MONASH University

Home News

# Testosterone could combat dementia in women

**18 June 2013**

Professor Susan Davis has discovered that testosterone therapy may protect women against cognitive decline.

In a new study, post-menopausal women on testosterone therapy showed a significant improvement in verbal learning and memory, offering a promising avenue for research into memory and ageing.

Led by Director of the Women's Health Research Program at Monash University, Professor Susan Davis, and presented at ENDO 2103, the research is the first large, randomised, placebo-controlled investigation into the effects of testosterone on cognitive function in postmenopausal women.

Testosterone has been implicated as being important for brain function in men and these results indicate that it has a role in optimising learning and memory in women.

Dementia, which was estimated to affect more than 35 million people worldwide in 2010, is more common in women than men. There are no effective treatments to prevent memory decline.

In the study, 96 postmenopausal women recruited from the community were randomly allocated to receive a testosterone gel or a visually identical placebo gel to be applied to the skin. Participants underwent a comprehensive series of cognitive tests at the beginning of the study and 26 weeks later.

All women performed in the normal range for their age at the beginning of the trial. There was a statistically significant and clinically meaningful improvement in verbal learning and memory amongst the women using the testosterone gel after 26 weeks.

Professor Davis said the results indicated that testosterone played an important role in women's health.

"Much of the research on testosterone in women to date has focused on sexual function. But testosterone has widespread effects in women, including, it appears, significant favourable effects on verbal learning and memory," Professor Davis said.

"Our findings provide compelling evidence for the conduct of larger clinical studies to further investigate the role of testosterone in cognitive function in women.

Androgen levels did increase in the cohort on testosterone therapy, but on average, remained in the normal female range. No negative side-effects of the therapy were observed.

The study was supported by the Judith Jane Mason & Harold Stannett Williams Memorial

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# Alzheimer's Disease and Estrogen Replacement Therapy

**Annlia Paganini-Hill, Ph.D.***

### Educational Objective:

*After completing this lesson, the participant will be aware of the current literature on estrogen replacement therapy and Alzheimer's disease. The extent and limitations of data on estrogen as a treatment for Alzheimer's disease and as a therapy to reduce Alzheimer's disease should be understood.*

## Introduction

Alzheimer's disease (AD) is an insidious dementing disorder that impairs memory, thinking, and behavior. This progressive degenerative brain disease is the most common cause of cognitive decline severe enough to interfere with usual daily activities. Memory loss is usually the first sign of the disorder. Affected individuals may recall in detail events from the distant past, but they cannot remember what occurred minutes earlier. In addition to increasing forgetfulness, afflicted patients typically have word-finding difficulties, problems doing complex tasks (such as keeping a checkbook), time disorientation, and a tendency to get lost. As the disease progresses, higher cognitive functions decline, resulting in difficulties doing even simple tasks (such as bathing). Eventually patients may lose the ability to communicate or recognize family members and may come to depend totally on caregivers.

Today AD affects 4.5 million Americans and claims more than 100,000 lives annually. AD can appear in middle age, but symptoms more often occur after age 65 years. The prevalence of AD then doubles approximately every 5 years,[1] resulting in nearly 50% of all persons over 85 years being afflicted.[2] With an aging population and no cure or prevention, the number

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*Please see last page for disclosure statement.

of patients with AD will increase to 14 million by the middle of the next century.

More women than men have AD. In contrast to dementia due to other causes, the age-specific prevalence of AD is one and a half to three times greater for women than for men.[1] In addition, women tend to live longer than men; the proportion of women increases from 55% at age 65 to 75% at age 95. Thus, the burden of AD falls particularly hard on women.

