

Potential Role for Estrogen Replacement in the Treatment of Alzheimer's Dementia

Lon S. Schneider, MD, Los Angeles, California, Martin R. Farlow, MD, Indianapolis, Indiana, Janice M. Pogoda, PhD, Truckee, California

In light of evidence that estrogen replacement therapy (ERT) might affect cholinergic function, we examined possible effects of ERT on clinical and cognitive responses to the cholinesterase inhibitor tacrine in women with Alzheimer's disease (AD). In a previously reported 30-week, randomized, double-blind, placebo-controlled, multicenter clinical trial, 14.5% of 318 women with evaluable data had been receiving ERT prior to randomization. Patients were randomly assigned to receive placebo or one of three ascending dosages of tacrine (maximum dosages of 80 mg/day, 120 mg/day, or 160 mg/day). Women completing the trial receiving ERT and tacrine improved more than women not receiving ERT who were randomized to tacrine or to placebo as assessed by cognitive ($p < 0.01$), clinical ($p = 0.02$), caregiver ($p = 0.006$), and mental status ($p = 0.07$) ratings. Using an intent-to-treat analysis, they improved significantly on cognitive ratings ($p = 0.01$). These results provide evidence that prior and continuing ERT may enhance response to tacrine in women with AD. Randomized trials are needed. © 1997 by Excerpta Medica, Inc. *Am J Med.* 1997;103(3A):46S-50S.

From the Department of Psychiatry and the Behavioral Sciences, Department of Neurology, School of Medicine, the Leonard Davis School of Gerontology (L.S.S.), and the Department of Preventive Medicine (J.M.P.), University of Southern California, Los Angeles, California; and from the Department of Neurology, Indiana University Medical Center, Indianapolis, Indiana (M.R.F.).

Supported in part by National Institute of Mental Health grant 19074, National Institute of Aging grant 05142 (Southern California Alzheimer's Disease Research Center Consortium), National Institute of Aging grant 101 33 (Indiana University School of Medicine Alzheimer's Disease Center), Warner-Lambert/Parke-Davis Pharmaceuticals, Inc, Ann Arbor, Michigan. The authors thank the Nichols Institute, Newport Beach, California, for plasma estradiol and estrone assays.

Presented in part at the American Academy of Neurology Annual Meeting, Seattle, Washington, May 10, 1995, and at the Gerontological Society of America Annual Meeting, Los Angeles, California, November 18, 1995; portions previously published in *Neurology* (Schneider LS, Farlow MR, Henderson VW, Pogoda JM. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. *Neurology* 46:1580-1584, 1996).

Requests for reprints should be addressed to Lon S. Schneider, MD, Departments of Psychiatry, Neurology, and Gerontology, University of Southern California School of Medicine, 2011 Zonal Avenue, HMR-1 01, Los Angeles, California 90033.

Cholinergic deficits are pronounced in Alzheimer's disease (AD), include a massive decline in cholinergic basalo-cortical projections, a substantial loss of cholinergic cell bodies in the nucleus basalis, reductions in cortical choline acetyltransferase (ChAT) activity, and seem to reflect early events in the disease process.¹ Clinical pharmacologic research, therefore, has emphasized potentiating central cholinergic function with the expectation of improving cognition. The acetylcholinesterase inhibitor, tacrine, is modestly effective at improving cognitive symptoms of the illness²⁻⁵ and has been marketed in the United States and elsewhere.

Similarly, estrogen may have cholinergic neurotrophic and neuroprotective effects and may enhance cognitive function. As described elsewhere in this supplement (Simpkins et al), in ovariectomized rats, estradiol replacement enhanced learning, reversed the decrease in neuronal choline uptake and ChAT caused by ovariectomy, prevented a decline in nerve growth factor and brain-derived neurotrophic factor mRNA, and showed a cytoprotective effect in cell cultures.⁶

