Effects of Estrogen on Cognition and Mood

A CME Slide Library From the Council on Hormone Education

• After reading these slides and notes, physicians and other health care providers will be able to
  – Discuss some of the features of cognitive aging and dementia.
  – List the physiological effects of estrogen that have the potential to affect brain functioning.
  – Discuss evidence on the effects of postmenopausal hormone therapy (HT) and endogenous estrogen on
cognition in postmenopausal women without dementia.
  – Discuss evidence on the effects of hormone use on the risk and treatment of Alzheimer’s disease (AD).
Effects of Estrogen on Cognition and Mood

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Effects of Estrogen on Cognition and Mood

Section 1:
Introduction
Cognition comprises multiple mental processes

- Attention
- Perception
- Working memory
- Executive function
- Spatial ability
- Language
- Learning
- Memory
  - Figural
  - Verbal


- Cognition is a comprehensive term used to describe the mental processes associated with the functions listed above.¹
- Although much discussion about cognitive function in postmenopausal women concerns learning and memory, cognition encompasses several other important mental processes (eg, working memory and executive function).
- Working memory allows for temporary, limited storage and manipulation of information used for complex cognitive tasks (eg, learning and reasoning).¹ Executive function includes the ability to think abstractly and to plan, begin, monitor, and cease complicated behavior.²
- Different areas of the central nervous system are involved in these various functions, and changes in estrogen levels that occur during premenopause, transitional menopause, and postmenopause do not affect all areas uniformly.

Normal Cognitive Aging

- ↓ Memory
- ↓ Motor/psychomotor speed
- ↓ Attention
- ↓ Visuospatial performance
- ↓ Visuomotor skills


• Normal cognitive decline occurs with aging, most notably in memory, psychomotor function, attention, and visuospatial and visuomotor skills.¹

• Although the cognitive functions listed above are typically affected by aging, symptoms that indicate a change from normal aging to cognitive impairment can be difficult to discern.

• Of the many parameters evaluated in cognitive testing, Petersen² suggests that memory is the most reliable indicator of progression from typical cognitive changes to impairment and more serious pathology. He also states that memory is the earliest predictor of ensuing AD.


Everyone with dementia has cognitive impairment, but not everyone with cognitive impairment has dementia.

Dementia represents a decline in memory and at least one other cognitive domain.

The decline interferes with occupational or social functioning.

Dementia is defined by the development of memory impairment together with at least one of the following cognitive disturbances: aphasia (ie, deterioration of language function), apraxia (ie, reduced ability to carry out motor activities in the absence of motor or sensory impairment), agnosia (ie, failure to recognize or identify objects in spite of intact sensory function), or a disturbance in executive functioning. These conditions signal a decline from previous functioning and must be severe enough to impede occupational or social functioning.

Dementia should be distinguished from the normal decline in cognitive functioning that happens with age.

Effects of Estrogen on Cognition and Mood

Section 2: Physiological Effects of Estrogen
Effects of Estrogen on Brain Function

- This section reviews some of the key areas in which estrogen has been shown to affect brain function, including physiological effects on the brain as well as effects on cognition, sleep, mood, and the onset of AD.
- We will begin with a discussion of some of estrogen’s neuroprotective functions and a review of estrogen’s effects on brain activation and cerebral blood flow.
The effects of estrogen on neural function involve multiple mechanisms:\(^1\):

- Protecting neurons from oxidative stress\(^2\)
- Protecting neurons from glutamate toxicity\(^3\)
- Increasing expression of neurotransmitters and neurotransmitter receptors\(^2\)
- Increasing expression of neurotrophic factors (and receptors) important for neuronal survival and function\(^4\)
- Increasing glucose transport and protecting against ischemic injury by increasing CBF\(^4\)
- Stimulating branching of neurites and promoting synaptogenesis\(^4\)


Estrogen and Cognition

- Estrogen receptors are found in brain regions involved with cognition
  - Cerebral cortex\(^1\)
  - Hippocampus\(^2\)
  - Basal forebrain\(^3\)

- Estrogen increases cholinergic\(^4\) and serotonergic\(^5,6\) activity in older women

- These findings suggest that estrogen may affect cognitive function


- There is strong evidence that estrogen receptors (ERs) are located in key brain regions involved with cognition.\(^1-3\)
- Estrogen receptors \(\alpha\) and \(\beta\) (ER\(\alpha\), ER\(\beta\)) are expressed in neurons and glial cells throughout the rostral-caudal extent of the brain and spinal cord. The cerebral cortex\(^1\) and hippocampus\(^2\) both contain ERs.
- Estrogen is thought to enhance cognitive function, in part by modulating the activity of acetylcholine in basal forebrain neurons (this system projects to the hippocampus and cerebral cortex and is involved in learning and memory). Shughrue et al\(^3\) reported that biologically active ERs are located in the basal forebrain, a finding that supports the likelihood that estrogen activity in the basal forebrain is involved in the processes of learning and memory.
- There is growing evidence that estrogen may protect against age-related cognitive decline and reduce the risk of developing AD in healthy postmenopausal women. One possible mechanism may be the preservation of cholinergic systems. Van Amelsvoort et al\(^4\) studied the effects of long-term unopposed estrogen on central cholinergic function in healthy postmenopausal women. Growth hormone responses to oral pyridostigmine were measured over a 3-hour period in 15 women on long-term estrogen and 15 untreated women. Growth hormone release after pyridostigmine was significantly greater in women treated with estrogen.
- In addition to the effects on cholinergic activity, estrogen modulates other neurotransmitter systems in the brain, such as the serotonergic and noradrenergic systems.\(^5-8\)

Estrogen is thought to have an impact on both psychological well-being and cognitive function. Though not fully understood, the biological basis of estrogen’s impact on cognitive function, as well as psychological well-being, may involve its interactions with central serotonergic systems. In a small cross-sectional study, van Amelsvoort et al.1 studied the effect of long-term unopposed estrogen on central serotonergic tone in healthy postmenopausal women and made comparisons with young women.

