

Hormone Replacement Therapy and the Risk of Dementia: The Women's Health Initiative Memory Study

Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and the incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2947–58.

Study Overview

Objective. To determine the effects of conjugated equine estrogen (CEE) alone and CEE plus medroxyprogesterone acetate (MPA) on incidence of probable dementia and mild cognitive impairment in older women.

Design. Prospective, randomized, double-blind, placebo-controlled clinical trials.

Setting and participants. This was a supplemental study to the Women's Health Initiative (WHI). All participants were community-dwelling women recruited from 39 of 40 WHI clinical centers. The study was conducted from June 1995 through 8 July 2002 (estrogen plus progestin trial; $n = 4532$) or through 29 February 2004 (estrogen alone trial; $n = 2947$). Eligible participants were aged 65 to 79 years and free of probable dementia at the time of enrollment.

Intervention. Participants in the estrogen-alone trial were given either 1 tablet of CEE 0.625 mg/day or matching placebo. In the estrogen plus progestin trial, participants were given either 1 tablet CEE plus MPA 0.625/2.5 mg per day or matching placebos.

Main outcome measures. Probable dementia and mild cognitive impairment as measured by a 4-phase protocol. In phase 1, participants underwent cognitive screening with a modified Mini-Mental State Examination (baseline and annually thereafter). Women who scored below an education-adjusted cut point were referred to phase 2. Phase 2 consisted of a battery of neuropsychologic testing and standardized interviews to assess acquired cognitive and behavioral impairments. In addition, a designated informant was interviewed separately regarding acquired cognitive or behavioral impairments in the participant. Phase 3 consisted of an evaluation by a local physician specialist with experience in diagnosing dementia. Participants were classified as having no dementia, mild cognitive impairment, or probable dementia. Women suspected of having probable dementia underwent phase 4, including noncontrasted computed tomography of the brain and laboratory blood tests to rule out reversible causes of cognitive decline. All cases judged as

probable dementia, 50% of mild cognitive impairment cases, and 10% of normal cases were independently reviewed by the central adjudicators.

Main results. Of 8094 age-eligible WHI participants, 7479 women consented to participate. 3693 participants were randomized to active treatment (CEE alone or CEE plus MPA), and 3786 were randomized to matching placebo. Baseline demographic characteristics were similar between the groups. In the treatment arms, 68 were diagnosed with probable dementia as compared with 40 in the placebo groups (hazard ratio [HR], 1.76 [95% confidence interval {CI}, 1.19–2.60]; $P = 0.005$). Incidence rates for probable dementia in the estrogen-alone trial were statistically similar to those in the estrogen plus progestin trial. After excluding participants with baseline modified Mini-Mental State Examination scores at or below the screening cut point, the HR was 1.77 (95% CI, 0.74–4.23; $P = 0.20$) in the estrogen-alone trial and 2.19 (95% CI, 1.25–3.84; $P = 0.006$) in the pooled trials. In the estrogen alone trial, 76 participants were diagnosed with mild cognitive impairment as compared with 58 in the placebo group (HR, 1.34 [95% CI, 0.95–1.89]). In the combined trial data, the HR was similar (1.25 [95% CI, 0.97–1.60]). For the composite endpoint of dementia or mild cognitive impairment, the HR was 1.41 for the pooled data (95% CI, 1.12–1.76; $P = 0.003$).

Conclusion. Estrogen therapy alone did not reduce dementia or the incidence of mild cognitive impairment and increased the risk for both endpoints. Pooling the data from estrogen alone and estrogen plus progestin resulted in increased risk of both endpoints.

Commentary

Previous studies have suggested that long-term hormone therapy may minimize cognitive decline and the onset of dementia in postmenopausal women [1,2]. As a result, in the mid-1990s, approximately 38% of postmenopausal women in the United States used hormone replacement therapy (HRT) to treat symptoms of menopause and prevent chronic conditions such as heart disease and osteoporosis [3]. The WHI study is a large, randomized, placebo-controlled trial

designed to study the risks and benefits of postmenopausal HRT. Shumaker and colleagues have conducted a trial to determine if the use of long-term HRT can prevent the onset of dementia and cognitive impairment.

This study showed that use of HRT either as estrogen alone or estrogen combined with progestin does not delay cognitive decline, and in fact, treatment was associated with an increased incidence of dementia compared with placebo. An important limitation of this study relates to the timing of HRT. Since women in this trial were aged 65 years or older at baseline, delayed onset of treatment relative to menopause may have allowed irreversible neurodegeneration to occur that HRT could not improve. Also, the higher risk of dementia in women receiving active treatment could be due to adverse effects of estrogen on vascular disease in the brain [4]. The possibility that HRT is associated with an increase in vascular disease in the brain could have important implications, as participants may have developed neurovascular disease but not yet have clinical manifestations such as cognitive impairment or dementia. Further follow-up of the participants in this trial is planned to determine whether an increased risk for dementia and cognitive impairment persists following HRT discontinuation.

Applications for Clinical Practice

The results of the Women's Health Initiative Memory Study demonstrate an increased risk of dementia and mild cognitive impairment with HRT use among women aged 65 to 79 years. Use of hormone therapy to prevent dementia or cognitive decline in women aged 65 years or older is not recommended.

—Review by Christianne L. Roumie, MD

References

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