

Neal Rouzier, M.D.

Hormones and the Brain Lecture #1

Study Group: Alzheimer's Threatens More Than Health



health & science

Study group: Alzheimer's threatens more than health

Disease could cost U.S. $1 trillion a year by 2050, report says

BY LESLEY CLARK
McClatchy Newspapers

WASHINGTON — Sargent Shriver once walked the halls of Congress pressing senators and members of the House of Representatives for more money for the Peace Corps, Head Start and Job Corps, his daughter, Maria Shriver, testified Wednesday.

"He knew every senator and every congressman by name. He knew their careers, their interests, their politics and, of course, their soft spots," California's first lady said. Now, at 93, the one-time adviser to two presidents doesn't remember his daughter, thanks to the ravages of Alzheimer's, the disease that a left him entirely dependent on others.

It was for her dad and millions like him that Shriver testified Wednesday, pushing for increased attention to Alzheimer's in the wake of a new report that suggests the disease "could very easily surpass even the current economic crisis in the damage it inflicts on individuals and our economy."

The report by the Alzheimer's Study Group projects that Alzheimer's related costs to Medicare and Medicaid alone will top more than $1 trillion annually by 2050.

"We have to put Alzheimer's on the front burner because if we don't, Alzheimer's will [illegible] will cripple our families, devastate our health care system, and decimate the legacy of our generation," Shriver told the Senate's Special Committee on Aging.

Her words on her father's behalf earned her a standing ovation from the dozens of Alzheimer's advocates who had packed the senate Senate hearing room, many of them wiping away tears as she spoke.

The study group — convened by Congress in 2007 and chaired by former Republican House Speaker Newt Gingrich and former Nebraska Democratic Sen. Bob Kerrey — recommends creating what it called an Alzheimer's Solutions Project to accelerate and focus national efforts, including an emphasis on research into preventing Alzheimer's. Research funding for the disease has been flat for five years.

"The human pain and financial burden of Alzheimer's is so great and the potential breakthroughs in science are so encouraging that a 'Manhattan Project' — approach to ending Alzheimer's is more than justified," Gingrich said, referring to the government project to develop a nuclear weapon during World War II. He noted that polio activities more than 50,000 Americans in the 1950s, but the disease largely was eradicated when a vaccine was found.

"An Alzheimer's preventive would dramatically overshadow even that great scientific victory of the polio vaccine."

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The Mysterious Effect of Reproductive Hormones on Cognitive Function: Scientific Knowledge in Search of an Application



and females. However, only males activated the left hippocampus and only females activated the right parietal and right prefrontal cortex. These findings lend support to the widely accepted notion that men and women behave differently when lost, suggesting that this behavioral difference is neurally based.

One of the most fascinating gender-related issues in neurology is the potential effect of estrogen on cognitive function. Based on the fundamental science of estrogen in the brain, it is tantalizing to postulate that estrogen could have a beneficial effect on preventing or delaying Alzheimer's disease. The remainder of this article will review the research on this question.

ESTROGEN AND THE ANATOMY OF THE BRAIN

Estrogen receptors are concentrated in the hypothalamus, preoptic area, anterior pituitary, CA1 region of the hippocampus, and basal forebrain cholinergic nuclei, and they are found to a lesser degree in the cerebral cortex, as well as in the caudate-putamen, midbrain raphe, brain stem locus ceruleus, and spinal cord. Except for the first three of these sites, the estrogen receptors at these locations would not be primarily involved in reproductive functioning. Therefore, what does estrogen do at these sites in the nervous system?

Through both a rapid "nongenomic" effect and a more delayed yet prolonged "genomic" effect, estrogen influences numerous neurotransmitter systems and modulates membrane excitability (see reference 11 for a complete review).[11] Estrogen affects the serotonergic system (by inducing serotonin receptors) and the noradrenergic system, accounting for its role in the cyclic mood variations of premenstrual syndrome and its mood augmentation in menopausal women. Estrogen modulates nigrostriatal dopamine levels, and its effect on the motor function of women with Parkinson's disease has been reported to be detrimental by some authors,[12,13] while others[14] suggest it is beneficial. Estrogen may actually increase dopamine levels by reducing catechol-*O*-methyltransferase (COMT) levels through interfering with COMT gene transcription. This increase in dopamine levels could then result in disease improvement.

Estrogen appears to be excitatory in its effects in the brain, correlating with the increase in seizures during the estrogen peak of ovulation that is reported by some women with epilepsy as part of a catamenial (ie, menstrually related) pattern. Estrogen particularly promotes de novo synapse formation on pyramidal neurons, involving excitatory *N*-methyl-D-aspartate (NMDA) receptors in the hippocampus. It also transiently down-regulates the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). These effects partly explain the seizure-permitting effects of estrogen on a disease for which the primary dysfunction is the balance between excitation and inhibition in the brain.

ESTROGEN AND ALZHEIMER'S DISEASE

The possible relationship between estrogen and Alzheimer's disease is complicated. The effect of estrogen on cognition and memory function itself could play a role, but the neuroprotective effects of estrogen in the brain may be even more important. The differentiation between memory-augmenting effects and neuroprotective effects is important to keep in mind when evaluating clinical work that uses estrogen for memory disorders.

Laboratory Research

Estrogens and progestins regulate synaptogenesis in the hippocampus, a brain area important for learning and incorporating new memories. In rats, hippocampal synapses are formed under the influence of estrogen during estrus, then broken down by the increase in progesterone during proestrus.[15] These experiments indicate that the synaptogenesis is transient (implicating a form of neuroplasticity) and is dependent on the presence of these hormones for its sustenance.

Estrogen has actions more site-specific for Alzheimer's disease, in which the primary and initial dysfunction occurs in the cholinergic basal forebrain nuclei of the frontal lobes. Estrogen up-regulates nerve growth factor receptors in the basal forebrain, promoting neuronal survival.[16] In ovariectomized rats, those treated with 17-beta-estradiol performed better on a memory task than untreated rats; the effect was associated with increased choline uptake and higher levels of choline acetyltransferase in the hippocampus and frontal cortex.[17]

Another potential effect of estrogen on neurotransmitters is that it can decrease monoamine oxidase activity in the amygdala and basomedial hypothalamus.[18] This effect would serve to modulate three important neurotransmitters that impact memory and learning: serotonin, norepinephrine, and dopamine.

The previously mentioned effect of estrogen on synaptic plasticity and dendritic spine density during estrous cycling in the rat is likely also important in the setting of ovarian failure, commonly known in the human as menopause. Oophorectomy in the rat produces a marked decrease in spine density of hippocampal CA1 neuronal dendrites.[19] Treatment with estradiol then produces new excitatory synapses, involving the participation of the NMDA subset of glutamic acid

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Harden CL. The mysterious effect of reproductive hormones on cognitive function: scientific knowledge in search of an application. J Gend Specif

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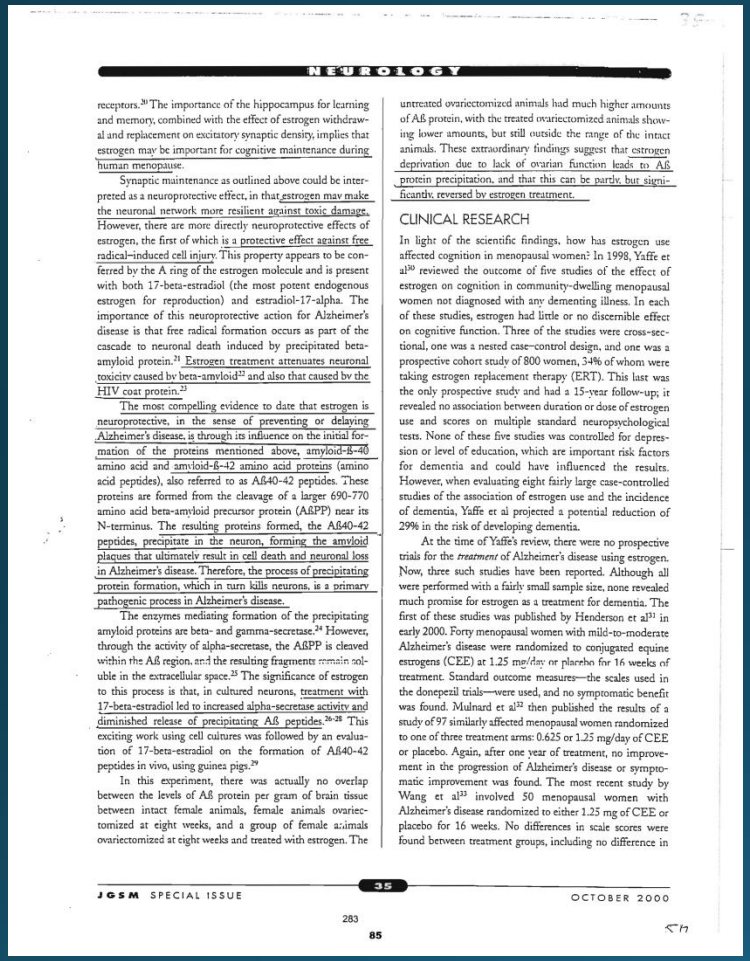

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receptors.[20] The importance of the hippocampus for learning and memory, combined with the effect of estrogen withdrawal and replacement on excitatory synaptic density, implies that estrogen may be important for cognitive maintenance during human menopause.

Synaptic maintenance as outlined above could be interpreted as a neuroprotective effect, in that estrogen may make the neuronal network more resilient against toxic damage. However, there are more directly neuroprotective effects of estrogen, the first of which is a protective effect against free radical–induced cell injury. This property appears to be conferred by the A ring of the estrogen molecule and is present with both 17-beta-estradiol (the most potent endogenous estrogen for reproduction) and estradiol-17-alpha. The importance of this neuroprotective action for Alzheimer's disease is that free radical formation occurs as part of the cascade to neuronal death induced by precipitated beta-amyloid protein.[21] Estrogen treatment attenuates neuronal toxicity caused by beta-amyloid[22] and also that caused by the HIV coat protein.[23]

The most compelling evidence to date that estrogen is neuroprotective, in the sense of preventing or delaying Alzheimer's disease, is through its influence on the initial formation of the proteins mentioned above, amyloid-ß-40 amino acid and amyloid-ß-42 amino acid proteins (amino acid peptides), also referred to as Aß40-42 peptides. These proteins are formed from the cleavage of a larger 690-770 amino acid beta-amyloid precursor protein (AßPP) near its N-terminus. The resulting proteins formed, the Aß40-42 peptides, precipitate in the neuron, forming the amyloid plaques that ultimately result in cell death and neuronal loss in Alzheimer's disease. Therefore, the process of precipitating protein formation, which in turn kills neurons, is a primary pathogenic process in Alzheimer's disease.

The enzymes mediating formation of the precipitating amyloid proteins are beta- and gamma-secretase.[24] However, through the activity of alpha-secretase, the AßPP is cleaved within the Aß region, and the resulting fragments remain soluble in the extracellular space.[25] The significance of estrogen to this process is that, in cultured neurons, treatment with 17-beta-estradiol led to increased alpha-secretase activity and diminished release of precipitating Aß peptides.[26-28] This exciting work using cell cultures was followed by an evaluation of 17-beta-estradiol on the formation of Aß40-42 peptides in vivo, using guinea pigs.[29]

In this experiment, there was actually no overlap between the levels of Aß protein per gram of brain tissue between intact female animals, female animals ovariectomized at eight weeks, and a group of female animals ovariectomized at eight weeks and treated with estrogen. The untreated ovariectomized animals had much higher amounts of Aß protein, with the treated ovariectomized animals showing lower amounts, but still outside the range of the intact animals. These extraordinary findings suggest that estrogen deprivation due to lack of ovarian function leads to Aß protein precipitation, and that this can be partly, but significantly, reversed by estrogen treatment.

