The Role of Hormone Replacement Therapy in the Prevention of Alzheimer Disease

Howard M. Fillit, MD

Alzheimer disease (AD) is the most common form of dementia among the elderly. A higher prevalence of AD in women than in men suggests a link between gonadal hormone levels and AD. Increasing evidence supports a role for estrogen in brain regions involved in learning and memory and in the protection and regulation of cholinergic neurons, which degenerate in AD. Despite the lack of consensus, many studies indicate that hormone replacement therapy may decrease the risk for or delay the onset of AD in postmenopausal women. Recent trials have suggested that estrogen treatment may have no significant effect on the clinical course of AD in elderly women with the disease. Thus, the role of estrogen therapy seems to be confined to primary rather than secondary prevention of AD. Ongoing clinical studies may help to determine the role of estrogen in the cognitive function of postmenopausal women and in the prevention of AD.
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Alzheimer disease (AD) is a neurodegenerative disorder that progressively affects intellectual functions. Alzheimer disease is manifested primarily in the impairment of cognitive functions such as memory and language. In 2000, AD affected an estimated 2.5 million to 4.5 million Americans,[1,2] resulting in a profound emotional, social, and economic burden. As life expectancy continues to increase in the United States, the delay or the prevention of this degenerative disorder will become even more pressing.

Alzheimer disease is more common in women,[3] with the prevalence of AD among women in the United States double that among men.[2] A recent meta-analysis of 7 sex-specific studies of incidence rates for AD concluded that AD is 1.5 times more likely to develop in women than in men.[4] These data suggest that low estrogen levels may be linked to the decline in cognitive function associated with dementia of the Alzheimer type.[5] Decreased estrogen levels after menopause is a risk factor for AD,[6] and neurobiological studies have found a link between estrogen and learning and memory functions.[7-13] For example, low estrogen levels negatively affect the performance of rodents on learning and memory tasks, whereas administration of estrogen reverses this effect.[14] Clinical research has focused on various roles for estrogen replacement therapy (ERT) (consisting of unopposed estrogens) and hormone replacement therapy (HRT) (consisting of estrogens in combination with a progestin): ERT/HRT in the cognitive function of healthy postmenopausal women[15-19]; the effect of ERT/HRT on the cognitive decline of elderly women, some of whom have mild cognitive impairment[20-24]; the link between ERT/HRT and the risk for development of AD[25-29]; and the use of estrogen to treat AD.[30-34]

A recent meta-analysis[35] found that, according to most studies, ERT/HRT has beneficial effects on learning and memory in postmenopausal women and is associated with a reduced risk for AD; a handful of studies, however, did not show significant effects.[35] In the absence of large randomized studies, no definitive evidence or consensus exists regarding the use of estrogen to prevent or to delay AD. It is also unclear whether any beneficial effects of estrogen on cognitive function occur immediately after menopause or later

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in life, and whether estrogen is effective in preventing the cognitive decline observed in normal aging and/or in pathological conditions. Inconsistent findings in these areas may be attributed to variations among any of the following variables: the size of the study population; the participants' ages, lifestyles, and educational levels; demographic features; the method of obtaining information about estrogen use, which may depend on participant recall; the route of administration of the hormone; the duration of the treatment; and the approach used to evaluate cognitive decline. More multicenter studies with a larger number of participants and standardized methods of diagnosis and evaluation are necessary to settle these issues.

This article reviews the neuroprotective and neurotrophic effects of estrogen, focusing on brain regions involved in learning and memory. It then discusses evidence regarding the effectiveness of ERT/HRT in preventing or delaying the onset of AD and surveys the nascent research on the use of estrogen to treat the disease.

