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Estrogen Replacement Therapy, Alzheimer's Disease, and Mild Cognitive Impairment

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This article highlights the latest findings regarding estrogen replacement therapy in the treatment and prevention of Alzheimer's disease (AD) and mild cognitive impairment in women. Despite considerable evidence from observational studies, recent randomized clinical trials of conjugated equine estrogens, alone and in combination with progestin, have shown no benefit for either the treatment of established AD or for the short-term prevention of AD, mild cognitive impairment, or cognitive decline. Based on the evidence, there is no role at present for estrogen replacement therapy in the treatment or prevention of AD or cognitive decline, despite intriguing results from the laboratory and from observational studies. However, numerous questions remain about the biologic effects of estrogens on brain structure and function. Additional basic and clinical investigations are necessary to examine different forms and dosages of estrogens, other populations, and the relevance of timing and duration of exposure.

Introduction

Alzheimer's disease (AD) affects more than 4 million Americans in the United States, and the number of people with this disorder is projected to quadruple by the middle of this century [1]. The prevalence of AD is higher in women as compared with men, largely a result of women's longer life expectancy. However, some investigations have also suggested that women may have a higher incidence or risk of AD, particularly at older ages. A study that pooled results from seven European studies showed higher AD incidence rates in women compared with men, especially in the very old. After the age of 85 years, the rates continued to increase for women but not for men [2]. More recent reports from the Rotterdam study [3] and the Cache County, Utah study [4] noted similar results: no differences in incidence rates by gender (up to ages 90 and 85 years for women and men, respectively), but higher rates for women at older ages. It has been proposed that the menopausal loss of normal estrogen production may be associated with a vulnerability of women to acquire AD, or even perhaps account for a greater incidence of symptoms, which are interpreted as AD [5].

Laboratory studies have shown a variety of mechanisms by which estrogens may be important for brain structure and function. Estrogen receptors are found throughout the brain in both men and women, particularly in brain regions that process memory. Estrogen has been shown to act as a trophic factor for cholinergic neurons, and it has anti-inflammatory and antioxidant properties. It modulates amyloid precursor protein metabolism, affects the vasculature, and inhibits apolipoprotein (apo) E levels in plasma [6]. Given these potential mechanisms, the important question is whether hormone replacement therapy (HRT) can prevent or treat cognitive impairment or dementia.

Estrogens occur naturally in several forms, including estradiol, estrone, and estriol. Of these, estradiol has the highest potency at the receptor, and may possibly be the most relevant for brain function. In the past, the most commonly prescribed form of estrogen replacement therapy (ERT) consisted of conjugated equine estrogens (CEE), which are a mixture of numerous estrogens without progestin. More recently, women with a uterus have been prescribed estrogen in combination with progestin. The effect of each of these preparations, however, may not be the same. The observational studies cited in the following sections generally grouped together all forms of estrogen.

Recent clinical trials have attempted to provide guidance on the usefulness and the risk profile of these compounds. The majority of these studies involved CEE with and without progestin. The results do not support the use of ERT for the treatment of AD or for the prevention of dementia, particularly in women over the age of 65 years. However, there are major gaps in our knowledge about estrogens and the brain that require further investigation.

Table 1. Placebo-controlled, randomized clinical trials of estrogen for treatment of AD

Study	Subjects, *n*	ERT, *mg/d*	Length of treatment	Results
Honjo *et al.* [10] / 1993	7	CEE 1.25 mg/d	3 wk	Selective improvement
Asthana *et al.* [11] / 1999	12	Transdermal 17β-estradiol 0.05 mg/d	8 wk	Selective improvement in attention and verbal memory
Henderson *et al.* [12] / 2000	42	CEE 1.25 mg/d	4 mo	No differences in cognition or function
Mulnard *et al.* [13•] / 2000	120	CEE 0.625 or 1.25 mg/d	12 mo	No differences in cognition, mood or function
Wang *et al.* [14] / 2000	50	CEE 1.25 mg/d	3 mo	No differences in cognition, mood, or cerebral blood flow
Asthana *et al.* [15] / 2001	20	Transdermal 17β-estradiol 0.05 mg/d	8 wk	Selective improvement in attention and memory

Estrogen and the Treatment of Alzheimer's Disease

Initial evidence for ERT as a possible treatment for AD came from several open-label clinical trials [7–9] and two randomized clinical trials [10,11] that showed selective cognitive improvement with ERT in women with AD. The initial studies were all of relatively brief duration, generally from 6 to 8 weeks of treatment, and the number of subjects assigned to estrogen was small, ranging from seven to 12. These intriguing studies provided the impetus for several larger, more rigorous trials to investigate ERT in the treatment of women with AD.

