



**Testimony**  
**Before the Subcommittee on Human Rights and**  
**Wellness**  
**Committee on Government Reform**  
**United States House of Representatives**

**Balancing Act: The Health**  
**Advantages of Naturally Occurring**  
**Hormones in Hormone Replacement**  
**Therapy**

*Statement of*

**Barbara Alving, M.D., MACP**

*Acting Director*

*National Heart, Lung, and Blood Institute*

*National Institutes of Health*

*U.S. Department of Health and Human Services*



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I am pleased to appear before this Committee in my capacity as Acting Director of the National Heart, Lung, and Blood Institute (NHLBI) and director of the NIH Women's Health Initiative (WHI), which has been administered by the NHLBI since 1997. I am here, first, to tell you what we learned from the WHI with regard to hormone therapy using conjugated equine estrogen and, second, to comment on alternative therapies that are now receiving attention.

The WHI began in 1991 to investigate approaches that might be helpful to older women in preventing common chronic diseases – coronary heart disease, breast and colorectal cancers, and osteoporosis. Estrogen “replacement” therapy is one such approach. For much of the 20<sup>th</sup> century, popular thinking was that restoring levels of estrogen, which ebb during middle age, would enable women to remain “forever young.” Although estrogen was initially prescribed to alleviate troublesome menopausal symptoms, a number of epidemiological studies provided evidence that women who took estrogen experienced a lower incidence of disease, particularly cardiovascular disease (CVD), and enjoyed better health overall than women who did not. Data from many basic science investigations provided plausible explanations for the observed CVD benefit, and an NHLBI-supported clinical trial documented improvements in CVD risk factors (e.g., cholesterol levels) that might account for such a benefit.

But, the observation that women who took estrogen tended to enjoy better health did not prove causality, and important questions remained. Does estrogen make women healthy? Or ... does being healthy (or, at least, health-conscious) make women take estrogen? The WHI hormone trial was designed to address these questions. It recruited about 27,000 healthy postmenopausal women, 50-79 years of age, and divided them into

one of two groups according to whether they had still had a uterus. Those who had a uterus were assigned to take either a pill containing estrogen and progestin (0.625 mg of conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate – Prempro) or a placebo; those who had undergone a hysterectomy took an estrogen pill (0.625 mg of conjugated equine estrogen – Premarin) or a placebo.

It is worth noting that at the outset of the WHI trial, many interested parties believed that an outcome favoring estrogen was a foregone conclusion. Indeed, some doctors and researchers argued that such a trial was unethical because it would require half of the participating women to take placebos and thereby deny them the presumed benefits of hormones. Nonetheless, arguments in favor of randomized, placebo-controlled, clinical trials prevailed – and, as we now know, they were justified.

The WHI trial of estrogen plus progestin was halted in 2002 after an average follow-up of 5.2 years. Compared with women who took a placebo pill, women taking the hormones experienced an excess risk of breast cancer and more episodes of heart attack, stroke, and blood clots. Although the hormone-treated women had lower rates of colorectal cancer and fractures, and overall death rates were equal, it was concluded that the hormone combination should not be recommended as a health-promoting regimen. Moreover, the WHI Memory Study (WHIMS), which focused on women aged 65 years and older, found an increased risk of dementia and no effect on cognitive impairment among recipients of estrogen plus progestin.

Subsequently, in the spring of 2004, the WHI estrogen-alone trial also was halted upon determination that the hormone therapy had no effect on coronary heart disease risk but increased the risk of stroke. The study also found that estrogen-alone therapy

significantly increased the risk of deep vein thrombosis, had no significant effect on the risk of breast or colorectal cancer, and reduced the risk of hip and other fractures.

Findings from the WHIMS, published just last month, indicated that estrogen therapy did not reduce incidence of dementia and had an adverse effect on cognitive function.

