Estrogen Levels Do Not Correlate With Improvement in Cognition
Leon J. Thal, MD; Ronald G. Thomas, PhD; Ruth Mulnard, RN, DNSc; Mary Sano, PhD; Michael Grundman, MD, MPH; Lon Schneider, MD

Objective: To investigate whether an association exists between estradiol and estrone levels and measures of cognitive functioning in women with Alzheimer disease (AD) treated with conjugated equine estrogen (Premarin; Wyeth-Ayerst, Philadelphia, Pa).

Methods: We studied 120 postmenopausal women who underwent hysterectomy and who had AD treated with Premarin for 1 year. Plasma estradiol and estrone levels were determined at multiple points during the 1-year treatment trial. The change from baseline level at 2 and 12 months was associated with the change score on 7 different assessments of cognitive functioning.

Results: At baseline, estradiol levels were low and there were no associations between the estradiol level and the 7 neuropsychological measures. A similar pattern was observed for estrone treatment. During treatment with 0.625 mg/d of Premarin, estradiol levels increased about 4-fold; while receiving 1.25 mg/d of Premarin, estradiol levels increased about 8-fold. A similar pattern was seen with estrone treatment. For both estradiol and estrone levels, there were no significant associations between the change in plasma level and the change in neuropsychological test scores at either 2 or 12 months.

Conclusion: Although Premarin elevated estradiol and estrone levels, there was no association between hormone levels and cognitive functioning after either 2 or 12 months of treatment.

Arch Neurol. 2003;60:209-212

A LZHEIMER DISEASE (AD) is the most common cause of dementia in the United States affecting approximately 4 million individuals. It occurs with higher frequency in women.1 Considerable evidence has emerged from epidemiological and preclinical studies suggesting that orally administered estrogens may be beneficial in improving cognition and mood in AD. This evidence includes up-regulation of choline acetyltransferase activity by estrogens,2 colocalization of estrogen and nerve growth factor receptors on cholinergic neurons,3 and improvement in neuropsychological functioning in postmenopausal women taking estrogens.4,5 However, 3 recent randomized, controlled clinical trials of conjugated equine estrogens (Premarin; Wyeth-Ayerst, Philadelphia, Pa) have failed to substantiate this claim.6-8 In contrast, 2 small controlled clinical trials using an estrogen patch reported improvement in attention and verbal memory on selected tasks although improvement was not seen on global cognitive or functional scales.9,10 In addition, plasma estradiol levels in a very small subset of patients in studies reported by Ashtana et al9,10 correlated with delayed recall, a measure of memory.

We previously reported on the rate of decline over a 1-year period in a relatively large multicenter trial examining the effects of Premarin in postmenopausal women who had AD.7 Although the overall results of this trial show no significant cognitive or global effects of conjugated equine estrogens over placebo treatment, women treated with Premarin did demonstrate increased plasma estradiol levels. It is possible that women with higher levels of circulating estrogens might have responded and that this response was masked in the overall group analyses. We report herein on a further analysis correlating the change in plasma estradiol levels with the change in a variety of global measures of cognition as well as with specific tests of memory, attention, and language to determine whether increasing circulating estradiol levels predicted response. These analyses were then repeated using estrone, the major estrogenic compound in Premarin. Results of the plasma estra-
At baseline, estradiol levels were low and equivalent in all 3 groups reflecting the postmenopausal status and the absence of estrogen supplementation (Figure). There were no significant associations between baseline estradiol levels and any of the 7 neuropsychological measures. An identical pattern was observed for estrone.

During treatment, patients receiving placebo maintained uniformly low levels of estradiol averaging approximately 5 pg/mL (18 pmol/L) (Figure). Individuals receiving 0.625 mg/d of Premarin had mean estradiol levels of approximately 20 pg/mL (73 pmol/L) and those receiving 1.25 mg/d of Premarin had levels averaging 33 to 40 pg/mL (128-147 pmol/L). All estradiol levels returned to pretreatment values by 3 months after discontinuing Premarin treatment. A similar pattern was seen with estrone with levels averaging approximately 175 pg/mL (648 pmol/L) while receiving 0.625 mg/d of Premarin and 350 pg/mL (1295 pmol/L) while receiving 1.25 mg/d of Premarin (data not shown).

