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Estrogen-Alone Hormone Therapy Could Increase Risk of Dementia in Older Women

Older women using estrogen-alone hormone therapy could be at a slightly greater risk of developing dementia, including Alzheimer's disease (AD), than women who do not use any menopausal hormone therapy, according to a new report by scientists with the Women's Health Initiative Memory Study (WHIMS). The scientists also found that estrogen alone did not prevent cognitive decline in these older women. These findings from WHIMS appear in the June 23/30, 2004, *Journal of the American Medical Association*[*](#).

"These studies further support last year's recommendations that menopausal hormone therapy should not be used to prevent cognitive decline or dementia in older postmenopausal women," stated Judith A. Salerno, MD, MS, Deputy Director of the National Institute on Aging (NIA). "Women should follow the Food and Drug Administration's recommendation that those who want to use menopausal hormone therapy to control their menopausal symptoms should use it at the lowest effective dose for the shortest time necessary."

The latest findings were reported by WHIMS Principal Investigator Sally A. Shumaker, PhD, Wake Forest University School of Medicine, and her colleagues at the 39 study sites. This research was funded by Wyeth Pharmaceuticals, which manufactures PremarinTM, the conjugated equine estrogens used in this trial, and Wake Forest University Baptist Medical Center. WHIMS is a substudy of the Women's Health Initiative (WHI) Hormone Trial, which is funded by the National Institutes of Health (NIH) at the Department of Health and Human Services (DHHS). The National Institute on Aging (NIA), a component of NIH, has been involved in reviewing the current findings as the lead NIH institute on age-related cognitive change and dementia.

The WHI Hormone Trial using estrogen plus progestin was stopped early in July 2002 when researchers found an increased risk of breast cancer, along with greater risks of heart disease, stroke, and blood clots, and determined that these risks outweighed the benefits of reduced risks of hip fracture and colorectal cancer. In May 2003, WHIMS investigators reported the results of the estrogen plus progestin part of their memory substudy^{**}. They found that estrogen plus progestin increased the risk of probable dementia in women 65 and older and did not preserve cognitive function. This part of WHIMS was also stopped in July 2002.

At the end of February 2004, the remaining parts of the WHI Hormone Trial and WHIMS, the estrogen-alone components, were halted because results were showing an increased risk of stroke and no reduction in the risk of heart disease in the women using estrogen alone. Scientists further believed that continuing the study until its planned conclusion next year would probably not add new information. In April 2004, the WHI investigators reported that they found an increased risk of blood clots, but no significant effect on breast or colorectal cancer and also a reduced risk of fractures in those women using estrogen alone.

Now, the WHIMS scientists have evaluated the cognition and dementia data from the estrogen-alone part of the trial. Some 2,947 women age 65 to 79 at the beginning of the trial received estrogen alone (a daily dose of 0.625 mg of PremarinTM) or a placebo. (The women received estrogen alone because they had all had hysterectomies at some time before beginning the study. A progestin is used with estrogen in menopausal hormone therapy in any woman with a uterus to prevent thickening and, sometimes, cancer of the lining of the uterus, the endometrium. Because the uterus is removed in a hysterectomy, there is no need for progestin when women who have had hysterectomies use menopausal hormone therapy.)

Participants were determined to be dementia free before they were enrolled in WHIMS. At the beginning and then annually for the more than 5-year average duration of the trial, WHIMS participants were evaluated to determine if they might have developed dementia or mild cognitive impairment (MCI). All women received the Modified Mini Mental State Exam (3MSE), and those suspected of having dementia also received an extensive clinical evaluation by a specialist physician.

At the end of the study, the risk of dementia in the estrogen-alone group was 49% higher than the risk in women using the placebo. That is, among 10,000 women using conjugated equine estrogens, 37 could be expected to develop dementia, compared to 25 in 10,000 women using the placebo — 12 extra cases of dementia in every 10,000 women using estrogen alone each year. This increased risk was not statistically significant.

Last year WHIMS scientists reported a 105% increase in the risk of dementia in older women using estrogen plus progestin compared to those using a placebo. That means, on average, each year in 10,000 women over age 65 using estrogen plus progestin there might be 45 cases of dementia compared to 22 cases in 10,000 older women on placebo.

Almost half of the dementia cases in the estrogen-alone study — 46% in older women using estrogen alone and 47% of those in older women using the placebo — were Alzheimer's disease (AD). Similarly, in the estrogen plus progestin study, 50% of the cases in older women using estrogen plus progestin and 57% of those in older women using placebo were classified as AD.

A second article on general cognitive function [***](#) from Mark A. Espeland, PhD, and other WHIMS investigators appears in the same issue of *JAMA*. It reports that beginning estrogen-alone hormone therapy after age 65 can have a small negative effect on overall cognitive abilities and that this negative effect may be greater in women with existing cognitive problems. The differences in scores on cognitive testing for the estrogen-alone and placebo groups were statistically significant, but the differences were so small that they are not considered clinically relevant by the investigators.

As with the earlier WHI and WHIMS result reports, these increases in risk must be viewed in perspective. Significant increases in risk are important for public health officials who are concerned with large groups in the population, where a small increase could have health implications for millions of people. For an individual woman, however, the increased risk is still quite small. (A detailed discussion of risk is presented in the NIA Fact Sheet, *Understanding Risk: What Do Those Headlines Really Mean?*, available online at <http://www.niapublications.org/engagepages/risk.asp>.)

Further, these findings relate to women age 65 and older taking this particular estrogen-alone hormone therapy. The cognitive risks and benefits for younger women using Premarin™ or other estrogen formulations are unknown. Any younger woman who is considering menopausal hormone therapy because of her menopausal symptoms should talk to her doctor about how the various Women's Health Initiative study findings relate to her own medical history and treatment.

General information on menopause, menopausal hormone therapy, and the Women's Health Initiative can be found on the NIH home page, www.nih.gov, by clicking on the link "Menopausal Hormone Therapy," or by going directly to www.nih.gov/PHTindex.htm.

The NIA leads the Federal research effort on aging in general and on aging and memory, including Alzheimer's disease. For more information on these topics, the public and media are invited to visit the NIA's websites. Information on memory and Alzheimer's disease may be viewed at www.alzheimers.org, the NIA's Alzheimer's Disease Education and Referral (ADEAR) Center website. The general public also may call the ADEAR Center toll free at 1-800-438-4380. General information on health and aging may be viewed at www.nia.nih.gov. Publications may be ordered online at www.niapublications.org or by calling the NIA Information Center toll free at 1-800-222-2225.

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