

# Use of Estrogens for the Prevention and Treatment of Alzheimer's Disease

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## Key Words

Dementia · Alzheimer's disease · Estrogens · Cognition · Treatment · Prevention · Central nervous system

## Abstract

This review examines the biological rationale for the use of estrogen replacement therapy (ERT) and the evidence for the efficacy of ERT in enhancing cognition, preventing Alzheimer's disease (AD) and treating AD in postmenopausal women. While the biological basis for ERT as a cognition enhancer is strong and multiply mediated, the clinical evidence for its use is not as compelling and must be weighed against possible side effects. Until the results of definitive large trials are available, the use of ERT alone or in combination with other treatments is worthy of consideration.

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## Introduction

Dementia worldwide affects about 5–8% of the population over 65 years of age. 15–20% of those over 75 and 25–50% of individuals over 85 [1]. Alzheimer's disease (AD) accounts for 50–75% of all dementia cases in the western world [1]. Considering the current trends of popu-

lation growth and changing life span, more than 14 million individuals worldwide may be suffering from AD by the middle of the next century [2]. The prevalence of AD is higher for women, even allowing for their greater longevity. However, there appears to be more men than women with early-onset familial AD, suggesting that environmental influences may be especially important for the development of AD in later life [3]. The fact that women usually live the last third of their adult lives in an estrogen-deficient state may provide an important clue.

We review the effects of estrogens on the central nervous system (CNS) and the evidence for estrogen's role as a cognition enhancer, potentiator of other cognition enhancers, and agent providing protection against the development of AD. We also question whether the findings of estrogen on cognition could be indirect and mediated through its effect on elevating mood. Finally, the question of unopposed estrogens versus combined with progesterone and the role of phytoestrogens are examined.

## Biological Effects of Estrogens on the CNS

Estrogen appears to have important roles in normal CNS activity. It may also affect the pathogenesis of AD through its actions on neurotransmitters, nerve growth, synapse morphology, neuromodulin and glucose metabo-

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lism. Estrogen may also have effects on cerebral blood flow as well as antioxidant properties.

#### *Estrogens and Acetylcholine*

The interaction between the cholinergic system and estrogen is of interest. The CNS, including the basal nucleus of Meynert, contains estrogen receptors. The major cholinergic projections to the frontal cortex originate from the nucleus of Meynert. This nucleus is remarkably acetylcholine-deficient in AD.

Cholinergic neurons appear to be sensitive to estrogens. Estrogen increases choline acetyltransferase (ChAT) activity in the basal forebrain of ovariectomized rats [4], while estrogen deprivation reduces the high-affinity choline uptake in the hippocampus of rats [5]. This reduction is reversible with short-term estradiol replacement. Long-term estradiol replacement seems to prevent the time-dependent decline in ChAT in the frontal cortex and to attenuate ChAT activity decline in the hippocampus [5].

#### *Estrogens and Nerve Growth*

In order to understand the effects of estrogens on nerve growth, the role of neurotrophins should be summarized. Nerve growth factor (NGF) is essential for early neuronal development and influences neuron differentiation and growth. Other important neurotrophins are identified: brain-derived neurotrophic factor (BDNF), and neurotrophins 3 and 4/5 (NT-3, NT-4/5) [6]. They bind to members of the trk receptor tyrosine kinase family, consisting of trkA (NGF), trkB (BDNF and NT-4/5) and trkC (NT-3). This results in the stimulation of mechanisms necessary for growth and survival of neurites, as well as stimulation of functions related to transmitter production and release [7].

Estrogen has an effect on NGF which regulates the basal forebrain cholinergic system in ovariectomized rats. Treatment in vivo with NGF-secreting cells causes sprouting of septal cholinergic neurons in basal forebrain neurons in monkeys [8]. Withdrawal of estrogen in ovariectomized rats results in a reduction in trkA (NGF receptor) messenger ribonucleic acid levels in specific basal cholinergic neurons [7]. The reduction is accompanied by decreased ChAT gene expression, suggesting a decline in cholinergic function, an effect reversed by estrogen.