A beneficial role for estrogen in AD, cognitive function, mood, and aging is suggested by observations of an inverse relationship of estrogen replacement therapy (ERT) dose and duration with dementia diagnoses on death certificates (see Henderson, this supplement); by preliminary trials suggesting a cognitive enhancing effect of estradiol, estrone, and conjugated estrogens in AD⁷⁻¹⁰ (Table I); and by trials in normal postmenopausal women (e.g., see reference 11). The vast majority of postmenopausal women do not receive ERT, despite its demonstrated efficacy in preventing osteoporosis and cardiovascular disease, and spend a substantial portion of their lives in an estrogen deficient state.¹²

To investigate the effects of ERT and cholinergic stimulation in AD, we analyzed data from women in a recent multicenter trial of the cholinesterase inhibitor, tacrine, to see if ERT use enhanced the treatment effects of tacrine.

METHODS

Patient Population

Eligible subjects were at least 50 years of age, met criteria for probable AD¹³ with baseline Mini-Mental Status Examination (MMSE)¹⁴ scores of 10-26 inclu-

TABLE 1

Preliminary Trials and Cases of Estrogen Therapy in Alzheimer's Disease

Author/Reference	Description
Fillit et al, 1986 ⁷	Seven AD women treated with estradiol (2 mg/day) over 6 weeks; 3 improved on attention, orientation, mood and social interaction. They were characterized by affective features, older onset (72 vs 61 years), osteoporosis, MMSE (14 vs 3.5). Side effects: withdrawal bleeding, breast tenderness.
Honjo et al, 1989 ⁸	Seven women with AD (mean age 80) were treated with estrone (1.25 mg/day) over 6 weeks. 6 showed improvement; an untreated comparison group did not.
Honjo et al, 1993 ⁹	A double-blind study of conjugated estrogen (1.25 mg/day) with medroxyprogesterone (2.5 mg for days 21–28) in 14 women with AD, and placebo in 15. The Hasegawa Dementia Scale, the New Screening Test for dementia, and the MMSE showed significant improvement, especially for memory.
Ohkura et al, 1994 ¹⁰	15 patients (mean age 71.9 years) were treated with 0.625 mg of conjugated estrogens b.i.d. for 6 weeks. Mean MMSE scores increased from 11.6 ± 1.9 to 13.8 ± 2.0 . The control group did not show a significant change. There was improvement on the Hamilton Depression Rating Scale.

AD = Alzheimer disease; MMSE = mini-mental state exam.

sive, were otherwise healthy, and had a caregiver who could complete patient assessments and ensure medication compliance. Subjects and their legal representatives or caregiver provided written informed consent (for eligibility details, see references 15,16).

Study Design

The 30-week, double-blind treatment period used a forced dose-titration at 6-week intervals. Subjects were randomly assigned to one of four treatment groups: Group 1 received placebo for the entire 30-week study. Group 2 received tacrine 40 mg/day for 6 weeks followed by 80 mg/day for the remaining 24 weeks. Group 3 received tacrine at 40 mg/day for 6 weeks, followed by 80 mg/day for 6 weeks, then 120 mg/day for the remaining 18 weeks. Group 4 began tacrine at 40 mg/day for 6 weeks, followed by 80 mg/day for 6 weeks, and 120 mg/day for 6 weeks, and then received 160 mg/day for the remaining 12 weeks of study. Study medication was administered in divided doses, four times daily.

Subjects were assessed on outcome measures every 6 weeks. Those who withdrew prior to 30 weeks after initial treatment were requested to return for assessments to allow for an intent-to-treat (ITT) analysis. Subjects were withdrawn from the study if serum ALT exceeded three times the upper limit of normal. Plasma samples collected at baseline were assayed for estradiol and estrone and at 30 weeks for tacrine.

Outcome Measures

The measures used were the Alzheimer's Disease Assessment Scale–Cognitive Scale (ADASc),¹⁵ a brief, objective neuropsychological assessment battery that evaluates memory, language, orientation, and praxis; the Clinician's Interview Based Impression of change (CIBI), a global, clinical, interview-based evaluation of change relative to baseline performed without input from family members, clinic

staff, or test scores²; the MMSE¹⁴; and the Caregiver's Impression of Change (CIC), a global evaluation by caregivers of patients' overall functioning as compared with their status at baseline.