In light of the WHI and WHIMS findings, the Food and Drug Administration (FDA) offers the following recommendations (updated April 19, 2004):

- Estrogens and progestins should not be used to prevent memory loss, heart disease, heart attacks, or strokes.
- Estrogens provide valuable therapy for many women, but carry serious risks, and therefore postmenopausal women who use or are considering using estrogen or estrogen with progestin treatments should discuss with their physicians whether the benefits outweigh the risks.
- For hot flashes and significant symptoms of vulvar and vaginal atrophy, these products are the most effective approved therapies. These products are also options for women whose significant risk of osteoporosis outweighs the risks of treatment; other treatments for prevention of postmenopausal osteoporosis are available.
- Estrogens and progestins should be used at the lowest doses for the shortest duration to reach treatment goals, although it is not known at what dose there may be less risk of serious side effects. Women are encouraged to talk to their health care provider regularly about whether treatment is still needed.
- There is a higher incidence of abnormal mammograms which require medical attention.

- Each woman's individual medical situation needs to be carefully discussed with her health care provider to make the best decision for her.

For prescription hormone formulations other than those studied in the WHI, the FDA advises the following: “Although ... other estrogens and progestins were not studied, it is important to warn postmenopausal women who take estrogens and progestins about the potential risks, which must be presumed to be the same.”

In the aftermath of the WHI findings, increased attention has been focused on the use of complementary and alternative medicine (CAM) to manage symptoms associated with the menopausal transition. Dietary supplements, including botanicals, are the most commonly used CAM modality for menopausal symptoms.

The National Center for Complementary and Alternative Medicine (NCCAM) supports basic and clinical research on the safety and efficacy of botanicals such as soy, black cohosh, and red clover in alleviating hot flashes, osteoporosis, and cognitive and affective problems. Other studies are generating laboratory data that are vital to understanding mechanism of action, characterizing the botanicals, identifying active constituents, and preparing standardized supplements. For example, two ongoing basic studies are looking at the effect of black cohosh extract on human breast tissue and its role as a serotonin modulator, and other research is looking at the effect of soy on breast and endometrial tissue as well as bone. In addition to individual research project grants, the NCCAM supports several research centers on women’s health.

The National Institute on Aging (NIA) is supporting a 4-year, randomized, controlled trial to evaluate the efficacy and safety of phytoestrogen-based approaches

(black cohosh, and a multibotanical preparation given with and without soy diet counseling) for treating vasomotor symptoms in perimenopausal and postmenopausal women.

Toxicity of black cohosh and other herbals and phytoestrogens is being evaluated by the National Institute of Environmental Health Sciences as part of an overall effort to establish the safety of herbal medicines.

The scientific literature on CAM therapies for menopause is equivocal, due to problems with small trials, short duration of treatment, large placebo effects, and imprecise measures for critical outcomes such as hot flashes. Investigations of the efficacy of soy to prevent cognitive changes, for example, have produced conflicting results, with the latest study (published in the July 7, 2004, issue of the Journal of the American Medical Association) finding no effect. The NCCAM has contracted with the Agency for Healthcare Research and Quality to conduct a review and assessment of the literature to provide a clearer picture of what is known about soy.

Clearly, additional research will be needed to provide safety and efficacy information on the range of CAM modalities being used by women to manage menopausal symptoms. The NIH is working to improve the rigor of future studies in this area. In collaboration with eight other NIH components, the NCCAM convened a working group of scientists to assess the quality of hot flash measurements currently in use and to make recommendations for research needed to improve these measurements. In addition the NCCAM, the NIA, and others at the NIH will co-sponsor a state-of-the-science meeting in March 2005 on the management of menopause-related symptoms.

Women are eagerly awaiting the outcome of federal efforts to uncover new approaches to address menopausal symptoms. Moreover, in discussions with gynecologists in the community, we have learned that women are seeking natural (biologically identical) hormone therapies via entities such as the Women's International Pharmacy (<http://www.womensinternational.com/about.html>).

Thank you for the opportunity to address these issues of great importance to women. I would be pleased to answer any questions the committee may have.