CLINICAL RESEARCH

In light of the scientific findings, how has estrogen use affected cognition in menopausal women? In 1998, Yaffe et al[30] reviewed the outcome of five studies of the effect of estrogen on cognition in community-dwelling menopausal women not diagnosed with any dementing illness. In each of these studies, estrogen had little or no discernible effect on cognitive function. Three of the studies were cross-sectional, one was a nested case–control design, and one was a prospective cohort study of 800 women, 34% of whom were taking estrogen replacement therapy (ERT). This last was the only prospective study and had a 15-year follow-up; it revealed no association between duration or dose of estrogen use and scores on multiple standard neuropsychological tests. None of these five studies was controlled for depression or level of education, which are important risk factors for dementia and could have influenced the results. However, when evaluating eight fairly large case-controlled studies of the association of estrogen use and the incidence of dementia, Yaffe et al projected a potential reduction of 29% in the risk of developing dementia.

At the time of Yaffe's review, there were no prospective trials for the *treatment* of Alzheimer's disease using estrogen. Now, three such studies have been reported. Although all were performed with a fairly small sample size, none revealed much promise for estrogen as a treatment for dementia. The first of these studies was published by Henderson et al[31] in early 2000. Forty menopausal women with mild-to-moderate Alzheimer's disease were randomized to conjugated equine estrogens (CEE) at 1.25 mg/day or placebo for 16 weeks of treatment. Standard outcome measures—the scales used in the donepezil trials—were used, and no symptomatic benefit was found. Mulnard et al[32] then published the results of a study of 97 similarly affected menopausal women randomized to one of three treatment arms: 0.625 or 1.25 mg/day of CEE or placebo. Again, after one year of treatment, no improvement in the progression of Alzheimer's disease or symptomatic improvement was found. The most recent study by Wang et al[33] involved 50 menopausal women with Alzheimer's disease randomized to either 1.25 mg of CEE or placebo for 16 weeks. No differences in scale scores were found between treatment groups, including no difference in

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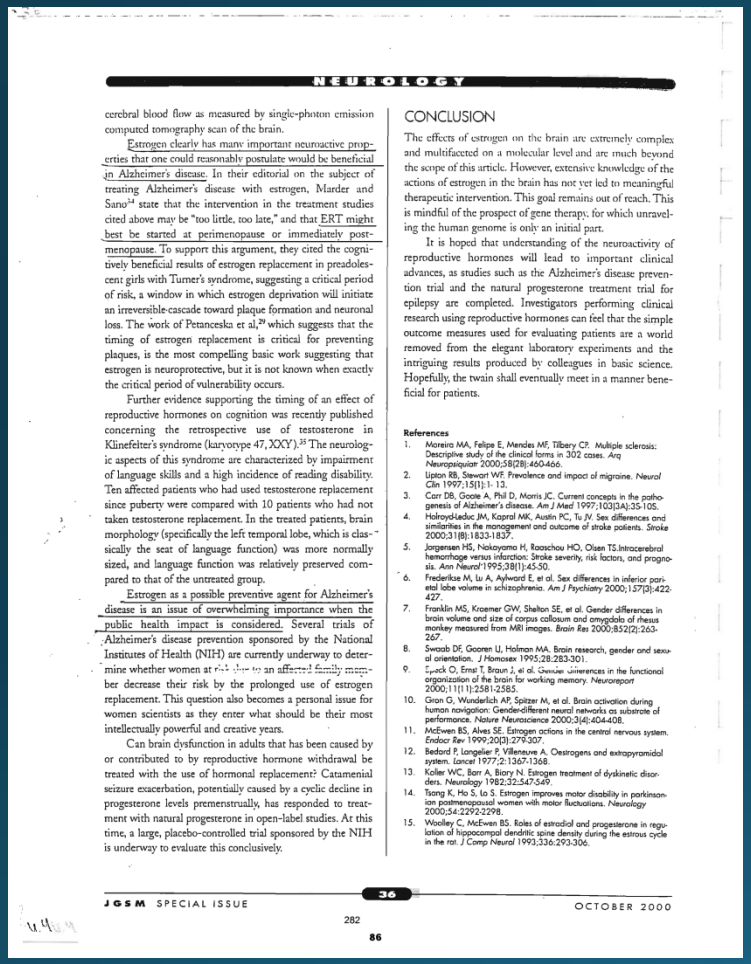

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cerebral blood flow as measured by single-photon emission computed tomography scan of the brain.

Estrogen clearly has many important neuroactive properties that one could reasonably postulate would be beneficial in Alzheimer's disease. In their editorial on the subject of treating Alzheimer's disease with estrogen, Marder and Sano[34] state that the intervention in the treatment studies cited above may be "too little, too late," and that ERT might best be started at perimenopause or immediately post-menopause. To support this argument, they cited the cognitively beneficial results of estrogen replacement in preadolescent girls with Turner's syndrome, suggesting a critical period of risk, a window in which estrogen deprivation will initiate an irreversible cascade toward plaque formation and neuronal loss. The work of Petanceska et al,[29] which suggests that the timing of estrogen replacement is critical for preventing plaques, is the most compelling basic work suggesting that estrogen is neuroprotective, but it is not known when exactly the critical period of vulnerability occurs.

Further evidence supporting the timing of an effect of reproductive hormones on cognition was recently published concerning the retrospective use of testosterone in Klinefelter's syndrome (karyotype 47, XXY).[35] The neurologic aspects of this syndrome are characterized by impairment of language skills and a high incidence of reading disability. Ten affected patients who had used testosterone replacement since puberty were compared with 10 patients who had not taken testosterone replacement. In the treated patients, brain morphology (specifically the left temporal lobe, which is classically the seat of language function) was more normally sized, and language function was relatively preserved compared to that of the untreated group.

Estrogen as a possible preventive agent for Alzheimer's disease is an issue of overwhelming importance when the public health impact is considered. Several trials of Alzheimer's disease prevention sponsored by the National Institutes of Health (NIH) are currently underway to determine whether women at risk due to an affected family member decrease their risk by the prolonged use of estrogen replacement. This question also becomes a personal issue for women scientists as they enter what should be their most intellectually powerful and creative years.

Can brain dysfunction in adults that has been caused by or contributed to by reproductive hormone withdrawal be treated with the use of hormonal replacement? Catamenial seizure exacerbation, potentially caused by a cyclic decline in progesterone levels premenstrually, has responded to treatment with natural progesterone in open-label studies. At this time, a large, placebo-controlled trial sponsored by the NIH is underway to evaluate this conclusively.

CONCLUSION

The effects of estrogen on the brain are extremely complex and multifaceted on a molecular level and are much beyond the scope of this article. However, extensive knowledge of the actions of estrogen in the brain has not yet led to meaningful therapeutic intervention. This goal remains out of reach. This is mindful of the prospect of gene therapy, for which unraveling the human genome is only an initial part.

It is hoped that understanding of the neuroactivity of reproductive hormones will lead to important clinical advances, as studies such as the Alzheimer's disease prevention trial and the natural progesterone treatment trial for epilepsy are completed. Investigators performing clinical research using reproductive hormones can feel that the simple outcome measures used for evaluating patients are a world removed from the elegant laboratory experiments and the intriguing results produced by colleagues in basic science. Hopefully, the twain shall eventually meet in a manner beneficial for patients.

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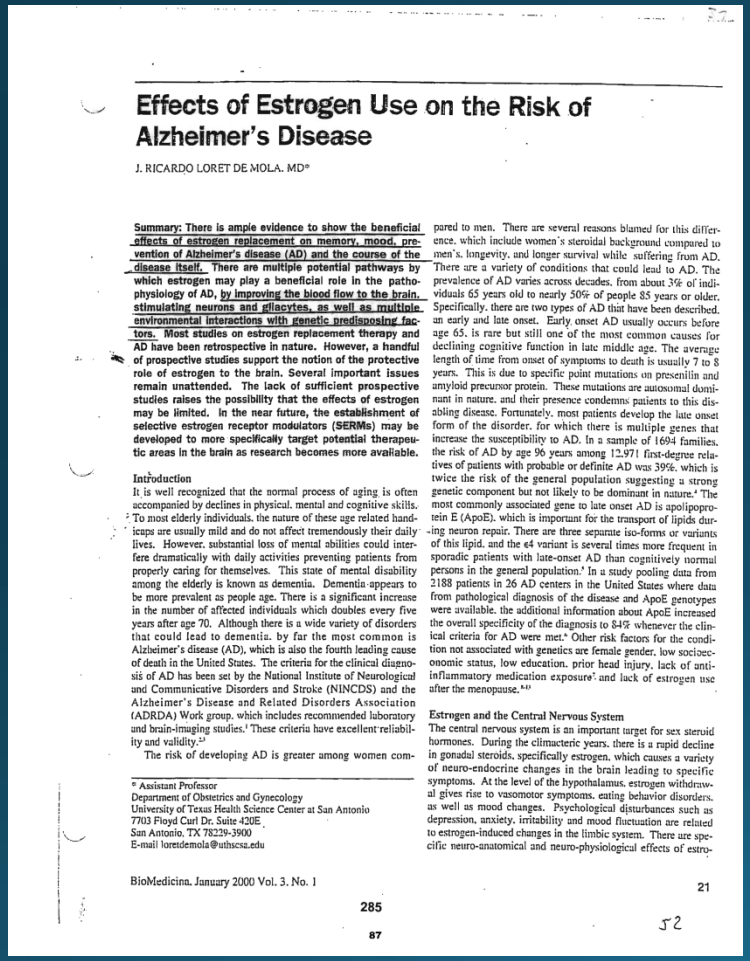
Effects of Estrogen Use on the Risk of Alzheimer's Disease



Effects of Estrogen Use on the Risk of Alzheimer's Disease

J. RICARDO LORET DE MOLA, MD*

Summary: There is ample evidence to show the beneficial effects of estrogen replacement on memory, mood, prevention of Alzheimer's disease (AD) and the course of the disease itself. There are multiple potential pathways by which estrogen may play a beneficial role in the pathophysiology of AD, by improving the blood flow to the brain, stimulating neurons and gliacytes, as well as multiple environmental interactions with genetic predisposing factors. Most studies on estrogen replacement therapy and AD have been retrospective in nature. However, a handful of prospective studies support the notion of the protective role of estrogen to the brain. Several important issues remain unattended. The lack of sufficient prospective studies raises the possibility that the effects of estrogen may be limited. In the near future, the establishment of selective estrogen receptor modulators (SERMs) may be developed to more specifically target potential therapeutic areas in the brain as research becomes more available.