Statistical Methods

A dose–response trend analysis using analysis of covariance models on mean outcome variables adjusted for baseline, site, and/or age assessed the hypothesis that women maintained on ERT who received tacrine performed better than women not on ERT who received tacrine who, in turn, performed better than women on placebo alone. Subsequent pairwise comparisons between placebo and treatment groups were tested using two-sample *t* tests on the adjusted mean outcome values. Ranks were used in nonparametric analyses for the CIBI and CIC.

Two analyses were conducted: (1) a modified ITT analysis in which all subjects who entered the trial and had at least one outcome assessment were assessed regardless of whether or not they completed the protocol; (2) a completer analysis, including only subjects who completed the protocol and had double-blind assessments at week 30. (Patients who withdrew early were asked to return for their originally projected week 30 assessment for the ITT analysis, so some may have been receiving open-label tacrine or other treatments.) Additional analyses included potential modifiers, such as tacrine dosage, duration of ERT use, effect of concomitant medroxyprogesterone use, and plasma tacrine levels.

RESULTS

Of 343 women who were randomized to treatment, 323 (94%) had at least one outcome assessment and were available for analysis. Of 51 (14.9%) who were receiving ERT at study entry, 46 were available for analysis. Of the 118 women who completed the 30-week trial and had evaluable data, 15 (12.7%) were receiving ERT.

TABLE II
Results of the Intent-to-Treat Analysis, Including Patients Randomized to Treatment and Available for 30 Week Assessment

Outcome	Intent-to-Treat			
	Placebo	Placebo + ERT	Tacrine	Tacrine + ERT
Sample size	83	9	194	37
ADASc*				
Difference vs baseline	+1.6	+4.1	+1.6	-0.9
Adjusted mean	31.7 (7.0)	33.1 (7.1)	31.7 (7.0)	28.3 (7.2)
Difference vs placebo	—	+1.4	0.0	-3.4
95% confidence interval	—	-3.5, 6.3	-1.8, 1.8	-6.2, -0.6
p Value vs placebo	—	0.60	0.94	0.02
Clinician's Interview-Based Impression of Change (CIBI) [†]				
Adjusted mean	4.30 (1.09)	3.89 (1.08)	4.25 (1.25)	4.02 (1.09)
Difference vs placebo	—	-0.41	-0.05	-0.28
95% confidence interval	—	-1.17, 0.35	-0.36, 0.26	-0.48, 0.38
Nonparametric p value	—	0.28	0.56	0.19
Caregivers Impression of Change (CIC) [‡]				
Adjusted mean	44.0 (20.9)	62.8 (20.6)	48.6 (23.2)	51.8 (20.4)
Difference vs placebo	—	18.8	4.6	7.8
95% confidence interval	—	4.2, 33.4	-1.4, 10.6	-1.0, 16.6
p Value vs placebo	—	0.009	0.09	0.07
MMSE [§]				
Difference vs baseline	-1.1	1.0	-0.9	0.0
Adjusted mean	16.8 (3.7)	18.9 (3.7)	17.0 (0.3)	17.8 (3.7)
Difference vs placebo	—	2.1	0.2	1.0
95% confidence interval	—	-0.5, 4.7	-0.8, 1.2	-0.5, 2.5
p Value vs placebo	—	0.11	0.67	0.17

Improvement on the ADASc and CIBI is indicated by the (-) sign.

* The ADASc is an objective scale that evaluates memory, language, orientation, and praxis (maximum severity score 70) (Rosen et al 1984). A decrease in ADAS score indicates improvement. Trend analysis, tacrine + ERT versus tacrine versus placebo, $p = 0.01$; 189 tacrine-only treated patients had available ADASc at week 30.

[†] The CIBI is without input from family members, clinic staff, or test scores. The patient is rated on a 7-point scale, compared to baseline: 1, very much better; 4, no change; 7, very much worse. Trend analysis, $p = 0.15$.

[‡] CIC at week 30 is a global evaluation of patients' overall functioning as compared with their status at baseline on a 0-100 scale. Trend analysis, $p = 0.08$. Sample sizes for the Caregivers Impression of Change were: Placebo, 81; ERT, 9; tacrine, 157; tacrine + ERT, 30.

