ALZHEIMER'S DISEASE AND ESTROGEN REPLACEMENT THERAPY: ANOTHER FACTOR TO CONSIDER

By

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Alzheimer's Disease and Estrogen Replacement Therapy: Another factor to consider

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Alzheimer's disease (AD) is rapidly becoming an important women's health issue based on recent epidemiological studies demonstrating the increased incidence among women. Several recent studies have shown a strong correlation between estrogen and the possible delay or prevention of Alzheimer's disease. This adds another factor for women and their health care providers to address when considering estrogen replacement therapy (ERT). ERT is already of great concern to women and remains a very controversial issue. The possibility of estrogen having a positive effect on cognition along with the cardioprotective effects and prevention of osteoporosis increase its benefits. Nurse practitioners play an important role in the prevention and early diagnosis of Alzheimer's disease. In the United States, Alzheimer's disease is the most common form of dementia. It is often misdiagnosed or unrecognized in the early stages. Practitioners are on the front-line and must sharpen their diagnostic skills to prevent the misdiagnosis of dementia, identifying patients at greater risk including women. A clear understanding of the pathophysiology of AD, and how estrogen may positively affect neuronal activity will be helpful in deciphering the latest information about diagnostic tests and new treatments.

A review of the literature indicates a strong relationship between estrogen and cognition. Several observational studies have revealed epidemiologic data regarding the increased prevalence of AD among women, and the significantly lower incidence of AD among women taking HRT. Clinical trials to date are also demonstrating promising evidence but have been unable to account for confounding factors. Studies in progress, such as the Women's Health Initiative will provide more accurate data upon which practitioners can base clinical decisions and counseling about HRT. Meanwhile, leading researchers have suggested that patients be informed of the possible benefits of estrogen replacement for the prevention or delay of AD.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE PAGE</td>
<td>i</td>
</tr>
<tr>
<td>SIGNATURE PAGE</td>
<td>ii</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>iii</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>v</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>PATHOPHYSIOLOGY</td>
<td>2</td>
</tr>
<tr>
<td>EPIDEMIOLOGY</td>
<td>3</td>
</tr>
<tr>
<td>COST OF CARE</td>
<td>4</td>
</tr>
<tr>
<td>DIAGNOSIS</td>
<td>5</td>
</tr>
<tr>
<td>TREATMENT</td>
<td>6</td>
</tr>
<tr>
<td>ANALYSIS OF LITERATURE</td>
<td>7</td>
</tr>
<tr>
<td>CONCLUSION</td>
<td>9</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>12</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>18</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>25</td>
</tr>
</tbody>
</table>
LIST OF TABLES

1. Observational studies ........................................................................................................ 20
2. Epidemiologic studies ......................................................................................................... 22
3. Experimental studies .......................................................................................................... 23
Alzheimer's Disease and Estrogen Replacement Therapy:

Another factor to consider

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Abstract

Alzheimer's disease (AD) is rapidly becoming an important health issue for women based on recent epidemiological studies demonstrating the increased incidence among women. Several recent studies have shown a strong correlation between estrogen replacement and the possible delay or prevention of Alzheimer's disease. This adds another factor for women and their health care providers to address when considering estrogen replacement therapy (ERT). ERT is already of great concern to women and remains a very controversial issue. The possibility of estrogen having a positive effect on cognition along with the cardioprotective effects and prevention of osteoporosis increase the benefits of ERT. Nurse practitioners play an important role in the possible prevention and early diagnosis of Alzheimer's disease. In the United States, Alzheimer's disease is the most common form of dementia. It is often misdiagnosed or unrecognized in the early stages, preventing early treatment and the possible delay of this devastating disease. Practitioners are on the frontline and must sharpen their diagnostic skills in order to identify patients at greater risk including women. A clear understanding of the pathophysiology of AD, and how estrogen may positively affect neuronal activity will be helpful in deciphering the latest information about diagnostic tests and new treatments.

A review of the literature indicates a strong relationship between estrogen replacement therapy and cognition. Several observational studies have revealed epidemiologic data regarding the increased prevalence of AD among women, and the significantly lower incidence of AD among women taking ERT. Clinical trials to date are also demonstrating promising evidence but have been unable to control confounding factors. Studies in progress, such as the Women's Health Initiative will provide more accurate data upon which practitioners can base clinical decisions and counseling about ERT. Meanwhile, leading researchers have suggested that patients be informed of the possible benefits of estrogen replacement for the prevention or delay of AD.
Introduction

Recent epidemiological studies demonstrated that Alzheimer's disease (AD) is rapidly becoming an important women's health issue. Increased incidence of the disease among women as well as the aging of the America population is the basis of this phenomenon. Recent studies have found a strong correlation between estrogen and improved cognitive function (Yaffe, Sawaya, Lieferburg, and Grady, 1998), adding another factor for women considering taking estrogen replacement therapy (ERT). ERT is an issue of great concern to women and remains very controversial. The possibility of estrogen having a positive effect on cognition in addition to the cardioprotective effects and prevention of osteoporosis weigh in favor of the benefits of ERT. Primary care practitioners must carefully weigh all the potential risks and benefits when counseling women about hormone replacement therapy.