Across all treated patients, levels of estradiol ranged from 0 to more than 100 pg/mL (0 to >367 pmol/L). This spread in estradiol levels allowed us to examine the change scores between cognitive measures across a wide range of plasma estradiol levels. There were no significant associations between the MMSE or ADAS-Cog change score and plasma estradiol change at either 2 or 12 months after initiating therapy. There was a significant negative association between change in delayed recall and change in estradiol level at 12 months but not at 2 months (Table). Further exploration of this relationship revealed that this association was largely dependent on 3 outliers in which large increases in plasma estradiol levels (55, 62, and 73 pg/mL [202, 227, and 268 pmol/L, respectively]) were associated with decreases in delayed word recall at 12 months (P = .75). There were no significant associations between the change scores in estradiol level and delayed recall disappeared (P = .05) that disappeared when the 3 outliers were removed (P = .88). In addition, there was a separate and independent main effect of apolipoprotein E on change in the delayed recall test results at 12 months for both estradiol and estrone that also disappeared when the 3 outliers were removed.

In this large, multicenter, randomized, controlled clinical trial, commonly used doses of Premarin elevated plasma estradiol levels approximately 4-fold at the low dose and approximately 8-fold at the higher dose, resulting in mean levels of approximately 20 pg/mL (73 pmol/L) while receiving 0.625 mg/d of Premarin and 40 pg/mL (147 pmol/L) while receiving 1.25 mg/d of Premarin.
Unlike our study, these subjects had not undergone hysterectomy. As in the present study, studies by Henderson et al⁶ and Wang et al⁷ failed to detect cognitive improvement. In contrast, 2 very small studies by Asthana et al⁹,10 reported improvement on tests of attention and memory in 12 and 20 women, respectively, randomized to treatment with an estradiol patch delivering 0.05 mg/d or 0.1 mg/d of estradiol-17β. The lower-dose patch produced plasma estradiol levels reaching about 70 pg/mL (257 pmol/L) while the higher-dose patch resulted in estradiol levels of approximately 120 pg/mL (440 pmol/L). A correlation was found between the level of plasma estradiol and the test results of delayed cued recall in 6 of 12 subjects receiving 0.05 mg/d of Premarin.⁹ In the second study, using the higher-dose patch, improvements were noted in tasks of attention, total recall, and figure copying but not in global status, mood, or functional assessments.¹⁰ In our study, we enrolled many more subjects and attained plasma estradiol levels using Premarin that were as high as the levels reported by Asthana et al.⁹,¹⁰ We failed to observe a significant positive association between change in plasma estradiol levels and performance on a variety of cognitive measures. Comparability across trials is apparent in that 2 of the 3 larger studies⁶,⁸ included patients who did not undergo hysterectomy and our study⁷ attained plasma estradiol levels over 140 pg/mL (>514 pmol/L), consistent with the findings of Asthana et al.⁹,¹⁰ Thus, we conclude that the results obtained by Asthana et al are most likely secondary to the use of small sample sizes and the presence of a few outliers.

**Accepted for publication October 17, 2002.**

**Author contributions:** Study concept and design (Drs Thal, Thomas, Grundman, and Schneider); acquisition of data (Drs Mulnard and Grundman); analysis and interpretation of data (Drs Thomas, Grundman, and Schneider); drafting of the manuscript (Drs Thal, Thomas, Sano, Grundman, and Schneider); critical revision of the manuscript for important intellectual content (Drs Thomas, Mulnard, Sano, Grundman, and Schneider); statistical expertise (Drs Thomas, Grundman, and Schneider); obtained funding (Drs Thal and Grundman); administrative, technical, and material support (Drs Thomas, Mulnard, Sano, and Grundman); study supervision (Dr Grundman).

This study was supported by grant AGO 10483 from the National Institute on Aging, Washington, DC.

We thank Wyeth-Ayerst for supplying Premarin and performing the plasma sample and hormone assays.

Corresponding author and reprints: Leon J. Thal, MD, Department of Neurosciences, University of California, San Francisco, CA 94143-0450.
Diego, School of Medicine, 9500 Gilman Dr, La Jolla, CA 92039 (e-mail: lthal@ucsd.edu).

REFERENCES


17. Mohs RC, Knopman D, Peterson RC, et al, for the Alzheimer’s Disease Cooperative Study. Development of cognitive instruments for use in clinical trials of antideimen-


24. Blessed G, Tomlinson BE, Roth M. The association between quantitative mea-
sures of dementia and of senile change in the cerebral grey matter of elderly sub-


tradiol therapy for senile dementia—Alzheimer’s type. Psychoneuroendocrinol-

27. Yaffe K, Grady D, Pressman S. Serum estrogen levels, cognitive performance, and risk of cognitive decline in older community women. J Am Geri-

28. Hogervorst E, Williams J, Budge M, Riedel W, Jolles J. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-

©2003 American Medical Association. All rights reserved.