Despite the enormous emotional, physical, social, and financial costs of AD, we know little about its cause or treatment. Besides age, family history of dementia is the most consistently recognized risk factor, more than doubling a person's risk when a parent or sibling is demented.[3] Mutations at specific genetic loci (on chromosomes 1, 14, and 21) cause uncommon forms of this illness that present before age 60 years. Polymorphisms of apolipoprotein E (a glycoprotein involved in lipid transport and neuronal repair) strongly influence AD risk: the presence of the ε4 allele confers a threefold higher risk. Few other risk factors are known. Table 1 gives a partial list of putative risk and protective factors. Although no preventable factor for AD has been identified, accumulating evidence suggests that, for women, postmenopausal estrogen replacement therapy (ERT) may be one intervention strategy to reduce the risk of AD.

## Estrogen as a Treatment for Alzheimer's Disease Symptoms

Ten intervention trials have evaluated the efficacy of estrogen for treating women with AD.[4-7] In each trial, outcome measures were limited to brief cognitive screening tests, duration was often short (3 weeks to 9 months), and the number of subjects was small (7 to 30). In all trials combined, 86 women were treated with estrogen. Only three studies were randomized, double-blind, placebo-controlled trials.[5-7] However, in each study some women (overall about two thirds) showed improved test scores with estrogen treatment. Women with mild or moderate dementia tended to show greater improvement than those severely demented. The AD symptoms ameliorated with ERT covered a broad spectrum of tasks: memory, attention, orientation in time and space, and calculation. Social interaction and interest in daily activities also increased. The effects were lost after treatment ceased. Although these small treatment studies showed a beneficial effect of estrogen, the lack of randomization or blinding in most trials tempers a decision that estrogen is efficacious for cognitive symptoms of AD.

## Estrogen's Effects on Alzheimer's Disease Risk

In addition to the therapeutic benefit of ERT observed among women with AD, accumulating evidence suggests a reduced AD risk among postmenopausal women using estrogen.

The first indication of a significant reduction in AD risk among women who had used ERT came from the Leisure World Cohort Study.[8,9] ERT decreased AD risk by 30%. Since this report, eight of nine subsequent studies reported lower AD risk among estrogen users[10-18] (Fig. 1). Among these studies, all but one estimated the relative risk of AD to be at least 45% lower among ERT users compared with nonusers.

Study design, however, limits interpretation of some of these findings. For example, patients in clinical series often differ from patients in the general population. Information biases might also have distorted results. In some studies, data on estrogen use were collected differently from cases (interview with a proxy informant) than from control subjects (interview with the control herself). Moreover, in cross-sectional studies, the temporal sequence between estrogen exposure

**Table 1.** *Risk and Protective Factors for Alzheimer's Disease**

| |
|---|
| **Putative risk factors** |
| Increasing age |
| Family history of dementia |
| ε4 allele of apolipoprotein E gene |
| Mutations at specific genetic loci on chromosomes 1, 14, and 21 |
| Family history of trisomy 21 |
| Female gender |
| Depression |
| Head trauma |
| Thyroid disease |
| Low education level |
| Solvent exposure |
| Aluminum exposure |
| **Putative protective factors** |
| Postmenopausal estrogen replacement therapy |
| Anti-inflammatory medications |
| Antioxidants |
| Smoking |

*The roles of many of these putative risk and protective factors remain controversial.