MECHANISMS OF AD

A number of underlying causes for the neuronal damage seen in AD have been proposed, including oxidative stress caused by free radicals, hormonal insufficiency, loss of trophic support, hypoxia, and trauma. Vascular disease, which diminishes regional cerebral blood flow, may also be a risk factor for AD.[36] In addition, Panidis et al[36] suggested that nearly 30% of cases of AD are attributable to genetic factors, particularly polymorphism of apolipoprotein E (ApoE). Of the 3 types of genes for ApoE (ε*2*, ε*3*, and ε*4*), the ε*4* allele is a known risk factor for AD.[37,38] The ε*4* allele is responsible for the production of the ApoE4 isoform, which can interact with amyloid β-protein (Aβ) to form AD-associated neuritic plaques.[39] Autopsy findings in patients with late-onset AD show increases in Aβ deposition in patients with ApoE ε*4*.[40]

Early AD mainly affects brain regions involved in learning and memory, such as the entorhinal cortex and the hippocampus.[41-43] The 2 main signs of the pathologic changes of AD include neuritic plaques mainly containing fibrillar Aβ, and neurofibrillary tangles composed of phosphorylated tau molecules that form paired helical filaments.[36,44-46] Amyloid β-protein is probably produced by the metabolism of the amyloid precursor protein (APP) at the β cleavage site.[47] Mutations of APP have been implicated in early-onset AD and can lead to aggregations of Aβ plaques early in the development of the disease.[48] Neurofibrillary tangles, which are found in aging brains in general, may mark a phase in neuronal degeneration, since they appear where neurons have died.[44] Neurofibrillary tangles and Aβ plaques can occur independently.[45] Other neurotoxic agents that may play a role in the degeneration associated with AD are hydrogen peroxide, a precursor for free radicals that have also been associated with the neuronal damage seen in AD,[49,50] and glutamate, the principal excitatory neurotransmitter, which may contribute to AD through excitotoxicity.[50]

Patients with AD also exhibit profound, progressive loss of cholinergic neurons in the nuclei of the basal forebrain,[45,51] which project to the hippocampus and the neocortex and are essential for learning and memory.[52,53] The loss of these neurons in the nuclei of the basal forebrain, and a corresponding decrease in cholinergic innervation of the hippocampal formation and the neocortex, are hallmarks of AD.[54-56] Whitehouse et al[51] demonstrated that neurons in the nucleus basalis of Meynert, which project directly to the cerebral cortex, are decreased by as much as 80% in the brains of patients with AD or dementia of the Alzheimer type. The cortical neuronal atrophy and decline of synaptic density in the cortex and hippocampus are likely correlates of dementia.[45]

The best available marker for cholinergic neurons in the basal forebrain is choline acetyltransferase (ChAT) activity.[51] Choline acetyltransferase synthesizes the neurotransmitter acetylcholine (ACh), which is involved in transmitting messages between the basal forebrain and the cortex, hippocampus, and amygdala.[36] Choline acetyltransferase also inhibits the expression of acetylcholinesterase, an enzyme that is involved in the metabolism of ACh.[57] Several studies have reported a significant decrease in ChAT activity in the postmortem brains of demented patients,[56] and levels of ACh are 90% lower in patients with AD.[36]

EFFECTS OF ESTROGEN ON BRAIN FUNCTION

There are multiple pathways to neuronal injury, dysfunction, and ultimately death in AD, many of which are potentially modified by estrogen. Evidence suggests that estrogen protects against various neurotoxic events and has a neurotrophic, regulatory role in the cholinergic system (**Table**).[12] New research supports additional protective and regulatory activities of estrogen on the expression of genes associated with AD.[58,65,84-87]

NEUROPROTECTIVE EFFECTS OF ESTROGEN

Although more research is needed on the specific mechanisms, recent data from an in vitro study indicate that estrogen is highly neuroprotective against a wide range of neurologic insults associated with AD.[50] Experimental evidence further suggests that the antioxidant potency of estrogen is inherent, independent of receptor binding.[49,94] The neuroprotective effects of estrogen against the oxidative damage and lipid peroxidation caused by toxins could be a mechanism to explain the reduced risk for AD seen in women using estrogen therapy.[50]

Estrogen is particularly effective against neuronal injury induced by the toxins Aβ[49,50,59-62,64] and glutamate.[10,49,50] Using an animal model, Thomas and Rhodin[64] recently found that low doses of conjugated equine estrogens prevented the abnormal deposition of Aβ in the cerebral vasculature and the adhesion and transmigration of leukocytes that mark an inflammatory reaction, which may have relevance for the chronic inflammation seen in AD. Estrogen has been shown to attenuate elevated cal-