Estrogen enhances neurite growth by selectively increasing tau protein level and stabilizing microtubules [9]. As a consequence, hypothalamic neurons can extend longer and more stable neurites. Also, the colocalization of intranuclear estrogen-binding sites and low-affinity NGF receptors in rats means that their ligands may act on the

same neuron (perhaps synergistically) to regulate the expression of specific genes that may influence neuronal survival, differentiation, regeneration and plasticity [10]. In vitro estrogen treatment of rat embryogenic septal neurons increased the number of primary and secondary neurites and mean total neurite length [11].

There are regional differences in estrogen's actions on neurotrophins. Estradiol replacement is more effective in maintaining a neurotrophin, brain-derived nerve factor (BDNF) mRNA in the hippocampus than in the neocortex [12].

#### *Estrogens and Neuromodulin*

Neuromodulin is a membrane-bound phosphoprotein which has been implicated in axonal elongation and synaptogenesis. Neuromodulin has been detected in the developing and adult preoptic area and basal hypothalamus – the regions associated with memory and learning. Neuromodulin and estrogen receptor mRNA are localized in similar regions of the hypothalamus. Estrogen modulates neuromodulin mRNA expression in those regions [13].

#### *Glucose Metabolism and Estrogens*

AD is associated with reduced brain metabolic activity, including reduced rates of glucose metabolism in different regions. Glucose ingestion may be associated with better performance of AD patients in certain memory tests [14]. In an animal study, estradiol in physiological levels modulated cerebral glucose homeostasis in ovariectomized rats [15]. Glucose uptake was elevated by 120% in estradiol-treated rats, in 7 out of 8 regions examined, when compared with placebo-treated animals. Impaired glucose transport compromises energy-dependent processes in synapses on which estrogen has a direct effect. Exposure of rat cortical synaptosomes to  $\beta$ -amyloid peptide caused 50% reduction in glucose transport but not if pretreated with 17 $\beta$ -estradiol [16].

#### *Estrogens and Cerebral Blood Flow*

A secondary effect of estrogen replacement is an increase in cerebral blood flow. AD is characterized by reduced regional cerebral blood flow (rCBF), especially in the parietal and temporal cortex. The most severe and earliest reduction of rCBF is in the temporal cortex with other cortical areas becoming involved as the disease progresses [17]. Estrogen replacement therapy significantly increases rCBF in AD patients in the right lower frontal region [18].

### *Estrogens as Antioxidants*

Another mechanism of estrogen's action is its antioxidant activity. Brain cells are at particular risk of damage caused by free radicals. The brain has an extremely high rate of oxygen consumption and its neuronal membranes have high contents of polyunsaturated fatty acids that are susceptible to lipid oxygenation. One of many changes occurring in an aging brain is oxidative damage caused by free radicals.

A commercial estrogen, 2-hydroxyestrone, is almost 3 times more active as an antioxidant than  $\alpha$ -tocopherol (vitamin E), which has the highest antioxidant activity among natural tocopherols [19]. Tocopherols are oxidized to tocopheroxyls, and estrogens with a hydroxy group (OH) at the aromatic ring have the ability to regenerate the tocopheroxyl to tocopherol [19]. Free heme compounds may be a source of oxidative stress in the AD brain because they irreversibly inhibit muscarinic acetylcholine receptors [20].  $\beta$ -Estradiol reduces free heme activity [20] and so reduces oxidative stress.

### *Estrogens and $\beta$ -Amyloid*

$\beta$ -Amyloid, which takes part in the pathogenesis of AD, also behaves as an oxidative stressor [21]. Elevation in hydrogen peroxide correlates with toxic consequences of AD  $\beta$ -amyloid interaction with nerve cells [21]. High concentrations of 17 $\beta$ -estradiol protect clonal hippocampal cells from oxidative damage and cell death at molecular and cellular levels [22]. Estrogens may protect the brain from toxicity of  $\beta$ -amyloid by stimulating  $\alpha$ -secretase [23], which in turn increases levels of soluble amyloid precursor protein and by reducing the pentraxin serum amyloid P component [24]. Pentraxin serum component has been found in atherosclerotic lesions and neurofibrillary tangles and may play a role in the aging process and AD.

