Effects of estrogen on cognition, mood, and cerebral blood flow in AD: A controlled study

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A controlled study

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Article abstract—*Objective:* To examine the effects of estrogen therapy on cognition, mood, and cerebral blood flow in patients with AD. *Background:* Some studies have suggested estrogen may be effective in the treatment of AD. However, most of these studies were not controlled adequately. *Methods:* Fifty female AD patients were recruited in a randomized, double-blind, placebo-controlled 12-week trial. Each member of the estrogen-treated group received conjugated estrogen (Premarin) 1.25 mg/day. The primary outcome measures were the Cognitive Ability Screening Instrument (CASI), Clinical Dementia Rating (CDR), and Clinician Interview-Based Impression of Change (CIBIC-plus). The secondary outcome measures were Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD), Hamilton Anxiety Rating Scale (HARS), Hamilton Depression Rating Scale (HDRS), and ^{99m}Tc hexamethylpropylene amine oxime SPECT of the brain. *Results:* No meaningful differences were found between the outcome measures (CASI, CDR, CIBIC-plus, BEHAVE-AD, HARS, HDRS, and cerebral blood flow) taken from the estrogen-treated group and those from the control group. *Conclusion:* A 1.25-mg/day dose of Premarin administered for 12 consecutive weeks does not produce a meaningful effect on cognitive performance, dementia severity, behavior, mood, and cerebral perfusion in female AD patients. Because estrogen therapy has been suspected of yielding adverse effects, and its therapeutic effectiveness is in doubt, additional evaluation of its role in AD treatment ought to be conducted. **Key words:** Estrogen—Dementia—AD—Cognition—Depression—Cerebral blood perfusion.

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Estrogen replacement therapy is widely used among postmenopausal women to prevent osteoporosis[1] and to reduce the risk of cardiovascular disease.[2] However, the role of estrogen in the prevention or treatment of AD has not been established conclusively.[3]

Animal studies suggest that estrogen might affect neuropsychological functions through several mechanisms, including stimulation of neurite outgrowth,[4] modulation of the neurotransmitters,[5] alteration of the lipoprotein components,[6] transformation of amyloid precursor protein solubility,[7] and protection against cerebral ischemia.[8]

Some clinical studies have shown that estrogen therapy improved cognitive function in postmenopausal[9] and climacteric women.[10] It has been suggested that this improvement may be attributed to the relief of menopausal symptoms.[9,11] Some other studies reported that women who received estrogen ran a lower risk in development of AD,[12,13] but the results were inconsistent and inconclusive.[3]

In connection with treatment of AD, previous studies reported that estrogen benefited AD patients in some aspects, but not in all measures of dementia severity.[14-19] One study demonstrated further that estrogen therapy enhanced cerebral blood flow of AD patients.[17] Having noted that most of these studies were open trials,[14,15,17-19] we conducted a randomized, double-blind, placebo-controlled study to evaluate the effects of estrogen on cognition, mood, and cerebral perfusion in AD patients.

Methods. The institutional review board of the Taipei Veterans General Hospital approved this study. The nature and purpose of the study were explained and made known to each patient and one of the patient's caregivers, and signed informed consent was obtained.

Patient population. Women with mild to moderate AD age 60 years and older were recruited. All met the diagnostic criteria of probable AD set by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associ-

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ation.[20] Their baseline Mini-Mental State Examination (MMSE)[21] scores were from 10 to 26, and their Clinical Dementia Ratings (CDRs)[22] were 1 or 2. None of the patients had a Hachinski ischemic score[23] of more than 4. All patients were instructed not to take other antidementia medication during the 12-week experimental period.

All patients were otherwise healthy as determined by physical and laboratory examinations. A patient was excluded if she had uncontrolled diabetes or hypertension, an active disease, or a past or family history of endometrial or breast cancer. Every patient received a gynecologic examination, including a cervical Papanicolaou smear, before and at the end of the trial.

Estrogen administration protocol. This trial was double blind and placebo controlled. Patients were randomized at a ratio of 1:1 to receive either conjugated estrogen (Premarin, Wyeth-Ayerst [Asia], Taiwan) 1.25 mg or placebo, orally once per day. The Premarin and placebo drugs were put in standard gelatin capsules to mask their identity and were dispensed every 2 weeks for 12 weeks.

Possible adverse events, including vaginal bleeding, vaginal itching, breast enlargement, endometrial cancer, breast cancer, thromboembolic events, hypertension, skin rash, and headache, were recorded.