Effects of Estrogen on Brain Regions Involved in Memory and Cognitive Function*

Effects	References (Year)
Neuroprotective effects against injury	
Amyloid β-protein	Jaffe et al[58] (1994); Goodman et al[59] (1996); Behl et al[49] (1997); Gridley et al[60] (1997); Keller et al[61] (1997); Bonnefont et al[62] (1998); Xu et al[63] (1998); Brinton et al[50] (2000); Thomas and Rhodin[64] (2000); Vincent and Smith[65] (2000)
Glutamate	Goodman et al[59] (1996); Singer et al[10] (1996); Behl et al[49] (1997); Brinton et al[50] (2000)
Hydrogen peroxide	Behl et al[49] (1997); Brinton et al[50] (2000)
Neurotrophic effects in the basal forebrain cholinergic system	
Enhances hippocampal functioning	Brinton[66] (1993); Brinton et al[67] (1997); Gibbs et al[68] (1997); Fader et al[69] (1998); Luine et al[70] (1998); Gibbs[71] (1999); Brinton et al[50] (2000); Newhouse et al[72] (2001); Eberling et al[73] (2001)
Increases neuronal outgrowth and dendritic spine density in the hippocampus	Woolley et al[7] (1990); Woolley and McEwen[8] (1993); Murphy and Segal[9] (1996); Murphy et al[13] (1998)
Regulates cholinergic neurons in the basal forebrain	Luine[57] (1985); O'Malley et al[74] (1987); Gibbs and Pfaff[75] (1992); Toran-Allerand et al[76] (1992); Miranda et al[77] (1993); Gibbs et al[78] (1994); McMillan et al[79] (1996); Gibbs[80] (1997); Gibbs[81] (1998); Gibbs and Aggarwal[11] (1998); Blurton-Jones et al[82] (1999); Gibbs[83] (2000)
Effects on genes associated with AD	
Regulates expression of apolipoprotein E	Srivastava et al[84] (1997); Stone et al[85] (1998); Teter et al[86] (1999)
Inhibits expression of mutant presenilin-7	Mattson et al[87] (1997)
Other effects	
Increases glucose transport	Bishop and Simpkins[88] (1995)
Enhances regional cerebral blood flow	Ohkura et al[89] (1995); Resnick et al[90] (1998); Maki and Resnick[91] (2000); Dubal and Wise[92] (2001)
Down-regulates the serotonin$_{1A}$ receptor within the serotonin system	Österlund et al[93] (2000)

*AD indicates Alzheimer disease.

cium levels induced by Aβ and glutamate and to suppress lipid peroxidation induced by iron and Aβ.[59] Xu et al[63] recently found that 17β-estradiol reduced the generation of plaque-forming Aβ by rodent and human neurons.

Estrogen may also protect neurons from Aβ toxicity by stimulating the proteolysis of APP.[58] Jaffe and colleagues[58] reported that estrogen promotes the metabolism of APP into its nonamyloidogenic part. A more recent study of the effect of estrogen on neuronal Swedish-mutated APP found that although estradiol increased nonamyloidogenic APP secretion in primary cortical neurons, Aβ production was undiminished, possibly owing to the interference of astrocytes.[65] Recent animal models of AD have also indicated a link between the excessive expression of APP and the loss of cholinergic function seen in AD.[95-97] Interactions among estrogen, APP, and nerve growth factor have been suggested to protect against the degeneration of cholinergic neurons,[98] but more research is needed to determine the mechanisms by which estrogen influences APP metabolism.

Estrogen also guards against intracellular hydrogen peroxide accumulation, preventing the degeneration of primary neurons and hippocampal cells.[49,50] It appears that 17β-estradiol acts directly on synapses to prevent oxidative impairment of sodium and potassium ions in adenosine triphosphatase activity, glucose transport, and glutamate transport.[61]

Finally, a recent report[73] that used magnetic resonance imaging to evaluate the effects of sex and estrogen use on hippocampal volume in 13 elderly women taking ERT, 46 women not taking any estrogen therapy, and 38 men found that the women taking ERT had significantly larger right anterior hippocampal volumes than the other 2 groups. Sex did not have a significant effect, supporting a neuroprotective effect of estrogen.