### *Synapses and Estrogen*

Estrogen has a positive effect on the synapses. In rats, estrogen treatment increases the number of dense-cored vesicles, the terminals containing dense-cored vesicles and the number of synapses [25]. Dense-cored vesicles represent synthesis, storage and transport sites for certain neuropeptides. Estrogens induce changes in the density of synapses in rats with levels of estradiol having a direct correlation with synapse density [26]. More importantly, these changes also occur in the hippocampus [26]. The decrease in the hippocampal spine density after oophorectomy in rats can be reversed with estrogen replacement therapy (ERT) [27].

An additional mechanism for estradiol's influence on learning and memory involves N-methyl-D-aspartate (NMDA) receptors. In rats, estradiol induces an increase in NMDA-binding sites, which results in an increased sensitivity to glutamate, an excitatory neurotransmitter, in the hippocampus [28]. NMDA synapses may be involved in learning and memory processes [29]. When estrogen increases dendritic spine density in the rat hippocampus, it also increases the number of NMDA receptors [29]. Estrogen may also induce glial and synaptic plasticity in the hypothalamus of ovariectomized primates [30].

### *Other Neurotransmitters*

Estrogen may affect other neurotransmitters. It directly influences dopamine receptors [31] and modulates dopamine activity [32]. Estrogen increases the density of 5-HT receptors in cerebral cortex of ovariectomized rats [33] and elevates serotonin levels in postmenopausal women [34]. Estrogen may enhance serotonergic transmission, by decreasing monoamine oxidase level as well as serotonin transport [35]. This may account for estrogen's positive effects on mood.

### *White Matter Changes (WMC)*

Estrogen-mediated morphological changes in the brain can be observed by means of magnetic resonance imaging (MRI). Many AD patients have WMC similar to those seen in cerebrovascular disease. These WMC may be ischemic, secondary to the amyloid angiopathy [36]. Postmenopausal women treated with estrogen have fewer and less extensive MRI white matter abnormalities than those not receiving ERT. There exists an inverse relationship between the total white matter hyperintensity area and the duration of estrogen treatment [37].

## **Studies on Cognition**

Estrogen has been demonstrated to have positive effects on many cognitive faculties in animals and humans. In vivo studies show that ERT may affect specific memory tasks [5, 38]. Estrogens have been shown to enhance nonspatial learning in animals [5] and humans [39–42]. Human studies, which we review here, have focused on the use of ERT by women who have passed the menopause and those who have had their ovaries removed.

### *ERT and Postmenopausal Women*

The frequent use of ERT by postmenopausal women has provided opportunities for naturalistic studies of estrogen's effects. A large 15-year prospective cross-sectional study of Rancho Bernardo community, investigated the possible influence of ERT on the cognitive function of elderly women enrolled in a study on heart disease factors [42]. The results were not supportive of the use of estrogen for improving cognition as none of the 12 tests of cognition was consistently associated with current or past use, duration or dose. Of 132 statistical analyses, only five statistically significant differences were found. Of 800 elderly females, only the women who had used estrogen for at least 20 years, scored significantly better on the fluency test compared with those who had never used estrogens. Paganini-Hill and Henderson [43] measured the plasma levels of estrone and estradiol in 292 women from a retirement community who performed the clock-drawing task. The levels did not differ significantly between women with normal and abnormal clocks. In a study of healthy postmenopausal women, Kempen and Sherwin [41] found 28 women on ERT performed statistically significantly better on immediate and delayed paragraph recall than 44 women not taking ERT. This suggested a specific verbal memory effect rather than global effect of ERT on cognition. In a study of 222 postmenopausal women participating in a stroke study, women taking ERT ( $n = 70$ ) had significantly better results on conceptualization, attention and visuopractical skills [36].

