

## **AAN: New Analysis Reverses Thinking on Estrogen and Alzheimer's**

**BOSTON, May 3 -- Women who took estrogen before age 65 may not be at a higher risk of later dementia after all.**

**Contradicting earlier findings of an association between the use of estrogen and the later development of Alzheimer's disease, a deeper analysis of the evidence that led to that conclusion has found the opposite, reported Victor W. Henderson, M.D., M.S., of Stanford University, and colleagues.**

**In fact, the new analysis suggests that women who used estrogen may have a nearly 50% lower risk of Alzheimer's, as long as they began using the hormone before age 65, they said at the American Academy of Neurology meeting here.**

**However, they cautioned against using the findings to change clinical practice.**

**The results of the new analysis of data from the Women's Health Initiative Memory Study, or WHIMS, came as something of a surprise, acknowledged Dr. Henderson.**

**Results of the WHIMS study, which enrolled 7,153 women aged 65 and up and was published in 2003, appeared to show that the overall use of estrogen was associated with an increased risk for all-cause dementia, and had no positive effect on global cognition.**

**Still, Dr. Henderson said, the WHIMS investigators wanted to probe more deeply to see whether there may have been undetected cognitive benefits among women who reported using either conjugated equine estrogen (Premarin) alone or estrogen plus progesterone (Prempro) prior to their enrollment in the study.**

**About 22% (961) of women in the estrogen/progestin arm of the WHIMS study had reported prior hormone use, as did about 45% (1,267) of women in the estrogen only trial.**

**In the deeper analysis reported by Dr. Henderson and colleagues, they found that the risk for all-cause dementia, which occurred in 106 women, was 0.54 (95% confidence interval, 0.32-0.91) for prior users compared with other women.**

**When they broke the data down by dementia type, they found that the hazard ratio for Alzheimer's disease among prior HRT users was 0.36 (95% CI, 0.16 to 0.85, statistically significant,  $P < 0.05$ ), and for other types of dementia the hazard ratio was 0.70 (95% CI, 0.36-1.39, not statistically significant).**

**Adjusting for possible confounding factors, they found that neither the timing of prior hormone initiation, age at first use, duration of use, recent use, or type of prior therapy were associated with these dementia outcomes.**

**Prior users, compared to nonusers, had minimally better baseline mean scores on the Modified Mini-Mental State examination in the estrogen-alone trial ( $94.95 \pm 4.42$  versus  $94.43 \pm 4.87$ ,  $P = 0.004$ ) but not in the estrogen-plus-progestin trial ( $95.68 \pm 3.86$  versus  $95.53 \pm 4.11$ ,  $P = 0.3$ ).**

Prior users tended to be slightly older than women who did not use estrogen until study assignment, and were also a few years longer past menopause. They also had slightly higher mean body mass index, and a slightly elevated risk of stroke or transient ischemic attack, Dr. Henderson noted.

"The conclusion here is that prior hormone usage was associated with a reduced rate of all-cause dementia and with Alzheimer's disease in the WHIMS trials," Dr. Henderson said, "and that there were some small and probably not very clinically important differences in terms of baseline cognition, and that the findings, we think have implications in terms of research that needs to be done in trying to determine the long-term cognitive outcomes of early hormone therapy usage."

Noting that the results of the current analysis are observational only, based on a relatively small number of dementia cases, Dr. Henderson cautioned that "the kind of evidence that we're reporting really isn't the kind of evidence that should be used to determine decisions in clinical practice," he said. "It's not strong enough to make that carryover."

Dr. Henderson speculated that the discrepancies between the current analysis and the overall WHIMS results might be related to beneficial effects of estrogen on some vascular factors.

#### Action Points

- Explain to patients who ask that the findings of the current analysis appear to contradict earlier indications that hormone replacement therapy may contribute to dementia. The findings need to be examined in much greater detail before therapeutic recommendations can be made.
- This study was published as an abstract and presented orally at a conference. These data and conclusions should be considered to be preliminary until they have been published in a peer-reviewed publication.