Efficacy measures. Every patient was evaluated by a neurologist, a psychiatrist, and a research assistant at baseline, and at the end of weeks 6 and 12 of treatment.

Primary outcome measures. Our trained assistants administered the Cognitive Abilities Screening Instrument (CASI)[24] to assess cognitive performance. CASI, written in Chinese, provides a quantitative assessment of attention, concentration, orientation, short-term memory, long-term memory, language ability, visual construction, category fluency, abstract thinking, and judgment. It has a score range of 0 to 100, and a higher score indicates a better performance. CASI has been used as a tool to assess longitudinal cognitive decline in community studies.[25,26] Some of its items are identical to or closely resemble those included in the MMSE, so that an estimated MMSE score (MMSE-CE) can be derived from these items. The MMSE-CE has been found to be nearly identical to the MMSE score obtained through conventional means.[27]

Neurologists recorded patients' histories and performed neurologic examinations. The Clinician's Interview-Based Impression of Change (CIBIC-plus)[28] was used to evaluate the general clinical status of patients relative to baseline. The severity of dementia was graded in accordance with the CDR.[22]

Secondary outcome measures. Psychometric assessments were performed at baseline and the end of week 12 by one psychiatrist. The Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD)[29] scale was used to assess common behavioral problems in AD patients. The Hamilton Depression Rating Scale (HDRS)[30] and Hamilton Anxiety Rating Scale (HARS)[31] were used to evaluate the affective condition of AD patients.

Regional cerebral blood flow (rCBF) measurements. rCBF was measured with SPECT at baseline and at the end of week 12. SPECT was performed using a rotating gamma camera (Helix HR, Elscint, Israel) after IV injection of 15 mCi ^{99m}Tc hexamethylpropylene amine oxime (HMPAO; Ceretec, Amersham International, UK). Data were obtained in a 64 × 64 pixel matrix through a 360-deg rotation at an angular interval of 6 deg. Transaxial slices of the brain were reconstructed from the brain base up to the vertex of the brain using a standard back-projection method and a Hanning filter. Five transaxial slices (two pixels thick, one pixel = 6.9 mm) were selected for each patient with one slice corresponding to the cerebellum (orbitomeatal [OM] line) and four supratentorial cerebral slices at 0.69, 1.4, 2.8, and 3.6 cm above the OM line. Eight regions of interest (ROIs), four in the right hemisphere and four in the left hemisphere, were set up symmetrically on each cerebral slice, making a total of 32 ROIs in the supratentorial area. Two symmetric ROIs were selected in each cerebellar hemisphere. The mean pixel counts (MPC) of these two ROIs represented cerebellar activity. The index for rCBF (corticocerebellar ratio [CCR]) was calculated from the ratio of cortical to cerebellar ROI MPC.

Laboratory tests. Blood samples were drawn from patients at baseline and at the end of the trial. Serum levels of estrone (E1), estradiol (E2), and dehydroepiandrosterone sulfate (DHEA-S) were measured by radioimmunoassay (RIA)[32,33] and served as an index of compliance and response to treatment. The minimum recorded level of RIA for E1 was 0.025 ng/mL, and was 20 pg/mL for E2.

Statistical analysis. SPSS for Windows (SPSS 8.0, IL) was used for data analysis. Efficacy was evaluated based on an intent-to-treat population, including all randomized patients who had at least one dose of the study drug and one postbaseline data point. The mean changes of outcome measures from baseline to weeks 6 and 12 were compared. Student's *t*-test was used to examine the differences in continuous measures between the estrogen-treated group and the placebo group. Categoric variables were analyzed by chi-square test.

Results. *Protocol deviations and withdrawal information.* Fifty women with AD were enrolled in the study. Twenty-five patients were randomized to the estrogen arm and the other 25 to the placebo arm (figure). Two patients in the placebo group discontinued prematurely. One was admitted to the hospital due to suffocation resulting in hypoxic encephalopathy at week 10. Another patient dropped out of the trial due to poor compliance. One patient in the estrogen-treated group did not take medication during the last 4 weeks due to massive vaginal bleeding. Nonetheless, she completed the week 12 evaluation as scheduled.

Baseline patient characteristics. The demographic and baseline cognitive performance data of the patients are shown in table 1. Only two patients had previous exposure to estrogen, but neither of them took estrogen within 1 month before the study. Patients in each group were comparable with respect to baseline characteristics and baseline outcome measures.