### *ERT and Surgically Menopausal Women*

Of 19 surgically menopausal women, 10 treated with estrogens had higher immediate paragraph recall scores compared to baseline [44], while there was a decrease in the scores of both immediate and delayed recall of paired associates in the 9 women receiving placebo. This decrease was related to a decline in their plasma estrone sulfate and estradiol levels. Short-term verbal memory improved independently of mood changes and most other menopausal symptoms in women receiving ERT after bilateral oophorectomy [44].

A large study of 6,110 women including 938 concurrent ERT users, which examined risk factors for atherosclerosis, found that in surgically menopausal women, ERT improved word fluency [39]. This effect was most marked in current users with a long ERT history and persisted after removal of the depression score from linear regression. A randomized double-blind study of conjugated estrogens in 36 asymptomatic women after hyster-

ectomy improved quality of life and mood but not memory [45].

In summary, the evidence for ERT improving cognition generally in menopausal women is lacking though there may be specific effects on verbal memory and mood.

### **Estrogens as Prevention of AD**

A number of case-control and prospective studies have examined a possible role of estrogens in prevention of AD. One case-control population-based study ( $n = 227$ ), which used computerized pharmacy data to assess estrogen use, did not find an association between AD and ERT [46]. The risk of AD was lowest for oral estrogens (odds ratio = 0.7, 95% CI not given) although the slightly varying odds ratio for different means of estrogens delivery were probably due to random variation.

A similar result (odds ratio = 0.69, 95% CI = 0.46–1.03) for oral preparations was reported in a case-control study of a retirement community [47]. In this study of 138 dementia cases (each matched with 4 controls) including 71 AD cases, the risk was lower for higher doses of estrogens, as well as for longer duration of ERT [47]. In another case-control study of 248 demented subjects each matched with 5 controls, the risk of AD and other dementias was significantly decreased in estrogen users (odds ratio = 0.65, 95% CI = 0.49–0.88) compared with nonusers [48]. The risk was reduced significantly with higher doses and longer duration of oral therapy, and also decreased where estrogen was administered nonorally. In both studies, the protective effects of ERT seemed to be time- and dose-related with long-term, high-dose users having the least risk of AD [47, 48]. However, both studies used death certificates and medical records for dementia diagnosis and neither had information on education.

Mortel and Meyer [49] reported an association between a lack of ERT and increased dementia risk in a case-control study. When 306 postmenopausal women including 93 AD and 65 vascular dementia cases were matched with 148 controls, women with dementia were 53% as likely to have used estrogens compared with control subjects. Another study from Henderson and Paganini-Hill [50], this time from an AD Research Centre, showed that 143 women with AD were significantly less likely to be taking ERT than 92 control subjects.

In a prospective community-based study by Tang et al. [51], none of the 23 women ( $n = 1,124$  women, including 156 women with a history of ERT use), who were already

taking estrogen at baseline, developed AD during the follow-up. The age at onset of AD was significantly later in women with a history of estrogen use than in those without it. The risk of AD for estrogen users was 5.8% versus 16.3% for nonusers, even after adjustment for education, ethnic origin and apolipoprotein E status. A source of bias was that estrogen use was assessed by history and it was more common among better educated women and less common in African-American women. Another prospective study, The Baltimore Longitudinal Study of Aging [52], reported that the risk of developing AD was 2.3 times higher in women who had never taken estrogens. However, the results from this study require replication as the sample of 472 was not representative in terms of education, socioeconomic status and estrogen use. The Italian Longitudinal Study on Aging [53] examined estrogen use in a randomly selected community sample of 1,568 postmenopausal women among who 92 AD cases were identified. The frequency of estrogen use was higher in healthy women compared with AD patients (odds ratio = 0.34, 95% CI = 0.07–0.77).

### **Estrogens as Treatment of AD** (table 1)

There is accumulating evidence from trials of estrogens as a treatment for AD that patients' cognitive function may be enhanced with ERT. Honjo et al. [54], reporting women with AD and lower levels of estrone sulfate than normal women, gave 7 women with AD a conjugated estrogen over 6 weeks and reported improvements in orientation, memory and calculation.