Secretion of prolactin induced by the specific serotonergic-releasing and re-uptake inhibiting agent, d-fenfluramine, provides an index of serotonergic responsivity and activity.2 Prolactin responses were measured in 3 groups of healthy women: 11 young women, 11 postmenopausal women on long-term estrogen (8 on slow-release estradiol implants, 3 on continuous oral CEE; mean age = 60 years), and 11 postmenopausal women who had not taken estrogen.

Prolactin responses were significantly decreased in women who had not taken estrogen compared to young healthy women. In contrast, prolactin responses were not different between estrogen-treated and young women. Overall, there was a significant relationship between older age and lower prolactin responsivity.

These results suggest that central serotonergic tone is reduced in healthy postmenopausal women who are estrogen-naïve, but not in postmenopausal women who have received prolonged estrogen alone. Thus estrogen may modulate age-related changes in serotonergic tone.


Cholinergic dysfunction has been implicated in the etiology of age-related memory impairment and AD. Van Amelsvoort et al studied the effect of prolonged use of unopposed estrogen on central cholinergic tone in healthy postmenopausal women.

Growth hormone responses to oral pyridostigmine (120 mg) were measured over a 3-hour period in 30 healthy postmenopausal women, 15 on long-term estrogen (mean length of use = 15 years) and 15 never-users.

Growth hormone release following pyridostigmine was significantly greater in estrogen-treated women than in never-users. In addition, within the estrogen-treated group, there was a significant positive correlation between duration of treatment and GH response.

The ability of long-term estrogen to enhance cholinergic function in postmenopausal women may be related to duration of treatment. Modulation of central cholinergic function may be one mechanism by which long-term estrogen might preserve cognitive function in healthy, postmenopausal women.

Increased Serotonin Receptor Binding With Estrogen

Statistical maps showing areas where receptor binding significantly increased ($P = .01$) after 10 weeks of estrogen alone in healthy postmenopausal women*

*Mean age = 54.5 years. Subjects received transdermal 17β-estradiol 0.075–0.15 mg.

• Serotonin 2A receptors in the prefrontal regions of the brain may affect cognitive functions, such as working memory and verbal fluency, and mood. These receptors may be increased by estrogen administration. Kugaya et al conducted a neuro-imaging study among 10 postmenopausal women (mean age = 54.5 years) to investigate the effect of estrogen on serotonin transmission and the impact of that effect on cognition and mood.

• Participants underwent PET measurements of serotonin 2A receptor binding before and after estrogen administration. Treatment consisted of a transdermal patch containing 0.075 to 0.15 mg of 17β-estradiol for a mean of 10.2 weeks. There was no control group. Cognitive assessments, usually performed the day before PET scans, included tests of verbal memory, executive cognition, and verbal fluency. Mood was assessed with the depression/dejection subscale of the Profile of Mood States and the Beck Depression Inventory.

• Serotonin 2A receptor binding was significantly increased after estrogen administration in the right prefrontal cortex (right precentral, inferior frontal, and medial frontal gyrus and the anterior cingulate cortex). In the inferior frontal gyrus, receptor up-regulation was significantly correlated with change in plasma estradiol ($P = .022$).

• Verbal fluency and certain areas of executive cognition (ie, attention/motor speed), but not mood, were significantly improved by estrogen without correlation with receptor changes.

• This study offers further evidence that estrogen increases serotonin 2A receptor binding in human prefrontal regions.

Estrogen Modulates Brain Activation in Postmenopausal Women

- Estrogen in therapeutic doses alters brain activation
- Results suggest that estrogen affects brain areas involved in working memory

n = 46; age range, 33 to 61 years.

• Functional MRI can detect differences in the magnetic properties of oxygenated blood compared with deoxygenated blood. During performance of cognitive tasks, blood flow and oxygen concentration (evidence of brain activation) are altered in the areas of the brain presumably involved in the task.

• This randomized, double-blind, crossover study evaluated brain activation patterns in 46 postmenopausal women (aged 33 to 61 years).

• Women were treated for 2 periods of 21 days each, one period with CEE 1.25 mg/d and the other with placebo; there was a 14-day washout period between treatment periods.

• Brain activation patterns were examined with functional MRI during performance of verbal and nonverbal working memory tasks.

• CEE increased brain activation in several areas involved with memory and cognition, including the anterior frontal lobe regions and inferior parietal lobule. The first image above illustrates increased activation in the frontal lobe region during the verbal storage component of a verbal working memory task. The second and third images show increased activation of the middle and inferior frontal gyri during performance of retrieval tasks for both verbal and nonverbal working memory tasks.

• There was no effect of estrogen on performance of cognitive tasks in this study.

In a study of 120 healthy, right-handed subjects aged 21 to 91 years, PET was used to investigate age- and sex-related differences in regional cerebral glucose metabolism.

Fifty-five men and 65 women participated in this observational study. There was no significant difference in age or intelligence between men and women. Plasma glucose concentrations were measured before PET scanning, which was used to evaluate metabolic rates in certain brain regions.

Compared with men, women had a significantly greater age-related decrease in hippocampal cellular glucose metabolism, which may lead to greater atrophy and volume loss. Significant sex differences were also found in other brain areas essential to higher cognitive functioning. These findings may explain some of the age-sex differences in human cognition and response to brain injury and disease.

