NCCAM
NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

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Complementary and Alternative Medicine at the NIH

Menopausal Symptoms and Alternative Therapies

On October 23–24, 2002, the National Institutes of Health (NIH) hosted a scientific workshop on menopausal hormonal therapy (HT).[1] The goals were to review the results of one treatment group, halted in May 2002, of the NIH Women's Health Initiative (WHI) clinical trial; to place those results within the context of other research, past and present; and to assess what is known about the use of menopausal HT, particularly as a preventive regimen, and what research still needs to address. During the workshop, Lorraine A. Fitzpatrick, M.D., professor of medicine at the Mayo Clinic and Foundation, provided information on the use of HT alternatives, including complementary and alternative medicine (CAM). Stephen E. Straus, M.D., Director of the National Center for Complementary and Alternative Medicine (NCCAM), summarized the Center's current research on HT alternatives, the challenges of such studies, and promising future directions.

Stephen E. Straus, M.D.
Director, NCCAM

Background on the WHI

The WHI, launched by NIH in 1991, is a group of different, and sometimes overlapping, prospective clinical trials[2] that make up one very large clinical trial. The WHI is examining various treatments that showed earlier scientific promise for preventing various diseases in and improving the quality of life of postmenopausal women. WHI investigators have been studying two distinct HT regimens, estrogen plus progestin (E+P) or estrogen alone, as well as the effects of a low-fat diet and vitamin D and calcium supplementation. The disease outcomes being studied include heart disease, breast and other cancers, bone problems from osteoporosis (especially fractures), blood clots in the legs and lungs, and stroke. The WHI is the largest clinical trial ever conducted in the United States, with an ethnically diverse population of 161,000 women aged 50–79 enrolled at 40 study sites.

Based on the results of previous studies, the U.S. Food and Drug Administration has approved the use of HT for relief of menopausal symptoms and for prevention of osteoporosis. Prior to the WHI, there had been many previous retrospective studies[3] suggesting that HT may provide additional health benefits, including a 40- to 50-percent reduction in risk for coronary heart disease (CHD). Previous studies also indicated improvements in bone mineral density (with reduced risks of spine and hip fractures) and benefits in other outcomes, but increased risks of breast cancer and clots in the legs and lungs.[4]

As was reported widely in the news media, the treatment group of the WHI that was stopped was studying an E+P tablet (marketed as Prempro).[5] Over 16,000 women were in this group; they were aged 50–79, postmenopausal, generally healthy, and they had an intact uterus (i.e., had not had a hysterectomy). In May 2002, the study's Data Safety and Monitoring Board[6] had recommended that the E+P treatment group be halted after only 5.2 years of followup instead of the planned 8.5 years because risks appeared to outweigh benefits in the study population. For every 10,000 women taking the E+P regimen, when compared with women who were not taking it, 7 more women developed CHD, 8 more had a stroke, 8 more had a pulmonary embolism (blood clot in the lung), and 8 more had invasive breast cancer. On the benefits side, six fewer women had colorectal cancers and five fewer had hip fractures. The global index (an overall measure of health outcomes) of this group of the trial also weighed heavier on the side of risk than benefit.

The authors of the scientific paper on these results noted, "This trial did not address the short-term risks and benefits of hormones given for the treatment of menopausal symptoms."[4] However, they found that E+P does not appear to be desirable as a primary prevention for CHD. Thus, despite the common wisdom of a decade ago that encouraged many women to use HT not only to allay their menopausal symptoms but also to prevent heart attacks, this first major study proved that the risk of heart disease was not reduced. Rather, it was increased in women who used HT for several years.

The news from the HT study is that prolonged use of this particular E+P regimen is not wise; however, the WHI study did not address whether short-term use is acceptable. It was noted that the WHI data apply to a specific treatment given to a group

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of women with specific characteristics. Statistical analysis indicates that the absolute risk to any individual is very small. The findings should not be assumed to apply to use of other HT doses, formulations, or routes of administration (e.g., patches or estrogen-only regimens) or to women who are perimenopausal or are having significant menopausal symptoms.