In a case-control study of 143 female AD patients (including 70 autopsy confirmed cases), those taking estrogens scored significantly better on the Mini-Mental State Examinations (MMSE): 16.6 versus 9.9 for untreated women [50]. This difference was maintained after controlling for education. Four nonrandomized, open label trials of ERT in female AD patients reported improved cognition [18, 54–56]. ERT also alleviated depressive symptoms in three studies [18, 55, 56] suggesting that the effect on cognition could have occurred through mood enhancement. However, in one study this was unlikely, as the mean baseline Hamilton Rating Scale for Depression was only 4 even though the score decreased further during the course of ERT [18].

One study [40] compared the performance of women with AD taking estrogens ( $n = 9$ ) and those not taking estrogens ( $n = 27$ ), matched for age, education and duration of dementia. The estrogen group scored significantly

better on a semantic memory task, digit spans forward and backwards and one of the drawing tasks. However, the sample sizes were small in this study and the women were not randomized to treatment groups.

The positive effects on cognition seem to last as long as ERT is being used [18]. In the study by Okhura et al. [18], the results for the estrogen-treated group ( $n = 15$ ) on MMSE (10 cases) and Hasagawa Dementia Scale (11 cases) were significantly better than in the control group. At 6 weeks, improvements were noted in orientation in time and space, recent and remote events, and calculation. These performances returned to pretreatment levels within 3 weeks of cessation of estrogen. The same authors [56] in a study of 7 women with mild to moderate dementia of Alzheimer's type (followed for 5–45 months) showed improvement in 4 out of 7 participants on MMSE and Hasagawa Dementia Scale, suggesting that long-term, low-dose ERT had a favorable effect on cognition. However, all these studies have very small numbers and larger investigations are awaited.

### *Estrogens and Antidementia Drugs*

In a posthoc analysis of tacrine clinical trial data [57], women who were taking tacrine plus ERT (concurrent or previous ERT users  $n = 37$ ) performed better than those taking tacrine alone ( $n = 194$ ), who outperformed those on placebo ( $n = 83$ ). Prior or concurrent ERT use was associated with a better performance on Clinical Interview Based on Impression of Change (to a significant level) and MMSE (trend only), even after adjusting for age and education. The response to tacrine plus ERT suggested that estrogen may be an adjunct treatment to acetylcholinesterase inhibitors in AD. In a retrospective study of 1,648 participants of a multicenter clinical trial clinically diagnosed as AD (including 89 ERT users), there was a slight enhancement of cognitive function with estrogen as measured by the Alzheimer's Disease Assessment Scale [58, 59].

### *Interactions of Estrogens with ApoE4*

The  $\epsilon 4$  allele of the apolipoprotein E (ApoE) gene increases the risk for AD in familial and sporadic forms of AD and may account for 50% of the attributable risk [60]. The interactions of ERT and ApoE status were examined in a study of 1,282 nondemented elderly women [51]. In the 604 women (53.7%) for whom genotypes were available, the presence of ApoE4 conferred an increased risk of AD, but their risk was substantially lower if women were taking ERT. Thus, compared to women not taking ERT, the relative risk of AD for those receiving ERT was 0.13