Family nurse practitioners play an important role in counseling women about ERT. As primary care providers, nurse practitioners have a potential role in the prevention and early diagnosis of AD, and other forms of dementia. The Agency for Health Care Policy and Research developed guidelines in response to the rapidly increasing numbers of adults ages 65 and older affected by some type of dementia (Clinical Guidelines, 1996). In the United States, AD is the most common form of dementia. It is often misdiagnosed or unrecognized in the early stages. Practitioners are at the front-line and must sharpen their diagnostic skills to identify patients at greater risk for AD. Evidence-based practice is necessary for nurse practitioners to stay up to date with the latest information about diagnostic tests and new treatments for AD. Both ERT and AD are important women's health issues and many factors must be considered including positive or negative clinical effects, cost of care, diagnostic tests, and treatment options.
Pathophysiology

The question of how estrogen plays a role in the delay or possible prevention of AD is yet to be completely answered. An understanding of the pathophysiology of AD is necessary in order to evaluate the possible effects of ERT. Dementia is an insidious, progressive degeneration of intellectual functioning causing multiple cognitive deficits. Alzheimer's disease (AD) represents approximately 50% to 60% of all dementia (Gambert, 1997). AD was first described by Alois Alzheimer in 1906 in a patient with severe dementia, and brain abnormalities, specifically neuritic plaques and neurofibrillary tangles (Aronson, 1988). The neuritic plaques have been identified as amyloid beta-peptide derived from the beta-amyloid precursor protein (APP) on chromosome 21 (Heston, 1997).

Genetic evidence indicates that AD is associated with increased beta amyloid plaques and about 10% of AD cases are familial with autosomal dominant inheritance (Farrer et al., 1997). Apolipoprotein E (APOE) genotype is associated with increased risk of AD in Caucasians according to meta-analysis by Farrer and other investigators (1997). Apolipoprotein E is a lipid transport molecule that has a strong affinity for the senile plaques seen with AD (Yaffe, 1997). This review (Farrer et al., 1997), noted a higher risk of AD among women that was not related to greater longevity. Presently APOE genotyping is used in patients clinically diagnosed with AD but it is not useful for predicting AD in cognitively normal patients (Roses, 1997). A specific neural thread protein call AD7c-NTP has been isolated from the brains of AD patients and also in the cerebral spinal fluid. Wands and de la Monte (1997) from Nymox Corporation have correlated an increased level of NTP correlated with increased dementia in neuronal cells causing neural sprouting and cell death. This protein may also be detected in the urine, adding to the possibility of an earlier and less invasive diagnostic test for AD (Wands & de la Monte, 1997).

The association of AD with decreasing estrogen levels is associated with the effect on neurotrophins, proteins that support neuronal growth and the maintenance of neural
axons and dendrites (McPhee, 1994). One theory suggests that beta amyloid and other oxidative factors initiate processes that lead to apoptosis, or cell suicide (Metz, 1998). It has also been hypothesized that estrogen may exert an effect on lipoproteins, and specifically APOE (Metz, 1998). In addition, estrogen has shown to have antioxidant and neuroprotective effects in animal studies.

The main effect of estrogen may be the control of the secretion of acetylcholine in the hippocampus by estrogen on choline acetyltransferase, an enzyme important in the synthesis of acetylcholine in the basal forebrain associated with memory (Seeman, 1997). In animal research by Gibbs (1997), ovariectomized rats demonstrated a significant decrease in choline acetyltransferase (ChAT). Estrogen replacement enhanced basal forebrain cholinergic activity and correlated to dose and duration of treatment (Gibbs, 1997). These animal studies further support the hypothesis that estrogen may improve cognitive function by improving cholinergic activity in the brain (Yaffe et al., 1998). Estrogen deficiency is a possible risk factor for neuronal loss but not necessarily the direct cause of AD (Birge, 1996). In summary, estrogen may effect brain function via a wide array of potential actions and mechanisms, including increased cerebral blood flow, and prevention of neuronal activity (Speroff et al., 1997).