Introduction

It is well recognized that the normal process of aging is often accompanied by declines in physical, mental and cognitive skills. To most elderly individuals, the nature of these age related handicaps are usually mild and do not affect tremendously their daily lives. However, substantial loss of mental abilities could interfere dramatically with daily activities preventing patients from properly caring for themselves. This state of mental disability among the elderly is known as dementia. Dementia appears to be more prevalent as people age. There is a significant increase in the number of affected individuals which doubles every five years after age 70. Although there is a wide variety of disorders that could lead to dementia, by far the most common is Alzheimer's disease (AD), which is also the fourth leading cause of death in the United States. The criteria for the clinical diagnosis of AD has been set by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) Work group, which includes recommended laboratory and brain-imaging studies.[1] These criteria have excellent reliability and validity.[2,3]

The risk of developing AD is greater among women compared to men. There are several reasons blamed for this difference, which include women's steroidal background compared to men's, longevity, and longer survival while suffering from AD. There are a variety of conditions that could lead to AD. The prevalence of AD varies across decades, from about 3% of individuals 65 years old to nearly 50% of people 85 years or older. Specifically, there are two types of AD that have been described, an early and late onset. Early onset AD usually occurs before age 65, is rare but still one of the most common causes for declining cognitive function in late middle age. The average length of time from onset of symptoms to death is usually 7 to 8 years. This is due to specific point mutations on presenilin and amyloid precursor protein. These mutations are autosomal dominant in nature, and their presence condemns patients to this disabling disease. Fortunately, most patients develop the late onset form of the disorder, for which there is multiple genes that increase the susceptibility to AD. In a sample of 1694 families, the risk of AD by age 96 years among 12,971 first-degree relatives of patients with probable or definite AD was 39%, which is twice the risk of the general population suggesting a strong genetic component but not likely to be dominant in nature.[4] The most commonly associated gene to late onset AD is apolipoprotein E (ApoE), which is important for the transport of lipids during neuron repair. There are three separate iso-forms or variants of this lipid, and the ε4 variant is several times more frequent in sporadic patients with late-onset AD than cognitively normal persons in the general population.[5] In a study pooling data from 2188 patients in 26 AD centers in the United States where data from pathological diagnosis of the disease and ApoE genotypes were available, the additional information about ApoE increased the overall specificity of the diagnosis to 84% whenever the clinical criteria for AD were met.[6] Other risk factors for the condition not associated with genetics are female gender, low socioeconomic status, low education, prior head injury, lack of anti-inflammatory medication exposure[7] and lack of estrogen use after the menopause.[8,9]

Estrogen and the Central Nervous System

The central nervous system is an important target for sex steroid hormones. During the climacteric years, there is a rapid decline in gonadal steroids, specifically estrogen, which causes a variety of neuro-endocrine changes in the brain leading to specific symptoms. At the level of the hypothalamus, estrogen withdrawal gives rise to vasomotor symptoms, eating behavior disorders, as well as mood changes. Psychological disturbances such as depression, anxiety, irritability and mood fluctuation are related to estrogen-induced changes in the limbic system. There are specific neuro-anatomical and neuro-physiological effects of estro-

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- Summary: There is ample evidence to show the beneficial effects of estrogen replacement on memory, mood, prevention of Alzheimer's disease (AD) and the course of the disease itself.
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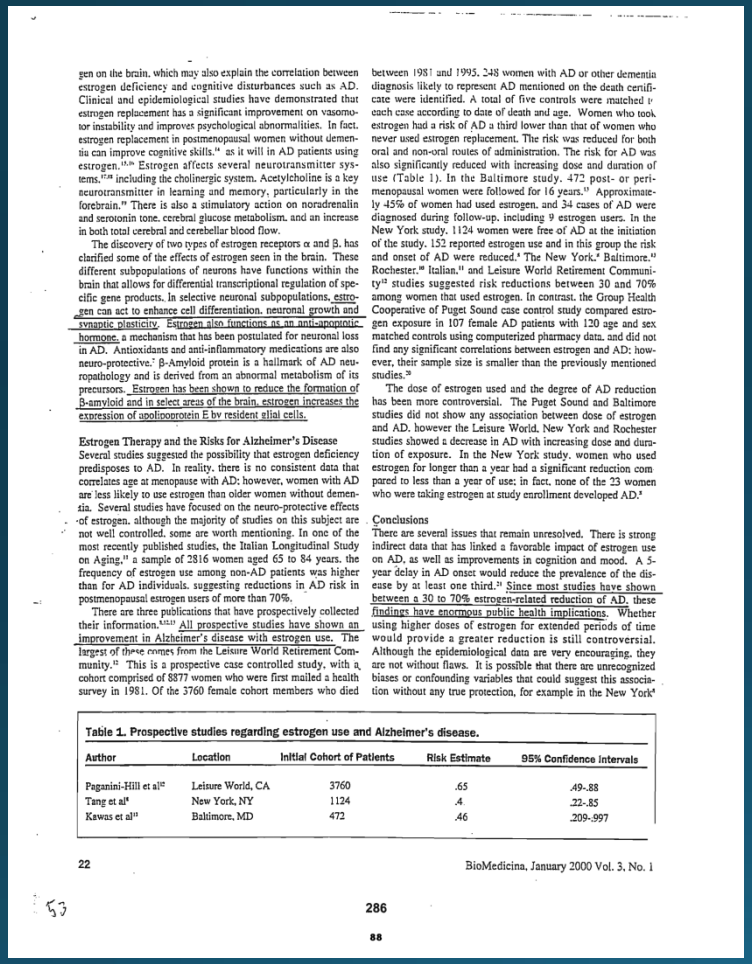

gen on the brain, which may also explain the correlation between estrogen deficiency and cognitive disturbances such as AD. Clinical and epidemiological studies have demonstrated that estrogen replacement has a significant improvement on vasomotor instability and improves psychological abnormalities. In fact, estrogen replacement in postmenopausal women without dementia can improve cognitive skills,[14] as it will in AD patients using estrogen.[15,16] Estrogen affects several neurotransmitter systems,[17,18] including the cholinergic system. Acetylcholine is a key neurotransmitter in learning and memory, particularly in the forebrain.[19] There is also a stimulatory action on noradrenalin and serotonin tone, cerebral glucose metabolism, and an increase in both total cerebral and cerebellar blood flow.

The discovery of two types of estrogen receptors α and β, has clarified some of the effects of estrogen seen in the brain. These different subpopulations of neurons have functions within the brain that allows for differential transcriptional regulation of specific gene products. In selective neuronal subpopulations, estrogen can act to enhance cell differentiation, neuronal growth and synaptic plasticity. Estrogen also functions as an anti-apoptotic hormone, a mechanism that has been postulated for neuronal loss in AD. Antioxidants and anti-inflammatory medications are also neuro-protective.[7] β-Amyloid protein is a hallmark of AD neuropathology and is derived from an abnormal metabolism of its precursors. Estrogen has been shown to reduce the formation of β-amyloid and in select areas of the brain, estrogen increases the expression of apolipoprotein E by resident glial cells.

Estrogen Therapy and the Risks for Alzheimer's Disease

Several studies suggested the possibility that estrogen deficiency predisposes to AD. In reality, there is no consistent data that correlates age at menopause with AD; however, women with AD are less likely to use estrogen than older women without dementia. Several studies have focused on the neuro-protective effects of estrogen, although the majority of studies on this subject are not well controlled, some are worth mentioning. In one of the most recently published studies, the Italian Longitudinal Study on Aging,[11] a sample of 2816 women aged 65 to 84 years, the frequency of estrogen use among non-AD patients was higher than for AD individuals, suggesting reductions in AD risk in postmenopausal estrogen users of more than 70%.

There are three publications that have prospectively collected their information.[9,12,13] All prospective studies have shown an improvement in Alzheimer's disease with estrogen use. The largest of these comes from the Leisure World Retirement Community.[12] This is a prospective case controlled study, with a cohort comprised of 8877 women who were first mailed a health survey in 1981. Of the 3760 female cohort members who died between 1981 and 1995, 248 women with AD or other dementia diagnosis likely to represent AD mentioned on the death certificate were identified. A total of five controls were matched to each case according to date of death and age. Women who took estrogen had a risk of AD a third lower than that of women who never used estrogen replacement. The risk was reduced for both oral and non-oral routes of administration. The risk for AD was also significantly reduced with increasing dose and duration of use (Table 1). In the Baltimore study, 472 post- or perimenopausal women were followed for 16 years.[13] Approximately 45% of women had used estrogen, and 34 cases of AD were diagnosed during follow-up, including 9 estrogen users. In the New York study, 1124 women were free of AD at the initiation of the study, 152 reported estrogen use and in this group the risk and onset of AD were reduced.[9] The New York,[9] Baltimore,[13] Rochester,[10] Italian,[11] and Leisure World Retirement Community[12] studies suggested risk reductions between 30 and 70% among women that used estrogen. In contrast, the Group Health Cooperative of Puget Sound case control study compared estrogen exposure in 107 female AD patients with 120 age and sex matched controls using computerized pharmacy data, and did not find any significant correlations between estrogen and AD; however, their sample size is smaller than the previously mentioned studies.[9]

The dose of estrogen used and the degree of AD reduction has been more controversial. The Puget Sound and Baltimore studies did not show any association between dose of estrogen and AD, however the Leisure World, New York and Rochester studies showed a decrease in AD with increasing dose and duration of exposure. In the New York study, women who used estrogen for longer than a year had a significant reduction compared to less than a year of use; in fact, none of the 23 women who were taking estrogen at study enrollment developed AD.[9]

Conclusions

There are several issues that remain unresolved. There is strong indirect data that has linked a favorable impact of estrogen use on AD, as well as improvements in cognition and mood. A 5-year delay in AD onset would reduce the prevalence of the disease by at least one third.[13] Since most studies have shown between a 30 to 70% estrogen-related reduction of AD, these findings have enormous public health implications. Whether using higher doses of estrogen for extended periods of time would provide a greater reduction is still controversial. Although the epidemiological data are very encouraging, they are not without flaws. It is possible that there are unrecognized biases or confounding variables that could suggest this association without any true protection, for example in the New York[9]

Table 1. Prospective studies regarding estrogen use and Alzheimer's disease.

Author	Location	Initial Cohort of Patients	Risk Estimate	95% Confidence Intervals
Paganini-Hill et al[12]	Leisure World, CA	3760	.65	.49-.88
Tang et al[9]	New York, NY	1124	.4	.22-.85
Kawas et al[13]	Baltimore, MD	472	.46	.209-.997

- Estrogen can act to enhance cell differentiation, neuronal growth and synaptic plasticity. Estrogen also functions as an anti-apoptotic hormone.
- Estrogen has been shown to reduce the formation of β-amyloid and in select areas of the brain, estrogen increases the expression of apolipoprotein E by resident glial cells.
- All prospective studies have shown an improvement in Alzheimer's disease with estrogen use!!!!!!!!!!!
- Since most studies have shown between a 30 to 70% estrogen-related reduction of AD, these findings have enormous public health implications.