**Table 1.** Studies on cognition

Group (first author)	Year	Design	Sample size	Findings
<i>Estrogens as prevention of AD</i>				
Brenner [46]	1994	Case-control	107 AD patients 120 controls	No association between estrogen use and AD
Paganini-Hill [47]	1994	Case-control	138 dementia patients 550 controls	Lower risk with higher doses of estrogens and longer duration of ERT
Henderson [50]	1994	Case-control	143 AD patients 92 controls	AD cases less likely to be taking ERT
Mortel [49]	1995	Case-control	158 dementia patients 148 controls	Dementia cases less likely to use ERT
Paganini-Hill [43]	1996	Case-control	248 dementia patients 1,193 controls	Risk of AD and other dementias significantly lower in ERT users, also with higher doses and duration of treatment
Tang [51]	1996	Prospective	1,124 including 156 with a history of ERT use	Age at onset of AD later in women with a history of ERT use
Kawas [52]	1997	Prospective	472 including 230 ERT users	Risk of developing AD higher in ERT never users
Baldereschi [53]	1998	Observational, cross-sectional	1,568 including 238 ERT users and 92 dementia cases	Higher estrogen use in healthy women
<i>Estrogens in AD patients</i>				
Fillit [55]	1986	Open trial	7	Improvements in orientation and attention in 3 patients
Honjo [54]	1989	Open trial	7	Improvements in orientation, memory, calculation
Henderson [50]	1994	Group comparisons	138 including 10 ERT users	Patients taking ERT scored better on MMSE
Okhura [18]	1994	Open trial	15 ERT group 15 controls	Improvements on MMSE and Hasagawa Dementia Scale with ERT
Okhura [56]	1995	Open trial	7	Long-term, low-dose ERT improves cognition
Henderson [40]	1996	Group comparisons	36 women including 9 ERT users	Better cognitive performance of ERT group
Doraiswamy [58]	1997	Unspecified drug for AD trial, double-blind, retrospective	1,648 including 89 ERT users	Slight enhancement of cognition with ERT
<i>ERT and postmenopausal women</i>				
Barret-Connor [42]	1993	15-year prospective, cross-sectional	800 ERT users	Better performance on fluency test, only for users of 20 years
Kempen [41]	1994	Cross-sectional	28 ERT users 44 nonusers	ERT group better on immediate and delayed paragraph recall
Paganini-Hill [43]	1996	Group comparisons	292	No difference in clock-drawing task with different estrogen serum levels
Schmidt-Fazekas [36]	1996	Group comparisons	70 ERT users 140 never users	ERT group better in conceptualization, attention, visuoperceptual skills
<i>ERT and surgically menopausal women</i>				
Ditkoff [45]	1991	Placebo, double-blind	Total of 36	No significant effect on Wechsler Adult Intelligence Scale
Phillips [44]	1992	Placebo, double-blind	10 ERT users 9 nonusers	Improvement in short-term memory in ERT group
Szklo [39]	1996	Prospective		Improvement in word fluency in surgically menopausal current ERT users

for Apoε4 heterozygotes, and 0.4 for other ApoE genotypes. None of the women homozygous for Apoε4 had been taking estrogens.

### **Estrogen and Progesterone**

The effect of progesterone on cognition is relevant as ERT is commonly combined with progesterone. The use of ERT with progesterone may produce worse results on cognition than estrogen-only treatment [56]. Paganini-Hill and Henderson [43] reported higher progesterone levels in women with the abnormal clock-drawing task. Further, the addition of progesterone may adversely influence the mood of postmenopausal women. Negative mood appears with concurrent progesterone intake or shortly after and correlates positively with progesterone dose [61]. Treatment with norethisterone, a progesterone, decreases menopausal symptoms such as flushes and sweats, but affects mood and concentration adversely [62].

### **Mood and Estrogens**

The possibility that estrogen's positive effects on cognition are mediated through its mood-enhancing actions has been mentioned. The evidence for this is still relatively weak and mainly comes from studies of postmenopausal women who are not clinically depressed.

In a randomized double-blind study of estrogen in asymptomatic surgically menopausal women ( $n = 36$ ), there was a decrease in depression scores in the estrogen-treated group [45]. Others [63–65] have also suggested that estrogens can be used in nondepressed surgically menopausal women for mood improvement. Placebo-controlled trials of ERT [66–71] reported improved mood and quality of life with ERT in postmenopausal women without significant depressive symptoms [35]. However, other placebo-controlled trials [72–75] did not find a positive effect of estrogen on mood in healthy postmenopausal women [35]. In depressed menopausal women there have been three controlled studies of estrogen [76–78], of which two reported positive effect on mood [77, 78] and one did not [76]. While ERT has been effectively used as an adjunct to the treatment of depression in women not responding to antidepressants only [61], its use in major depression remains controversial and requires further investigation.

