, Anasti JN. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. Obstetrics & Gynecology 1999;94:225-8.
44. Loprinzi CL, Barton DL, Rhodes D. Management of hot flashes in breast-cancer survivors. The Lancet Oncology 2001; 2(4): 199-204.
45. Modelska K, Cummings S. Tibolone for postmenopausal women: systematic review of randomized trials. The Journal of Clinical Endocrinology & Metabolism 2002; 87(1): 16-23.
46. Berendsen HH. The role of serotonin in hot flushes. Maturitas 2000; 36(3): 155-64.
47. Slopien R, Meczekalski B, Warenik-Szymankiewicz A. Relationship between climacteric symptoms and serum serotonin levels in postmenopausal women. Climacteric 2003; 6(1): 53-7.
48. Loprinzi CL, Kugler JW, Sloan JA, *et al.* Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059-63
49. Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA 2003;289(21):2827-34.
50. Loprinzi CL, Sloan JA, Perez EA, *et al.* Phase III evaluation of fluoxetine for treatment of hot flashes. Journal of Clinical Oncology 2002;20(6):1578-83.
51. Guttuso T, Kurlan R, McDermott MP, Kieburtz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. Obstetrics & Gynecology 2003;101(2):337-45.
52. Pandya KJ, Raubertas RF, Flynn PJ, *et al.* Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. Annals of Internal Medicine 2000;132(10):788-93.
53. Jacobson JS, Troxel AB, Evans J, *et al.* Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. Journal of Clinical Oncology 2001;19(10):2739-45.
54. Nikander E, Kilkkinen A, Metsä-Heikkilä M, *et al.* A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. Obstetrics & Gynecology 2003;101(6):1213-20.
55. Albertazzi P, Pansini F, Bonaccorsi G, *et al.* The effect of dietary soy supplementation on hot flushes. Obstetrics & Gynecology 1998;91(1):6-11.
56. Tice JA, Ettinger B, Ensrud K, *et al.* Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) study: a randomized controlled trial. JAMA 2003;290(2):207-14.
57. Barton DL, Loprinzi CL, Quella SK, *et al.* Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. Journal of Clinical Oncology 1998;16(2):495-500.
58. Crandall C. Vaginal estrogen preparations: a review of safety and efficacy for vaginal atrophy. Journal of Women's Health 2002;11(10):857-77.
59. Grady D, Brown JS, Vittinghoff E, *et al.* Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study. Obstetrics & Gynecology 2001;97(1):116-20.
60. Brown JS, Vittinghoff E, Kanaya AM, *et al.* Urinary tract infections in postmenopausal women: effect of hormone therapy and risk factors. Obstetrics & Gynecology 2001;98(6):1045-52.
61. Robinson D, Cardozo LD. The role of estrogens in female lower urinary tract dysfunction. Urology 2003;62(4 Suppl 1):45-51.
62. Hendrix SL. Urinary incontinence and menopause: an evidence-based treatment approach. Disease-A-Month 2002; 48:622-636.
63. Eriksen B. A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. American Journal of Obstetrics & Gynecology 1999; 180(5):1072-9.