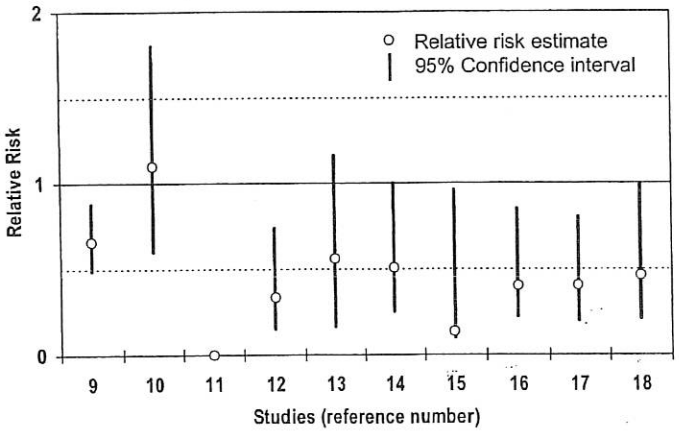


**Figure 1**
Estrogen replacement therapy and Alzheimer's disease: epidemiologic studies.

and AD onset is ambiguous. A physician might, in the presence of AD, eliminate estrogen as a discretionary medication. Conversely, preliminary reports in popular and professional publications linking estrogen deficiency to AD might lead patients and physicians to advocate estrogen for palliating AD symptoms. In either instance, current estrogen use would provide a poor measure of total estrogen exposure.

The strongest support for the estrogen hypothesis comes from longitudinal studies of women initially free of the disease. In addition to the Leisure World Cohort Study, three research teams have provided complete reports on AD risk when information on ERT was collected prospectively before the onset of dementia symptoms. Although one study[10] failed to confirm an association with ever use of estrogen, three found AD risk significantly reduced by 35% to 60%.[9, 16, 18]

The first of these four longitudinal studies, the Leisure World Cohort Study, includes 8877 women who self-reported information on ERT when they enrolled in the cohort in the early 1980s.[8, 9] With follow-up through 1995,[9] 3760 of these women had died, 248 with diagnoses suggesting AD indicated on their death certificates. Each case was individually matched by birth and death year to five women who had died without mention of these diagnoses. ERT reduced AD risk by 35% (odds ratio [OR]=0.65, 95% confidence interval [CI] 0.49 to 0.88). Although AD is certainly underreported on death certificates, this should attenuate the relative risk estimate to the null, suggesting perhaps an even greater reduction than that observed.

In a case-control study from a large Seattle health maintenance organization, Brenner et al.[10] compared estrogen pharmacy records of 107 incident AD cases and 120 age-matched control subjects. Although they found no association of AD risk with ever use of estrogen (OR=1.1, 95% CI 0.6 to 1.8), the risk was reduced by 30% (OR=0.7, 95% CI 0.4 to 1.5) among oral estrogen users.

Among 1124 nondemented older women in a community-based Manhattan cohort, Tang and associates[16] identified 167 incident AD cases during a follow-up period of 1 to 5 years. Among oral estrogen users, AD risk was reduced by 60% (OR=0.40, 95% CI 0.22 to 0.85), and age at onset was significantly higher among estrogen users who became demented than among never users.

Kawas et al.[18] identified 34 incident AD cases among 472 older women participating in the Baltimore Longitudinal Study of Aging and followed for up to 16 years. The relative risk of AD among ever users of ERT (oral or transdermal) compared with never users was reduced by over one half (OR=0.46, 95% CI 0.209 to 0.997).

### *Dose-Response Effect*

Findings of a dose-response relationship would strengthen the argument for a causal relationship between ERT and reduced AD risk. Although data on dose-response effects are sparse, the Leisure World Cohort Study found a significant trend of decreasing risk with increasing dose of the oral conjugated equine estrogen used for the longest time[9] (Fig. 2). The risk was 0.78 for women who used low-dose estrogen (≤ 0.625 mg) and 0.54 for high-dose estrogen (≥ 1.25 mg) compared with nonusers. The risk also decreased significantly with increasing years of ERT: 0.83 for ≤ 3 years, 0.50 for 4 to 14 years, 0.44 for ≥ 15 years (Fig. 3). The Manhattan cohort[16] also found a significant trend of decreasing risk with increasing duration. Women who had taken estrogen for 1 year or less (average 4 months) had an AD risk of 0.47; women who had taken estrogen for more than 1 year (average 13.6 years) had a risk of 0.13. However, the smaller Baltimore Longitudinal Study of Aging found no duration effect.[18]