### *Phytoestrogens*

Phytoestrogens are very popular herbal medicines and are perceived as safe. The four classes of phytoestrogens (isoflavones, lignans, coumestans, resorcylic acid lactones) can be found in soy products, grains, legumes, fruit and vegetables [79]. Although phytoestrogens are thousands of times less potent than estradiol [79], they have been reported to improve menopausal symptoms [80]. At present, there are no studies examining possible use of phytoestrogens for improving mental health of postmenopausal women.

### **Side Effects**

The beneficial effects of estrogens on physical health are well known, such as offering protection against cardiovascular disease and osteoporosis [81]. It has been also suggested that they may prevent colorectal cancer [82] and maintain skin thickness [83]. These benefits must be balanced against risks or side effects. Endometrial hyperplasia is a side effect of unopposed estrogens [84], but ERT with progesterone has been suggested to affect adversely cognition. On the other hand, surveillance for endometrial cancer is technically easy through endometrial biopsy, and endometrial cancer which follows unopposed ERT seems to be well differentiated. An increased risk of endometrial cancer is not a concern in ERT with progesterone [81], but withdrawal bleeding after progesterone may be undesirable in women with dementia. The risk of breast cancer in ERT users is controversial. Doses of estrogens known to protect against osteoporosis and cardiovascular disease are, at present, not known to be associated with any clear-cut increased risk of breast cancer [85].

### **Discussion**

Converging biological, preventative and clinical data supporting the positive effects of estrogen on AD are encouraging but not definitive for a number of reasons. Firstly, there are many inconsistencies among studies regarding: sample selection (from drug trial, population-based, volunteer or unrelated research samples); diagnosis of AD (clinical, death certificates, pathological); treatment regimens (unspecified ERT preparations, opposed versus unopposed estrogens, different doses, varying lengths of treatment, small number of subjects); outcome measures (tests of memory, attention, mood); subject

demographics, specifically age and education; concurrent or previous use of other medications such as anti-inflammatory drugs, and monitoring of estrogen blood levels. Secondly, statistical significance found in studies with large samples does not always necessarily represent clinical significance. Thirdly, the beneficial effects of estrogen on cognition may be secondary to the effects of ERT on mood.

There are similarities between the use of estrogen for depression and for dementia, both of which have been researched for a considerable period. ERT appears to enhance the response to specific antidementia drugs and the dosage found to be effective in depression is similar to the one required in AD. Even though the beneficial effect of ERT on mood has been often reported [35], ERT is not widely used for depression, except by gynecologists.

Questions raised by ERT use, its potential benefits and risks may well be answered once two randomized, double-blind, placebo-controlled trials of ERT are completed. The Women's Health Initiative, established by National Institute of Health in the USA, is the largest prevention study ever conducted [86]. Recruitment of 27,500 women aged 50–79 for this 15-year prospective study was scheduled to be completed in 1998. A subsample of 8,000 enrolled women will also take part in a memory study. The other trial, run by US Alzheimer's Disease Coopera-

tive Study Unit, is investigating the influence of ERT on cognitive function in 120 postmenopausal women with mild to moderate AD [86].

## Conclusion

The evidence of estrogen's effects on brain in general and cognition specifically, combined with the tantalizing findings of estrogen's protective effects against AD emerging from retrospective case-control studies, and the positive results from small AD treatment studies are too strong to ignore. Current therapy for AD is limited and mainly symptomatic, e.g. cholinesterase inhibitors which offer significant but modest benefits [87]. Meanwhile, the use of ERT is worth considering as a prevention and treatment [1]. Women with hereditary predisposition to AD or those at high risk of osteoporosis or cardiovascular disease may be more inclined to consider ERT prophylaxis, though definitive data are not yet available. Caution is still warranted in view of the lack of long-term prospective data, large clinical trials and scrutiny of side effects. Evidence for the use of ERT either alone or in combination with other treatments is eagerly awaited as is the development and testing of nonfeminizing estrogen analogs for men.

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