NEUROTROPHIC EFFECTS OF ESTROGEN

In addition to the neuroprotective properties, estrogen exerts trophic and regulatory effects on basal forebrain cholinergic neurons.[11] A number of studies have shown that the regulatory role of estrogen in the basal forebrain influences hippocampal morphology and function. Luine and colleagues[70] have suggested that, in addition to the direct effects of estrogen on the hippocampus, estrogen initiates hippocampal effects that are mediated by areas projecting to the hippocampus. They found that the performance of rats on spatial memory tasks, which are dependent on hippocampal function, improved significantly after long-term estradiol treatment; however, increases in monoaminergic and amino acid neurotransmitter activity were seen in the frontal cortex and the basal forebrain rather than in the hippocampus.[70] These results are consistent with those of other studies[69,71] in which administration of estradiol to ovariectomized rats improved their performance on spatial memory tasks—in one study,[71] after 3.5 and 12 months of continuous treatment—and reduced the cognitive-impairing effects of scopolamine hydrochloride. These experimental studies were supported by a recent randomized, placebo-controlled study[72] among 15 postmenopausal women that showed that the effects of scopolamine hydrochloride (2.5 μg/kg given as a one-time dose) were blunted in subjects treated with 17β-estradiol (1 mg/d) for 3 months. Long-term benefits in hippocampal function may be due to the influence of short-term changes in cholinergic activity, induced by estrogen, that project to the hippocampus, and may help explain the reduction in the risk for and severity of AD in postmenopausal women who have taken ERT.[71]

Dendritic spines, the principal loci of neuronal interactions and communication in the central nervous system, are among the central targets of the mechanisms of action of estrogen. A dramatic decrease in dendritic spine density has been observed in the ventromedial hypothalamic neurons of ovariectomized rats that was reversed by administering estrogen.[99] This is consistent with findings that the density of synapses and synaptic spines fluctuates during the estrous cycle, increasing in response to estrogen.[7,8] More recent studies[9,13] on rat hippocampal neurons in culture have confirmed that estrogen plays a critical role in a process that yields a 2-fold increase in dendritic spine density. This process may be mediated by brain-derived neurotrophic factor; however, the effects of estrogen on brain-derived neurotrophic factor regulation in this brain region are not yet fully understood.[13,100] The functional consequence of increased dendritic spine density is reflected in the improvement of rodent performance in behaviors related to hippocampal function. Estrogen enhances the induction of long-term potentiation in awake animals, a model of synaptic plasticity in the hippocampus with potential relevance to learning and associative memory.[101]

Evidence of the local effects of estrogen in the hippocampus and the neocortex has also been established. Estrogen appears to interact closely with neurotrophins, which also promote neuronal growth and block apoptosis, in the basal forebrain. In the 1980s, O'Malley and colleagues[74] proposed that estrogen modulated the production, release, and uptake of ACh by cholinergic neurons. Administering estrogen to ovariectomized rats induced the potassium-evoked release of ACh,[68] which is inhibited by Aβ,[102] in the hippocampus and the overlying cortex. The enhanced release of ACh in these areas is reflected in direct, trophic effects of estrogen on hippocampal neurons. Brinton[66] reported filopodial growth in hippocampal neurons within 5 minutes of exposure to 17β-estradiol, and has since demonstrated with others significantly increased hippocampal and neocortical neurite outgrowth, viability, and survival after exposure to 17β-estradiol and conjugated equine estrogens.[50,67] Effective protection of rodent neuronal cells in vitro from toxic complexes formed by the combination of acetylcholinesterase and Aβ by 17β-estradiol has also been demonstrated.[62]