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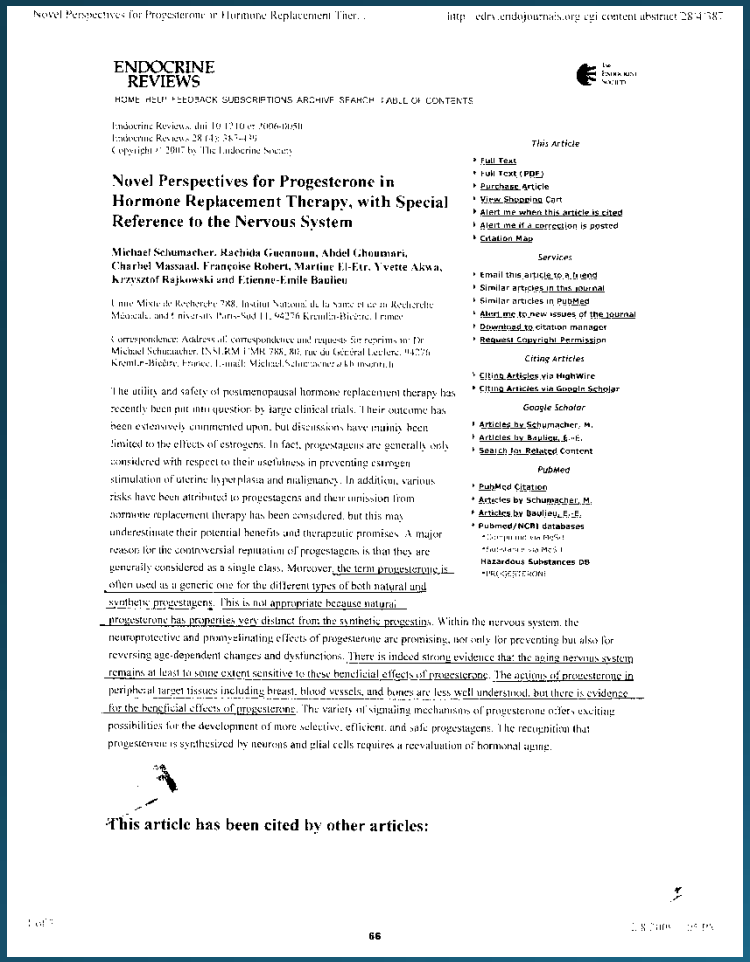
Novel Perspectives for Progesterone in Hormone Replacement Therapy, with Special Reference to the Nervous System



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Novel Perspectives for Progesterone in Hormone Replacement Therapy, with Special Reference to the Nervous System

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The utility and safety of postmenopausal hormone replacement therapy has recently been put into question by large clinical trials. Their outcome has been extensively commented upon, but discussions have mainly been limited to the effects of estrogens. In fact, progestagens are generally only considered with respect to their usefulness in preventing estrogen stimulation of uterine hyperplasia and malignancy. In addition, various risks have been attributed to progestagens and their omission from hormone replacement therapy has been considered, but this may underestimate their potential benefits and therapeutic promises. A major reason for the controversial reputation of progestagens is that they are generally considered as a single class. Moreover, the term progesterone is often used as a generic one for the different types of both natural and synthetic progestagens. This is not appropriate because natural progesterone has properties very distinct from the synthetic progestins. Within the nervous system, the neuroprotective and promyelinating effects of progesterone are promising, not only for preventing but also for reversing age-dependent changes and dysfunctions. There is indeed strong evidence that the aging nervous system remains at least to some extent sensitive to these beneficial effects of progesterone. The actions of progesterone in peripheral target tissues including breast, blood vessels, and bones are less well understood, but there is evidence for the beneficial effects of progesterone. The variety of signaling mechanisms of progesterone offers exciting possibilities for the development of more selective, efficient, and safe progestagens. The recognition that progesterone is synthesized by neurons and glial cells requires a reevaluation of hormonal aging.

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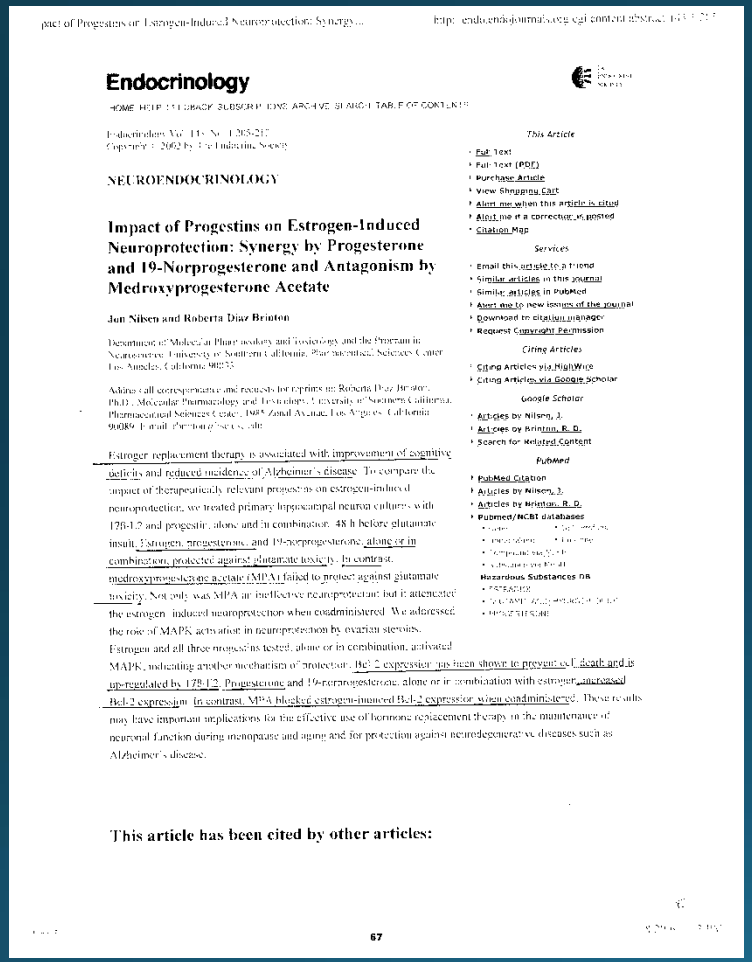
Impact of Progestins on Estrogen-Induced Neuroprotection: Synergy by Progesterone and 19-Norprogesterone and Antagonism by Medroxyprogesterone Acetate



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NEUROENDOCRINOLOGY

Impact of Progestins on Estrogen-Induced Neuroprotection: Synergy by Progesterone and 19-Norprogesterone and Antagonism by Medroxyprogesterone Acetate

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Estrogen replacement therapy is associated with improvement of cognitive deficits and reduced incidence of Alzheimer's disease. To compare the impact of therapeutically relevant progestins on estrogen-induced neuroprotection, we treated primary hippocampal neuronal cultures with 17β-E2 and progestin, alone and in combination, 48 h before glutamate insult. Estrogen, progesterone, and 19-norprogesterone, alone or in combination, protected against glutamate toxicity. In contrast, medroxyprogesterone acetate (MPA) failed to protect against glutamate toxicity. Not only was MPA an ineffective neuroprotectant, but it attenuated the estrogen-induced neuroprotection when coadministered. We addressed the role of MAPK activation in neuroprotection by ovarian steroids. Estrogen and all three progestins tested, alone or in combination, activated MAPK, indicating another mechanism of protection. Bcl-2 expression has been shown to prevent cell death and is up-regulated by 17β-E2. Progesterone and 19-norprogesterone, alone or in combination with estrogen, increased Bcl-2 expression. In contrast, MPA blocked estrogen-induced Bcl-2 expression when coadministered. These results may have important implications for the effective use of hormone replacement therapy in the maintenance of neuronal function during menopause and aging and for protection against neurodegenerative diseases such as Alzheimer's disease.

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Nilsen J, Brinton RD. Impact of progestins on estrogen-induced neuroprotection: synergy by progesterone and 19-norprogesterone and antagonism by medroxyprogesterone acetate. Endocrinology. 2002 Jan;143(1):205-212.

- Estrogen replacement therapy is associated with improvement of cognitive deficits and reduced incidence of Alzheimer's disease.
- Estrogen & progesterone … alone or in combination, protected against glutamate toxicity. In contrast, medroxyprogesterone acetate (MPA) failed to protect against glutamate toxicity.
- Bcl-2 expression has been shown to prevent cell death and is up-regulated by 17β-E2. Progesterone also increased Bcl-2 expression. In contrast, MPA blocked estrogen-induced Bcl-2 expression when coadministered.

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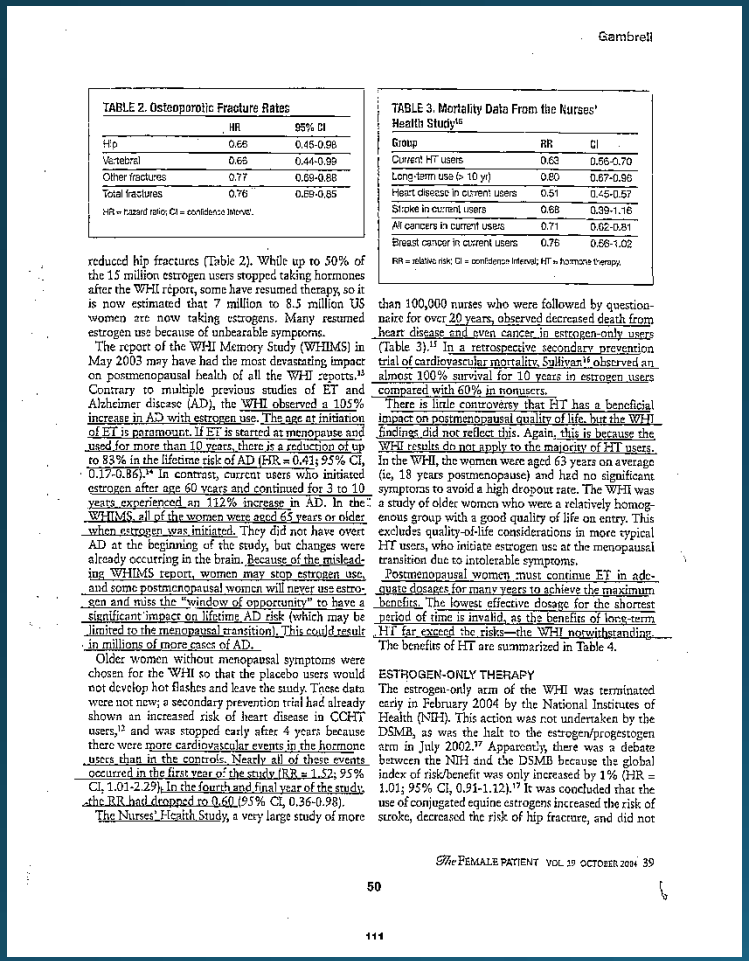

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TABLE 2. Osteoporotic Fracture Rates

	HR	95% CI
Hip	0.66	0.45-0.98
Vertebral	0.66	0.44-0.99
Other fractures	0.77	0.69-0.86
Total fractures	0.76	0.69-0.85

HR = hazard ratio; CI = confidence interval.

TABLE 3. Mortality Data From the Nurses' Health Study[16]

Group	RR	CI
Current HT users	0.63	0.56-0.70
Long-term use (> 10 yr)	0.80	0.67-0.96
Heart disease in current users	0.51	0.45-0.57
Stroke in current users	0.68	0.39-1.16
All cancers in current users	0.71	0.62-0.81
Breast cancer in current users	0.76	0.56-1.02

RR = relative risk; CI = confidence interval; HT = hormone therapy.

reduced hip fractures (Table 2). While up to 50% of the 15 million estrogen users stopped taking hormones after the WHI report, some have resumed therapy, so it is now estimated that 7 million to 8.5 million US women are now taking estrogens. Many resumed estrogen use because of unbearable symptoms.

The report of the WHI Memory Study (WHIMS) in May 2003 may have had the most devastating impact on postmenopausal health of all the WHI reports.[13] Contrary to multiple previous studies of ET and Alzheimer disease (AD), the WHI observed a 105% increase in AD with estrogen use. The age at initiation of ET is paramount. If ET is started at menopause and used for more than 10 years, there is a reduction of up to 83% in the lifetime risk of AD (HR = 0.41; 95% CI, 0.17-0.86).[14] In contrast, current users who initiated estrogen after age 60 years and continued for 3 to 10 years experienced an 112% increase in AD. In the WHIMS, all of the women were aged 65 years or older when estrogen was initiated. They did not have overt AD at the beginning of the study, but changes were already occurring in the brain. Because of the misleading WHIMS report, women may stop estrogen use, and some postmenopausal women will never use estrogen and miss the "window of opportunity" to have a significant impact on lifetime AD risk (which may be limited to the menopausal transition). This could result in millions of more cases of AD.

Older women without menopausal symptoms were chosen for the WHI so that the placebo users would not develop hot flashes and leave the study. These data were not new; a secondary prevention trial had already shown an increased risk of heart disease in CCHT users,[12] and was stopped early after 4 years because there were more cardiovascular events in the hormone users than in the controls. Nearly all of these events occurred in the first year of the study (RR = 1.52; 95% CI, 1.01-2.29). In the fourth and final year of the study, the RR had dropped to 0.60 (95% CI, 0.36-0.98).