This study compared changes in rCBF in 12 HT users and 16 nonusers, with a 2-year interval between assessments. Among HT users, 10 received CEE 0.625 mg/d, one received estradiol 0.5 mg/d, and one received a triple estrogen formulation. Six also received progesterone. PET measurements of rCBF were conducted at rest and during performance of cognitive tests (verbal and figural recognition memory tasks) to assess the effects of estrogen on rCBF. Measurements were recorded at year 1 and year 3. At year 1, HT users and nonusers had different activation patterns at rest and during the performance of figural and verbal memory tasks. Over time, HT users showed increased rCBF to several brain areas (see highlighted areas in above illustration) including the right hippocampus; bilateral middle temporal gyrus; left medial frontal gyrus; right inferior frontal gyrus; and left cerebellum. Overall, HT users performed better on memory tests. Older women who have been identified as having decreased hippocampal rCBF may be at an increased risk for developing AD. Previous studies using PET and SPECT have shown decreased hippocampal activity in individuals at increased risk for AD. This study shows the opposite effect, indicating that HT may be neuroprotective.
Effects of Estrogen on Cognition and Mood

Section 3:
Estrogen and Cognition
• This section reviews the effects of estrogen on various measures of cognitive performance in postmenopausal women.
Perimenopausal Women Notice Cognitive Changes

- 230 women enrolled in the Seattle Midlife Women’s Health Study were interviewed (mean age, 47 years)
- 62% reported an undesirable change in memory
- Changes included:
  - Difficulty recalling words or numbers
  - Forgetting events and actions
  - Difficulty concentrating
- Women attributed these changes to stress, health, and age rather than hormonal changes


- Women’s perceptions of midlife memory changes were evaluated in the Seattle Midlife Women’s Health Study. The majority of the women interviewed were in menopausal transition (mean age, 47 years).
- Participants were asked a series of open-ended questions about memory changes and what factors they felt were responsible for the changes.
- Sixty-two percent of the women reported undesirable changes in memory. Analysis of the data showed that difficulty with verbal memory (ie, difficulty remembering words or numbers) was the most noteworthy subjective change.
- When asked what they thought were the reasons for the memory changes they were experiencing, women most frequently mentioned stress from role overload, getting older, and physical health problems including low blood pressure, hearing problems, thyroid disorders, and generalized fatigue.
- This study demonstrates that women in midlife are aware of changes in memory but are likely to attribute the changes to factors other than hormonal fluctuation.
In cross-sectional analyses, verbal memory was tested in 326 women (aged 52 to 63 years). Recall scores did not differ by menopausal status, serum estrogen levels, or use of HT (never vs current vs past use). Timing of HT initiation may be important: a post hoc analysis of current HT users showed that women who initiated HT before their last menstrual period performed better than those who did so after menopause.

Melbourne Women’s Midlife Health Project


A recent report from the Melbourne Women’s Midlife Health Project, a cross-sectional, population-based study, addressed the relationship of menopausal stage, estrogen exposure, and verbal memory, as well as the issue of the importance of the timing of estrogen initiation on memory. The effect of estrogen exposure on immediate and delayed verbal recall was tested in 326 women (52 to 63 years) through a word list recall task. Surgically menopausal women were excluded. Menopausal status was assessed based on prospective menstrual diaries. Menopausal stages were defined according to the following:
- Early menopausal = menstruation in the preceding 3 months + a change in menstruation pattern
- Late menopausal = 3 to 12 months of amenorrhea
- Early postmenopausal = 12 to 60 months of amenorrhea
- Late postmenopausal = >60 months of amenorrhea

Women were also classified as never, past, or current users of HT. Current users were classified according to duration of HT and to whether they initiated HT during the menopausal transition or after their final menstrual period.

Memory was assessed at year 8. Memory scores did not differ significantly by menopausal status, endogenous estrogen exposure, current or previous use of HT, or duration of HT use.

A post hoc analysis did show that memory was significantly better ($P \leq .01$) in the 59 current users of HT who began using it during the menopausal transition (ie, before their final menstrual period) than for the 17 who began it after menopause. These results are consistent with data showing that estrogen influences verbal memory when given soon after surgical menopause.1,2

Recently, Meyer et al4 conducted the first longitudinal study tracing the cognitive performance of women as they undergo menopause. Participants in the Chicago site of the Study of Women’s Health Across the Nation (aged 42 to 52 years) were assessed for working memory and perceptual speed with the Digit Span Backward and Symbol Digit Modality tests, respectively. Cognitive assessments were available for 803 women. The results showed no significant incremental change in scores on either cognitive task as participants progressed from one menopausal stage to another.

Several studies have examined the effect of estrogen on cognitive function and/or CBF.

For example, Jacobs et al. and Maki et al. reported improved performance on tests of memory and cognitive function for HT users compared with nonusers in observational studies of elderly postmenopausal women.

Resnick and colleagues used PET to directly measure cross-sectional differences in rCBF at rest and during performance of verbal and figural delayed recognition memory tasks in HT users and nonusers. Maki and colleagues followed those same women longitudinally over the next 2 years and found that HT users showed increased rCBF to the hippocampus, parahippocampal gyrus, and middle temporal lobe. These areas are among those that show preclinical changes in individuals at risk for AD. Shaywitz and colleagues used functional MRI to examine brain activation patterns during performance of verbal and nonverbal working memory tasks in a randomized clinical trial among women treated with estrogen alone and those given placebo.

In all studies, use of HT altered brain activation in certain areas of the brain involved with memory and cognition, and HT users had different patterns of rCBF compared with nonusers.


Female Advantage in Verbal Memory Is Related to Serum Estradiol Level

Non-Demented Elderly Men and Women (mean age, 74 years)

To address the issue of whether certain areas of cognitive function—in particular, verbal memory—are related to gender, and whether hormone levels might explain this relationship, Hogervorst et al investigated the relationship between serum total testosterone and total estradiol levels and visual and verbal function in 145 non-demented elderly volunteers. Participants (mean age = 74; women, n = 66; men, n = 79) were not currently using HT; 16% of the women had used HT (more than 1 year before the study).

As shown in the chart on the left, delayed verbal recall was significantly higher for women than men ($P = .02$). Women also performed significantly better than men on total free verbal recall ($P = 0.004$). There was a nonsignificant trend for men to be better than women at graded naming ($P = .06$).

Better delayed verbal recall was significantly correlated ($P < .01$) with higher levels of total estradiol in women, but not in men, as demonstrated in the scatter plots on the right. Other verbal memory tests, such as total free verbal recall, were not correlated with estradiol levels in women. There was a negative relationship of serum total testosterone levels with verbal recall in men and women.