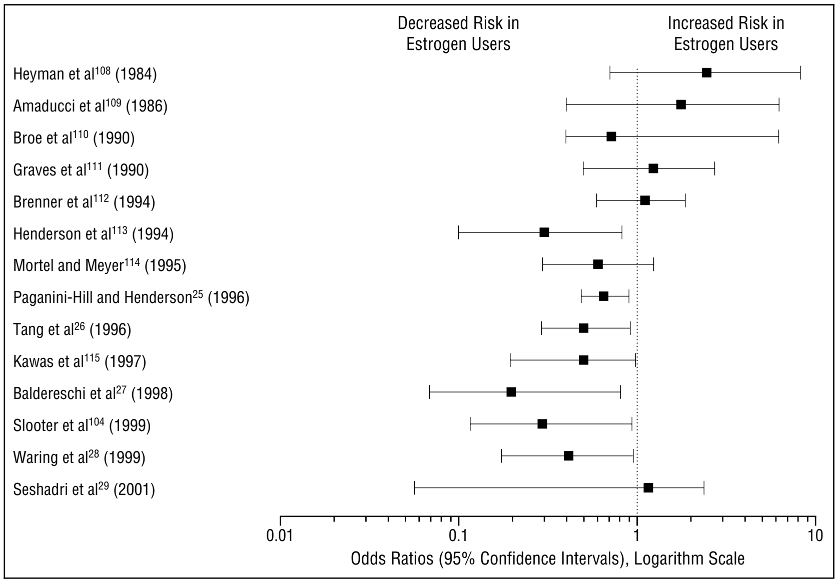
Estradiol was also found to increase ChAT activity in certain basal forebrain cholinergic nuclei in female rats.[57] A recent study, however, reported that although the administration of estradiol increased ChAT expression and high-affinity choline uptake in the cholinergic system of ovariectomized rats after 2 weeks, no changes were found after 4 weeks of continuous or repeated estrogen treatment.[83] Furthermore, continuous estrogen therapy administered for 13 months led to a decrease in high-affinity choline uptake, especially in the hippocampus.[83] Although these findings indicate that enhancement of cholinergic function by estrogen may be short-term, other data show that 4 weeks of estrogen treatment in rats produces consistent decreases in levels of the low-affinity nerve growth factor receptor $p75^{NGFR}$, an effect of increased ChAT levels that plays a crucial role in regulating cholinergic activity.[80]

Toran-Allerand and colleagues[103] consider estrogen to be a neuronal growth factor that shares many characteristics of neurotrophins, enabling convergence of estrogen- and neurotrophin-signaling pathways. The decline of gonadal steroid levels in both sexes with aging may thus contribute to the loss of neuronal systems integral to cognitive function.[103]

EFFECTS OF ESTROGEN ON GENES ASSOCIATED WITH AD

Recent studies have investigated the effects of estrogen on the expression of ApoE4. Estradiol up-regulated ApoE gene expression by increasing levels of ApoE messenger RNA in an animal model of AD[84]; in a similar animal model, estradiol enhanced synaptogenesis, possibly through an ApoE-dependent mechanism.[85] Teter and colleagues[86] have recently confirmed these findings by studying the interaction of ApoE and estrogen in mouse hippocampal slice cultures. Neuronal sprouting increased in ApoE-dependent areas, possibly as a consequence of the up-regulation by estrogen of ApoE expression to enable the recycling of membrane lipids for use by sprouting neurons.[86] A population-based case-control study investigating a possible link between estrogen and early-onset AD, which included 53% ApoE *ϵ3/ϵ4* or ApoE *ϵ4/ϵ4* carriers, found a stronger inverse correlation between estrogen use and early-onset AD in this group (odds ratio [OR], 0.37; 95% confidence interval [CI], 0.08-1.58) than in women with the ApoE3 *ϵ3/ϵ3* genotype (OR, 0.60; 95% CI, 0.19-1.88).[104] However, another study found no reduction in the risk for cognitive decline among women with the ApoE *ϵ4* allele who used ERT/HRT, although hormone users without the ApoE *ϵ4* allele exhibited less cognitive decline.[38] Moreover, Lendon and Lambert[105] recently reported that estrogen enhanced expression of the *ϵ4* allele. The possible mechanisms involved in the interaction of estrogen and ApoE are the subject of ongoing research.