The Nurses' Health Study, a very large study of more than 100,000 nurses who were followed by questionnaire for over 20 years, observed decreased death from heart disease and even cancer in estrogen-only users (Table 3).[15] In a retrospective secondary prevention trial of cardiovascular mortality, Sullivan[16] observed an almost 100% survival for 10 years in estrogen users compared with 60% in nonusers.

There is little controversy that HT has a beneficial impact on postmenopausal quality of life, but the WHI findings did not reflect this. Again, this is because the WHI results do not apply to the majority of HT users. In the WHI, the women were aged 63 years on average (ie, 18 years postmenopause) and had no significant symptoms to avoid a high dropout rate. The WHI was a study of older women who were a relatively homogenous group with a good quality of life on entry. This excludes quality-of-life considerations in more typical HT users, who initiate estrogen use at the menopausal transition due to intolerable symptoms.

Postmenopausal women must continue ET in adequate dosages for many years to achieve the maximum benefits. The lowest effective dosage for the shortest period of time is invalid, as the benefits of long-term HT far exceed the risks—the WHI notwithstanding. The benefits of HT are summarized in Table 4.

ESTROGEN-ONLY THERAPY

The estrogen-only arm of the WHI was terminated early in February 2004 by the National Institutes of Health (NIH). This action was not undertaken by the DSMB, as was the halt to the estrogen/progestogen arm in July 2002.[17] Apparently, there was a debate between the NIH and the DSMB because the global index of risk/benefit was only increased by 1% (HR = 1.01; 95% CI, 0.91-1.12).[17] It was concluded that the use of conjugated equine estrogens increased the risk of stroke, decreased the risk of hip fracture, and did not

- WHI observed a 105% increase in AD with estrogen use.
- The age at initiation of ET is paramount. If ET is started at menopause and used for more than 10 years, there is a reduction of up to 83% in the lifetime risk of AD (HR=0.41).
- Estrogen after age 60 years and continued for 3 to 10 years experienced an 112% increase in AD (should be dementia).
- WHIMS, all of the women were aged 65 years or older when estrogen was initiated.

Gambrell RD. The women's health initiative reports: Critical review of the findings. The Female Patient. 2004;29:25-41.

- Because of the misleading WHIMS report, women my stop estrogen use, and some postmenopausal women will never use estrogen and miss the "window of opportunity" to have a significant impact on lifetime AD risk (which may be limited to the menopausal transition).
- This could result in millions of more cases of AD.
- More cardiovascular events in the hormone users than in the controls. Nearly all of these events occurred in the first year of the study (RR=1.52).
- In the fourth and final year of the study, the RR had dropped to 0.60.
- The Nurses' Health Study…over 20 years, observed decreased death from heart disease and even cancer in estrogen-only users.

- In a retrospective secondary prevention trial of cardiovascular mortality, Sullivan observed an almost 100% survival for 10 years in estrogen users compared with 60% in nonusers.
- There is little controversy that HT has a beneficial impact on postmenopausal quality of life, but the WHI findings do not reflect this.
- This is because the WHI result do not apply to the majority of HT users.
- Postmenopausal women must continue ET in adequate dosages for many years to achieve the maximum benefits.
- The lowest effective dosage for the shortest period of time is invalid, as the benefits of long-term HT far exceed the risks – the WHI notwithstanding.

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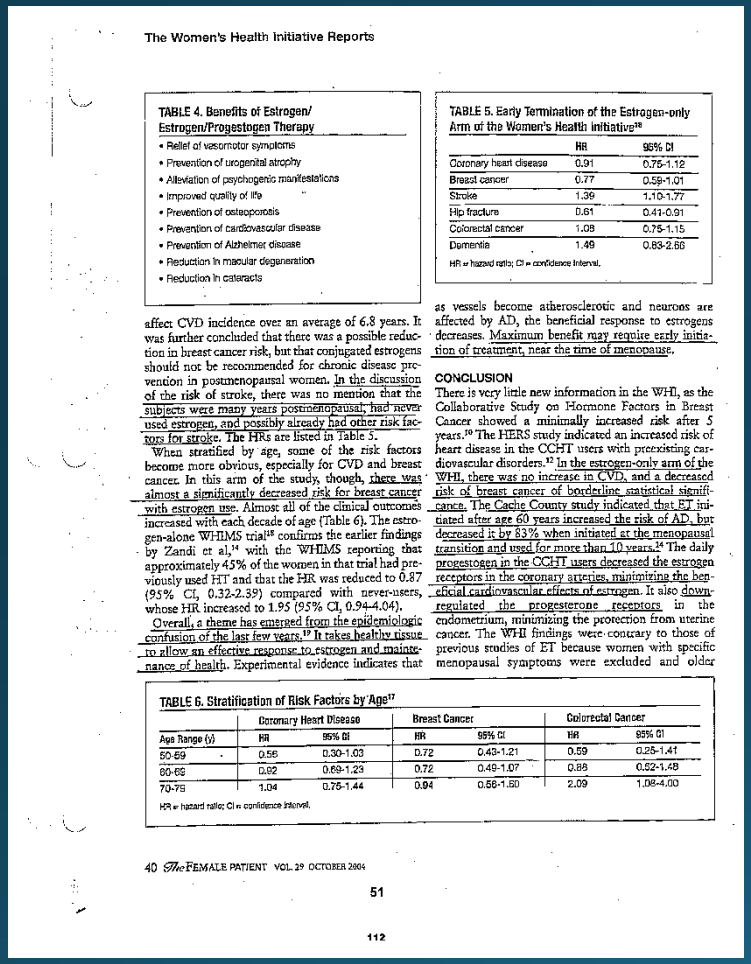

The Women's Health Initiative Reports

TABLE 4. Benefits of Estrogen/ Estrogen/Progestogen Therapy

- Relief of vasomotor symptoms
- Prevention of urogenital atrophy
- Alleviation of psychogenic manifestations
- Improved quality of life
- Prevention of osteoporosis
- Prevention of cardiovascular disease
- Prevention of Alzheimer disease
- Reduction in macular degeneration
- Reduction in cataracts

TABLE 5. Early Termination of the Estrogen-only Arm of the Women's Health Initiative[16]

	HR	95% CI
Coronary heart disease	0.91	0.75-1.12
Breast cancer	0.77	0.59-1.01
Stroke	1.39	1.10-1.77
Hip fracture	0.61	0.41-0.91
Colorectal cancer	1.08	0.75-1.15
Dementia	1.49	0.83-2.66

HR = hazard ratio; CI = confidence interval.

affect CVD incidence over an average of 6.8 years. It was further concluded that there was a possible reduction in breast cancer risk, but that conjugated estrogens should not be recommended for chronic disease prevention in postmenopausal women. In the discussion of the risk of stroke, there was no mention that the subjects were many years postmenopausal, had never used estrogen, and possibly already had other risk factors for stroke. The HRs are listed in Table 5.

When stratified by age, some of the risk factors become more obvious, especially for CVD and breast cancer. In this arm of the study, though, there was almost a significantly decreased risk for breast cancer with estrogen use. Almost all of the clinical outcomes increased with each decade of age (Table 6). The estrogen-alone WHIMS trial[18] confirms the earlier findings by Zandi et al,[14] with the WHIMS reporting that approximately 45% of the women in that trial had previously used HT and that the HR was reduced to 0.87 (95% CI, 0.32-2.39) compared with never-users, whose HR increased to 1.95 (95% CI, 0.94-4.04).

Overall, a theme has emerged from the epidemiologic confusion of the last few years.[17] It takes healthy tissue to allow an effective response to estrogen and maintenance of health. Experimental evidence indicates that as vessels become atherosclerotic and neurons are affected by AD, the beneficial response to estrogens decreases. Maximum benefit may require early initiation of treatment, near the time of menopause.

CONCLUSION

There is very little new information in the WHI, as the Collaborative Study on Hormone Factors in Breast Cancer showed a minimally increased risk after 5 years.[10] The HERS study indicated an increased risk of heart disease in the CCHT users with preexisting cardiovascular disorders.[12] In the estrogen-only arm of the WHI, there was no increase in CVD, and a decreased risk of breast cancer of borderline statistical significance. The Cache County study indicated that ET initiated after age 60 years increased the risk of AD, but decreased it by 83% when initiated at the menopausal transition and used for more than 10 years.[14] The daily progestogen in the CCHT users decreased the estrogen receptors in the coronary arteries, minimizing the beneficial cardiovascular effects of estrogen. It also down-regulated the progesterone receptors in the endometrium, minimizing the protection from uterine cancer. The WHI findings were contrary to those of previous studies of ET because women with specific menopausal symptoms were excluded and older

TABLE 6. Stratification of Risk Factors by Age[17]

	Coronary Heart Disease		Breast Cancer		Colorectal Cancer	
Age Range (y)	HR	95% CI	HR	95% CI	HR	95% CI
50-59	0.56	0.30-1.03	0.72	0.43-1.21	0.59	0.25-1.41
60-69	0.92	0.69-1.23	0.72	0.49-1.07	0.88	0.52-1.48
70-79	1.04	0.75-1.44	0.94	0.56-1.60	2.09	1.08-4.00

HR = hazard ratio; CI = confidence interval.

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- In the discussion of the risk of stroke, there was no mention that the subjects were many years postmenopausal, had never used estrogen, and possibly already had other risk factors for stroke.
- There was almost a significantly decreased risk for breast cancer with estrogen use.

Gambrell RD. The women's health initiative reports: Critical review of the findings. The Female Patient. 2004;29:25-41.

- Overall, a theme has emerged from the epidemiologic confusion of the last few years. It takes healthy tissue to allow an effective response to estrogen and maintenance of health.
- Maximum benefit may require early initiation of treatment, near the time of menopause.
- In the estrogen-only arm of the WHI, the was no increase in CVD, and a decreased risk of breast cancer of borderline statistical significance.

- The Cache County study indicated that ET initiated after age 60 years increased the risk of AD, but decreased it by 83% when initiated at the menopausal transition and used for more than 10 years.
- Progestogen in the CCHT users decreased the estrogen receptors in the coronary arteries, minimizing the beneficial cardiovascular effects of estrogen. It also down-regulated the progesterone receptors.

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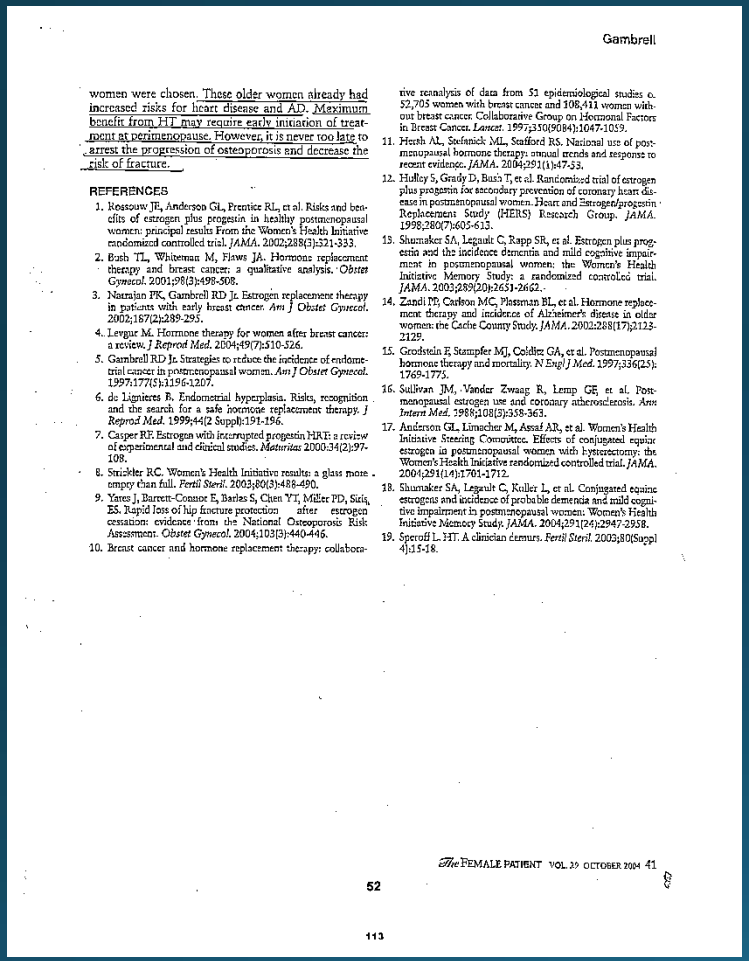

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women were chosen. These older women already had increased risks for heart disease and AD. Maximum benefit from HT may require early initiation of treatment at perimenopause. However, it is never too late to arrest the progression of osteoporosis and decrease the risk of fracture.