Epidemiology

According to present epidemiologic data the only definite AD risk factors that have been identified include age, familial aggregation (environmental and genetic) and the apolipoprotein E gene-e4 allele (Fragtiglioni, 1998). It has been well established that the prevalence of AD increases rapidly with age (Fragtiglioni, 1998). The incidence data of AD from the Kungsholm project (Fragtiglioni et al., 1997) was 19.6 per 1,000 person-years for women, and 12.4 for men aged 75-79, increasing to 86.7 for women, and 15.0 for men aged 90 or older. The implications for the year 2050 are staggering, when the number of people with AD will more than double from 4 million up to 10 million (McCann et al., 1997). The majority of those affected will most likely be women since women now make up 72% of the U.S. population over 85 years of age (McCann et al., 1997). Presently as many as 30-50% of women over the age of 85 suffer from dementia.
often more severe than their male counterparts (McCann et al., 1997). The Framingham study by Bachman et al. (1993) was a longitudinal study that followed a cohort of more than 5,000 adults ages 30-62 from 1950 to 1990 to determine the incidence of AD in the general population. The rate of AD rose from 7 per 1,000 at ages 65-69, doubling every successive 5 years to 118 per 1,000 for age 85-89 (Bachman et al., 1993). More recent data cited by Fratiglioni (1998) reveals prevalence rates of 1-2% in persons aged 65-74 years, 4-5% in those 75-84 years, and 10-13% in those over the age of 85. Women over the age of 84 had the highest prevalence of severe dementia (Fratiglioni, 1998). AD has a survival rate of 8-10 years after diagnosis and has been reported as the fourth leading cause of death in adults in the U.S. (Gambert, 1997).

Cost

The economic cost of Alzheimer's is estimated to be $90 billion annually in the U.S. based on statistics from the National Institute of Aging (AHCPR, 1996). The increased prevalence of AD and the rapidly increasing number of elderly will lead to higher financial and psychosocial costs. The psychosocial cost that families and patients bear is not easily quantified. Since women have increased longevity they are also more likely to be living alone and in poverty, placing them at even greater risk of morbidity due to lack of medical care (McCann et al., 1997). The greatest impacts of these emotional and financial burdens often fall upon female caregivers who may not have adequate financial or emotional support (McCann et al., 1997). Persons with even mild dementia require constant surveillance and custodial care, and those with more severe disease require higher amounts of specialized care, staff, and support (Fratiglioni, 1998). Presently, nursing homes nationwide are spending millions of dollars to develop specialized units to care for Alzheimer's patients since it is the most common reason for nursing home placement. The cost of care is prohibitive for most patients and their families forcing them to rely on the government for assistance (Gambert, 1997).
Diagnosis

Presently the diagnosis of AD is based on the exclusion of all other dementias or medical illnesses, and primarily relies on patient history, physical exam, and Mini-Mental Status Exam results or other neuropsychological tests. Recent studies comparing the clinical diagnosis of AD with autopsy results revealed errors in diagnosis ranging from 10-19% (Gambert, 1997). Results were obtained from studies that utilized the standardized clinical criteria from the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA). One study (Mangino & Middlemiss, 1997) found that seven out of eight patients did not meet these criteria, and indicated one out of ten patients were incorrectly diagnosed or underdiagnosed. Tierney et al., (1996) found that neuropsychological testing was more useful in predicting memory impairment than APOE genotyping in a prospective two year longitudinal study of 123 memory impaired nondemented patients. Researchers recommended APOE genotyping may be used to identify persons at increased risk for AD but not helpful in determining the development or diagnosis of AD (Tierney et al., 1996).

The NINCDS-ADRA Criteria for the diagnosis of probable AD consists of: (Mangino & Middlemiss, 1997)

- Inclusion Criteria: dementia established by clinical exam and documented by Mini-Mental Status Examination, or similar exam, and confirmed by neuropsychologic tests; deficits in 2 or more areas of cognition, progressive worsening of memory, no disturbance in level of consciousness; onset between 40-90 years of age; absence of systemic disorders or other brain diseases

- Supporting Criteria: progressive deterioration of specific cognitive functions (i.e.: language, motor skill, and perception); impaired activities of daily living, family history of similar disorders, normal lumbar puncture, normal pattern in EEG, evidence of cerebral atrophy on CT scan with progression documented
• Exclusion Criteria: sudden, apoplectic onset, focal neurologic findings (i.e.: hemiparesis, sensory loss, or visual field deficits), or seizures, and gait disturbances at the onset or very early in course of disease

AHCPR (1996) developed guidelines in 1992 to address the difficulty in diagnosing dementia and the increasing incidence of AD and related dementias. The panel’s principal objective was to improve the early detection of AD, and identify other treatable conditions (AHCPR, 1996). According to diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), there must be evidence of decline in multiple cognitive domains, not only memory (AHCPR, 1996). For primary care providers, previous knowledge of the patient’s level of functioning and close follow-up is paramount in diagnosing dementia. The present guidelines from AHCPR (1996) for the initial assessment of clients include:

• focused history to determine onset, progression, and duration of symptoms

• thorough physical exam including neurological assessment

• information from family and caregivers to supplement possible memory loss

• mental status test (i.e: Mini-Mental Status Exam)

