



Effects of Estrogen Plus Progestin on Risk of Dementia

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measurement. Our suggestion that tests revealing elevated levels of PSA be repeated after a few weeks would have the effect of making the test criterion more “stringent” and thus increasing its specificity, just as the impetus to schedule a biopsy would be reduced for those men whose subsequent test result is normal. We acknowledge that this suggestion is merely a commonsense interpretation of the implications of these results and not based on the data. We agree with Hakama and Auvinen that the merit of PSA screening for prostate cancer should be informed by the results of randomized trials.

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Effects of Estrogen Plus Progestin on Risk of Dementia

To the Editor: Dr Shumaker and colleagues¹ from the Women’s Health Initiative Memory Study (WHIMS) reported that combined equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) increased the risk for probable dementia in postmenopausal women aged 65 years or older. They also found that this regimen did not prevent mild cognitive impairment. These findings are consistent with our data that MPA antagonizes the neuroprotective and memory mechanisms of estrogen.²⁻⁴ These studies, conducted while the WHIMS trial was in progress, indicate that progestins have differing profiles of biochemical and genomic activation that lead to differential effects on beneficial estrogen-inducible mechanisms.⁵ Results of these analyses could be used to predict efficacy of hormone therapy formulations for prevention of Alzheimer disease (AD). The challenge remains to develop a therapeutic strategy for promoting the beneficial effects of estrogen in the brain while preventing untoward consequences of estrogen in other organ systems.

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To the Editor: Although the results of the WHIMS trial¹ may seem surprising, they are consistent with the results of previous observational studies of hormone therapy and risk of AD.

In their case-control study, Brenner et al² found no relationship between incident AD and use of hormone therapy within a 10-year interval. Similar 10-year results were reported from the UK General Practice Research Database.³ By contrast, 2 prospective studies^{4,5} have suggested that lifetime hormone use (presumably including perimenopausal and early postmenopausal use) may be beneficial.

We suggested a resolution to this conflict in our recent analyses of data from the Cache County Study.⁶ We found adjusted hazard ratios (HRs) of 2.12 and 2.41 for dementia among current users of hormone therapy with exposures of less than 3 and of 3 to 10 years, respectively. These values are similar to the HR of 2.05 reported in the WHIMS. However, we also found much lower HRs of 0.17 to 0.32 among former users of hormone therapy who reported 3 or more years of exposure. Therefore, we concluded that “our results and those of all prior observational studies are consistent with a loss of (protective) HRT [hormone replacement therapy] effect from exposures near the onset of dementia,” and concluded that “the benefits of HRT (in randomized prevention trials) may take years to appear, and a considerable latency period may intervene between treatment and effect. Thus, caution would be in order when interpreting null or disappointing early trial results.”

We fear that the WHIMS results will prematurely spell the end of any practical interest in the use of hormone therapy for prevention of AD. We caution, first, that the WHIMS results relate specifically to use of combined equine estrogens with medroxy-progesterone acetate (72% of hormone therapy users in Cache County took oral unopposed estrogens). Second, the results are only applicable to women with concurrent or very recent exposure to hormone therapy. Considering all available data, including particularly the new trial data, we concur that women should not initiate estrogen plus progestin treatment in old age with hopes of preventing AD. Nonetheless, earlier use may reduce the risk of AD a decade or more later. Continued monitoring of incident AD for another decade in the WHIMS cohort should provide much-needed evidence.

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