Jacques Rossouw, M.D., acting director of the WHI at the time of the conference, stated, "Women with a uterus who are currently taking E+P should have a serious talk with their doctor to see if they should continue it. If they are taking this hormone combination for short-term relief of [menopausal] symptoms, it may be reasonable to continue since the benefits are likely to outweigh the risks. Longer-term use or use for disease prevention must be reevaluated, given the multiple adverse effects noted in WHI."

CAM for Menopausal Symptoms

The workshop included information on the use of CAM for management of menopausal symptoms. Especially since the release of the WHI results, many women have been wondering whether there are safe and effective CAM alternatives. Lorraine A. Fitzpatrick, M.D., spoke on alternative therapies (both conventional drug and CAM), drawing on the state of the science and her clinical experience. She noted:

"Therapies that don't work very well, if at all"—vitamin E, evening primrose oil, soy isoflavones, dong quai, red clover, ginseng, yam cream, and Chinese medicinal herbs.

"Therapies that might work, but data from appropriate trials are not available" (i.e., better research is needed)—black cohosh and vitex (chasteberry). Dr. Fitzpatrick noted that she does offer black cohosh as an option to patients who want to take something "natural" rather than drugs; however, there are issues with herbal preparations (discussed below).

Soy protein/isoflavones. Soy contains isoflavones, plant steroids that are chemically similar to estrogen. When taken in conjunction with a low-fat diet, soy protein containing phytoestrogens can lower "bad" cholesterol levels. This finding has led to its popularity among postmenopausal women. Dr. Fitzpatrick said there is a lack of sound scientific data to support using soy as a replacement for HT. It is known that: (1) Genistein and daidzein, two phytoestrogens in soy, have estrogenlike effects on select tissues but very minor effects in comparison to placebo. (2) Long-term effects of soy phytoestrogens on estrogen-sensitive tissues are unknown. (3) Soy components stimulate breast tumors in mice.

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Our mission: The National Center for Complementary and Alternative Medicine (NCCAM) is dedicated to exploring complementary and alternative healing practices in the context of rigorous science, training CAM researchers, and disseminating authoritative information to the public and professionals.

Lorraine A. Fitzpatrick, M.D.
Mayo Clinic and Foundation

Phytoestrogens. These are plant compounds that have some similarities to human estrogens and may work in the body by some of the same mechanisms as estrogen. However, they are weaker than animal and some synthetic estrogens and are not stored in tissue, but easily broken down. Phytoestrogens consist of more than 20 compounds in over 300 plants, including various herbs (parsley and garlic), grains (soybeans, wheat, and rice), fruits (dates, cherries, and apples), and drinks (coffee and wine). Retrospective studies suggest that phytoestrogens are associated with a reduction in certain chronic diseases. However, their effects in any woman will vary for many reasons, such as product concentration, the woman's estrogen status, and the flora in her digestive tract. For those who use phytoestrogens, Dr. Fitzpatrick noted, moderation is key; overuse has been reported to cause vaginal bleeding.

Problems with research studies on botanical (herbal) preparations. Doses and formulations have varied widely among studies, making meaningful comparisons difficult. There is a lack of consensus among experts regarding dosage, safety, the interactions of herbs and drugs, and how long to treat. Studies have varied greatly in quality and have tended to be short in duration. More research of higher quality is needed.

Potential problems with botanical products. These include "myths that natural equals safe and thousands of years of use equals safe"; botanicals are not regulated to the same degree as drugs; they can be mislabeled, underlabeled, and/or inconsistent; and toxic metals or conventional Western drugs have been found to contaminate some preparations. Also, there is much that is not yet known about the interactions of these botanical products with bodily systems or conventional drugs. It is generally recommended to stop all herbal products at least 2 weeks prior to elective surgery because of potential interactions.

Other CAM treatments. Other CAM therapies that either are being scientifically studied or have been reported to have benefit for easing menopausal symptoms include meditation, acupuncture, hypnosis, biofeedback, applied relaxation (a relaxation technique), deep breathing exercises, and paced respiration (a technique of slow breathing using the stomach muscles).

NCCAM's Research

Stephen E. Straus, M.D., Director of NCCAM, presented information on the use of CAM, the scientific evidence, issues of research studies on botanical products, NCCAM research on women's health, and future research directions in CAM for government, industry, and academia.