Primary outcome measures. The mean changes in all of the outcome measures are shown in table 2. No differences were found in the changes of CASI (1.0 ± 8.0 versus 0.5 ± 8.2, $p = 0.850$) and MMSE-CE (0.2 ± 3.3 versus 0.2 ± 2.5, $p = 0.975$) scores between the estrogen and placebo groups at the end of the study. None of the subscales of CASI showed significant improvement in the estrogen-treated group. The changes of CIBIC-plus (−0.2 ± 1.0 versus −0.2 ± 0.8, $p = 0.944$) and CDR (0.0 ±

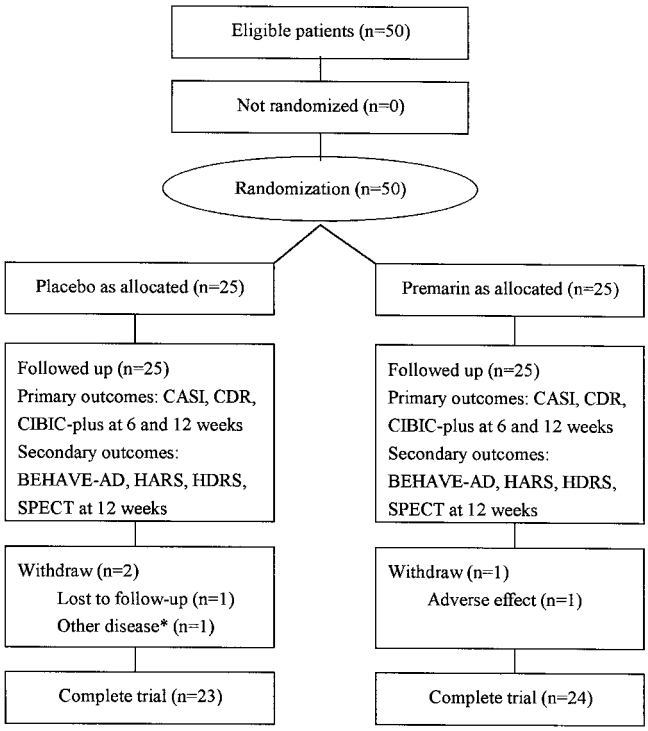

*Figure. Trial profile. *Other disease = suffocation resulting in hypoxic encephalopathy; CASI = Cognitive Assessment Screening Instrument; CDR = Clinical Dementia Rating; CIBIC-plus = Clinician Interview-Based Impression of Change; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale.*

0.4 versus 0.1 ± 0.4, $p = 0.366$) were similar between the two groups.

Secondary outcome measures. In the psychometric assessments, the estrogen group had greater but nonsignificant improvements in the HDRS (−1.2 ± 5.8 versus 0.4 ± 4.8, $p = 0.335$) and HARS (−0.8 ± 4.7 versus 0.4 ± 2.6, $p = 0.277$) scores at the end of the study. No intergroup difference was noted in the BEHAVE-AD score.

Thirty-four patients (17 in the estrogen-treated group and 17 in the placebo group) had a ^{99m}Tc HMPAO SPECT pattern consistent with AD, with a characteristic pattern of decreased perfusion over the bilateral temporoparietal regions. The CCR changes of the 32 ROIs in the two groups did not show any group difference. We further grouped the 32 cerebral ROIs into four cortical regions: frontal, anterior temporoparietal, posterior temporoparietal, and occipital. Changes in mean CCR in these four cortical regions (frontal: 0.00 ± 0.12 versus 0.01 ± 0.12, $p = 0.829$; anterior temporoparietal: 0.00 ± 0.15 versus 0.04 ± 0.13, $p = 0.391$; posterior temporoparietal: 0.01 ± 0.13, versus 0.02 ± 0.12, $p = 0.447$; occipital: 0.02 ± 0.18 versus 0.06 ± 0.14, $p = 0.492$), and in the whole brain (0.01 ± 0.14 versus 0.04 ± 0.12, $p = 0.475$) showed no differences between the two groups.