When making a diagnosis of dementia and differentiating delirium, practitioners may find the mnemonic DEMENTIA helpful (Gambert, 1997): Drug use, Emotional disorder (depression), Metabolic disorders (thyroid, diabetes, etc.), Eye or ear disorders, Nutritional disorders (folate deficiency) and normal-pressure hydrocephalus (reversible with early intervention), Tumors and trauma, Infection, Atherosclerosis and alcoholism. Obviously there are many possible causes for cognitive impairment. Delirium is one of the most treatable causes of cognitive impairment and is not to be confused with a true dementia. It often has an abrupt onset and is precipitated by a single factor such as hypoxia or sepsis (Mangino & Middlemis, 1997). At the present time clinical diagnosis of dementia is made by exclusion of all other causes although tests are being developed to improve the accuracy of diagnosis. The use of NTP testing is not being used on a regular
basis in the clinical setting but may be useful in the diagnosis of younger patients with mild symptoms. Recommended laboratory tests include: complete blood count, chemistry profile, calcium, renal and hepatic function tests, vitamin B12, thyroid function, rapid plasma reagin (RPR) test, and erythrocyte sedimentation rate, with toxicology screen and HIV testing as optional. Additional testing may include lumbar puncture, EEG, and brain imaging (i.e.: CT scan, MRI scan, or single photon emission CT scan) (Kettl, 1997).

Classification of AD is often based on MMSE scores. Patients with a MMSE of greater than 20 are considered early stage, scores between 11-19 are considered middle stage, and scores of less than 10 are severely impaired or late stage (Kettl, 1997). MMSE scores are also useful in determining patient response to treatments. Normal disease progression varies but is usually a gradual decline in cognitive abilities over a 7-10 year period resembling a reversal of normal human development (Kettl, 1997). AD in the late stages generally requires nursing home placement in a specialized care unit.

Treatment

Researchers and pharmaceutical corporations are eagerly searching for new treatments for AD. Estrogen therapy continues to generate a great deal of interest as recent studies (Sherwin, 1997) confirm its potential role in prevention or delay of AD. Many therapies are being evaluated including: estrogen, NSAIDS, vitamin E, tacrine and donezipil (Grinspoon et al., 1995). The American Psychiatric Association (APA) recommends donezipil, a cholinesterase inhibitor, as first line treatment for mild to moderate symptoms of AD, lasting for longer than 6 months, because of its decreased side effects, and easier once a day dosing compared to tacrine (Lovestone, Graham, and Howard, 1997). A 24 week, double blind, placebo-controlled study of donezipil demonstrated a statistically significant improvement in cognitive function in patients
with mild to moderately severe AD (Rogers, Farlow, Doody, Mohs, and Friedhoff, 1998). Another placebo-controlled study showed a significantly higher MMSE score in AD patients receiving alpha-tocopherol (vitamin E) at a dose of 1,000IU bid (Knopman, 1998). According to these preliminary findings vitamin E may be recommended in most patients with AD. The only identified safety concern was a possible exacerbation of coagulopathies in some patients (Knopman, 1998).

Colditz et al. (1995) examined the use of estrogen and progestins with the risk of breast cancer in the Nurses' Health Study. This 1976 to 1992 prospective study (n = 121,700 women) found that older women who were candidates for estrogen had a greater risk for breast cancer from age 60-64 if they had taken estrogen for five or more years (Colditz et al., 1995). Limitations of this study included its methodology of self-report data and differences in rates of mammogram screening. The relative risk of breast cancer was 1.71 (Colditz et al., 1995) which may not outweigh the risk of heart disease, AD, or osteoporosis but must be considered and discussed. A more recent study, the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, found that the risk of atypical endometrial hyperplasia was about 1% among women randomly assigned to placebo or any of the estrogen/progestin combinations (Davidson, 1995). In comparison, women receiving estrogen alone had a 34% risk of endometrial hyperplasia. Present recommendations (Davidson, 1995) for HRT include: estrogen for women who have had a hysterectomy, and combined therapy of estrogen and progestin for women with an intact uterus after careful evaluation of individual risk factors.

A recent placebo controlled clinical trial of tacrine, a cholinesterase inhibitor, compared women receiving tacrine and ERT, to women taking tacrine alone, or placebo only (Schneider, Farlow, Pogoda, and Poirier, 1997). APOE genotype was also analyzed, and the MMSE utilized to determine significant changes. Study results were clinically significant for the group of women who were non-APOE genotype, and taking ERT and tacrine (see Table 3). The APOE 4 group differences were small regardless of ERT status (Schneider et al., 1997). A separate review of combination therapies including cholinesterase inhibitors, vitamin E, anti-inflammatory agents, gingko biloba , and
estrogen revealed a lack of statistically significant findings for any of these agents (Doraiswamy & Steffens, 1998). This further emphasizes the need for controlled clinical trials to address the efficacy and safety issues of AD treatments.
Analysis of Research Literature and HRT