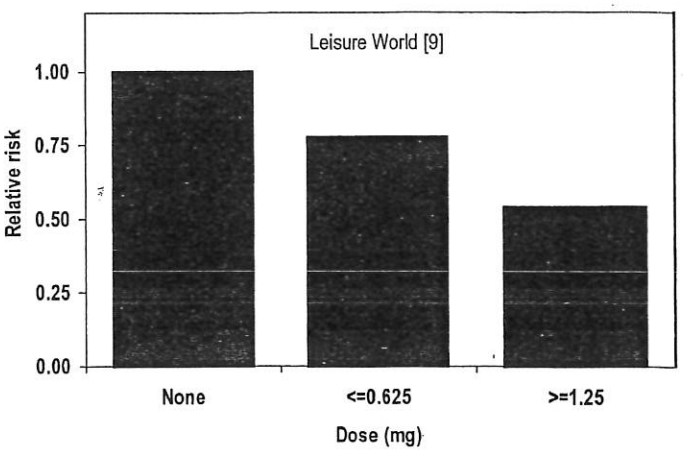


**Figure 2**
Dose of estrogen replacement therapy and Alzheimer's disease risk.

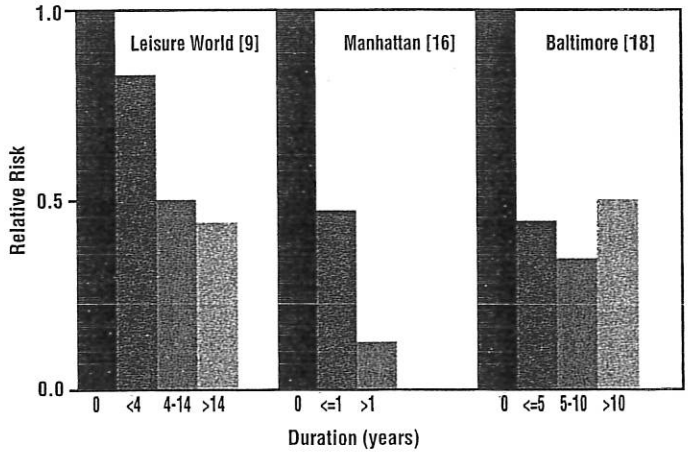


**Figure 3**
Duration of estrogen replacement therapy and Alzheimer's disease risk.

### *Effects of Formulation and Route of Administration*

Minimal information relates formulation of estrogen or route of administration to AD risk (Fig. 4). Brenner and colleagues[10] classified estrogen users by route and formulation into oral conjugated estrogen users, other oral estrogen (diethylstilbestrol and ethinyl estradiol) users, vaginal conjugated estrogen users, and other vaginal estrogen (dienestrol) users. No OR among women using these formulations and routes of administration was statistically significant (Fig. 4). The CIs were wide and overlapped considerably. However, among oral conjugated estrogen users the AD risk was reduced by 30% (OR=0.7, 95% CI 0.3 to 1.4). In the Leisure World Cohort Study all administration routes (oral only, oral plus injection and/or cream, and injection/cream only) showed reduced risks.[9] Estrogen users in the Manhattan cohort included only oral users.[16] In the Baltimore Longitudinal Study of Aging both oral and transdermal estrogen users were considered, but separate risk estimates were not given.[18]

## Estrogen's Effects on the Brain

Alzheimer's disease is associated with severe neuropathologic changes, a deficiency in the neurotransmitter acetylcholine, and brain cell death.[19, 20] The two most salient pathologic abnormalities of AD are neurofibrillary tangles within neuronal cell bodies of the cerebral cortex and hippocampus and neuritic plaques with a β-amyloid core within the neuropil between cell bodies. The prominent association of inflammatory cytokines, complement proteins, and acute-phase reactants with the AD lesions suggests an inflammatory process.[21]