Serum level of hormones. Estrogen therapy elevated the serum level of E1 (0.05 ± 0.08 versus 0.01 ± 0.02 ng/mL, $p = 0.013$) and E2 (97.0 ± 122.6 versus −16.6 ± 59.5 pg/mL, $p < 0.001$) after 12 weeks of treatment. This finding indicates that compliance was good in the estrogen group. The changes in serum DHEA-S level were not different (−0.1 ± 0.8 versus 0.1 ± 0.8 μmol/L, $p = 0.471$) between the two groups.

***Table 1** Demographic data and baseline outcome measures in the estrogen and placebo groups*

Parameter	Estrogen	Placebo	*p* Value
Age, y	72.6 ± 9.1	71.0 ± 9.1	0.471
Education, y	6.9 ± 5.4	4.9 ± 5.2	0.246
Body weight, kg	52.9 ± 8.1	56.3 ± 6.5	0.103
Age at menarche, y	15.8 ± 2.0	16.2 ± 2.3	0.496
Age at menopause, y	49.0 ± 4.4	51.2 ± 3.8	0.497
E1, ng/mL	0.027 ± 0.005	0.026 ± 0.004	0.604
E2, pg/mL	26.3 ± 19.1	34.6 ± 55.5	0.481
DHEA-S, μmol/L	2.0 ± 1.5	1.7 ± 1.5	0.451
CASI score	57.5 ± 15.7	56.3 ± 14.6	0.780
MMSE-CE, score	16.1 ± 4.3	16.2 ± 4.2	0.894
CDR	1.3 ± 0.5	1.2 ± 0.4	0.571
BEHAVE-AD score	4.9 ± 5.7	4.7 ± 5.5	0.900
HDRS score	7.1 ± 4.5	7.5 ± 4.9	0.766
HARS score	6.4 ± 4.7	7.2 ± 4.3	0.515
Mean CCR	0.8 ± 0.2	0.8 ± 0.1	0.479

Values are mean ± SD.

E1 = estrone; E2 = estradiol; DHEA-S = dehydroepiandrosterone sulfate; CASI = Cognitive Assessment Screening Instrument; MMSE-CE = CASI-estimated Mini-Mental State Examination score; CDR = Clinical Dementia Rating; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; CCR = corticocerebellar ratio.

Adverse events. All adverse events are listed in table 3. One patient suffocated and died from aspiration pneumonia 1 month after suffocation. The estrogen-treated group had nearly as many adverse events as the placebo group except in the case of vaginal bleeding, which occurred in 11 of 25 estrogen-treated patients (44.0%). On reporting vaginal bleeding, a patient would receive a comprehensive gynecologic examination. The patient continued taking medication if no abnormality was found. Only one patient withdrew from the study due to vaginal bleeding. Neither breast cancer, endometrial cancer, nor thromboembolic events were noted during the study period.

Discussion. Through this randomized, double-blind, placebo-controlled study, we found that estrogen brought about no significant benefit in female AD patients. This result conflicts with the findings of previous studies, most of which indicated that estrogen therapy improved some of the measures of dementia severity.[14-19]

The explanation for this conflict may involve several issues. Perhaps the most important is the study design. Most of the previous studies used an open-label design.[14,15,17-19] In our study the fact that the placebo group also showed mild improvement in cognitive performance suggests that this improvement might be related to the practice or learning effect.

Table 2 *The mean (± SD) changes of all outcome measures during the study period*

	6 Weeks		12 Weeks	
Parameter	Estrogen	Placebo	Estrogen	Placebo
Total CASI score	0.4 ± 5.2	−0.7 ± 8.2	1.0 ± 8.0	0.5 ± 8.2
Short-term memory	−0.4 ± 2.5	0.1 ± 2.7	1.1 ± 2.5	0.2 ± 2.5
Long-term memory	0.3 ± 1.3	−0.3 ± 2.3	−0.1 ± 1.7	−0.1 ± 1.0
Attention	0.5 ± 1.2	0.4 ± 1.5	0.3 ± 1.3	0.4 ± 1.3
Orientation	0.1 ± 2.8	−0.1 ± 1.9	−0.1 ± 3.5	0.0 ± 2.8
MENMA	0.6 ± 1.7	−0.1 ± 1.9	0.3 ± 2.0	0.4 ± 1.9
Abstraction and judgment	−0.4 ± 1.6	0.3 ± 1.3	−0.1 ± 1.6	0.1 ± 2.0
Language	−0.3 ± 1.6	−0.3 ± 1.5	−0.1 ± 1.9	−0.3 ± 1.7
Visual construction	0.0 ± 1.3	0.2 ± 3.3	0.2 ± 2.3	0.1 ± 2.6
ANML	0.4 ± 1.9	−0.7 ± 1.8	−0.1 ± 1.6	−0.4 ± 1.8
MMSE-CE score	0.3 ± 2.8	−0.7 ± 2.6	0.2 ± 3.3	0.2 ± 2.5
CIBIC-plus score	−0.2 ± 0.9	−0.2 ± 0.8	−0.2 ± 1.0	−0.2 ± 0.8
Clinical Dementia Rating	0.0 ± 0.3	0.0 ± 0.4	0.0 ± 0.4	0.1 ± 0.4
BEHAVE-AD score	—	—	−0.4 ± 3.8	−0.8 ± 5.0
HARS score	—	—	−0.8 ± 4.7	0.4 ± 2.6
HDRS score	—	—	−1.2 ± 5.8	0.4 ± 4.8
Mean corticocerebellar ratio	—	—	0.01 ± 0.14	0.04 ± 0.12