The mounting evidence in favor of estrogen therapy for possible prevention or delay of the progression of AD comes from many sources. The earliest evidence was noted in 1952 when Caldwell and Watson studied the psychologic effects of estrogen (Jones & Ashbar, 1997). The treatment group (n = 15) showed improvement in associated learning. The weaknesses included methodological problems and small sample size limiting the possible conclusions. Previous literature reviews, however, revealed positive effects of estrogen on specific areas of cognitive functioning (Sherwin, 1997). A literature review by Sherwin (1997) concluded that there is substantial evidence to support the positive effect of estrogen and maintenance of memory in healthy women. The comparison of studies is difficult due to the wide range of estrogen doses, methodology, and psychometric testing. A recent review of the literature by Haskell, Richardson, and Horwitz (1997) strongly suggests a relationship between estrogen and cognition with a majority of the observational studies revealing positive effects with HRT. Unfortunately, the observational studies do not specify dosages used, and were unable to account for other confounding variables.

Several epidemiological studies (see table 2) have identified populations at increased risk for AD including women, genetic predispositions, and age-related risks (Fratiglioni et al., 1997; Herbert, 1995; Bachman, et al. 1993). Animal studies (see table 3) have demonstrated that estrogen affects the development and function of the central nervous system, in particular the basal forebrain, a region important for cognitive function (Haskell, et al., 1997). The randomized clinical trials to date have not controlled for potential confounding factors such as depression or vasomotor symptoms (Haskell et al., 1997). In an effort to organize findings more logically, this present review of the literature will examine groups of studies based on their methodology.

Observational Studies

Several prospective studies have been completed evaluating the effect of estrogen on cognition and support the use of estrogen. Kawas et al (1997) did a prospective longitudinal study (see table 1) over a 16 year period in Baltimore, Maryland and observed a reduced risk of AD for women who were using estrogen. The subjects
included 514 post or peri-menopausal women ages 28-94, predominantly white (92%), college educated (63%), and 45% of the sample reported use of HRT. Methods involved multidisciplinary evaluations, physical and neuropsychological testing, and self report of HRT. Variables examined included: age of menarche, age and duration of menopause, and history of hysterectomy. The Cox proportional hazards regression model was chosen for analysis of data to estimate the relative risk of AD with HRT. Results revealed no statistically significant changes in the AD rate when adjusted for education level attained, age of menopause, menarche, surgical menopause, or duration of estrogen treatment. The relative risk for AD was 0.457 (95% CI) when HRT users were compared to nonusers. The individual dosage or route of estrogen was not evaluated due to the variability among subjects. The advantage of obtaining longitudinal data prospectively was addressed but the data did not reveal a significant effect related to the duration of estrogen as expected (Kawas et al. 1997). The authors reported using neuropsychological assessments and appropriate laboratory and imaging studies for diagnosis but not the specific type of psychometric testing done to determine presence of AD.

The Italian Longitudinal Study on Aging by Baldereschi et al. (1997), investigated the relationship between AD and estrogen replacement therapy; their findings supported their hypothesis that estrogen is associated with a decreased prevalence of AD in postmenopausal women. Their population-based, cohort study consisted of 2,816 women aged 65-84 years randomly selected and stratified by 5 year age groups (Baldereschi et al., 1997). A cross-sectional survey was completed over a 2 year period, and the women were screened using the MMSE, and diagnosed with AD according to the DSM-III-R criteria (Baldereschi et al., 1997). The inverse association between estrogen use and incidence of AD remained statistically significant after adjusting for age, education, age of menarche and menopause, smoking and alcohol habits, and body weight after 50 years of age (Baldereschi et al., 1997). These researchers noted the presence of potential confounding factors and biases associated with observational studies and recommended prospective, clinical trials (Baldereschi et al., 1997).
An epidemiological overview (see table 2) by Seeman (1997) evaluated the male/female differences in psychopathology including AD. A number of differences were noted among men and women and the rate of illness. Findings by Seeman (1997) indicated that the loss of estrogen makes women more vulnerable to AD although no specific data were reported. The Nurse's Health Mortality Study examined the relationship between hormone replacement therapy and mortality over a 16 year period (Colditz, 1995). Data collection involved biennial questionnaires and each participant that died was matched with 10 controls at time of death. Results demonstrated a lower risk of death for hormone users compared to nonusers. The greatest reduction in mortality was among current hormone users with coronary risk factors. It was also noted that the survival benefit diminished with longer duration of use among those women at lower risk of coronary disease (Grodstein et al., 1997)

Paganini and Henderson (1996) completed a prospective case-controlled study from 1981-1995 at a retirement community in southern California. The cohort included 8877 women who were sent a health survey requesting information about medical history, health habits, menstrual history, and use of estrogen therapy. Cohort members were resurveyed and hospital admissions reviewed. Death certificates and the National Death Index were used to determine diagnosis of AD. Five controls were matched to each case of AD based on year of birth and year of death. Diagnoses of AD were noted on 248 death certificates of the 3760 cohort members that died during this study. Results indicated a significantly reduced risk of AD and related dementia among estrogen users. Variables evaluated included: use of ERT, dosage and route, duration of therapy, age of menarche, and body weight. Credible conclusions are difficult due to the method of data collection and the lack of information regarding onset of AD and the possibility of misdiagnosis on death certificates.