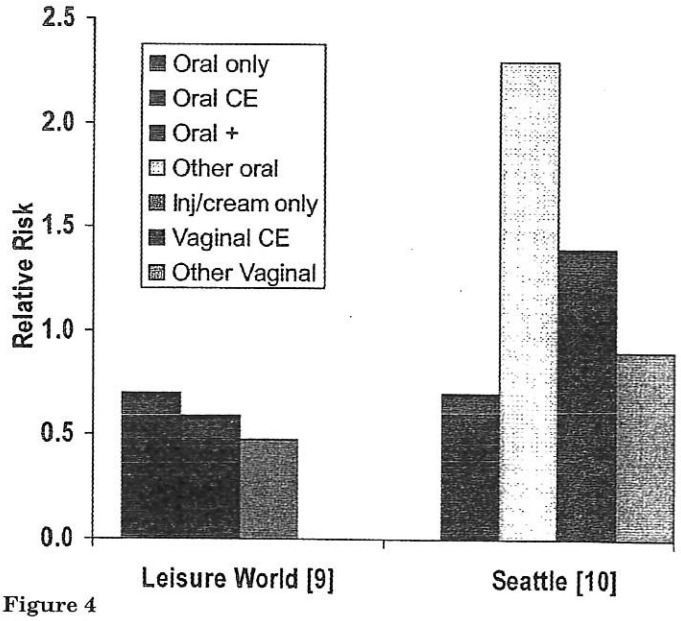


**Figure 4**
Type and route of estrogen replacement therapy and Alzheimer's disease risk.

**Table 2.** *Effects of Estrogen on the Brain*

| |
|---|
| Increases dendritic spine density |
| Promotes synapse formation |
| Modulates nerve growth factor activity |
| Influences several neurotransmitter systems including the acetylcholine system |
| Increases apolipoprotein E levels |
| Antioxidant |
| Anti-inflammatory |
| Promotes the breakdown of the amyloid precursor protein so there is less β-amyloid |
| Enhances blood flow |
| Augments glucose uptake and metabolism |
| Reduces glucocorticoid elevations |

In the adult nervous system, sex steroids play an important role in the dynamic process of formation and remodeling of neuronal circuits and in neurotransmitter activity. Estrogens readily cross the blood-brain barrier, where they can interact with both nuclear and membrane-bound estrogen receptors. Studies in experimental animals and cell culture systems have established estrogen's role in the preservation and growth of neuronal elements that are analogous to regions of the brain most affected by the neurodegenerative changes of AD. In addition, behavioral studies of estrogen effects on learning and memory in animals are consistent with the hormone-dependent neuronal changes. Potential effects of estrogen on the brain are summarized in Table 2.

Estrogen regulates growth proteins associated with axonal elongation, enhances the outgrowth of nerve processes, and promotes synapse formation between nerve cells. Ovariectomy in adult female rats decreases dendritic spine density in the CA1 region of the hippocampus, a region prominently affected in AD. This effect is prevented by estrogen replacement. Postsynaptic response and firing of CA1 neurons are also higher in ovariectomized rats given estrogen than in controls.

Estrogen influences several neurotransmitter systems, including those using acetylcholine, noradrenaline, serotonin, dopamine, glutamate, and γ-aminobutyric acid. Acetylcholine is a key neurotransmitter in neural networks that are heavily affected by neurofibrillary tangles in AD. In ovariectomized rats, estrogen increases choline acetyltransferase (an enzyme needed to synthesize acetylcholine) in the basal forebrain and its projection target areas, but male rats do not show a response. Estrogen also reverses learning deficits induced by a cholinergic antagonist.

The risk conferred by the apolipoprotein ε4 allele appears greater in women than in men. This gender difference may be mediated in part by estrogen. Estrogen increases brain levels of apolipoprotein E, an effect that might facilitate neuronal repair after brain injury.

Other actions of estrogen may also influence AD risk. Estrogen's antioxidant actions could blunt β-amy-

loid neurotoxicity and the damaging effects of free radicals that accumulate with aging. Its anti-inflammatory actions may moderate inflammatory processes implicated in neurotic plaque formation. In vitro, estrogen promotes the breakdown of the amyloid precursor protein to fragments less likely to accumulate as neurotoxic β-amyloid. It enhances cerebral blood flow and augments cerebral glucose transport and metabolism, which may improve cognitive performance. Estrogen also blunts the deleterious glucocorticoid elevations induced by stress, which are harmful to hippocampal neurons.