In 2000, the results of three double-blind, randomized clinical trials of CEE in women with AD were released. Each of these larger controlled studies failed to find a therapeutic effect. In the first study, 42 women with mild to moderate AD were followed for 16 weeks in a randomized clinical trial of 1.25 mg/d of CEE versus placebo [12]. There were no significant differences found between the two treated groups on measures of cognition, the Clinical Global Impression of Change (CGIC), or the caregiver's rating of functional status at week 4 or week 16.

The trial with the longest duration, and largest sample of women, was conducted by the sites of the Alzheimer's Disease Cooperative Study (ADCS) [13•]. In this 12-month study, 120 hysterectomized women 60 years of age or older with mild to moderate AD were randomized to receive placebo, 0.625 mg/d of CEE, or 1.25 mg/d of CEE. After 12 months, no differences were found between the subject groups on the CGIC ($P = 0.43$), the Mini-Mental Status Examination (MMSE) ($P = 0.51$), or the Alzheimer's Disease Assessment Scale–cognitive subscale ($P = 0.13$). Although the MMSE appeared to show improvement in the estrogen-treated group at 2 months, the difference disappeared as the study proceeded. Moreover, at the end of the 12-month exposure, women in the estrogen-treatment group had worse scores on the Clinical Dementia Rating scale ($P = 0.01$).

In the third study, 50 women with AD were followed for 12 weeks of randomized exposure to 1.25 mg/d of CEE or placebo. In addition to measuring cognition and mood, this study also investigated cerebral blood flow, measured by single photon emission computed tomography [14]. Among the global, behavioral, and brain imaging measures performed, no significant differences were found between the groups, consistent with the two earlier studies that year. As a result of these studies, ERT is not clinically indicated for the treatment of AD.

The larger clinical trials all investigated CEE, which is the most commonly used form of ERT. Other forms of estrogen for the treatment of AD have been investigated in smaller pilot studies only. In a randomized 8-week trial of 20 women with AD, 0.10 mg/d of transdermal 17β-estradiol was associated with selective improvement of attention and memory scores [15], which was consistent with previous pilot studies of a lower dose [7,11]. Additional studies, many underway, are necessary to further evaluate various types of estrogen and schedules of administration. Table 1 summarizes the key features of some of the randomized, placebo-controlled trials of estrogens in women with AD that have been published to date.

Estrogen and Dementia Prevention: Observational Studies and Clinical Trials

The disappointing results for estrogen in the treatment of AD, however, did not provide any information on whether ERT could be useful for the prevention of disease.

Although ERT may not be an effective treatment for established AD, it could still hold the hope and scientific rationale to be an agent of prevention for dementia, affecting pathophysiologic processes at earlier stages of the disease. Clinical support for this possibility was substantiated by a large number of observational studies showing differences in risk for women who had reported the use of ERT. These observational investigations include studies where information regarding ERT use was collected after the development of dementia (prevalent cases), as well as studies where the information on ERT use was collected prospectively before the development of dementia (incident cases). Table 2 sum-

marizes the results from published observational studies investigating risk of AD and ERT usage. Several of these observational studies found that increasing duration of use afforded greater protection against AD. Furthermore, an investigation from the Cache County study also found that the increased protection was primarily in women with prior rather than current use [16•]. A meta-analysis of available studies at the time also showed a protective effect, particularly in the investigations with incident cases [17].

With the growing evidence from observational studies, clinical trials were initiated to examine ERT and AD prevention. In the United States, the Women's Health Initiative (WHI) provided the opportunity to conduct a nested clinical trial. This study, called the Women's Health Initiative Memory Study (WHIMS) [18••], examined whether ERT reduced the risk of dementia in healthy women aged 65 to 79 years at baseline. The study used CEE for women with hysterectomy and CEE with medroxyprogesterone acetate (MPA) for women with a uterus. Originally planned to have 9 years of follow-up, the study enrolled 2947 women into the estrogen-alone trial and 4532 women into the combination CEE plus MPA arm. The CEE plus MPA study was prematurely terminated in July 2002 after approximately 5 years because of increased risk for coronary heart disease outcomes, stroke, venous thromboembolism, and breast cancer. The CEE-alone trial was terminated in February 2004 because an excess risk of stroke in the treated group was deemed to be unacceptable in healthy women participating in research. When the data from WHIMS were analyzed, CEE alone and CEE plus MPA were associated with an increased incidence of dementia (primarily AD) compared with placebo, although the association did not reach statistical significance in the smaller CEE-alone group (RR = 1.49; 95% CI, 0.83 to 2.66) [18••]. When data from the CEE-alone and the CEE plus MPA trials were pooled, the overall risk for dementia was 1.76 times higher for women taking estrogen than for women taking placebo (RR = 1.76; 95% CI, 1.19 to 2.60) [19•].