An earlier case-control study by the same researchers also found decreased risk of AD with estrogen replacement (Henderson & Paganini, 1994). Subjects included 143 elderly women with probable AD and 92 women who met nondemented criteria at Alzheimer's Disease Research Center in Los Angeles, CA. Methods involved
neurological and psychological testing comparing subjects with AD to nondemented controls. The Mini-Mental Status Exam was used during enrollment and medication history was obtained directly from subjects and confirmed with prescription labels. Results demonstrated that AD subjects were significantly less likely to use ERT (p = 0.19-0.49) (Henderson & Paganini, 1994). Demented patients taking estrogen did perform significantly better on the MMSE than control group. The researchers noted several limitations, including the lack of a population-based sample and retrospective retrieval of information.

The Atherosclerosis Risk in Communities (ARIC) Study is a large multicenter longitudinal investigation that also assessed the association of ERT with cognitive functioning (Szklo et al., 1996). The samples came from four communities totaling 15,792 subjects aged 45-64 of which 8,685 were women. Baseline information was obtained in 1987 and retested every two years. Variables included: menopausal status, use of ERT, health status, fibrinogen, and sport index. Cognitive scores were obtained from three neuropsychological tests: the delayed word recall (DWR), Revised Wechsler Adult Intelligence Scale (WAIS-R), and the word fluency test (WF). The researchers (Szklo et al., 1996) concluded that the differences in scores on the WF test were consistent with previous claims of improved verbal memory with ERT. They noted the weaknesses were possible selection bias of subjects, and recall bias regarding use of ERT.

Tang et al. (1996) evaluated the effects of estrogen on the risk of AD and age of onset, using a prospective longitudinal design. The subjects were from a convenience sample of 1124 elderly women meeting the criteria for the study living in NYC receiving Medicare. The criteria included: no evidence of cognitive dysfunction, no history of stroke or Parkinson's. ERT history was obtained from a risk factor questionnaire and diagnosis of dementia was completed by an independent group of physicians. The Cox proportional hazard model was used for data analysis to determine the relative risk of AD. After adjusting for education, ethnic origin, and apoe E genotype, women who took ERT for greater than one year had a significantly decreased risk of AD (7% vs 16.3%, p < 0.01) compared to nonusers (Tang, 1996).
Experimental Studies

Experimental studies (see table 3) may provide more compelling evidence for the effects of estrogen on cognition. Schmidt et al. (1996) performed a cross-sectional study comparing postmenopausal estrogen users and non-users. The sample consisted of 70 women currently using estrogen and 140 women who have never used estrogen from a large-scale stroke prevention study in Austria among randomly selected community members. Methods used for comparison included: neuropsychological test scores from the Mattis Dementia Rating Scale, blood pressure monitoring, ECG, echocardiograms, extensive lab tests, and MRI. Results revealed that estrogen users performed better than nonusers on most of the neuropsychological testing. The MRI results showed a clinically significant inverse relationship of total white matter hyperintensity in women treated with estrogen possibly related to decreased hypercholesterolemia and decreased ischemic brain damage. Although the improved performance on the neuropsychological tests may not be of clinical significance the MRI results may indicate important markers in dementia (Schmidt et al., 1996). Study limitations included possible confounding factors (Schmidt et al., 1996).

Phillips and Sherwin (1992) studied the effects of estrogen on memory function in surgically menopausal women. Subjects included 19 women needing a hysterectomy and bilateral oopherectomy for benign disease. Study design was double blind randomized clinical trial in which ten women received estrogen injections and nine women received a placebo injection. Estradiol levels were collected and neuropsychological tests were given at each test session. Four subtests of the Wechsler Memory Scale were administered under identical test conditions. In addition a menopausal index and multiple affect adjective checklist was administered to identify vasomotor symptoms and depression. Results suggested that estrogen influenced verbal memory function specifically immediate and delayed recall of associated learning (p < 0.05). Limitations included short term analysis, small sample size, and supraphysiologic levels of estrogen (Phillips & Sherwin, 1992).
Estrogen effects on the brain have been noted in experimental animal studies. According to Singh et al. (1994) estrogen specifically affects the basal forebrain and levels of choline acetyltransferase (ChAT) levels associated with memory and learning. The effects of estrogen on female rats were compared, measuring levels of choline acetyltransferase and testing active avoidance performance. Results demonstrated impairment of nonspatial learning after five weeks of estrogen deprivation in young female rats that was reversible with estrogen replacement (Singh et al., 1994). There was also an effect noted on ChAT activity in the hippocampus suggesting the importance of estrogen in the proper function of basal forebrain cholinergic neurons that undergo severe degeneration with AD. Another animal study by Gibbs (1996) revealed estrogen effects on the basal forebrain cholinergic neurons. An evaluation of increasing dosages and duration of treatment revealed increased positive effects (Gibbs, 1996). Simpkins et al. (1997) also conducted a study using the animal model with similar results and concluded that the multiple behavioral effects of estrogen warrant clinical trials of ERT in humans with AD.

