

Two new studies show that commonly prescribed forms of postmenopausal hormone therapy may slightly accelerate the loss of brain tissue in women 65 and older beyond what normally occurs with aging (see also Wake Forest University Baptist Medical Center).

The studies' findings appear as companion papers in the Jan. 13 issue of *Neurology*, the medical journal of the American Academy of Neurology. Both papers report on analyses from the Women's Health Initiative Memory Study, a substudy of the National Institutes of Health's (NIH's) landmark Women's Health Initiative (WHI) hormone therapy clinical trials.

Previous studies showed that hormone therapy in the form of conjugated equine estrogens (CEEs), with or without added progestin, increased the likelihood that older women would have difficulty with thinking skills and memory and experience dementia or cognitive impairment. Because these drugs are known to increase women's risk for strokes, it had been assumed that these drugs adversely affected women's memory by increasing the rates of "silent strokes" and brain lesions, changes in tissue that occur when blood flow to an area of the brain is reduced or blocked.

Instead, investigators found that the volumes of brain lesions were not significantly increased among women prescribed hormone therapy, but that the total volumes of brain tissue in regions critical to memory were slightly smaller.

CEEs, which are components of Premarin<sup>TM</sup> and PremPro<sup>TM</sup>, have been used extensively for treating menopausal symptoms.

In the first of the two studies, a research team led by Laura H. Coker, Ph.D., of Wake Forest University Baptist Medical Center, did not find support for the hypothesis that hormone therapy was linked to increases in small vascular lesions in the brain or silent strokes.

"We asked," Coker said, "what is the most likely mechanism of the negative effect of hormone therapy on thinking and memory? We thought it was silent cerebrovascular disease. So we designed a study to obtain MRI scans of women's brains to look for increased volumes of brain lesions among those participants who had taken hormone therapy, compared

to those who had not." More than 1,400 women, ages 71 to 89, who had previously participated in the WHI hormone therapy studies for an average of four to six years, participated. "This is not what we expected to find," Coker said.

In the companion paper, researchers report that the women who had taken hormone therapy had slightly smaller brain volumes in two critical areas of the brain: the frontal lobe and the hippocampus. Both areas are involved in thinking and memory skills, and loss of volume in the hippocampus is a risk factor for dementia.

"Our findings suggest one possible explanation for the increased risk for dementia in older women who had previously taken post-menopausal hormone therapy in the Women's Health Initiative Memory Study," said Susan Resnick, Ph.D., of the National Institute on Aging, which is part of NIH. Resnick was the lead author for the second paper. "Our findings suggest that hormone therapy in older post-menopausal women has a negative effect on brain structures important in maintaining normal memory functioning. However, this negative effect was most pronounced in women who already may have had some memory problems before using hormone therapy, suggesting that the therapy may have accelerated a neurodegenerative disease process that had already begun."

Current recommendations are that hormone therapy be used only if needed to treat menopausal symptoms, and taken at the lowest dose and for the shortest time possible to relieve symptoms, which generally appear in women age 48 to 55. Women age 65 and older should not begin hormone therapy because the risks outweigh possible benefits. The new information suggests that older women who were already having some cognitive problems at the time they began hormone therapy are most at risk for negative effects on the brain. However, the findings also suggest that women who were healthy at the time they began hormone therapy were less likely to have any adverse effects on the brain, Resnick said.

Researchers will next set out to determine whether the negative effects of hormone therapy on brain volumes continue over time through follow-up MRI studies of the women studied. In addition, it will be important to examine younger women who took hormone therapy closer to the timing of menopause to determine whether they show a different pattern of effects on cognitive function and brain structure, Coker said.

Keywords: Aging, Central Nervous System Disease, Cerebrovascular Disease, Clinical Trial Research, Dementia, Endocrinology, Estrogen, Hormones, Menopause, Neurology, Therapy,

Treatment, Urology, Women's Health, Wake Forest University Baptist Medical Center.

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