The Preventing Postmenopausal Memory Loss and Alzheimer's with Replacement Estrogens study (PREPARE) was also designed to examine the utility of CEE, with or without progestin, to delay AD and memory loss in women 65 years or older with a family history of AD in a first-degree relative. Because of the results of WHIMS, the PREPARE trial was also prematurely halted. The participants are currently being consented for long-term follow-up, without revealing the treatment assignment, to investigate if there is a benefit with remote exposure as was suggested in data Cache County study [16•]. In progress in the United Kingdom is the Women's International Study of Long Duration Oestrogen After Menopause (WISDOM), a randomized prevention trial that was initiated in 2000, with an add-on study similar to WHIMS, called WISDOM-Cognition, in which endpoints of dementia and cognitive function are measured. Results from this trial are not yet available, with the projected follow-up period concluding in 2009.

Estrogen and Prevention of Mild Cognitive Impairment

Mild cognitive impairment (MCI) is a term used to describe individuals with cognitive losses who do not meet criteria for dementia. Most commonly, the syndrome involves memory loss, which is deemed beyond that generally attributed to normal aging [20]. Clinic patients with MCI have a higher risk of developing dementia than individuals without memory loss. In addition to dementia, WHIMS evaluated the relationship between ERT and the development of MCI and evaluated whether CEE alters global cognitive function in older women, as had been suggested by numerous previous studies and a meta-analysis showing selective improvement in verbal memory, vigilance, reasoning, and motor speed [21].

Despite the promise of these previous studies, in the WHIMS study, 76 participants were diagnosed with MCI in the CEE-alone group compared with 58 in the placebo group (RR = 1.34; 95% CI, 0.95 to 1.89). When data from the two trials were pooled, the RR was similar (1.25; 95% CI, 0.97 to 1.60). Thus, MCI also appeared more frequently in women on HRT [18••]. Moreover, for women aged 65 years or older, hormone therapy (CEE plus MPA or CEE alone) had an adverse effect on global cognition as measured by the Modified MMSE (3MSE), a test of global cognitive function. This effect was greater among women with lower cognitive function at baseline [22,23].

Animal and Basic Science Studies of Estrogen Replacement Therapy

Basic science investigations have enlightened our understanding of estrogen's beneficial role on brain function as measured at the cellular, molecular, and animal model organismal levels. Reduced levels of estrogen in numerous models have demonstrated consequences for neuronal function, survival, and synaptogenesis [24].

The time interval between estrogen loss and the initiation of HRT may be an important issue relevant to estrogen's biologic activity within the brain. For example, synaptic density in the rat hippocampus was shown by Silva *et al*. [25] to be much greater when there was no significant hypoestrogenic phase following oophorectomy (4-day delay vs 12-day delay before initiation of estrogen replacement). Similarly, estrogen deprivation reduced physical activity as well as upregulation of brain-derived neurotrophic factor mRNA in rats, a finding that was enhanced when estrogen deprivation exceeded 7 weeks. With this "prolonged" absence of estrogen, the rat hippocampus seems to lose the capacity to respond normally to stimuli such as exercise [26]. One could postulate that long-standing adaptation to estrogen deficiency (at time points distant to the onset of menopause) coincides with dysfunctional, damaged neurons that are beyond the capacity of estrogen replacement to restore [27].

Table 2. Observational studies of the association between estrogen replacement and risk of Alzheimer's disease

Study	Subjects, *n*	OR / RR	95% CI	Comment
Prevalent cases				
Heyman *et al.* [39]	120	2.4	0.7–7.8	No association
Amaducci *et al.* [40]	213	1.7	0.4–6.9	No association
Broe *et al.* [41]	340	0.8	0.4–1.6	No association
Graves *et al.* [42]	260	1.2	0.5–2.6	No association
Brenner *et al.* [43]	127	1.1	0.6–1.8	No association
Henderson *et al.* [44]	235	0.2	0.1–0.5	Significant risk reduction
Mortel and Meyer [45]	306	0.6	0.3–1.2	No association
Lerner *et al.* [46]	264	0.6	0.3–0.9	Significant risk reduction
Baldereschi *et al.* [47]	2816	0.3	0.1–1.0	Significant risk reduction
Incident cases				
Paganini-Hill and Henderson [31]	355			Significant risk reduction with
< 7 y		0.7	0.5–1.2	longer duration
7 y		0.5	0.3–0.9	
Tang *et al.* [48]	1124			Significant risk reduction with
< 1 y		0.5	0.2–1.1	longer duration
1 y		0.1	0.0–0.9	
Kawas *et al.* [33]	472	0.5	0.2–1.0	Significant risk reduction
Waring *et al.* [34]	444			Significant risk reduction with
< 6 mo		0.9	0.4–1.6	longer duration
≥ 6 mo		0.4	0.2–1.0	
Seshadri *et al.* [49]	280	1.2	0.6–2.4	No association
Zandi *et al.* [16•]	1866			
< 3 y		0.8	0.4–1.6	Significant risk reduction with
3–10 y		0.6	0.3–1.2	longer duration
> 10 y		0.4	0.2–0.9	
Current		1.1	0.6–1.9	Significant risk reduction with
Prior		0.3	0.2–0.7	prior use
Lindsay *et al.* [50]	2079	1.4	0.5–4.0	No association
Review article				
Yaffe *et al.* [17]				
Prevalent	1991	0.8	0.5–1.3	Significant risk reduction
Incident	1596	0.5	0.3–0.8	among incident studies