Gaps in Current Knowledge

Presently the majority of research studies are unable to determine a direct cause and effect relationship between estrogen and AD, although evidence continues to mount in favor of the potential benefits of HRT. The need for further randomized clinical trials has already been discussed and such trials are currently in progress. Other areas to be addressed are the ethical and practical considerations surrounding clinical trials of both Alzheimer's disease and HRT. An example of this dilemma is the sluggish enrollment in the Women’s Health Initiative possibly related to the widespread news coverage about estrogen's effects. Many women are reluctant to take part in a trial in which they may receive the placebo instead of estrogen (Skolnick, 1997). Some leading ethicists believe there is enough clinical evidence of estrogen's benefit that it is ethically questionable to give subjects a placebo. Leading Alzheimer’s researchers agree that there are ethical dilemmas in placebo-controlled trials and are making efforts to carefully design trials but they are not in agreement that retrospective studies can be a basis for medical practice
Another important issue is the adherence (or lack of) in taking ERT, as noted by several studies (Rubin, 1998). Results from one survey indicated that only 15% of the 105 postmenopausal women interviewed were currently taking ERT and 38% said they had never received any information nor were offered ERT even though 78% had been seen by their gynecologist in the last year (Rubin, 1998). This may be an even greater issue with patients at risk for AD or onset of early symptoms. As primary care providers it is vitally important that patients and their families have a clear understanding of all the potential risks and benefits and are given informed choices.

Current Research

Review of the research literature indicates a continuing need for large, randomized clinical trials and longitudinal studies. Presently an ancillary study of the Women's Health Initiative (WHI), called the Memory Study is designed to investigate whether ERT may decrease the incidence of AD and dementia in postmenopausal women and delay the progression of the disease in women already diagnosed with AD (Pollner, 1996). The WHI Memory study plans to enroll at least 8000 women, who will be given a MMSE and further neuropsychological testing depending on MMSE score with the results initially set to be analyzed the year 2007 (Pollner, 1996). This is one of the largest and most complex studies ever conducted with 29 centers participating nationwide. Participants will be screened annually by a physician and expanded psychometric assessment developed by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD).