Mattson et al[87] have shown that 17β-estradiol blocks the expression of mutant presenilin-1, a pro-apoptotic gene linked to early-onset AD that was found in a study of transgenic mice to have a synergistic effect with mutated APP, leading to decreased cholinergic function.[96] In conjunction with findings that 17β-estradiol protects neurons against *nip*-2, another gene that promotes cell death,[106] this research suggests a direct, receptor-independent role for estrogen in preventing neuronal loss associated with AD. More specifically, 17β-estradiol delayed cellular glucose deprivation induced by *nip*-2[106] through a mechanism that may have relevance to AD, since glucose transport and metabolism are diminished in the disease.[107] In their study of the antiapoptotic action of estrogen, Mattson and colleagues[87] found an additional protective capacity of



Odds ratios (squares) and 95% confidence intervals (horizontal lines) from studies of the risk for the development of Alzheimer disease among postmenopausal women using estrogen therapy. Adapted with permission from Yaffe et al.[116]

17β-estradiol to stabilize mitochondrial function.

OTHER EFFECTS OF ESTROGEN ON THE BRAIN

Studies of cognitive function in individuals have established that, during memory processing, estrogen increases glucose transport[88] and regional cerebral blood flow,[89-91] which are decreased in AD. Recently, Maki and Resnick[91] examined longitudinal changes in regional cerebral blood flow in 12 ERT/HRT users and 16 nonusers during the performance of verbal and figural recognition memory tasks. In addition to obtaining higher scores than nonusers on a battery of standardized memory tests, the ERT/HRT users exhibited enhanced regional cerebral blood flow in the hippocampus, the parahippocampal gyrus, and the temporal lobe, regions fundamental to memory function that can reveal preclinical abnormalities in individuals at risk for AD. These results were similar to those found in 2 earlier studies,[89,90] suggesting a key mechanism through which ERT/HRT may decrease the risk for AD. In their recent comparison of the effect of estradiol on middle-aged and young female rats, Dubal and Wise[92] suggested that estrogen achieves neuroprotective effects by modulating regional blood flow, which may be maintained after menopause by ERT.

In summary, numerous studies confirm that estrogen exerts a wide range of neuroprotective and neurotrophic influences on brain regions and neuronal subtypes involved in memory and cognitive function that are negatively affected by AD. These studies have provided the basis for investigations of the effects of estrogen on cognitive impairment in the course of normal as well as pathologic aging of postmenopausal women.

ERT/HRT AND THE RISK FOR AND ONSET OF AD

As mentioned earlier, AD is more likely to develop in women older than 65 years than in their male counterparts,[3,4] possibly due to reduced estrogen levels.[5] The association between ERT/HRT and the risk for AD remains controversial, although most investigations suggest that ERT/HRT reduces the risk for AD (**Figure**). A recent meta-analysis[35] of 14 studies reported an OR of 0.56 (95% CI, 0.46-0.68) for the relative risk for the development of AD. The results of the studies analyzed were heterogeneous, and poor recall of ERT/HRT use may have confounded the results. A major 1998 meta-analysis[116] of the effect of ERT/HRT on the risk for the development of AD in postmenopausal women, which examined 8 case-control studies[6,108-114] and 2 prospective cohort studies,[26,115] reported a summary OR of 0.71 (95% CI, 0.52-0.98) for the development of dementia among estrogen users. Both prospective cohort studies and 1 case-control study[113] reported a significantly lower risk for dementia in women who had ever used estrogen. Of the remaining studies, 3 reported no significant increase among estrogen users,[6,110,114] 2 reported no difference in risk,[112,113] and 2 found no significant increased risk for dementia among estrogen users compared with nonusers.[108,109] Because of significant heterogeneity in the findings, which may be attributable to study design, a separate analysis was performed of the 2 study types. The summary OR for the case-control studies was 0.80 (95% CI, 0.56-1.16) for diagnosis of AD; for the prospective studies, the summary OR was 0.48 (95% CI, 0.29-0.81). The 3 studies that investigated the relationship between the duration of estrogen use and protection against dementia found inconsistent results,[6,26,115] although in a follow-up investigation of their earlier study, Paganini-Hill and Henderson[25] found a decreased risk among long-term users of ERT.