None of the variables in the table showed significant differences between the estrogen-treated and the placebo groups by Student's *t*-test.

CASI = Cognitive Assessment Screening Instrument; MENMA = concentration/mental manipulation; ANML = list generating fluency; MMSE-CE = CASI-estimated Mini-Mental State Examination; CIBIC-plus = Clinician Interview-Based Impression of Change; BEHAVE-AD = Behavioral Pathology in AD; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale.

The only placebo-controlled study[16] revealed improvement on only one dementia scale, but not on two others.

Furthermore, all of the studies were limited by sample size. Although one study[17] recruited more than 50 patients (total 62), only 9 patients received estrogen therapy. We enrolled 50 AD patients, of whom 25 received estrogen therapy. But even this number may be insufficient. Based on our results, the mean treatment difference in CASI score between the two groups was 0.5 with an SD of 8.1. With 80% power and a two-sided probability of 0.05 for type I error, we figure the number of patients required to detect a meaningful difference in a 12-week period is 4,121 for each group. Therefore, the possibility of type II error causing a negative result in this study is negligible.

Table 3 *Adverse events in the estrogen-treated and the placebo groups*

Parameter	Estrogen, n	Placebo, n	*p* Value
Vaginal bleeding	11	0	0.001
Vaginal itching	3	3	1.000
Breast enlargement	9	4	0.107
Hypertension	11	13	0.571
Nausea	1	0	0.312
Skin rash	8	5	0.333
Headache	19	16	0.355
Suffocation	1	0	0.312

Although the duration of the treatment regimen in this study (12 weeks) was longer than most previous trials (3 to 6 weeks), it may not be long enough to allow estrogen to exert its effect. One study[18] reported that estrogen therapy lasting 5 to 45 months did improve cognitive performance in AD patients; therefore, the effect of estrogen on cognition may become significant clinically only after a relatively long treatment duration.

Some authors suggested that estrogen therapy had only beneficial effects on some limited domains of cognitive performance, such as verbal memory,[34] visual memory,[35] or recall of names.[36] The short-term memory subscale of CASI included a three-item verbal memory test and a five-item visual memory test. Using this subscale we found no improvement in the estrogen-treated group. Because our CASI subscales provided only simple tests in these domains, we maintain that additional study is needed for a definitive evaluation.

HDRS and HARS scores of estrogen-treated patients showed mild but not significant improvement as therapy for psychological symptoms. Several previous studies reported that estrogen improved emo-

tional condition in postmenopausal women.[9,11] In the study by Fillit et al.,[14] estrogen responders consisted of a group of patients with high HDRS scores (21 versus 9). Our patients had a mean HDRS score of only 7. This may be one reason that our AD patients did not respond well to estrogen.

Another study[17] reported estrogen might increase CBF in the right lower frontal region and primary motor region of the right hemisphere. In that study,[17] only estrogen-treated patients received brain SPECT examination. In our study, the changes of CBF in the estrogen-treated group were not significantly different from such changes in the placebo group.

Although the results of this study suggest that estrogen therapy is not effective in improving cognitive performance and dementia severity, estrogen might still play a role in the treatment of AD. For example, estrogen might have a synergistic effect when used in combination with a cholinesterase inhibitor. In the post hoc analysis of a clinical trial for tacrine,[37] women who received both estrogen and tacrine demonstrated a significantly greater improvement in cognitive performance and dementia severity than those receiving tacrine alone. Furthermore, it is possible that estrogen may be beneficial in the primary prevention of AD. A meta-analysis suggested that estrogen users had a 29% lower risk of developing dementia.[3] Although estrogen might not overwhelm the AD disease process, it may delay or arrest cognitive decline in noncognitively impaired women.

