

Hormone replacement therapy: Study reveals increased dementia risk

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Postmenopausal women over the age of 65 using combined hormone therapy face significantly increased risks of dementia and strokes, according to new findings from a sub-study 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 issue of *Journal of the American Medical Association (JAMA)*, found that older women taking Prempro, the most commonly used form of estrogen plus progestin, were twice as likely to develop dementia, including Alzheimer's disease, than their placebo-taking counterparts.

Combination hormone therapy, also known as hormone replacement therapy (HRT), has been prescribed for decades ostensibly to mitigate menopausal symptoms, prevent heart disease, strokes, osteoporosis and was heralded as a means of "slowing the aging process" and preventing dementia.

The study, entitled "Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women," additionally found that the therapy does not protect against mild cognitive impairment. It concluded: "These findings, coupled with previously reported WHI data, support the conclusion that the risks of estrogen plus progestin outweigh the benefits."

A May 27 press release from the National Institutes of Health (NIH), a division of the US Department of Health and Human Services, concurred: "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."

More than 4,500 women 65 or older from 39 medical centers took part in the WHI memory study, which

began in 1995, and were randomly assigned either Prempro or a placebo. Administration of the drugs was halted in July 2002, when researchers discovered that the estrogen plus progestin group showed, among other findings: a 41 percent increase in strokes, a 29 percent increase in heart attacks, a doubling of blood clot rates, a 22 percent increase in total cardiovascular disease and a 26 percent increase in breast cancer.

Scientists also found that after four years of follow-up, there were 40 cases of probable dementia among the 2,229 hormone users and 21 among the 2,303 women in the placebo group. The dementia risk began increasing one year after the hormone treatment was initiated, with Alzheimer's disease being the most common diagnosis and vascular dementia ranking second. Both groups exhibited similar risks of developing mild cognitive impairment, a dementia precursor.

According to the NIH, investigators took into consideration factors that might influence cognitive status, such as socioeconomic issues, educational attainment, prior estrogen or progestin use history and involvement of other pertinent medication.

As of July 2002, when administration of the hormonal drug cocktail was ceased, some 6 million women in the US were being prescribed the therapy by their physicians. At that time the study results found that the adverse effects of the combination drugs applied to all women, irrespective of age, ethnicity or prior disease status.

A third WHI study, which followed 16,600 postmenopausal women age 50 to 79 for over five years, demonstrated a 31 percent increase of stroke risk in hormone users over placebo takers. The greater risk was present despite accounting for high blood pressure, cardiovascular disease, smoking, diabetes and other

factors.

“These results are quite staggering,” Dr. Lewis Kuller of the University of Pittsburgh Graduate School of Public Health, who headed up a local branch of the study, told a Pittsburgh newspaper in May. Fuller said that the stroke finding could help explain why hormone therapy augments the risk of dementia. He explained that the medications might cause changes in the blood vessels of the brain. Small infarcts (blood flow blockages) that are not easily detected could in turn lead to cognitive changes and eventual dementia.

“Right now any oral estrogen is basically not a winner until proven otherwise,” commented Kuller.

Dr. Gerardo Heiss, professor of epidemiology at the University of North Carolina, who helped design the overall Women’s Health study, reiterated that the strength of the findings, both the new ones and last year’s, was due to the large number of study participants. Heiss and colleagues found that “there was no subgroup of women who were not at increased risk of stroke if they were taking the combination therapy.”

“Overall, this paper indicates that the increased risk of ischemic stroke [which accounts for 80 percent of strokes] among women who were taking the hormone therapy is consistent with the reported increased risk in coronary heart disease and also with dementia attributable to an increased propensity to small strokes and cerebral infarcts,” stated Heiss.

The report’s lead author Dr. Sally Shumaker recommended “that older postmenopausal women not take the combination hormone therapy to prevent dementia” and hoped “doctors will incorporate what we’ve learned in their recommendations to patients.”

On May 8, Jennifer Hayes, PhD, director of the Center for Women’s Health at Baylor College of Medicine in Houston and leader of that part of the WHI study that explored quality of life issues related to hormone replacement therapy, spoke to *ABC News*. Said Hayes: “We picked the most commonly used measure of quality of life in the world. This measure has eight subscales: general health; physical functioning, emotional or mental health; role limitations due to physical problems; role limitations due to emotional problems; bodily pain; social functioning; energy and fatigue. In addition, we used a depression measure, a sleep disturbance measure, a cognitive impairment measure, and a question about

satisfaction with sex.”

“The effects of health-related quality of life were just very, very small. Out of the 13 separate measures that we looked at, there was a significant effect in only one. We had 574 women between the ages of 50 and 54 who reported moderate-to-severe hot flashes when they came into the study. In that group, we found a 5 percent improvement in sleep.”

Hayes continued: “I talked to women for whom hormone therapy has made all the difference in their quality of life during the phase where their hot flashes are most bothersome. But I don’t know that there is a ‘safe period’ to take it. We found that the rate of stroke, heart attack and blood clots occurred in the first two years. Breast cancer takes longer to develop.”

The formulation Prempro, manufactured by Wyeth Pharmaceuticals, was used in the study, explained Hayes, because some 85 percent of women taking estrogen with a progestin were on this drug. “Now there are some other options, including patches and estrogens and progestins from other sources, from plant-based estrogens and progesterones. The problem is we don’t have any data on those formulations or routes of administration. So until we do, the US Food and Drug Administration has cautioned that they should be treated the same. All combination hormones must have a black box warning in their physician labeling that highlights the increased health risks.”



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