[§] The MMSE is a brief, structured, examination of cognitive function (maximum severity score 0, maximum correct score 30). Trend analysis, $p = 0.06$; $n = 193$ tacrine patients.

ERT = estrogen replacement therapy; MMSE = mini-mental state exam.

Estrogen Replacement Therapy

Conjugated estrogens (Premarin) was the most commonly used estrogen replacement, used by 86% of subjects, followed by estradiol used by 12%, estrone sulfate by 2%. The median duration of usage was 11 years. The number of subjects who may have used ERT 3 months prior to the trial, and the proportion of women who had previous hysterectomies are unknown. Eight patients received concomitant medroxyprogesterone.

Baseline Characteristics

Patients in each group were comparable with each other with respect to baseline characteristics, including body weight, duration of illness, and cognitive test scores, except that those receiving ERT tended to be younger (67 years \pm 9 vs 74 years \pm 8), and significantly fewer ERT-treated patients did not complete high school (4% vs 16%).

There were no significant differences in body weight or duration of illness with respect to treat-

ment assignment or ERT status (60.4 vs 60.6 kg, $p = 0.91$, and 1.24 vs 1.57 years, $p = 0.28$, ERT vs non-ERT status, respectively). Overall MMSE score was 18 ± 4.7 , and ADASc was 30 ± 12 .

Intent-to-Treat Analysis

A statistically significant dose-trend was observed for the ADASc (**Table II**; $p = 0.01$). Overall, women who were receiving ERT and tacrine responded significantly better at 30 weeks than women not receiving ERT who were randomized to placebo (mean difference -3.4 , $p = 0.02$) or to tacrine (-3.4 , $p = 0.01$). There were statistical trends in favor of tacrine plus ERT for the CIBI, the CIC, and the MMSE (see Table I).

Completer Analysis

Significant dose-trends were observed for the ADASc (**Table III**; $p = 0.005$), CIBI ($p = 0.02$), and the CIC ($p = 0.006$), and nearly significant for the MMSE ($p = 0.07$). On the ADASc, women who were

TABLE III

Outcome of Evaluable Subjects (Patients Who Completed the 30 Week Protocol)

	Completer Subjects			
	Placebo	Placebo + ERT	Tacrine	Tacrine + ERT
Sample size	53	7	50	8
ADASc ⁺				
Difference vs baseline	+1.0	+4.6	-0.8	-4.6
Adjusted mean	28.9 (6.5)	31.3 (6.6)	27.0 (6.5)	22.3 (6.6)
Difference vs placebo	—	+2.4	-1.9	-6.6
95% confidence interval	—	-3.2, 8.0	-4.5, 0.7	-11.6, -1.6
p Value vs placebo	—	0.41	0.13	0.009
CIBI [†]				
Adjusted mean	4.29 (1.16)	3.86 (1.14)	3.96 (1.20)	3.33 (1.16)
Difference vs placebo	—	-0.43	-0.33	-0.96
95% confidence interval	—	-1.37, 0.51	-0.79, 0.13	-1.84, -0.08
Nonparametric p value	—	0.29	0.08	0.08
CIC [‡]				
Adjusted mean	43.1 (22.1)	71.3 (21.8)	48.3 (22.8)	66.6 (21.9)
Difference vs placebo	—	28.2	5.2	23.5
95% confidence interval	—	10.4, 46.0	-3.7, 14.1	6.7, 40.3
Nonparametric p value	—	0.005	0.27	0.02
MMSE [§]				
Difference vs baseline	-0.7	1.3	0.9	1.6
Adjusted mean	17.8 (3.4)	20.3 (3.4)	19.4 (3.4)	20.3 (3.5)
Difference vs placebo	—	2.5	1.6	2.5
95% confidence interval	—	-0.3, 5.3	0.3, 2.9	-0.1, 5.1
p Value vs placebo	—	0.07	0.02	0.07

* Trend analysis, tacrine + ERT versus tacrine versus placebo, $p = 0.005$. A total of 50 placebo patients and 6 placebo + ERT patients were available for the ADASc analysis; 4 of the 8 tacrine + ERT patients were receiving 120 mg/day, and 2 were receiving 160 mg/day at 30 weeks. Both groups showed significant improvement compared to placebo (120 mg/day: -7.3, $p = 0.05$; 160 mg/day: -9.4, $p = 0.06$).