In sum, the advantage of women over men in certain tests of verbal memory may be a function of the activational effect of estrogen on the brain.

To investigate whether the rate of loss of BMD predicts cognitive decline, Lui et al conducted a multicenter, prospective cohort study involving 4,462 women aged ≥70 participating in the Study of Osteoporotic Fractures. Total BMD of the hip was measured at ~2 and 6 years after enrollment and expressed as annualized percentage rate of bone change. A 3MSE was given at 6 and 10 years (mean follow-up = 4.5 years); cognitive decline was defined as a decline of ≥3 points on the 3MSE score.

As this slide demonstrates, the risk of cognitive decline increased by quartile of percentage change in total hip BMD. Twenty percent of women in the highest quartile of change had cognitive decline, compared to only 12% in the lowest quartile. The relationship between BMD and cognitive decline remained significant after adjustment for age, education, history of stroke, functional status, BMI, and smoking status (OR = 1.4; 95% CI, 1.1-1.8). Adjusting for or excluding past or current estrogen users did not modify the association between bone loss and cognitive decline.

The advantage of using BMD, an endogenous measure of lifelong estrogen exposure, as a proxy for estrogen is the avoidance of the so-called “healthy user” bias inherent in prospective, observational studies.

Focusing particularly on impairment of verbal memory and its relationship to loss of BMD, Zhang et al studied 4,304 subjects aged ≥60 years in the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994), a cross-sectional survey combined with a standardized medical examination. Verbal memory was assessed using delayed recall of a 3-item word list and a 6-item story. Verbal memory impairment was defined as a combined score of <4.

The prevalence of verbal memory impairment decreased as BMD increased. With adjustment for age, sex, and other covariates, the odds ratios of verbal memory impairment for each quintile of increasing BMD were 0.64 (95% CI, 0.43-0.95), 0.65 (95% CI, 0.45-0.92), 0.55 (95% CI, 0.35-0.87), and 0.44 (95% CI, 0.28-0.69), respectively (P for trend < .001).

These results reinforce the idea that women with the greatest lifelong exposure to estrogen, as indicated by the highest quintile of BMD, are the most likely to show preservation of cognitive functioning.
• Recently, data were reported from several randomized, clinical trials of the effects of HT in younger mid-life women, shedding light on the question of whether peri- or early menopausal women—ie, those who typically receive HT—benefit cognitively from therapy.

• Shaywitz et al. recently reported the results of a randomized, double-blind, placebo-controlled trial, the first to examine the effects of estrogen specifically on reading ability as well as on short-term memory. Sixty postmenopausal women aged 32.8 to 64.9 years (mean 51.2 years) were generally healthy, had their last menstrual period at a mean of 38.9 months before baseline, and had not received any HT for at least 3 months before the study.

• Women were primarily evaluated for oral reading as measured by the Gray Oral Reading Tests (third edition) and for immediate and delayed verbal recall using the Logical Memory and Paired Associate Learning subtests of the Wechsler Memory Scale and by a Sentence Span task. Additional measures included vocabulary, attention, nonverbal memory, and visual mental rotation.

• Participants were treated for two periods of 21 days each, one with CEE 1.25 mg/d and the other with placebo, with 14 days of washout between treatment periods.

• Since the investigators could not control for the practice effects or carryover effects of estrogen that might have affected test performance in the second period, they restricted their analysis to the first period. During that time, the group receiving CEE showed significantly better oral reading \( (P = .002) \) and verbal memory performance \( (P = .01) \) than the placebo group. However, after reanalysis using Full-Scale IQ as a covariate, the difference in verbal memory was not significant.

• Plasma concentrations of estrogen were not correlated with cognitive performance.

• *Pueraria lobata* (PL) is a traditional Chinese herbal remedy for menopausal symptoms and an ingredient in preparations for conditions affecting menopausal women, such as osteoporosis, coronary heart disease, and some hormone-dependent cancers. *Pueraria lobata* contains isoflavones, which belong to the phytoestrogen group.

• The effects of 3 months of treatment with PL (equivalent to 100 mg isoflavones) on lipid profile, sex hormone levels, bone turnover markers, and indices of cognitive function were compared to those of CEE 0.625 mg/d plus MPA 5 mg/d for the last 14 days of each 28-day period.

• 127 community-living, postmenopausal women aged 50 to 65 years were allocated, in random order, to receive E+P (n = 43), PL (n = 45), or no treatment (n = 39). Patients were not blinded their treatments. Among other assessments, women were given a menopausal symptoms questionnaire; the MMSE; neuropsychological tests covering memory, attention, motor speed, and word-finding ability; the Boston Naming Test; Trail-Making tests of attention, mental flexibility, visual search, and motor function; the Hong Kong List-Learning Test (HKLT), which examines short- and long-delayed recall and learning rates and strategies; and a quality of life (SF36) assessment at baseline and after 3 months.

• In contrast to PL, E+P significantly improved short- and long-delayed verbal recall, as measured by the HKLT, compared to no treatment (*P* < .05), while flexible thinking was improved in the PL but not the E+P group compared to control. These results offer further support to the idea that HT may have a beneficial effect on verbal memory in particular in mid-life women.
HT Is Associated With Improved Memory and Modulations in Brain Activation

Mean Age, 65 Years

![Graph showing comparison between HT Users and HT Nonusers](image)

- Women in this study were all aged ≥55 years (mean age, 65 years) and were participants in the Baltimore Longitudinal Study of Aging.
- Neuroimaging and neuropsychological evaluation were performed annually for 9 years. At each visit, 12 neuropsychological tests were administered to participants to assess verbal knowledge, language, learning and memory, visuospatial abilities, and perceptuomotor speed.
- Neuropsychological tests included the BVRT, which measures immediate figural memory, and the CVLT, which measures immediate and delayed recall.
- As shown in the bar graphs on the left, HT users exhibited better recall on the CVLT than did nonusers, and HT users had fewer total errors on the BVRT compared with nonusers.
- The images on the right depict rCBF as measured by PET. PET measurements were conducted at rest and during performance of verbal and figural delayed recognition memory tasks. Compared with nonusers, HT users exhibited different rCBF activation patterns during the performance of memory tasks. In the figure above, the areas highlighted by crosshairs indicate regions of altered activation in women taking HT.