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- These older women already had increased risks for heart disease and AD.
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- However, it is never too late to arrest the progression of osteoporosis and decrease the risk of fracture.

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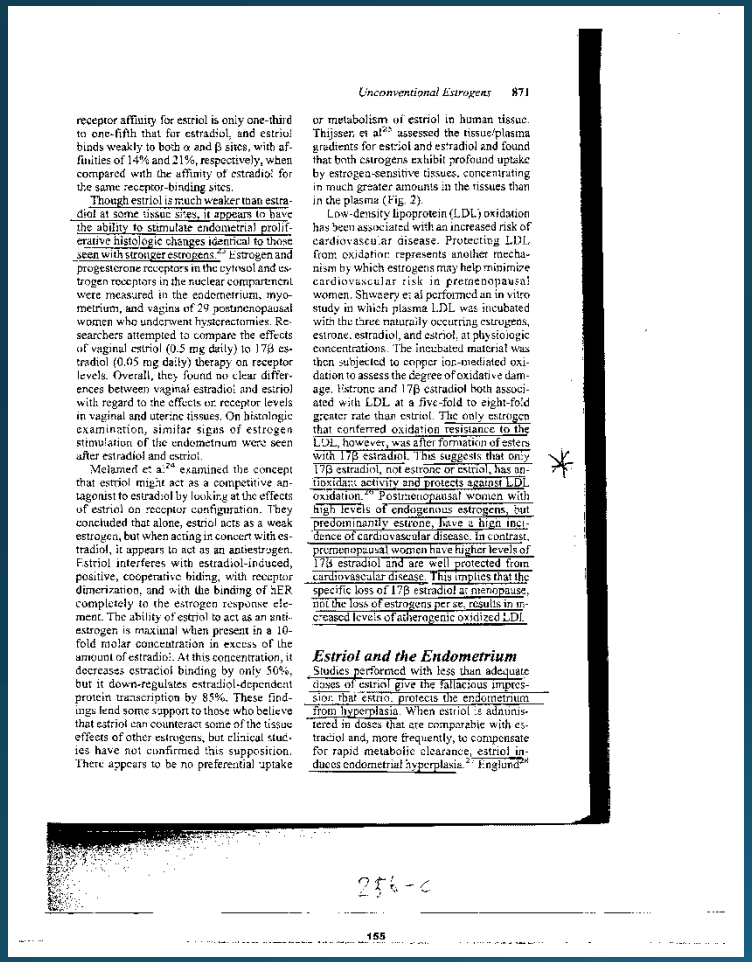
Unconventional Estrogens



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receptor affinity for estriol is only one-third to one-fifth that for estradiol, and estriol binds weakly to both α and β sites, with affinities of 14% and 21%, respectively, when compared with the affinity of estradiol for the same receptor-binding sites.

Though estriol is much weaker than estradiol at some tissue sites, it appears to have the ability to stimulate endometrial proliferative histologic changes identical to those seen with stronger estrogens.[22] Estrogen and progesterone receptors in the cytosol and estrogen receptors in the nuclear compartment were measured in the endometrium, myometrium, and vagina of 29 postmenopausal women who underwent hysterectomies. Researchers attempted to compare the effects of vaginal estriol (0.5 mg daily) to 17β estradiol (0.05 mg daily) therapy on receptor levels. Overall, they found no clear differences between vaginal estradiol and estriol with regard to the effects on receptor levels in vaginal and uterine tissues. On histologic examination, similar signs of estrogen stimulation of the endometrium were seen after estradiol and estriol.

Melamed et al.[24] examined the concept that estriol might act as a competitive antagonist to estradiol by looking at the effects of estriol on receptor configuration. They concluded that alone, estriol acts as a weak estrogen, but when acting in concert with estradiol, it appears to act as an antiestrogen. Estriol interferes with estradiol-induced, positive, cooperative biding, with receptor dimerization, and with the binding of HER completely to the estrogen response element. The ability of estriol to act as an antiestrogen is maximal when present in a 10-fold molar concentration in excess of the amount of estradiol. At this concentration, it decreases estradiol binding by only 50%, but it down-regulates estradiol-dependent protein transcription by 85%. These findings lend some support to those who believe that estriol can counteract some of the tissue effects of other estrogens, but clinical studies have not confirmed this supposition. There appears to be no preferential uptake or metabolism of estriol in human tissue. Thijssen et al[25] assessed the tissue/plasma gradients for estriol and estradiol and found that both estrogens exhibit profound uptake by estrogen-sensitive tissues, concentrating in much greater amounts in the tissues than in the plasma (Fig. 2).

Low-density lipoprotein (LDL) oxidation has been associated with an increased risk of cardiovascular disease. Protecting LDL from oxidation represents another mechanism by which estrogens may help minimize cardiovascular risk in premenopausal women. Shwaery et al performed an in vitro study in which plasma LDL was incubated with the three naturally occurring estrogens, estrone, estradiol, and estriol, at physiologic concentrations. The incubated material was then subjected to copper ion–mediated oxidation to assess the degree of oxidative damage. Estrone and 17β estradiol both associated with LDL at a five-fold to eight-fold greater rate than estriol. The only estrogen that conferred oxidation resistance to the LDL, however, was after formation of esters with 17β estradiol. This suggests that only 17β estradiol, not estrone or estriol, has antioxidant activity and protects against LDL oxidation.[26] Postmenopausal women with high levels of endogenous estrogens, but predominantly estrone, have a high incidence of cardiovascular disease. In contrast, premenopausal women have higher levels of 17β estradiol and are well protected from cardiovascular disease. This implies that the specific loss of 17β estradiol at menopause, not the loss of estrogens per se, results in increased levels of atherogenic oxidized LDL.

Estriol and the Endometrium

Studies performed with less than adequate doses of estriol give the fallacious impression that estriol protects the endometrium from hyperplasia. When estriol is administered in doses that are comparable with estradiol and, more frequently, to compensate for rapid metabolic clearance, estriol induces endometrial hyperplasia.[27] Englund[28]

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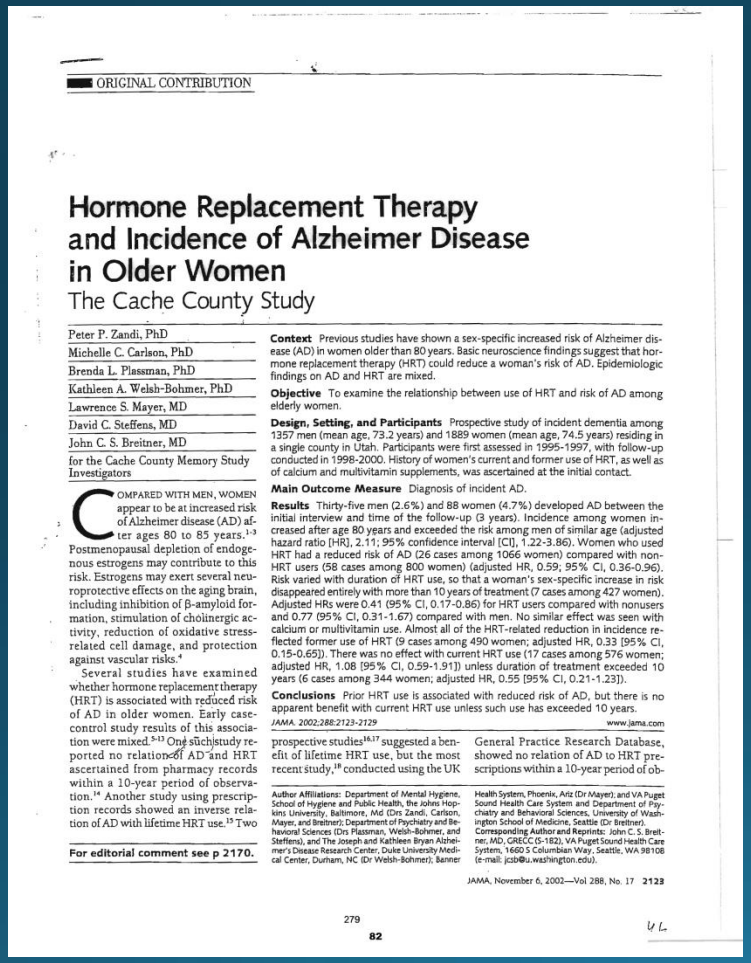
- The only estrogen that conferred oxidation resistance to the LDL, however, was after formation of esters with 17β estradiol.
- This suggests that only 17β estradiol, not estrone or estriol, has antioxidant activity and protects against LDL oxidation.

- Postmenopausal women with high levels of endogenous estrogens, but predominantly estrone, have a high incidence of cardiovascular disease.
- In contrast, premenopausal women have higher levels of 17β estradiol and are well protected from cardiovascular disease.
- This implies that it is the specific loss of 17 beta estradiol at menopause, and not the loss of estrogens per se, that results in increased levels of atherogenic oxidized LDL.

Hormone Replacement Therapy and Incidence of Alzheimer Disease in Older Women



ORIGINAL CONTRIBUTION

Hormone Replacement Therapy and Incidence of Alzheimer Disease in Older Women

The Cache County Study

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Context Previous studies have shown a sex-specific increased risk of Alzheimer disease (AD) in women older than 80 years. Basic neuroscience findings suggest that hormone replacement therapy (HRT) could reduce a woman's risk of AD. Epidemiologic findings on AD and HRT are mixed.

Objective To examine the relationship between use of HRT and risk of AD among elderly women.

Design, Setting, and Participants Prospective study of incident dementia among 1357 men (mean age, 73.2 years) and 1889 women (mean age, 74.5 years) residing in a single county in Utah. Participants were first assessed in 1995-1997, with follow-up conducted in 1998-2000. History of women's current and former use of HRT, as well as of calcium and multivitamin supplements, was ascertained at the initial contact.

Main Outcome Measure Diagnosis of incident AD.