OR—odds ratio; RR—risk ratio.

The supporting evidence for the impact of estrogen on cognitive performance is not limited to the rodent model. Hippocampal spine density was highly responsive to estrogen in both young and aged female ovariectomized rhesus monkeys [28], whereas choline acetyltransferase induction was regionally specific within the cholinergic basal forebrain neurons of aged animals [29] when estradiol was administered as a protocol that mimicked the normal physiologic cycle with timed intermittent peaks. In young primates, using the same physiologic protocol, the spine density of the prefrontal cortex was also enhanced following estradiol administration, despite the lack of concurrent influence on spine density in the primary visual cortex [30]. Consistent with these primate studies, estradiol has largely been the preferred form of estrogen replacement used in experimental animal models, removing the tremendous variability of the many compounds used in human investigations.

Estrogen Replacement Therapy and the Prevention of Alzheimer's Disease: Reconciling Results of Observational Studies and Clinical Trials

Repeatedly, observational studies of volunteer cohorts and population-based samples have suggested that women who subscribe to HRT after menopause have a reduced risk for development of AD as compared with nonusers of the hormones [16•,31–34]. However, data from randomized clinical trials have not demonstrated benefit for women who have AD or women seeking to prevent or delay the development of dementia or cognitive loss. How might we explain these disparate results?

Some of the answers to these issues may lie in inherent differences between the observational studies and randomized clinical trials with respect to the design of the study. In observational studies of estrogen, women initiate HRT on their own or in response to their physician's advice. Thus, the women using HRT may be differ-

ent from the women not using HRT in many regards, including education, overall physical health, or other known and unknown factors. In randomized trials, however, randomization assures that on average, known and unknown factors are equally distributed between the intervention and placebo groups, so any difference seen between the groups is more likely attributable to the intervention itself and not to other factors. It is thus possible that the women represented in observational studies who had self-selected HRT may have been different in some regard than the women who were recruited and randomized in the clinical trial. Hence, the characteristics of the women using HRT and not the HRT itself may have accounted for the apparent reduction in risk of dementia.

Other potential reasons for the difference in the results from observational studies and randomized trials may have been the timing for initiation of estrogen replacement following menopause and the hormone choices and regimen (continuous vs cyclical administration) [35••]. Although the randomized clinical trial has the advantage of minimizing the alternate explanations for the observed effects, it has the disadvantage that it cannot test a wide variety of doses, duration of use, or regimens. The WHIMS studied the effect of one type [36–38] of estrogen (CEE) used for a relatively short time (5 years) at one dose (0.625 mg/d). As seen in some of the observational studies, larger doses, increased duration, and earlier use had increased benefit against dementia development. Basic science studies continue to suggest that hormonal therapy may be relevant to AD and cognitive decline. Recent investigations promote the notion that estrogen may exert positive effects only if given within a limited, perimenopausal timeframe and perhaps requiring cyclical administration. Challenged by the findings from ongoing basic science investigations, it is apparent that additional clinical studies are indicated and may yet reveal a relationship of hormones to the development of cognitive impairments and AD.

Conclusions

Despite a large body of evidence from animal, basic science, and observational studies, current evidence does not support a role for hormonal therapy in the prevention or treatment of AD. Complex, unresolved issues remain about the biologic and clinical effects of ERT in the brain. The data to refute this role come from a large, randomized controlled trial. This randomized clinical trial studied the effect of one type of estrogen (CEE), used for a relatively short time (5 years) at one dose (0.625 mg/d). However, additional studies in the laboratory and clinic are necessary to further evaluate the potential effects of hormone replacement given in forms other than CEE, with alternative schedules of administration and various timings of therapy initiation.

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