Young women (mean age, 34 years) who were to be treated with the gonadotropin-releasing hormone analog LAD were tested for cognitive function before treatment and after 3 and 5 months of receiving LAD.

Baseline cognitive function scores did not differ significantly between the two groups.

Three months of ovarian suppression with LAD resulted in a significant decline in performance on typical tests of verbal memory (paragraph recall).

After 2 months of treatment with estrogen, scores returned to baseline (month 5).

Scores on other tests of verbal memory (delayed paragraph recall and paired associates test) were similarly decreased by LAD and improved by estrogen.

Effects of estrogen on memory were evaluated in this randomized, double-blind study of premenopausal women (n = 19) who required total abdominal hysterectomy and bilateral salpingo-oophorectomy for benign disease.

Estrogen levels and scores on memory tests were assessed before surgery and after 2 months of treatment with either estradiol (estradiol valerate 10 mg IM monthly) or placebo.

 Portions of the Wechsler Memory Scale were used to test memory.

On the associate learning test, both immediate and delayed recall scores remained stable in the women treated with estradiol but decreased significantly in those given a placebo.

Scores on the immediate and delayed paragraph recall tests increased in the estradiol-treated group but did not change in the placebo group.

No hormonal effect was observed on scores of either immediate or delayed visual recall.

The data suggest that some aspects of memory are affected by abrupt decreases in serum estrogen levels.
This prospective, observational study by Maki et al evaluated the effect of HT on cognitive abilities, including memory.

Subjects were participants in the Baltimore Longitudinal Study of Aging and were postmenopausal and nondemented at the time of testing and for up to 7 years afterward.

Users of HT showed significantly better performance \( (P < .01) \) on several measures of verbal learning and memory compared with never-users.

There were no significant differences on other cognitive test scores, including tests of attention (Digit Span), mental rotations (card rotations), and memory for designs (BVRT).

Duration of HT was not correlated with any dependent measures. However, women receiving adjuvant progestin performed better than did women receiving estrogen alone on a test of visuospatial abilities.
Effects of HT on Tests of Verbal Abilities in Postmenopausal Women

Mean Age, 74 Years

- In this longitudinal study among 727 women, most participants had received estrogen treatment around the time of menopause and most had used unopposed CEE. Among the current and past users, 37 women (5% of the total sample) had used estrogen for longer than 1 year, 44 women (6%) had used estrogen for less than 1 year, and 12 women (2%) were using estrogen at the time of evaluation.
- Subjects underwent cognitive testing at baseline and again 2 to 3 years later. Average age at baseline was 74.2 years.
- Outcome measures were the Selective Reminding Test (a measure of verbal memory), the Similarities subtest of the revised Wechsler Adult Intelligence Scale (verbal abstract reasoning), and a short version of the Boston Naming Test (data not shown).
- When the statistical effect of demographic variables (age, education, and ethnicity) was controlled, ever-users of HT performed significantly better than did never-users at baseline.
- At follow-up evaluation, delayed recall scores for ever-users improved (+0.64), whereas scores for never-users declined (-0.41; \( P < .001 \); data not shown).
- Women who had used HT scored significantly higher at baseline on cognitive tests compared with never-users, and their performance on verbal memory tests improved over time.

Estrogen Is Associated With Better Figural Memory

**Cross-Sectional**

<table>
<thead>
<tr>
<th>Age-Corrected z Score for Total Errors on BVRT*</th>
<th>Current Estrogen Users</th>
<th>Never Users</th>
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<td><img src="image1" alt="Graph" /></td>
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<td>n = 172</td>
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**Longitudinal**

<table>
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<th>BVRT Total Errors</th>
<th>Estrogen at T2</th>
<th>No Estrogen</th>
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</thead>
<tbody>
<tr>
<td><img src="image2" alt="Graph" /></td>
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</table>

*Benton Visual Retention Test, a measure of short-term visual memory. †P < .05.

• Observational data on hormonal status and visual memory were reported in 288 postmenopausal women in the Baltimore Longitudinal Study of Aging. One hundred and sixteen women (mean age = 61.8 years) who reported that they were receiving estrogen were compared to 172 never-users (mean age = 67.7 years). Participants were given the BVRT, a measure of short-term visual memory, visual perception, and constructional skills.

• As shown by the cross-sectional data depicted on the left graph, women who were receiving estrogen had significantly (P = .043) fewer errors on the BVRT.

• Of the current estrogen users, 18 had taken the BVRT 6 years previously, before they had initiated treatment, making it possible to conduct a longitudinal analysis of the effect of estrogen on age-associated change in memory. Eighteen women with repeat test scores who had never used estrogen served as the comparison group. As seen in the right graph, estrogen appeared to protect against changes in performance on the BVRT attributable to aging. Women who did not initiate estrogen showed the typical age-related decrease on this measure.

• These cross-sectional and longitudinal findings suggest that estrogen may protect against memory decline in nondemented postmenopausal women and offer further support for a beneficial role of estrogen on cognitive function in aging women.

Effects of Current and Past HT on Cognitive Function

Change in 3MSE scores after 4 to 6 years:
- Past users had a smaller decline compared with never-users ($P < .05$)
- Never and current users had similar declines

<table>
<thead>
<tr>
<th></th>
<th>Current User (n = 802)</th>
<th>Never-User (n = 4441)</th>
<th>Previous User (n = 1935)</th>
<th>P-Value</th>
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<tr>
<td>Age of HT initiation (years)</td>
<td>52.2 ± 10.8</td>
<td>—</td>
<td>48.8 ± 7.7</td>
<td>.001</td>
</tr>
<tr>
<td>Duration of use (years)</td>
<td>14.3 ± 9.9</td>
<td>—</td>
<td>5.2 ± 6.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% Impaired on 3MSE</td>
<td>14.3</td>
<td>20.5</td>
<td>14.5</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

Mean age at baseline: 72 years.