[†] Trend analysis, $p = 0.02$.

[‡] Trend analysis, $p = 0.006$; 51 placebo patients had caregiver ratings.

[§] Trend analysis, $p = 0.07$; 49 tacrine patients were available for analysis.

Abbreviations as in Table II.

receiving ERT and tacrine responded significantly better at 30 weeks than women not receiving ERT who were randomized to placebo (mean difference -6.6 or to tacrine (-4.7). On the CIC, patients receiving tacrine plus ERT improved 23.5 points compared to placebo and 18.3 points compared to tacrine alone on a 100-point scale of change. (Elsewhere we have compared the results of the ITT and completer analyses.¹⁶

Effects of Potential Modifiers

Linear regression analysis indicated that, among the completers, increasing tacrine dose, ERT use, and nonuse of progesterone were independently related to better week 30 outcome on the ADASc. Duration of ERT use was not related to outcome.

Plasma Levels

As reported elsewhere,¹² estradiol and estrone plasma levels were significantly higher in the ERT-treated patients (median estradiol: 12.5 ng/mL vs 7.0, $p = 0.009$, median estrone: 53.5 vs 28.0, $p = 0.003$). Tacrine plasma levels at the end of the study were not significantly different in tacrine-treated patients

receiving ERT compared to those not receiving ERT (34.9 vs 27.6 ng/mL, $p = 0.25$).

DISCUSSION

Women receiving ERT and tacrine may perform better on cognitive and clinical assessments than women receiving tacrine alone or placebo. The magnitude of both the ADASc improvement with ERT plus tacrine compared to placebo and the improvement from baseline after 30 weeks was about twice that reported overall in the multicenter trial.²

ERT may augment the effect of tacrine through cholinergic neurotrophic and neuroprotective actions, neurotransmitter effects, or downregulation or decreases in β adrenergic receptors and serotonin (5-HT₂) receptors.¹⁷ Other speculative mechanisms include possible antiinflammatory effects of estrogen^{18,19} (since inflammatory processes may play a substantial role in the illness^{20,21}), and a decrease in circulating levels of apolipoproteins.²² In particular, the E4 allele of apolipoprotein E (ApoE4) has been associated with increased risk for AD.²³ A pharmacokinetic interaction with tacrine may be involved as well.

This was essentially an observational study of ERT, where tacrine treatment was the only randomized intervention. Potential sources of bias include ERT treatment and differences in age and education among ERT users. Women generally received ERT for many years prior to the trial. The proportion of AD women receiving ERT in this trial, however, is comparable to the 12% reported in the population-based sample of the Cardiovascular Health Study.²⁴ A majority of patients probably were prescribed ERT following hysterectomy with oophorectomy. Although the ERT patients were somewhat younger and better educated, the overlaps in age and education were substantial, and differences were statistically adjusted in the analyses as needed. Other factors that could not be controlled included the estrogen preparation used, dose, reason for treatment, duration of treatment, age at menopause, age of subjects, and uterine or ovarian status. These are important considerations in the biology of postmenopausal women, since a chronic estrogen deficiency state may have profound effects on cholinergic neuronal function or the ability to respond to cholinergic stimulation.

These results support the need for clinical trials examining the possible additive beneficial effects of ERT to cholinergic treatments for AD and lends support to previous pilot trials of estrogen alone (Table I). To understand the effects of tacrine in women who have been receiving chronic ERT, a study should randomize them to a cholinesterase inhibitor or placebo. A long-term postmenopausal effect of exogenous estrogen may make this latter group more likely to respond to cholinesterase inhibitors than patients who have been estrogen deficient for many years and started on ERT only recently. A study only of women with AD who have had hysterectomies or oophorectomies but who have not been placed on ERT would be inadequate.