Conclusion

What is the role then, of primary care practitioners in counseling pre-menopausal and menopausal women about HRT and the possible risk factors associated with AD? Does HRT decrease the risk of AD and does the risk of AD out weigh the risk of breast or endometrial cancer? These questions remain unanswered. In a recent symposium, some of the leading researchers in these areas acknowledge the positive effects of estrogen as although they are very wary of drawing more specific conclusions (Speroff, 1998). The positive effects noted from recent randomized clinical trials are promising but limited in
their application. Dr Berga (1998) addressed the issue of dementia facing elderly women and stated that presently estrogen is the only agent available that may prevent this debilitating condition. It is recommended that eligible patients be informed of the possible benefits of estrogen in the prevention of AD in addition to discussing the potential risks (Speroff, 1998). For primary care practitioners, the issue of AD and HRT should be addressed with all female patients that may be at risk. It will be very important to diagnose patients early, identify possible risk factors, and consider the benefits and risks of treatments available. Further research will provide more concrete evidence but the potential benefits of HRT appear to outweigh the risks for patients at high risk of AD. In regards to prevention, each case must be evaluated on an individual basis.
<table>
<thead>
<tr>
<th>Observational studies</th>
<th>Author</th>
<th>Method</th>
<th>Results</th>
<th>Discussion</th>
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</thead>
<tbody>
<tr>
<td>1997 Italian Longitudinal Study on Aging</td>
<td>Baldereschi et al.</td>
<td>Population based cohort study 2,816 women aged 65-84 yrs</td>
<td>decreased risk of AD odds ratio 0.24 (95% CI)</td>
<td>adjusted for age, educ, age of menarche, and menopause, smoking, etoh use, and body wt</td>
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<tr>
<td>1997 Baltimore longitudinal study of Aging</td>
<td>Kawas et al</td>
<td>prospective study 514 women over 16 yrs</td>
<td>decreased risk of AD, RR 0.46 based on 34 cases of AD including 9 ERT users</td>
<td>no effect noted for duration of ERT usage. No information re: type of psychometric testing</td>
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<tr>
<td>1996 Leisure World Retirement community</td>
<td>Paganini-Hill, Henderson</td>
<td>case-control prospective cohort study of 8877 women</td>
<td>248 cases of AD out of 3760 deaths, odds ratio: 0.65; (95% CI)</td>
<td>evaluated dose and duration of ERT and found decreased risk</td>
</tr>
<tr>
<td>1994 ERT in older women comparisons between AD and nondemented</td>
<td>Henderson, Paganini-Hill</td>
<td>case-control study 143 women with AD compared to 92 nondemented subjects MMSE</td>
<td>decreased risk of AD with ERT use (7% Vs 18% in nondemented control group (p=0.19-0.49)</td>
<td>methodological limitations, retrospective analysis</td>
</tr>
<tr>
<td>1996 ERT and cognitive functioning in ARIC study</td>
<td>Szklo et al</td>
<td>large prospective longitudinal study, 6,110 subjects women</td>
<td>weak positive association with WF scores and ERT users</td>
<td>large sample specific neuro testing, possible bias of subjects and self</td>
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<tr>
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<td>1996 NYC longitudinal study</td>
<td>Tang et al</td>
<td>retrospective study, 1282 nondemented women, ERT usage, dementia diagnosis, APOE genotyping</td>
<td>decreased risk of AD among ERT users 5.8% vs 16.3% in non users; RR 0.40 after adjusted for education and APOE</td>
<td>observational design limitations, self report of ERT use</td>
</tr>
<tr>
<td>Epidemiologic studies</td>
<td>Author</td>
<td>Method</td>
<td>Results</td>
<td>Discussion</td>
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<tr>
<td>1997 Effects of age, sex, ethnicity on the association of apoeE genotype and AD</td>
<td>Farrer et al.</td>
<td>Meta-analysis by 40 research teams, 5930 subjects with AD, 8607 without AD</td>
<td>Odds ratio for homozygous apoeE4 genotype 12.5-14.9% among Caucasian subjects, not significant for non Caucasian</td>
<td>Increased AD among Caucasian subjects with apoeE4 genotype, increased AD among women regardless of genotype</td>
</tr>
<tr>
<td>1997 Apolipoprotein E phenotype and cognitive decline of elderly women</td>
<td>Yaffe et al.</td>
<td>Prospective cohort study, 1750 white women</td>
<td>Increase decline of AD 1.6 times &gt; in E4 carrier on Trails B test, 2.4 times &gt; decline in MMSE</td>
<td>Limited generality based on selection bias, confirms previous studies</td>
</tr>
<tr>
<td>1995 The prevalence of dementia changing in Rochester, MN</td>
<td>Beard et al.</td>
<td>Retrospective study 1960-1990, 521 subjects met diagnostic criteria/Poisson Regression Analysis</td>
<td>RR 1.14 in 1980</td>
<td>Small sample size, unable to account for confounding factors or increased incidence</td>
</tr>
<tr>
<td>1997 Very old women at highest risk of AD: the Kungsholm Project, Stockholm</td>
<td>Fratigioni</td>
<td>Prospective study over 5 yrs, 1473 non-demented subjects &gt; 75 yrs MMSE/DSM-III-R criteria</td>
<td>Increased risk 60% for each 5yr interval/ women &gt; 90yrs: 67.9/1000 person/years men &gt; 90yrs: 16.9/1000</td>
<td>Limited diagnostic validity, high attrition rate and restricted geographic area</td>
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<tr>
<td>1995 Age specific</td>
<td>Hebert et al.</td>
<td>Prospective cohort study, 642 subjects</td>
<td>Incidence rate 0.6%(65-69yrs) 1.0%(70-74)</td>
<td>AD rate 14 times higher for 85+ age group</td>
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</tbody>
</table>
References


Farrer, L.A., Cupples, L.A., Haines, J.L., Hyman, B., Kukull, W.A., Mayeux, R.,
sex, and ethnicity on association between APOE genotype and AD. Journal of American
Medical Association, 278, 1349-1355.


Fratiglioni, L., Viitanen, M., von Strauss, E., Tontodonati, V., Herlitz, A., and
Winblad, B. (1997). Very old women at highest risk of dementia and Alzheimer’s


Gibbs, R.B. (1996). Effects of estrogen on basal forebrain cholinergic neurons vary as a
function of dose and duration of treatment. Brain Research, 757, 10-16.

Letter, 11, 1-5.

Grodstein F, Stampfer MJ, Colditz GA, Willett, W.C., Manson, J.A., Joffe, M.,
Rosner, B., Fuchs, Ch., Hankinson, S.E., Hunter, D.J., Hennekens, H., and Speizer F.E.
Medicine, 336, 1769-75

treatment on cognitive function in women: a critical review of the literature. Journal of
Clinical Epidemiology, 50, 1249-1264.

Henderson VW, Paganini-Hill A., Emanuel, C.K., Dunn, M.E., and Buckwalter, J.G.
(1994). Estrogen replacement therapy in older women- comparisons between AD cases
and nondemented control subjects. Archives Neurology 51, 896-899.


Pollner, F. (1996). Memory study on Alzheimer Disease adds interest to WHI. *Annals of Internal Medicine, 125*(8), I-55-56.