*χ-square analysis comparing equivalence of proportions across all groups. Second 3MSE testing was 6 years later.

Note: Decline in 3MSE scores 4 to 6 years after baseline was not predicted by current use of HT; greater education, younger age, and past HT use were statistically significant predictors of less decline.


- Participants for this study\(^1\) were selected from a larger pool of subjects enrolled in the Study on Osteoporotic Fractures. The mean age of participants was 72 years.
- Evaluation of cognitive function included administration of a 3MSE, Trails B test, and Digit Symbol Substitution. Participants were evaluated at baseline and again 4 to 6 years later.
- At baseline, current and past users of HT had better 3MSE scores ($P < .05$ and $P < .001$, respectively) compared with never-users. However, scores on 3MSE and Trails B were not influenced by duration of estrogen use at baseline.
- At re-evaluation, past users showed significantly smaller ($P < .05$) declines in 3MSE and Trails B performance compared with never-users, who demonstrated declines similar to those of current HT users.
- In contrast to current and never-users, past users showed a significantly slower rate of cognitive decline over the course of the study. Current users initiated HT later than did previous users (52 ± 10.8 years of age, versus 49 ± 7.7 years of age), suggesting that early exposure to HT might be critical for maintaining cognitive status.
- Other reports have suggested that there may be a limited window of time, possibly early in the postmenopause, during which estrogen is most likely to affect cognitive decline.\(^2\)\(^-\)\(^6\)

The Cache County Study was a prospective, observational study that examined the incidence of dementia (ie, AD) among a group of older, postmenopausal women in a relatively homogenous population in Cache County, Utah. All of the women were Caucasian, ≥65 years old, with very low prevalence of alcohol and tobacco use. Fifty-two percent of users were currently taking HT at baseline. The most common form of HT, taken by 77% of current users, was an oral unopposed CEE 0.625 mg/d.

At the beginning of the study (1995-1997), 2,928 women were interviewed and cognitive assessment was performed, which included administration of a 3MSE. Two hundred twenty-six women were found to have dementia at baseline.

This figure illustrates the effect of HT on cognitive decline as shown by differences in 3MSE scores for HT users and nonusers who completed the 1995-1997 evaluation (Time 1) and were re-evaluated during Time 2 (1998).

The inverse association between HT use and decline in 3MSE score was negligible in the youngest group of women (65-74 years old), moderate in women between the ages of 75 and 84, and most notable among the oldest group of women (≥85 years old).
A randomized, placebo-controlled study evaluated the effect of estrogen on memory in 37 postmenopausal women (mean age, 65 ± 4.9 years). None were current users of HT and only one participant had used estrogen in the past (6 years before entering the study). The subjects were tested with several tests of memory function, randomized to transdermal estradiol (0.1 mg/day) or placebo for 3 weeks, and retested.

Change from baseline scores for tests of visual associative learning and memory for spatial location are represented above. Women who received estradiol for 3 weeks improved significantly ($P = .05$) on a composite measure combining all 3 memory tasks compared with women who received placebo. Improvement was also observed on a task of mental rotation (data not shown) but not on several tests of frontal lobe function (eg, planning skills).

Randomized Controlled Trial of E+P and Cognitive Function in Women With Coronary Heart Disease

**Mean Age, 71 Years**

**Setting**
- Add-on study to Heart and Estrogen/progestin Replacement Study (HERS)

**Participants**
- 1063 postmenopausal women

**Treatment**
- E+P (n = 517) or placebo (n = 546)

**Results**
- After 4.2 years, 1 (verbal fluency) out of 6 cognitive tests showed significance (in favor of placebo)

*P = .02 compared with E+P group.

- A subgroup of postmenopausal women with established coronary disease who participated in the Heart and Estrogen/progestin Replacement Study (HERS) took part in this study.
- Participants were randomized to receive CEE 0.625 mg with MPA 2.5 mg or placebo. The 3MSE and the Verbal Fluency, Boston Naming, Word List Memory, Word List Recall, and Trails B exams were given at the end of the 4.2-year study.
- Participants were between 44 and 79 years old at testing (mean age, 71 years).
- HT did not result in improved cognitive function in women with coronary disease. Except in the case of verbal fluency (P = .02), age-adjusted mean scores on 5 of the 6 tests of cognitive function were not significantly different between the two groups.
- The effect of E+P on cognition in women without coronary disease cannot be determined from this study. Women with CHD may have a greater risk of cognitive decline and dementia resulting from both AD and vascular disease.
- Because cognitive function was not measured at baseline, change in cognitive function from baseline to the end of the trial between the treatment groups could not be compared.
- Genetic variants of apolipoprotein were not measured in this study. The apolipoprotein E, ε4 (APOE ε4) genotype has been linked to both cognitive decline and CHD, and unopposed estrogen has a reduced protective effect against AD in APOE ε4–positive women. Thus, it is possible that these results may reflect a prevalence of APOE ε4 women in this population.

Deficits in Processing Speed and Memory in Women Receiving Hormone Treatments for Breast Cancer

3-Year Treatment

*P < .05. Patients had received surgery for early-stage breast cancer, 67% had received radiotherapy, and none had received adjuvant chemotherapy.
Patient group received either anastrazole or tamoxifen.

• Although the use of hormonal treatments for breast cancer is common, few data are available on the impact of such treatments on cognition. Because several regions of the brain are rich in estrogen receptors, the long-term use of therapies that affect ovarian hormones may have consequences for cognition.

• Shilling et al. conducted an unblinded pilot study among women taking part in the Anastrozole, Tamoxifen, and Combined (ATAC) trial. Women receiving hormonal treatment for breast cancer and a group of women without the disease were given cognitive assessments that measured a range of memory and attention functions. Breast cancer patients were randomized to tamoxifen plus placebo or anastrozole plus placebo. All patients had received surgery for early stage breast cancer and 67% had received radiotherapy. None had received adjuvant chemotherapy.