Results Thirty-five men (2.6%) and 88 women (4.7%) developed AD between the initial interview and time of the follow-up (3 years). Incidence among women increased after age 80 years and exceeded the risk among men of similar age (adjusted hazard ratio [HR], 2.11; 95% confidence interval [CI], 1.22-3.86). Women who used HRT had a reduced risk of AD (26 cases among 1066 women) compared with non-HRT users (58 cases among 800 women) (adjusted HR, 0.59; 95% CI, 0.36-0.96). Risk varied with duration of HRT use, so that a woman's sex-specific increase in risk disappeared entirely with more than 10 years of treatment (7 cases among 427 women). Adjusted HRs were 0.41 (95% CI, 0.17-0.86) for HRT users compared with nonusers and 0.77 (95% CI, 0.31-1.67) compared with men. No similar effect was seen with calcium or multivitamin use. Almost all of the HRT-related reduction in incidence reflected former use of HRT (9 cases among 490 women; adjusted HR, 0.33 [95% CI, 0.15-0.65]). There was no effect with current HRT use (17 cases among 576 women; adjusted HR, 1.08 [95% CI, 0.59-1.91]) unless duration of treatment exceeded 10 years (6 cases among 344 women; adjusted HR, 0.55 [95% CI, 0.21-1.23]).

Conclusions Prior HRT use is associated with reduced risk of AD, but there is no apparent benefit with current HRT use unless such use has exceeded 10 years.

JAMA. 2002;288:2123-2129 www.jama.com

COMPARED WITH MEN, WOMEN appear to be at increased risk of Alzheimer disease (AD) after ages 80 to 85 years.[1-3] Postmenopausal depletion of endogenous estrogens may contribute to this risk. Estrogens may exert several neuroprotective effects on the aging brain, including inhibition of β-amyloid formation, stimulation of cholinergic activity, reduction of oxidative stress-related cell damage, and protection against vascular risks.[4]

Several studies have examined whether hormone replacement therapy (HRT) is associated with reduced risk of AD in older women. Early case-control study results of this association were mixed.[5-13] One such study reported no relationship of AD and HRT ascertained from pharmacy records within a 10-year period of observation.[14] Another study using prescription records showed an inverse relation of AD with lifetime HRT use.[15] Two prospective studies[16,17] suggested a benefit of lifetime HRT use, but the most recent study,[18] conducted using the UK General Practice Research Database, showed no relation of AD to HRT prescriptions within a 10-year period of ob-

For editorial comment see p 2170.

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Zandi PP, Carlson MC, Plassman BL, et al. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. JAMA. 2002 Nov 6;288(17):2123-2129.

Estrogen & Alzheimer's Disease: The Forgotten Study

The Cache County Study. JAMA 2002; 288:2123-2129

- Findings of this study similar to 2 other major studies.
- The incidence of AD was reduced 50% in HRT users.
- HRT users for more than 10 years experienced a 5 fold lower incidence of AD.

- HRT exposure within 10 years of AD yields little benefit.
- HRT worthless with established AD.
- Benefits require > 10 years prior use.
- Study confirms that HRT should be started at menopause and continued indefinitely.
- Experts claim to use HRT for the shortest time possible and stop!
- Who's right?

E2 is protective if started early!

Conclusion cont…

- If current HRT use is halted as per expert recommendations, I predict an exponential increase in AD in 20-30 years.
- The economic impact on healthcare will be enormous.
- Therefore: I recommend HRT use for all women, but use the safe, appropriate hormones only.

Testosterone and Memory

- T supplementation increased working memory in men
- Similar to the same protective effects of estrogen in women

Janowsky J et al. Sex steroids modify working memory. J Cogn Neurosci 2000 May;12(3): 407-14

Testosterone and Alzheimer's

- TRT prevents the production of beta amyloid precursor protein. (in men)

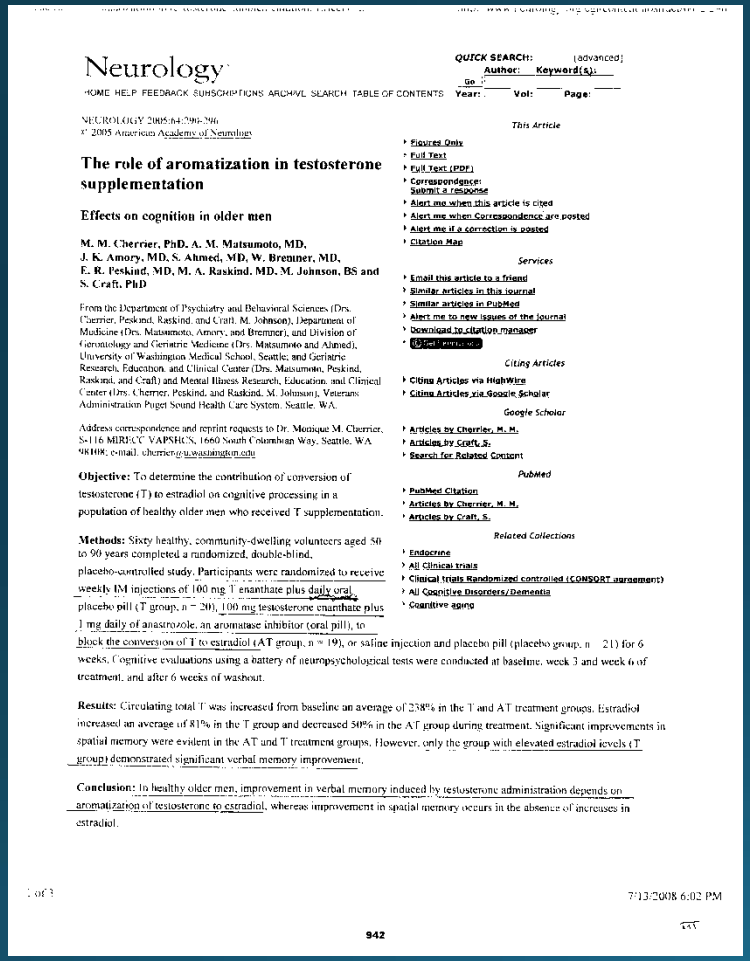
Gouras GK et al. Testosterone reduces neuronal secretion of Alzheimer's beta-amyloid peptides. Proc Natl Acad Sci USA 2000 Feb 1; 97(3):1202-5

Testosterone and Cognitive Function

- T correlated with cognitive function and TRT improves it.

Barrett-Connor E et al. Endogenous sex hormones and cognitive function in older men. J Clin Endocrinol Metab 1999 Oct;84(10):3681-5

The Role Of Aromatization In Testosterone Supplementation



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NEUROLOGY 2005;64:290–296
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The role of aromatization in testosterone supplementation

Effects on cognition in older men

M. M. Cherrier, PhD, A. M. Matsumoto, MD, J. K. Amory, MD, S. Ahmed, MD, W. Bremner, MD, E. R. Peskind, MD, M. A. Raskind, MD, M. Johnson, BS and S. Craft, PhD

From the Department of Psychiatry and Behavioral Sciences (Drs. Cherrier, Peskind, Raskind, and Craft, M. Johnson), Department of Medicine (Drs. Matsumoto, Amory, and Bremner), and Division of Gerontology and Geriatric Medicine (Drs. Matsumoto and Ahmed), University of Washington Medical School, Seattle; and Geriatric Research, Education, and Clinical Center (Drs. Matsumoto, Peskind, Raskind, and Craft) and Mental Illness Research, Education, and Clinical Center (Drs. Cherrier, Peskind, and Raskind, M. Johnson), Veterans Administration Puget Sound Health Care System, Seattle, WA.

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Objective: To determine the contribution of conversion of testosterone (T) to estradiol on cognitive processing in a population of healthy older men who received T supplementation.

Methods: Sixty healthy, community-dwelling volunteers aged 50 to 90 years completed a randomized, double-blind, placebo-controlled study. Participants were randomized to receive weekly IM injections of 100 mg T enanthate plus daily oral placebo pill (T group, n = 20), 100 mg testosterone enanthate plus 1 mg daily of anastrozole, an aromatase inhibitor (oral pill), to block the conversion of T to estradiol (AT group, n = 19), or saline injection and placebo pill (placebo group, n = 21) for 6 weeks. Cognitive evaluations using a battery of neuropsychological tests were conducted at baseline, week 3 and week 6 of treatment, and after 6 weeks of washout.

Results: Circulating total T was increased from baseline an average of 238% in the T and AT treatment groups. Estradiol increased an average of 81% in the T group and decreased 50% in the AT group during treatment. Significant improvements in spatial memory were evident in the AT and T treatment groups. However, only the group with elevated estradiol levels (T group) demonstrated significant verbal memory improvement.

Conclusion: In healthy older men, improvement in verbal memory induced by testosterone administration depends on aromatization of testosterone to estradiol, whereas improvement in spatial memory occurs in the absence of increases in estradiol.

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- Clinical trials Randomized controlled (CONSORT agreement)
- All Cognitive Disorders/Dementia
- Cognitive aging

- Participants were randomized to receive weekly IM injections of 100 mg T enanthate or 100 mg testosterone enanthate plus 1 mg daily of anastrozole, an aromatase inhibitor (oral pill), to block the conversion of T to estradiol.

Cherrier MM, Matsumoto AM, Amory JK, et al. The role of aromatization in testosterone supplementation: effects on cognition in older men. Neurology. 2005 Jan 25;64(2):290-6.

- Only the group with elevated estradiol levels (T group) demonstrated significant verbal memory improvement.
- In healthy older men, improvement in verbal memory induced by testosterone administration depends on aromatization of testosterone to estradiol.

Significance of Oestrogens In Male (patho)physiology



Ann. Endocrinol., 2003 ; 64, 2 : 126-135
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Significance of oestrogens in male (patho)physiology

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Significance of oestrogens in male (patho)physiology

L.J.G. Gooren, A.W.F.T. Toorians

Ann. Endocrinol., 2003 ; 64, 2 : 126-135

Traditionally conceptualized as 'female hormones', oestrogens appear to have significant effects in the male biological system. Favorable effects have been noted on bone, brain and cardiovascular physiology while a potential role in the prostate pathology of the aging male has been seriously suspected. Oestrogens in male are predominantly the products of peripheral aromatization of testicular and adrenal androgens. While the testicular and adrenal production of androgens declines with aging, levels of total plasma oestradiol do not decline. This is to be ascribed to the common increase in fat mass with aging (the substrate of peripheral aromatization) and an increased aromatase activity with aging. But free or bioavailable oestrogens may decline due to an increase in sex hormone binding globulin.

Oestrogens produce significant beneficial effects on skeletal growth and bone maturation. In old age oestrogens are better predictors of bone fractures than androgens. Oestrogens exert effects on the brain on cognitive function, co-ordination of movement, pain and affective state, and are maybe protective of Alzheimer's disease. Oestrogen effects on the cardiovascular system include those on lipid profiles, fat distribution, endothelin-beta factors produced by the vascular wall (such as endothelins), nitric oxide, blood platelets, inflammatory factors and coagulation.

The potentially adverse effects of oestrogens on the prostate may be due to a shift in the oestrogen / androgen ratio with aging.

Sources of oestrogens in men are endogenous androgens, or in case of androgen deficiency, exogenous androgens. Dietary phytoestrogens or selective estrogen receptor modulators, as drugs, may be significant as well.

INTRODUCTION

Oestrogens in men, which are largely a product of peripheral aromatization of androgens, receive increasing attention. Traditionally conceptualized as 'female hormones', oestrogens appear to have unexpected but important effects on the male reproductive system; (for review see Couse and Korach) [17]. Oestrogen receptor knockout mice show abnormalities of the testis and accessory sex organs; (for review Tuconi *et al.*) [55].