Although several noncontrolled clinical trials suggest that estrogen may be effective in the treatment of AD, our study shows conflicting results. Large randomized trials with a long treatment duration are necessary to determine whether estrogen therapy benefits AD patients.

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References

1. Felson DT, Zhang Y, Hannan MT, Kiel DP, Wilson PWF, Anderson JJ. The effect of postmenopausal estrogen therapy on bone density in elderly women. N Engl J Med 1993;329: 1141–1146.
2. Stampfer MJ, Colditz GA, Willet WC, et al. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. N Engl J Med 1991; 325:756–762.
3. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. JAMA 1998;279:688–695.
4. McEwen BS, Woolley CS. Estradiol and progesterone regulate neuronal structure and synaptic connectivity in adult as well as developing brain. Exp Gerontol 1994;29:431–436.
5. Luine VN. Estradiol increases choline acetyltransferase activity in specific basal forebrain nuclei and projection areas of female rats. Exp Neurol 1985;89:484–490.
6. Applebaum–Bowden D, McLean P, Steinmetz A, et al. Lipoprotein, apolipoprotein, and lipolytic enzyme changes following estrogen administration in postmenopausal women. J Lipid Res 1989;30:1895–1906.
7. Jaffe AB, Toran–Allerand CD, Greengard P, Gandy SE. Estrogen regulates metabolism of Alzheimer amyloid beta precursor protein. J Biol Chem 1994;269:13065–13068.
8. Sullivan TJ, Karas RH, Aronovitx M, et al. Estrogen inhibits the response-to-injury in a mouse carotid artery model. J Clin Invest 1995;96:2482–2488.
9. Campbell S, Whitehead M. Estrogen therapy and the menopausal syndrome. Clin Obstet Gynecol 1977;4:31–47.
10. Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology 1992;17:485–495.
11. Ditkoff EC, Crary WG, Cristo M, Lobo RA. Estrogen improves psychological function in asymptomatic postmenopausal women. Obstet Gynecol 1991;78:991–995.
12. Tang MX, Jacobs D, Stern Y, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 1996;348:429–432.
13. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 1997;48:1517–1521.
14. Fillit H, Weinreb H, Cholst I, et al. Observations in a preliminary open trial of estradiol therapy for senile dementia (Alzheimer's type). Psychoneuroendocrinology 1986;11:337–345.
15. Honjo H, Ogino Y, Naitoh K, et al. In vivo effects by estrone sulfate on the central nervous system—senile dementia (Alzheimer's disease). J Steroid Biochem 1989;34:521–525.
16. Honjo H, Ogino Y, Naitoh K, et al. An effect of conjugated estrogen to cognitive impairment in women with senile dementia–Alzheimer's type: a placebo-controlled double blind study. J Jpn Menopause Soc 1993;1:167–171.
17. Ohkura T, Isse K, Akazawa K, Hamamoto M, Yaoi Y, Hagino N. Evaluation of estrogen treatment in female patients with dementia of the Alzheimer's type. Endocr J 1994;41:361–371.
18. Ohkura T, Isse K, Akazawa K, Hamamoto M, Yaoi Y, Hagino N. Long-term estrogen replacement therapy in female patients with dementia of the Alzheimer type: 7 case reports. Dementia 1995;6:99–107.
19. Henderson VW, Watt L, Buckwalter JG. Cognitive skills associated with estrogen replacement in women with Alzheimer's disease. Psychoneuroendocrinology 1996;21:421–430.
20. Mckahnn G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINADS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939–944.
21. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
22. Hughe CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–572.
23. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. Arch Neurol 1975;32:632–637.
24. Teng EL. Cross-cultural testing and the Cognitive Abilities Screening Instrument (CASI). In: Yeo G, Gallagher–Thompson D, eds. Ethnicity and the dementias. Washington, DC: Taylor & Francis, 1996:77–85.
25. Graves AB, Rajaram L, Bowen J, McCormick WC, McCurry SM, Larson EB. Cognitive decline and Japanese culture in a cohort of older Japanese Americans in King County, WA: the Kame Project. J Gerontol Soc Sci 1999:54B:S154–S161.
26. Liu HC, Fuh JL, Wang SJ, et al. Prevalence and subtypes of dementia in a rural Chinese population. Alzheimer Dis Assoc Disord 1998;12:127–134.
27. Graves AB, Larson EB, Kukull WA, White LR, Teng EL. Screening for dementia in the community in cross-national studies: comparison between the Cognitive Abilities Screening Instrument and the Mini-Mental State Examination. In: Corain B, Iqbal K, Nicolini M, Winblad B, Wisniewski H, Zatta P, eds. Alzheimer's disease: advances in clinical and basic research. Chichester, UK: Wiley & Sons, 1993:113–119.
28. Schneider LS, Olin JY, Doody RS, et al. Validity and reliability of the Alzheimer's disease cooperative study clinical global impression of change. Alzheimer Dis Assoc Disord 1997; 11(suppl. 2):S22–S32.
29. Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E,