• Ninety-four patients and 35 non-cancer controls were assessed. Groups did not differ significantly in age or estimated full-scale intelligence. The patient group did not differ from controls on measures of working memory, attention, and visual memory but was significantly impaired compared to the control group on measures of processing speed (P = .032) and verbal memory (P = .026). Cognitive performance in the patient group was not significantly related to length of time on trial or measures of psychological morbidity.

• Because this study was unblinded, changes in cognitive performance cannot be reliably assigned to either tamoxifen or anastrozole. However, preliminary results suggest that the anti-estrogen effects of tamoxifen and/or anastrozole may cause a specific deficit in verbal memory, in contrast to the pattern seen with healthy women.

Relative Risk of Cognitive Decline During the 3-Year MORE Trial: Raloxifene Versus Placebo

Mean Age at Baseline, 66 Years*

- Overall, there were no differences between groups on cognitive tests (6 measures)
- There was no significant effect of raloxifene on risk of decline in cognitive function on 5 out of 6 tests
  - However, women in the raloxifene groups showed less decline in delayed verbal recall over time
- Although differences were small, in post hoc analyses, women >70 years who took raloxifene performed significantly better on tests of delayed verbal recall and attention

n = 7478.

*Age range, 31 to 80 years.


Yaffe et al investigated whether raloxifene would have a beneficial effect on cognition in postmenopausal women similar to that associated with estrogen.

- This randomized, placebo-controlled trial evaluated cognitive test scores among a group of women receiving raloxifene for 3 years.
- The 7478 participants were enrolled in the MORE study. Participants were randomized to receive either 60 or 120 mg of raloxifene daily, or placebo.
- Cognitive function testing was performed at baseline, 6 months, and 1, 2, and 3 years into the study. The tests administered, and the primary areas they measure, were as follows:
  - Short Blessed Test: orientation, concentration, memory
  - Trail Making Test, Parts A and B (Trails A and Trails B): visuospatial scanning, sequential processing, motor speed, executive function, attention
  - Word List Memory Test, and Word List Recall Test: learning, immediate memory, delayed memory
  - Word List Fluency Test: verbal production, semantic memory, language
- Mean baseline cognitive scores were not significantly different among the 3 groups, and there was no significant difference in cognitive test scores between the 3 groups after 3 years of treatment.
- The RR of decline in cognitive function was not significantly different between the two raloxifene groups (combined) and the placebo group. However, women in either raloxifene group tended to have lower risk of decline on tests of attention and verbal delayed recall compared with women in the placebo group.

Effects of Estrogen Alone on Cognitive Impairment Risk Depend on APOE Genotype

*Time to cognitive impairment adjusted for age, education, race, and stroke history. Cognitive impairment was defined by 3MSE score of <80.


- The APOE ε4 allele is known to be a genetic risk factor for cognitive decline and AD. This study looked at the association between increased risk of cognitive decline and APOE ε4 and evaluated whether estrogen use may modify this association.

- Participants were 2,716 postmenopausal women over 65 years of age (mean age, 72 years), who were part of the Cardiovascular Health Study. Annual cognitive testing consisted of administration of an 3MSE examination. Investigators analyzed change in 3MSE score as a function of unopposed estrogen use and APOE genotype.

- Over the 6-year period, current estrogen users declined 1.5 points on the 3MSE, compared with never-users, who declined 2.7 points over the same period (P = .02)

- Among APOE ε4–negative women, current estrogen use reduced risk of cognitive impairment compared with that of never-users by 41% (hazard ratio [HR], 0.59; 95% CI, 0.36–0.99). In contrast, among APOE ε4-positive women, current estrogen use did not reduce risk of cognitive impairment (HR, 1.33; 95% CI, 0.74–2.42).

- Estrogen use was associated with a reduction in risk of cognitive decline among APOE ε4-negative women but not among APOE ε4–positive women.

- The presence of APOE ε4 is associated with atherosclerosis in the CNS.
Clinical studies have shown that elevated homocysteine increases the risk of incident dementia, myocardial infarction, and stroke, and that estrogen reduces levels of homocysteine. However, it is not known whether reduction of homocysteine is a mechanism by which estrogen may influence cognitive functioning in postmenopausal women.

Serum values of homocysteine, HT status, and two measures of cognitive functioning, the Modified Mini-Mental State Exam and the Delayed Word Recall Test, were measured in 1041 elderly women of Latino background. The women (mean age = 70.3 years) were participants in the Sacramento Area Latino Study on Aging (SALSA), an observational cohort study. Eighty percent of HT users were taking CEE 0.625 mg.

In women not taking HT (n = 819), the study found an inverse association between homocysteine and scores on the 3MSE. The 3MSE was 11.8 points lower and the Delayed Word Recall Test (DELREC) was 1.98 points lower for every 10 µmol/L increase in homocysteine.

Subjects on HT (21%; n = 222) did not show this same negative relationship between cognitive test performance and homocysteine. HT users had 3MSE scores 1.88 points higher (P < .001), DELREC scores 0.12 points higher (P = .06), and homocysteine levels 1.19 µmol/L lower (P < .001) than those not on HT. The DELREC scores in particular demonstrate that, across levels of homocysteine typically associated with poor cognitive performance, HT users maintained their verbal memory.

In sum, HT users performed very well on tests of delayed verbal recall even at the highest levels of homocysteine. In this study, serum homocysteine levels were associated with poorer cognitive performance only among postmenopausal women not taking HT.
Two analyses were recently published from the WHIMS, a randomized, double-blind, placebo-controlled, clinical trial involving participants from the estrogen and CEE/MPA arms of the WHI. The design and patient characteristics were identical for both analyses. The first paper\(^1\) reported on the effect of CEE/MPA on probable dementia, the primary outcome. The second\(^2\) evaluated the effect of CEE/MPA on global cognitive function using changes in 3MSE scores over time, and was conducted to help explain the primary results. It should be noted that 3MSE scores were not formally planned secondary end points and the study was not specifically powered to detect differences in 3MSE scores resulting from treatment.