REFERENCES

1. Hefti F, Schneider LS. Rationale for the planned clinical trials with nerve growth factor in Alzheimer's disease. *Psychiatr Devel.* 1989;4:297-315.
2. Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI, for the Tacrine Study Group. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. *JAMA.* 1994;271:985-991.
3. Egger SA, Levy R, Sahakian BJ. Tacrine in Alzheimer's disease. *Lancet.* 1991;337:989-992.
4. Farlow M, Gracon SI, Hershey LA, Lewis KW, Sadowsky CH, Dolan-Ureno J. A 12-week, double-blind, placebo-controlled, parallel-group study of tacrine in patient with probable Alzheimer's disease. *JAMA.* 1992;268:2523-2529.
5. Davis KL, Thal LJ, Gamzu E, et al. Tacrine in patients with Alzheimer's disease: a double-blind, placebo-controlled multicenter study. *N Engl J Med.* 1992;327:1253-1299.
6. Simpkins JW, Singh M, Bishop J. The potential role for estrogen replacement therapy in the treatment of the cognitive decline and neurodegeneration associated with Alzheimer's disease. *Neurobiol Aging.* 1994;15(suppl 2):S195-197.
7. Fillit H, Weinreb H, Cholst I, Luine V, McEwen B, Amador R, Zabriskie J. Observations in a preliminary open trial of estradiol therapy for senile dementia—Alzheimer's type. *Psychoneuroendocrinology.* 1986;11:337-345.
8. Honjo H, Ogino Y, Naitoh K, et al. In vivo effects by estrone sulfate on the central nervous system—senile dementia (Alzheimer's type). *J Steroid Biochem.* 1989;34:521-525.
9. Honjo H, Ogino Y, Tanaka 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.
10. Ohkura T, Isse K, Akazawa K, Hamamoto M, Yaoi Y, Hagino N. Evaluation of estrogen treatment in female patients with dementia of the Alzheimer type. *Endocrine J.* 1994;41:361-371.
11. Kampen DL, Sherwin BB. Estrogen use and verbal memory in healthy postmenopausal women. *Obstet Gynecol.* 1994;83:979-983.
12. Belchetz PE. Hormonal treatment of postmenopausal women. *N Engl J Med.* 1994;330:1062-1071.
13. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan E. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group. *Neurology.* 1984;34:939-944.
14. 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.
15. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatr.* 1984;141:1356-1364.
16. Schneider LS, Farlow MR, Henderson VW, Pogoda JM. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. *Neurology.* 46:1580-1584.
17. Luine VN, Khychevskaya R, McEwen BS. Effect of gonadal steroids on activities of monoamine oxidase and choline acetylase in rat brain. *Brain Res.* 1975;86:293-306.
18. Josefsson E, Tarkowski A, Carlsten H. Anti-inflammatory properties of estrogen. *Cell Immunol.* 1992;142:67-78.
19. Screpanti I, Santoni A, Gulino A, Herberman RB, Frati L. Estrogen and antiestrogen modulation of the levels of mouse natural killer activity and large granular lymphocytes. *Cell Immunol.* 1987;106:191-202.
20. McGeer PL, Rogers J. Anti-inflammatory agents as a therapeutic approach to Alzheimer's disease. *Neurology.* 1992;42:447-448.
21. Aisen PS, Davis KL. Inflammatory mechanisms in Alzheimer's disease: implications for therapy. *Am J Psychiatr.* 1994;151:1105-1113.
22. Sherwin BB, Gelfand MM. A prospective one-year study of estrogen and progesterone in postmenopausal women: effects on clinical symptoms and lipoprotein lipids. *Obstet Gynecol.* 1989;73:759-766.
23. Poirier J, Davignon J, Bouthillier D, et al. Apolipoprotein E polymorphisms and Alzheimer's disease. *Lancet.* 1993;342:697-699.
24. Manolio TA, Furberg CD, Shemanski L, et al. Associations of postmenopausal estrogen use with cardiovascular disease and its risk factors in older women. *Circulation.* 1993;88:2163-2171.