Thus, the established role of estrogen in neuronal growth and repair, neurotransmitter activity, learning, and memory suggests plausible biologic mechanisms for the observed effect of ERT on ameliorating AD symptoms and reducing risk of the disease.

## Summary

The burden of AD falls particularly hard on women. Considerable evidence suggests that estrogen might be beneficial in both the treatment and prevention of this disease in postmenopausal women. In clinical trials, although small and generally not randomized, estrogen appears to improve several AD symptoms in some women. The epidemiologic data show a strong association of about a 50% risk reduction among estrogen users. The findings of a dose/duration effect of decreasing risk with increasing dose/duration suggest a causal relation. Little information is available to determine the optimum formulation or administration route of the estrogen compound. Studies in experimental animals and cell cultures provide plausible biologic mechanisms for the observed effects in humans. Larger treatment trials in affected women and prospective randomized trials in older nondemented women are needed to confirm initial findings that estrogen is an efficacious treatment for AD and a prevention strategy against AD.

Physicians and their postmenopausal patients already have substantial reasons to consider ERT (e.g., to reduce heart disease risk and prevent osteoporosis). Although the issue is far from settled, the evidence hints at an exciting new benefit of estrogen—its apparent ability to prevent AD.

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## Questions for Volume 18, Lesson 24

1. **The prevalence of Alzheimer's disease**
   A. is greater in men than in women
   B. is less than that of other dementing diseases
   C. about doubles every 5 years after age 65
   D. is about 14 million in the United States
   E. decreases with age because a greater proportion of people die in each age group

2. **The risk of Alzheimer's disease**
   A. is doubled if a parent has Alzheimer's disease
   B. is not related to any environmental exposures
   C. is tripled if the individual has the apolipoprotein E ε3 allele
   D. is low if the individual does not have one of the specific genetic mutations known to cause Alzheimer's disease
   E. can be specifically calculated for each individual

3. **Clinical trials of estrogen in the treatment of women with Alzheimer's disease**
   A. number more than 80
   B. include many randomized, double-blind, placebo-controlled trials
   C. conclusively show that estrogen is efficacious in treating women with the disease
   D. found that estrogen's effect was limited to improvement in a few specific tasks
   E. suggest that estrogen is beneficial in treating symptoms in women

4. **Estrogen replacement therapy and Alzheimer's disease risk**
   A. are inversely associated
   B. are associated but not causally related
   C. have little relation
   D. are associated because of confounding variables
   E. have been extensively studied

5. **Limitations of some epidemiologic studies of ERT and Alzheimer's disease include**
   A. selected cases are representative of affected individuals in the general population
   B. estrogen information collected before onset of dementia symptoms
   C. control subjects used more estrogen than cases
   D. estrogen data collected differently from cases than from control subjects
   E. longitudinal design

6. **The *best* studies we have on ERT and Alzheimer's disease risk are**
   A. clinical trials
   B. longitudinal studies
   C. case-control studies
   D. cohort studies
   E. totally consistent in finding a reduced risk among estrogen users

7. **The epidemiologic studies of ERT and Alzheimer's disease risk**
   A. prove cause and effect
   B. all find a reduced risk among women who have used ERT
   C. generally show a 30% or lower risk among estrogen users compared with nonusers
   D. are limited to oral estrogen preparations
   E. provide many data on the effect of various doses

8. **Estrogen's effects on the brain**
   A. are limited by the blood-brain barrier
   B. support the hypothesis that estrogen reduces Alzheimer's disease risk
   C. may affect the pathogenesis but not the progression of Alzheimer's disease
   D. have no effect on learning and memory
   E. are well established in humans

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