Dr. Straus presented new data on CAM from the Study of Women's Health Across the Nation (SWAN), a 10-year prospective study being funded by various components of NIH, including NCCAM.[7] Among 3,302 women aged 42–52 of various racial/ethnic backgrounds at 7 sites nationwide, almost half (48.5 percent) had used CAM in the past year. The study yields data on the use of nutritional remedies, herbal remedies, psychological methods, physical methods, and folk medicine/traditional Chinese medicine by the participants, including among different racial/ethnic groups. Among perimenopausal women studied in California, an average of 20 percent had used an herbal product in the past year.

Next, Dr. Straus gave a brief overview of the scientific evidence for the use of CAM alternatives to HT. He reaffirmed Dr. Fitzpatrick's conclusions that small clinical trials have indicated that some CAM products may relieve menopausal symptoms. Basic science studies have identified agents, such as soy isoflavones, that are estrogenic and other products that may have hormonal (progestational or antisteroidogenic) activities. Nonetheless, no long-term studies have been conducted yet to determine whether these products are effective or safer than conventional HT.

Choosing which botanical products to study, Dr. Straus observed, is affected by certain issues and needs: to identify appropriate parts, species, and cultivars of the plant for study; to decide whether to study a whole extract or a fraction (e.g., one chemical); to ensure that the substance to be studied is grown and harvested under the best possible conditions; to establish how the substance will be extracted, standardized, and purified to help ensure quality control; and to define the best formulation, dose, and length of administration for the study.

Women's health is an important area of NCCAM research. More than 15 clinical, basic, and laboratory studies are being supported by NCCAM on HT alternatives for women's health conditions, including evaluations of black cohosh and red clover; how soy consumption influences menopausal symptoms; herb-drug interactions; the effects of isoflavones on bone density and breast cancer; and the interactions between soybean phytochemicals and tamoxifen in breast cancer.[8]

Dr. Straus proposed some key objectives for future research by industry, government, and academia on CAM therapies. There is a need to study and understand more fully the quality-of-life problems imposed by menopause. Well-characterized and standardized products are needed to use in studies. Better understanding is needed of the chemical constituents, mechanisms, and pharmacology of botanicals. Dose-ranging studies should be conducted to identify optimal doses. Clinical trials are needed of the efficacy of CAM therapies for menopausal symptoms and quality of life. The question of how safe botanical alternatives are for women with hormone-sensitive cancers needs to be investigated. Finally, large, collaborative clinical trials are needed to study the long-term activity and safety of products that are proven to be reliably effective.

Dr. Straus commented to *Complementary and Alternative Medicine at the NIH,* "We have learned only through careful, prospective studies that long-term use of E+P is not as safe as previously claimed." He added, "There is a high level of interest among women and their health care providers in botanical alternatives to HT. However, at this time, there is not enough rigorous scientific evidence to conclude that these botanicals are safe and beneficial; there is only suggestive evidence from small, short-term studies. Through NCCAM's current and future research, we will learn more about how these botanical products work, their safety, and what their health benefits might be for menopausal and postmenopausal women. I join in the recommendation that women should consult their health care providers about options for managing symptoms of menopause that are troublesome to them, as well as options for lowering postmenopausal health risks."

Notes

1. HT was formerly known as HRT (hormone replacement therapy).
2. To find out more about clinical trials, see the NCCAM fact sheet *About Clinical Trials in Complementary and Alternative Medicine.* In a prospective clinical trial, participants are divided into groups that are either exposed or not exposed to the health care intervention(s) of interest. All participants are followed over time for the effect(s) of the intervention(s).
3. A retrospective study is one in which the outcomes of interest occurred in the participants before the study began.
4. Writing Group for the Women's Health Initiative Investigators. "Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial." *Journal of the American Medical Association.* 2002. 288(3):321–33.
5. The study drug was a tablet taken once daily containing conjugated equine estrogen 0.625 mg and medroxyprogresterone acetate 2.5 mg, manufactured by Wyeth Pharmaceuticals.
6. Data Safety and Monitoring Boards (DSMBs) are part of the requirements for the oversight and monitoring of all multisite clinical trials supported or sponsored by NIH. A DSMB is an independent, external committee that monitors findings from the trial and makes recommendations with regard to continuing or concluding a trial, based on benefits versus risks.
7. Bair, Y.A., Gold, E.B., Greendale, G.A., et al. "Ethnic Differences in Use of Complementary and Alternative Medicine at Midlife: Longitudinal Results From SWAN Participants." *American Journal of Public Health.* 2002. 92(11):1832–40.
8. NCCAM extramural grants for fiscal year 2002 are posted at nccam.nih.gov/research/extramural/index.