It is becoming increasingly clear that oestrogens have an important effect on the final phases of skeletal maturation and bone mineralization in puberty. In addition, some studies in aging men show that oestrogen levels have a higher correlation with bone mineral density (BMD) than androgen levels; (for review see Riggs *et al.*) [67]. Impaired oestrogen action in men leads to dyslipidaemia and to impaired flow-dependent vasodilatation in peripheral arteries in response to an ischaemic stimulus probably resulting from endothelial dysfunction [79]. Evidence suggests that the effects of oestrogen on the vascular system are not entirely receptor-mediated [44]. Oestrogen effects on the brain are also becoming increasingly recognized [60]. In view of the effects of oestrogen on many important organ systems in the (aging) male, further research into the role of oestrogens is necessary. A better understanding of oestrogen recep-

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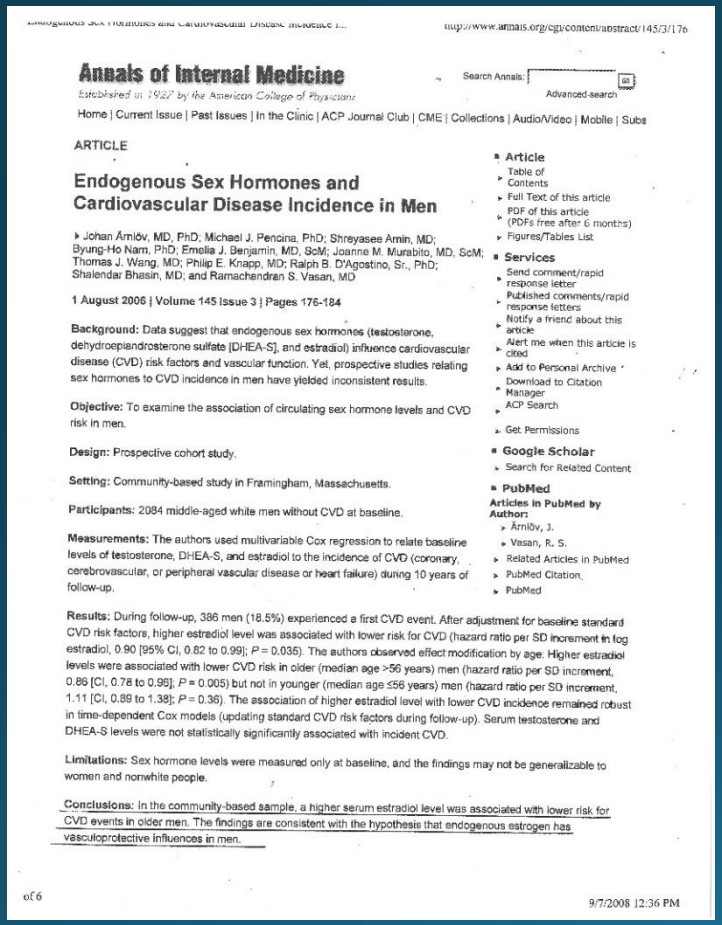
- Oestrogens appear to have significant effects in the male biological system. Favorable effects have been noted on bone, brain and cardiovascular physiology.
- But free or bioavailable oestrogens may decline due to an increased in sex hormone binding globulin.

Gooren LJ, Toorians AW. Significance of oestrogens in male (patho)physiology. Ann Endocrinol. 2003 Apr;64(2):126-35.

- Oestrogens produce significant beneficial effects on skeletal growth… on the brain, on cognitive function, co-ordination of movement, pain and affective state, and are protective against Alzheimer's.
- Effects on the cardiovascular system include those on lipid profiles, fat distribution, endocrine factors produced by the vascular wall.
- Oestrogen levels have a higher correlation with bone mineral density (BMD) than androgen levels. Impaired oestrogen action in men leads to dyslipidaemia.

Endogenous Sex Hormones and Cardiovascular Disease Incidence in Men



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ARTICLE

Endogenous Sex Hormones and Cardiovascular Disease Incidence in Men

Johan Ärnlöv, MD, PhD; Michael J. Pencina, PhD; Shreyasee Amin, MD; Byung-Ho Nam, PhD; Emelia J. Benjamin, MD, ScM; Joanne M. Murabito, MD, ScM; Thomas J. Wang, MD; Philip E. Knapp, MD; Ralph B. D'Agostino, Sr., PhD; Shalendar Bhasin, MD; and Ramachandran S. Vasan, MD

1 August 2006 | Volume 145 Issue 3 | Pages 176-184

Background: Data suggest that endogenous sex hormones (testosterone, dehydroepiandrosterone sulfate [DHEA-S], and estradiol) influence cardiovascular disease (CVD) risk factors and vascular function. Yet, prospective studies relating sex hormones to CVD incidence in men have yielded inconsistent results.

Objective: To examine the association of circulating sex hormone levels and CVD risk in men.

Design: Prospective cohort study.

Setting: Community-based study in Framingham, Massachusetts.

Participants: 2084 middle-aged white men without CVD at baseline.

Measurements: The authors used multivariable Cox regression to relate baseline levels of testosterone, DHEA-S, and estradiol to the incidence of CVD (coronary, cerebrovascular, or peripheral vascular disease or heart failure) during 10 years of follow-up.

Results: During follow-up, 386 men (18.5%) experienced a first CVD event. After adjustment for baseline standard CVD risk factors, higher estradiol level was associated with lower risk for CVD (hazard ratio per SD increment in log estradiol, 0.90 [95% CI, 0.82 to 0.99]; $P = 0.035$). The authors observed effect modification by age. Higher estradiol levels were associated with lower CVD risk in older (median age >56 years) men (hazard ratio per SD increment, 0.86 [CI, 0.78 to 0.95]; $P = 0.005$) but not in younger (median age ≤56 years) men (hazard ratio per SD increment, 1.11 [CI, 0.89 to 1.38]; $P = 0.36$). The association of higher estradiol level with lower CVD incidence remained robust in time-dependent Cox models (updating standard CVD risk factors during follow-up). Serum testosterone and DHEA-S levels were not statistically significantly associated with incident CVD.

Limitations: Sex hormone levels were measured only at baseline, and the findings may not be generalizable to women and nonwhite people.

Conclusions: In the community-based sample, a higher serum estradiol level was associated with lower risk for CVD events in older men. The findings are consistent with the hypothesis that endogenous estrogen has vasculoprotective influences in men.

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- Vasan, R. S.
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- Conclusions: In the community-based sample, a higher serum estradiol level was associated with lower risk for CVD events in older men.
- The findings are consistent with the hypothesis that endogenous estrogen has vasculoprotective influences in men.

GH and the Brain

- GH exerts profound effects on CNS
- Improves:
  - Cognitive capabilities
  - Memory
  - Alertness
  - Motivation, work capacity
- GH receptors present in the brain
  - Hypothalamus, choroid plexus, hippocampus
- GH crosses the blood brain barrier

Nyberg F. Growth Hormone in the brain: Characteristics of Specific brain targets for the hormone and their functional significance. *Front Neuroendocrinol* 2000 Oct;21(4):330-48

GH & THE BRAIN

- IGF-1 correlated with cognitive function in men average age 69
- GH deficiency correlated with
  - Poor emotional and psychosocial functioning

ALEMAN A. et al. Insulin-Like Growth Factor-1 and Cognitive Function in Healthy Older Men *J Clin Endocrinol Metab* 84:471-475, 1999

GH and Alzheimer's

- **IGF-1 exerts cytoprotection against A beta amyloid induced neuronal cell death**

Takako Nikura et al. Insulin-like growth factor 1(IGF-1) Protects Cells from apoptosis by Alzheimer's V6421 Mutant Amyloid Precursor protein through IGF-1 receptor in an IGF-binding protein-sensitive manner. J Neuroscience, 2001; 21(6):1902-1910.

Free Testosterone and Risk for Alzheimer Disease in Older Men



Free testosterone and risk for Alzheimer disease in older men

S.D. Moffat, PhD; A.B. Zonderman, PhD; E.J. Metter, MD; C. Kawas, MD; M.R. Blackman, MD; S.M. Harman, MD, PhD; and S.M. Resnick, PhD

Abstract—*Objective:* To investigate the relationships between age-associated decreases in endogenous serum total testosterone (T) and a free T index (FTI) in men and the subsequent development of Alzheimer disease (AD). *Method:* The authors used a prospective, longitudinal design with follow-up in men since 1958. Participants were from the Baltimore Longitudinal Study of Aging, a community-dwelling volunteer sample with baseline ages of 32 to 87 years. All subjects were free of AD at baseline T assessment. Five hundred seventy-four men assessed at multiple time points were followed for a mean of 19.1 years (range, 4 to 37 years). Diagnoses of AD were based on biennial physical, neurologic, and neuropsychological evaluations. *Results:* Diagnosis of AD was associated inversely with FTI by itself and after adjustments for age, education, smoking status, body mass index, diabetes, any cancer diagnoses, and hormone supplements. In separate analyses, total T and sex hormone binding globulin were not significant predictors after adjustment with covariates. Increases in the FTI were associated with decreased risk of AD (hazard ratio = 0.74; 95% CI = 0.57 to 0.96); a 26% decrease for each 10-nmol/mol FTI increase. *Conclusions:* Calculated free testosterone concentrations were lower in men who developed Alzheimer disease, and this difference occurred before diagnosis. Future research may determine whether higher endogenous free testosterone levels offer protection against a diagnosis of Alzheimer disease in older men.

NEUROLOGY 2004;62:188–193

A sizable literature now exists relating age-related alterations in the endocrine environment to cognitive changes[1-3] and the onset of Alzheimer disease (AD) in women.[4-7] The comparative dearth of similar research in men may be attributable primarily to the fact that testosterone replacement therapy (TRT) has been used much less commonly in men than hormone therapy in women. Moreover, TRT has not been administered for time periods that are sufficiently long to establish linkages to AD. Nevertheless, androgen levels in men decrease substantially with age, raising the question of whether this decrease may contribute to the development of AD.[8-9] Although numerous studies have demonstrated contributions of testosterone (T) to selected cognitive functions in young[10-12] and old men,[13-15] to date there have been no studies assessing prospectively the risk for AD associated with the so-called "andropause."

Decreased total T levels have been reported in men with AD compared with age-matched control subjects.[16] However, these data are ambiguous because the depleted T levels may be a consequence rather than a cause of the disease. To assess the impact of T decline in the subsequent manifestation of AD, it is essential to obtain measures of T that *precede* the development of the disease.

In the present study, we followed 574 men whose ages at baseline T assessment ranged from 32 to 87 years for a mean duration of 19.1 years. We collected multiple serum samples for determination of total T, sex hormone binding globulin (SHBG), and the calculated free T index (FTI) and evaluated presence or absence of a diagnosis of AD as the principal outcome variable. We report here the first prospective longitudinal study assessing the impact of long-term total and estimated free T levels on the development of AD.

Methods. *Subjects.* Subjects were men who volunteered to participate in the Baltimore Longitudinal Study of Aging (BLSA), a study performed by the National Institute on Aging (NIA).[17] Participants were community dwelling and returned every 2 years to the Gerontology Research Center of the NIA for comprehensive medical and neuropsychological evaluations. Androgen data were available for a large number of BLSA men whose blood samples were assayed as part of a study of prostate health and disease.

See also pages 170 and 301

From the Laboratory of Personality and Cognition (Drs. Moffat, Zonderman, and Resnick) and Laboratory of Clinical Investigation (Dr. Metter), National Institute on Aging, Intramural Research Program, Baltimore, MD; Institute of Gerontology and Department of Psychology (Dr. Moffat), Wayne State University, Detroit, MI; Department of Neurology (Dr. Kawas), University of California, Irvine, CA; Laboratory of Clinical Investigation (Dr. Blackman), National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD, and Kronos Longevity Research Institute (Dr. Harman), Phoenix, AZ.

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- Calculated free testosterone concentrations were lower in men who developed Alzheimer's disease, and this difference occurred before diagnosis.

Moffat SD, Zonderman AB, Metter EJ, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology. 2004 Jan 27;62(2):188-193.

Testosterone and Memory

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- TRT prevents the production of beta amyloid precursor protein. (in men)

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