# Past hormone therapy in older women

## Does the brain recover from adverse effects?

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Women transitioning into menopause, particularly those who experience hot flashes, face the challenging decision about whether or not to initiate hormone therapy (HT). Those who choose to take HT must also decide how long to continue treatment. The Women's Health Initiative Memory Study (WHIMS), the only randomized controlled trial of the effects of HT on incident dementia, found that conjugated equine estrogen (CEE), when combined with medroxyprogesterone acetate, doubled the risk of dementia in women who initiated treatment at age 65 years and later.[1] Unopposed CEE (i.e., without medroxyprogesterone acetate) did not increase the incidence of dementia, but a pooled analysis of both treatment arms revealed a 76% increased incidence of dementia.[2]

There was speculation that the HT-related increase in dementia in these older women was due to subclinical stroke, but the WHIMS-MRI study showed no increase in ischemic lesion volume with HT vs placebo.[3] Instead, HT was associated with smaller hippocampal and prefrontal cortex volumes.[4] The increased risk of dementia in women randomized to HT was associated with smaller hippocampal volumes and total brain volume, whereas greater ischemic lesion load generally and in the frontal lobe in particular was associated with increased risk of dementia in women taking placebo.[5] An important remaining question was whether the effects of HT on the hippocampus and frontal lobes of women aged 65 and older are sustained or whether the brain recovers after treatment discontinuation.

In this issue of *Neurology*®, Coker et al.[6] present a follow-up study to the original WHIMS-MRI study to address that important question. The focus was on change in total brain volume in women aged 65 years and older who were enrolled in WHIMS and who completed CEE-based hormone treatments or placebo approximately 8 years earlier.[6] This longitudinal MRI investigation demonstrated that frontal lobe volume neither recovers nor continues to be adversely affected by HT discontinued 4.7 years earlier. Whereas the original study found lower hippocampal volumes with HT compared with placebo, in the follow-up study that effect did not reach statistical significance ($p = 0.08$). Similar to the original WHIMS-MRI report, there was no effect of HT on white matter lesions, which continued to increase at age-appropriate rates in all study groups. Another way to interpret the findings is that the adverse effects of HT on the brains of older women are limited to the time period they received CEE-based treatments.

Secondary analyses provided insights into factors that might exacerbate the negative effects of HT on brain structure in older women. First, total brain volume was predominantly reduced in women whose pretreatment scores on a measure of global cognitive status were low and not in women with high pretreatment scores. Second, in women with a history of cardiovascular disease, HT was associated with increases in white matter lesion volume and total brain lesion volume. These findings suggest that older women who show accelerated cognitive decline or cardiovascular disease might be particularly at risk of harmful effects of HT on brain structure.

It is important to consider the external generalizability of WHIMS and WHIMS-MRI to routine clinical care. Even before WHIMS, it was uncommon to initiate HT in a woman older than 65 years. Age is an important determinant of the effects of CEE-based therapies on cognition. WHIMS investigators recently demonstrated that these therapies produced no sustained benefit or risk to cognitive function for younger women aged 50 to 55 years, suggesting that the adverse effects of HT on the brain may be limited to older women.[7] Although some women initiate HT early in the menopausal transition and continue until after age 65, WHIMS and WHIMS-MRI cannot address the effect of early and continued use of HT on dementia or brain volume. Two recent observational studies indicated a lower risk of Alzheimer dementia in women who used HT only during the menopausal transition but not in women who continued to use HT after that period.[8,9] Those findings suggest that use of HT for a limited time around the menopausal transition might be associated with the most optimal cognitive outcomes and that any benefits might be lost with

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continued use into late life. However, we must recognize that there are no randomized trial data to address the issue of how long a woman who initiates HT early in the menopausal transition can remain on HT and maintain optimal brain health.

The study authors recognized that the clinical significance of the persistent effects of HT on frontal volumes is unclear. Frontal lobe volumes were not linked to dementia in WHIMS.[5] In the simplest terms, the persistent effect of HT on the frontal lobe is equivalent to volume lost in the placebo group over a 3-year period. However, there is the possibility that a negative impact of HT on hippocampal volumes may persist, and decreased hippocampal volume was associated with increased risk of dementia in the HT arm of WHIMS. This issue is important because the WHIMS-MRI follow-up study likely presents an underestimation of HT's effect on brain structure because the study enrolled only 59% of the women from the original cohort, and the re-enrolled women were younger and healthier than women in the original cohort.

A limitation of the study is absence of pretreatment assessments of brain measures to ensure the lack of any group differences at baseline. However, given similar cognitive performances across the treatment groups at baseline, we find it unlikely that there were differences in brain volumes among the CEE and placebo groups before HT was initiated. Overall, WHIMS-MRI shows how brain and white matter lesion volumes on MRI can be used to measure the biological effects of estrogens on the brains of postmenopausal women and guide informed clinical decision making regarding the use of HT.


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