As the authors point out, observational studies are prone to confounding and compliance bias, which may influence their assessment for the risk of development of AD. In addition, despite the fact that HRT is prescribed more commonly than unopposed ERT in the United States, none of these studies included a significant proportion of HRT users. Two studies from the meta-analysis, however, merit more detailed consideration. The population-based investigations of Paganini-Hill and Henderson,[6,25] which show a decreased risk for AD with estrogen treatment, included a cohort of 8877 women and the completion of health surveys by the individuals rather than by proxy informants, an approach that provides more accurate data about the use of estrogen. The risk for AD was found to be 35% lower in estrogen users.[25] Tang and colleagues[26] followed up 1124 older women for 1 to 5 years and identified 167 incident cases of AD. The risk for AD was reduced by 50% among subjects who had used estrogen (OR adjusted for education, ethnicity, and ApoE genotype). A direct relationship between the duration of hormone treatment and the risk for AD was also reported; the risk was lower among women who had used estrogen for 1 to 5 years than among subjects who had used estrogen for 1 year or less. When demented patients who had used and those who had never used estrogen were compared, the age of AD onset was significantly delayed among estrogen users.

One of the 2 case-control studies in the 1998 meta-analysis[116] that reported no difference in risk[111,112] raised the possibility that the route of administration may influence whether estrogen protects against AD. Brenner and colleagues[112] compared the use of estrogen in 107 cases with AD and 120 age-matched control subjects and found no association between the use of estrogen and the risk for AD. However, the point estimate for AD was decreased by 30% when the results were analyzed for intake of oral estrogen alone. In contrast to these findings, the decrease in the risk for AD did not depend on the route of estrogen intake in the study by Paganini-Hill and Henderson.[6]

Two population-based, case-control studies published after the 1998 meta-analysis report conflicting findings. Results from a study by Waring and colleagues[28] regarding the use of ERT/HRT and the risk for development of AD are consistent with the findings from Tang and associates.[26] Among 222 women from the Rochester Epidemiology Project records-linkage system who were diagnosed as having AD from 1980 to 1984, the frequency of estrogen use was half that of the age-matched control group (n=222) at 10% vs 5% (OR, 0.42; 95% CI, 0.18-0.96). In contrast, a nested case-control study by Seshadri et al[29] found no reduced risk for development of AD among current ERT/HRT users. Starting with a large base cohort (n=221 406) from the General Practice Research Database in the United Kingdom, 59 women were verified as having a new diagnosis of AD from 1992 to 1998 and matched to 221 controls. Fifteen (25%) of the 59 cases and 53 (24%) of the 221 controls were current hormone users, yielding an OR of 1.18 (95% CI, 0.59-2.37) for the risk for development of AD among current ERT/HRT users. The inconsistency in findings between these 2 studies indicates that this issue remains unresolved pending results from further studies.

Two recent studies suggest that ERT/HRT use is associated with a reduced risk for development of AD, but both have limitations due to study methods. Baldereschi and colleagues[27] used results of the Mini-Mental State Examination for an initial screen in 2816 Italian women aged 65 to 84 years; those with positive findings underwent clinical assessment for dementia and AD. The frequency of hormone use was significantly higher among nondemented patients than those with AD after adjustment for age, education, age at menarche, age at menopause, cigarette and alcohol use, body weight at 50 years of age, and number of children (OR 0.28; 95% CI, 0.08-0.98). These findings were prone to recall bias regarding the elderly subjects' use of estrogen, especially among those who were cognitively impaired, although next of kin were questioned in these cases. In a longitudinal study of 3128 women who were outpatients at the California State Alzheimer's Disease Diagnostic and Treatment Centers, hormone users had significantly lower rates of diagnosis of AD at baseline and after 1 year, compared with nonusers.[117] Moreover, patients who had not used estrogen showed increased cognitive deterioration from baseline to follow-up, whereas no significant change in cognitive function occurred among the estrogen users during this period. However, no significant difference was found between the performance of estrogen users and nonusers who had been diagnosed as having AD at baseline. Complete follow-up data were available for only a very small number (n=16) of hormone users; nevertheless, these data suggest that estrogen may protect against cognitive decline in the earlier stages.