For More Information

The workshop may be viewed at videocast.nih.gov (go to "Past Events"). Speakers' slides and other print information are posted at www4.od.nih.gov/orwh/workshop2002.html. Material from various Federal agencies pertaining to menopausal HT may be accessed at www.nih.gov/PHTindex.htm. An NCCAM consumer advisory, "Alternative Therapies for Managing Menopausal Symptoms," is at nccam.nih.gov/health/alerts/menopause. *Questions and Answers About Black Cohosh and the Symptoms of Menopause,* a fact sheet by NCCAM and the NIH Office of Dietary Supplements, is available at ods.od.nih.gov/factsheets/blackcohosh.html. NCCAM publications may also be obtained from the NCCAM Clearinghouse (see pg. 2).

Complementary and Alternative Medicine at the NIH
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NEWS FOR RESEARCHERS

NCCAM announces **three new programs for CAM research centers.** Up to $5.3 million in funding is available in 2003. For more information, go to nccam.nih.gov/research/announcements.

Centers of Excellence for Research on Complementary and Alternative Medicine. Centers of Excellence will support program project grants (P01) to elucidate the mechanisms of action of CAM modalities. These awards will provide new opportunities for experienced molecular or cellular biologists, imaging scientists, immunologists, neurobiologists, pharmacologists, physiologists, and other scientists to investigate fundamental questions related to CAM. Letters of intent are due March 29, 2003; receipt date is April 29, 2003.

Developmental Centers for Complementary and Alternative Medicine. Developmental Centers will support U19 cooperative agreements in which CAM and conventional institutions and investigators partner to conduct exploratory and developmental research projects. These awards will provide opportunities for CAM institutions and investigators to strengthen their research expertise and infrastructure while enabling conventional researchers to gain clinical and cultural perspectives critical to the conduct of CAM research. Letters of intent are due March 14, 2003; receipt date is April 15, 2003.

Planning Grants for International Centers for Research on Complementary and Alternative Medicine. Planning grants for International Centers will support U.S. and international institutions to jointly plan and pilot multiproject exploratory and developmental studies of traditional/alternative healing approaches. The planning grants will lay the groundwork for developing applications for an International Center for Research on CAM that will be called for in 2004. Letters of intent are due February 28, 2003; receipt date is March 28, 2003.

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From NCCAM's Office of Clinical and Regulatory Affairs:

NCCAM has issued a new **Policy Announcement on the Quality of Natural Products.** This document provides guidance on several issues that investigators who are seeking funding from NCCAM for studies involving natural products must consider when designing their studies and preparing applications. Go to nccam.nih.gov/research/policies/naturalproducts.

New NCCAM Terms of Awards for Clinical Trials have been developed and are effective for awards made after December 1, 2002. The Terms apply to all NCCAM-supported trials of therapeutic or preventive interventions involving human subjects. They are designed to ensure compliance with Federal regulations to protect the safety of clinical trial participants and to ensure the high-quality conduct of trials. Go to nccam.nih.gov/research/policies/terms-of-awards.

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NCCAM has initiated, with the National Institute of Allergy and Infectious Diseases, a **Preclinical Antiviral Testing Program for Complementary and Alternative Medicine.** The program also collaborates with the U.S. Army Medical Research Institute on Infectious Diseases. It offers an opportunity for testing of potential CAM agents *in vitro* for their activity against various types of viruses, specifically category A, B, and C pathogens (as defined by the Centers for Disease Control and Prevention) and HIV. More information is at nccam.nih.gov/research/news/antiviral.