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Rates of Dementia Increase Among Older Women on Combination Hormone Therapy

Older women taking combination hormone therapy had twice the rate of dementia, including Alzheimer's disease (AD), compared with women who did not take the medication, according to new findings from a memory substudy of the Women's Health Initiative (WHI). The research, part of the Women's Health Initiative Memory Study (WHIMS) and reported in the May 28, 2003, *Journal of the American Medical Association (JAMA)*, found the heightened risk of developing dementia in a study of women 65 and older taking Prempro™, a particular form of estrogen plus progestin hormone therapy.

The study also found that the combination therapy did not protect against the development of Mild Cognitive Impairment, or MCI, a form of cognitive decline less severe than dementia.

"Because of possible harm in some areas and lack of a demonstrated benefit in others, we have concluded that combination hormone therapy should not be prescribed at this time for older, postmenopausal women to maintain or improve cognitive function," says Judith A. Salerno, M.D., M.S., Deputy Director of the National Institute on Aging (NIA) at the National Institutes of Health (NIH), U.S. Department of Health and Human Services.

The findings were reported by WHIMS Principal Investigator Sally A. Shumaker, Ph.D., Wake Forest University School of Medicine, Winston-Salem, NC, and colleagues at the 39 sites involved in the study.

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The memory substudy WHIMS was funded by Wyeth Pharmaceuticals, which manufactures Prempro™, which it provided for use in the WHI trials. The larger WHI trials are supported by the National Heart, Lung, and Blood Institute (NHLBI) of the NIH. The NIA has been involved in reviewing the current findings as the NIH's lead institute on age-related memory change and dementia.

Importantly, the women in the combined estrogen plus progestin (E+P) arm of the WHI and substudies such as WHIMS are no longer taking the combination therapy as part of the research trials. In July 2002, all combination therapy components of the WHI were halted when it was found that increased risk of breast cancer, heart disease, stroke, and blood clots among participating women on combined estrogen plus progestin therapy outweighed benefits for hip fractures and colorectal cancer.

As they did in the July 2002 report on increased risk of breast cancer, heart disease, and stroke, researchers stress with today's announcement that the data should be viewed in perspective. While the increased risk of dementia is significant when calculated over a large population of women, the risk to any individual older woman is actually relatively small. (For a detailed discussion of relative versus absolute risk, see the NIA Fact Sheet *Understanding Risk: What Do All Those Headlines Mean?* online at www.nia.nih.gov.)

The current findings address combined estrogen plus progestin therapy, specifically Prempro™, among women 65 years of age and older. For younger women, the cognitive risks and benefits of this combination therapy are unknown. Short-term hormone therapy in younger women for some symptoms of menopause has been approved by the U.S. Food and Drug Administration and the new findings do not directly address decisions about such treatment. Researchers and officials at the NIH suggest that women of any age consult with a physician about their individual risks and benefits.

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The memory study findings on women 65 and older showed that over a 5-year period:

- The risk for dementia among women taking estrogen and progestin was twice that of women taking placebo pills. This represents an increase per year from 22 women per 10,000 at risk of dementia in the placebo group to 45 women per 10,000 in the combination therapy group, an additional 23 cases per 10,000 per year among women taking combination therapy. Sixty-one cases of dementia were diagnosed among the 4,500 women participating in the study; 66 percent of those cases occurred among women on combination therapy while 34 percent occurred in women taking placebo.
- Most of the dementia found among women participating in the study was classified as probable Alzheimer's disease, with vascular dementia ranking second. There were 20 cases of Alzheimer's disease among the 40 dementia cases in women in the combination therapy group (50 percent of the cases); in women on placebo, 12 of the 21 cases (57 percent) of dementia were deemed Alzheimer's disease.
- There was no significant difference in the risk of being diagnosed with MCI alone when the placebo and combination therapy groups were compared.

About 4,500 women participated in the WHIMS substudy of women 65 and older. Once the women met the criteria for participation, including screening tests to make sure they did not have dementia at the study's start, they were randomly assigned to take estrogen plus progestin therapy (one pill per day of conjugated equine estrogen (CEE), 0.625 mg, plus medroxyprogesterone acetate (MPA), 2.5 mg – brand name Prempro™) or a look-alike placebo. Cognitive status was evaluated annually, and women who showed signs of decline were examined in greater depth to further characterize their cognitive status.

The researchers looked at several other factors that might influence cognitive status, including socioeconomic status, educational attainment, prior estrogen or progestin use history, and use of cholesterol lowering medications or aspirin or other non-steroidal anti-inflammatory drugs. These factors were not significantly different between the therapy

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group and the placebo group and did not account for the differences in rates of cognitive decline, the researchers said.

A second report in the same issue of *JAMA* showed general cognitive status to be adversely affected by the combination therapy in older women. WHIMS investigator Stephen Rapp, Ph.D., Wake Forest University School of Medicine, and colleagues at the other sites examined the participants' performance on an often-used test, the Modified Mini-Mental State Exam (3MS). All participants' average performance on the cognitive tests actually improved over time, which researchers suggest may be due to a "practice effect" as a result of taking the same tests every year. However, the rate of increase in the performance of women on the 3MS was somewhat lower for women in the combination therapy group when compared with women receiving the placebo.

About 3,000 women are continuing to participate in a second arm of the WHIMS research, a study of the effects on cognition of estrogen-only therapy in women who have had a hysterectomy. A Data Safety Monitoring Board will continue to monitor the risks and benefits for that part of the study.

The NIH is considering implications of the dementia findings for other clinical studies involving E + P.

More details on the studies' findings and their implications for women can be found in a question-and-answer format prepared by the NIA for consumers. Readers and viewers can see the additional material after the media embargo of 4 p.m. ET, May 27, at the NIA website www.nia.nih.gov or can receive a paper copy by calling the NIA's Alzheimer's Disease Education and Referral (ADEAR) Center at 1-800-438-4380.

General information on hormone therapy and the Women's Health Initiative specifically can be found on the NIH home page, www.nih.gov, by clicking on the link "Menopausal Hormone Therapy."

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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 ADEAR Center website. The general public also may call the ADEAR Center toll free at 1-800-438-4380 for information and publications. General information on health and aging may be viewed at www.nia.nih.gov, and publications may be ordered by calling the NIA Information Center toll free at 1-800-222-2225.

The media may contact the NIA Office of Communications and Public Liaison at 301-496-1752. An audio conference for media only will be held on Tuesday, May 27, from 11 a.m. until noon, with Dr. Judy Salerno of the NIA and other experts on the study available to take questions from media prior to the 4 p.m. ET reporting embargo. Reporters can participate and/or listen to the WHIMS conference call by calling 1-888-632-5950 (1-713-481-1320 for international callers) approximately 15 minutes prior to the session and will be instructed by operators how to participate. A replay of the audio conference will be available two hours after the audio conference, through June 3, by calling 1-877-519-4471 (1-973-341-3080 for international callers).

Radio editors, please note: An audio report will be available after May 27, 4 p.m. ET, from the NIH Radio News Service, by calling 1-800-MED-DIAL, or 1-800-633-3425.

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