A recent population-based study in the Netherlands was, to our knowledge, the first to examine the effect of estrogen use on the risk for early-onset AD. In comparing patients with AD (n=109) with age- and residence-matched controls (n=119), Slooter and colleagues[104] found a significant inverse correlation between estrogen treatment and early-onset AD (adjusted OR, 0.34; 95% CI, 0.12-0.94), suggesting that more research is needed in this specific area.

TREATMENT OF AD WITH ESTROGEN

Despite the significant neuroprotective and neurotrophic effect of estrogen, particularly in vitro, described already, human studies of the effect of estrogen as therapy for AD have been equivocal.[5,30-35] Some studies, primarily short-term ones, have suggested that estrogen use results in short-term improvements in cognition.[30-33,118,119] In contrast, 3 recent randomized, double-blind clinical trials analyzing the effects of estrogen on the clinical course of AD found no significant benefit with estrogen treatment.[34,120,121] These findings may be surprising in view of the increasing evidence showing protective benefits of estrogen on neurons involved in learning and memory and studies showing a significantly reduced risk for AD among women using ERT or HRT. However, an agent that reduces the risk for AD will not necessarily influence the clinical course of the disease once it is established, since the mechanisms involved may be different. The administration of estrogen after neuronal injury has been initiated or has progressed (eg, after AD is expressed) may have no benefit, but estrogen may protect neurons at the initial phases or before the onset of the disease.

Thus, the initial timing of hormone treatment may be crucial. In the study by Mulnard and colleagues,[34] ERT was not initiated immediately after hysterectomy, and the subjects were older than 60 years. The mean ages were 77 years for the estrogen group and 78 years for the placebo group in the study by Henderson et al[120] and 73 years for the estrogen group and 71 years for the placebo group in the study by Wang et al.[121] Estrogen may be most effective as a preventive agent immediately or shortly after menopause. Using an animal model, Gibbs[122] determined that estrogen treatment initiated immediately after or 3 months after ovariectomy—but not after 10 months—improved performance on a spatial memory task. This research suggests that a key window of opportunity for the initiation of hormone treatment in the prevention of cognitive decline in humans may exist, a hypothesis that warrants further investigation. This situation is somewhat analogous to the prevention of osteoporosis, ie, the earlier estrogen treatment is initiated after menopause, the more beneficial its effect, since bone that is already lost cannot be replaced to any significant degree.[123] Because the prevalence of osteoporosis rises dramatically with age, early intervention is necessary to forestall bone loss as long as possible.

CONCLUSIONS

Evidence supports a central role for estrogen in brain regions involved in memory and other cognitive tasks and in protection from AD-associated toxins and genes. A number of observational studies have suggested a significantly reduced risk for development of AD among women who have used ERT/HRT. The Women's Health Initiative Study of Cognitive Aging, a randomized, placebo-controlled trial among 2900 women that will assess cognitive outcomes with ERT/HRT use, is expected to provide substantial evidence regarding the influence of estrogen-based therapy on cognition and AD. That study is ancillary to the Women's Health Initiative Memory Study, which in turn is an arm of the Women's Health Initiative that is sponsored by the National Institutes of Health, Bethesda, Md. The Women's Health Initiative Memory Study will investigate the effect of conjugated equine estrogens on cognitive function and on the risk for the development of AD and other dementia among more than 8000 postmenopausal women, with a minimum follow-up of 6 years.[50,124] The Women's International Study of Long-Duration Oestrogen After the Menopause, also under way, is not due to report results until 2010.[125] These large clinical studies will provide valuable information regarding the potential effects of ERT/HRT on preserving cognitive function in postmenopausal women.

At present, most observational evidence, which is supported by neurobiological research findings on the action of estrogen, indicates that ERT/HRT mitigates the degeneration that may lead to AD. The lack of evidence of a role of estrogen in the treatment of AD suggests that ERT/HRT should be initiated as early as possible after menopause, before the onset or the progression of the disease. Thus, the relationship of postmenopausal hormone therapy to AD is somewhat parallel to its relationship to osteoporosis in that, in both cases, ERT/HRT seems to have a role in primary prevention.

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Corresponding author and reprints: Howard M. Fillit, MD, The Institute for the Study of Aging, Inc, 767 Fifth Ave, Suite 4600, New York, NY 10153 (e-mail: hfillit@rslmgmt.com).

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