Georgotas A. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatry 1987; 48(suppl 5):9–15.
30. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
31. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55.
32. Honjo H, Kitawaki J, Itoh M, et al. Serum and urinary oestrone sulfate in pregnancy and delivery measured by a direct radioimmunoassay. Endocrinol (Copenh) 1986;112:423–430.
33. Gattaneo S, Forti G, Fiorelli G, et al. A rapid radioimmunoassay for determination of dehydroepiandrosterone sulfate in human plasma. Clin Endocrinol 1975;4:505–512.
34. Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. Psychoneuroendocrinology 1988;13:345–357.
35. Resnick SM, Metter EJ, Zonderman AB. Estrogen replacement therapy and longitudinal decline in visual memory: a possible protective effect? Neurology 1997;49:1491–1497.
36. Robinson D, Friedman L, Marcus R, Tinklenberg J, Yesavage J. Estrogen replacement therapy and memory in older women. J Am Geriatr Soc 1994;42:919–922.
37. Schneider LS, Farlow MR, Henderson VW, Pogoda JM. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. Neurology 1996;46: 1580–1584.

Reduced prevalence of AD in users of NSAIDs and H2 receptor antagonists

The Cache County Study

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Article abstract—*Objective:* To test the hypothesis that nonsteroidal anti-inflammatory drugs (NSAIDs) and histamine H2 receptor antagonists (H2RAs) are associated with a decreased risk of AD in late life. *Background:* Sustained use of non-aspirin NSAIDs has been repeatedly associated with a reduced occurrence of AD. Similar effects with aspirin have been weaker. One prior study showed a strong association between use of H2RAs and reduced AD prevalence. *Methods:* In a population study of AD in Cache County, UT, we used a sequenced plan of sampling and case ascertainment to identify 201 cases of AD and 4425 participants with no indication of cognitive impairment. Independently, an interview and medicine chest inventory assessed use of several medicines including aspirin, non-aspirin NSAIDs, H2RAs, and three classes of "control" drugs not thought to be associated with AD. Follow-up questioning probed possible indications for use of these drugs. *Results:* Compared with cognitively intact individuals, the AD cases had significantly less reported current use of NSAIDs, aspirin, and H2RAs. Stronger associations appeared when subjects reported use of both NSAIDs and aspirin (no H2RAs), two different NSAIDs (no H2RAs), or two different H2RAs (with neither aspirin nor NSAIDs). There was little or no such association with use of the control medicines. Adjustment for usage indication did not influence these findings, and there was no appreciable variation with number of *APOE* ϵ4 alleles. *Conclusions:* As predicted, use of NSAIDs and aspirin were specifically associated with reduced occurrence of AD. Notably, a previous observation of an inverse association of AD and use of H2RAs was also affirmed. Definitive evidence for a preventive action of these agents will require randomized prevention trials. **Key words:** AD—Aspirin—Cyclo-oxygenase—Excitotoxicity—Histamine—Histamine H2 receptor antagonists—Inflammation—NMDA-type glutamate receptors—Nonsteroidal anti-inflammatory drugs.

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Genetic predisposition is the strongest evident cause of AD, but there is some evidence that neuroprotective interventions might delay onset or reduce risk of AD. Among suggested neuroprotective interventions, the best known are the non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs)[1-4] and postmenopausal hormone replacement therapy.[5,6] Antioxidant vitamins may also be beneficial.[7-9] One study showed an unexpected delay in onset of AD among sustained users of histamine H2 receptor antagonists (H2RAs),

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