The 3MSE was administered annually to study participants. The mean time between randomization and the last 3MSE before study discontinuation was 4.2 years.

The 3MSE mean total scores in both groups increased slightly over time. Women in the CEE/MPA group had smaller average increases than those receiving placebo \((P = .03)\); however, these differences were described as being not clinically important.

Censoring women after adjudicated dementia, mild cognitive impairment, stroke, or nonadherence had no effect on the results. Prior HT use, its duration, or the timing of the initiation of HT also did not affect the results.

These findings of no meaningful difference in overall cognitive test scores among women assigned to CEE/MPA are consistent with recent data from WHI on 3MSE scores after one year of treatment.\(^2\)

A substantial and probably clinically important decline \((\geq 2\) SDs\) in 3MSE total scores was observed more frequently in the CEE/MPA (6.7\%) group compared with the placebo group (4.8\%) \((P = .008)\).

Whether these findings on global cognitive function apply equally to HT initiated before age 65 years cannot be directly addressed by these data.


HT and Cognition: Early vs Late Initiation

**Early Initiation**
- E-alone → better verbal memory in surgical menopause, gonadal suppression\(^1,2\)
- E+P → improved verbal memory in women aged 50–65 years\(^3,4\)

**Later Initiation**
- E+P in older women → no benefit on verbal memory\(^5,6\) in older postmenopausal women

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• In 2003, reports were published from two randomized clinical trials\(^1,2\) in early mid-life women that address the impact of an early initiation of HT on cognitive test performance. This slide differentiates the results of studies in early mid-life women from results of studies conducted in older postmenopausal women.

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Effects of Estrogen on Cognition and Mood

Section 4:

Estrogen and Mood
• This section reviews the effects of estrogen on mood in postmenopausal women.
Estrogen and Neurotransmitter Systems Affecting Mood

**Sero-tonergic System**
- ↑ Serotonin uptake capacity
- ↑ Tryptophan availability to brain
- Modulates serotonin receptor expression
- ↓ Age-related decline in serotonergic responsivity

**Catecholaminergic System**
- Modulates dopamine release
- ↑ Norepinephrine release

**Estrogen**

↓ Monoamine oxidase activity


- As illustrated above, estrogen actions that affect mood occur at many levels and in several locations in the CNS:
  - Tritiated imipramine binding sites in the brain modulate the presynaptic uptake of serotonin. Sherwin and Suranyi-Cadotte showed that estrogen increased the number of tritiated imipramine binding sites on human platelets, suggesting that a similar increase in the number of CNS binding sites (and subsequent increase in serotonin uptake) may account for the positive effect of estrogen on mood in postmenopausal women.
  - Aylward et al reported that reduced free tryptophan concentrations and associated depression in postmenopausal women are both improved by administration of estrogen.
  - Activation of ERs in the rat hippocampus and frontal cortex decreases serotonin receptor function in those regions. Although the mechanism is currently undefined, the decrease in serotonin receptor function is rapid, suggesting a non-genomic effect.
  - Responses to the specific serotonergic releasing agent and re-uptake inhibitor, d-fenfluramine, were significantly decreased in women who had not taken estrogen compared with young healthy women, but were not different between postmenopausal women treated with estrogen and young women. These results suggest that central serotonergic responsivity is reduced in healthy postmenopausal women who have not taken estrogen, but not in postmenopausal women who have received prolonged estrogen treatment. This may offer one reason why estrogen can decrease vulnerability to mood disorders.
  - Ohtani et al demonstrated that estrogen increased dopamine availability in female rats. Similarly, Paul et al showed that 17β-estradiol increased dopamine release and norepinephrine release. Investigators suggested that estrogen may facilitate catecholamine release within the hypothalamus.
  - Luine et al reported that estradiol decreased monoamine oxidase in the hypothalamus and amygdala of female rats. The clinical importance of this finding was explored by Klaiber et al. These investigators conducted a double-blind, crossover study of 38 nondepressed menopausal women. While estrogen had a positive effect on mood in menopausal women (linked to decreases in monoamine oxidase activity), the concurrent administration of a progestin diminished this effect.

Estrogen and Depression

- Estrogen reported to improve postpartum depression\(^1\)
- Estrogen may improve mood in postmenopausal women without clinical depression\(^2,3\)
- Estrogen may improve symptoms in perimenopausal women with depressive symptomatology\(^4\)
- Data are not sufficient to justify use of estrogen as primary treatment for clinical depression


- Depression is more common in women than in men, and in some cases, episodes of depression may coincide with periods of drastic hormonal fluctuation in women, particularly the premenstrual, postpartum, and perimenopausal periods.
- Gregoire et al\(^1\) reported that estrogen effectively treated postnatal depression. In 1994, Studd and Smith\(^2\) also suggested that women with a history of postnatal depression can have estrogen-responsive mood disorders later in life.
- Two studies in surgically menopausal women suggested that estrogen lowered depression scores\(^3\) and improved mood\(^4\) in women without clinical depression.
- Soares et al\(^5\) demonstrated improvement in symptoms of depression for 68% of perimenopausal women undergoing estrogen treatment.
- Although it has been reported that reductions in estrogen levels alone did not correlate with increases in depressed mood,\(^6\) this connection remains a topic of interest, as does the possible use of estrogen to treat some symptoms of clinical depression.

In a randomized, double-blinded study designed to test the effects of adding MPA to CEE on mood, 48 healthy, naturally menopausal women were assigned to one of 4 cyclic, sequential E+P or unopposed estrogen regimens for 1 year. Participants received either 1) CEE 0.625 mg/d plus placebo (n = 10); 2) CEE 1.25 mg/d plus placebo (n = 12); 3) CEE 0.625 mg/d plus MPA 5 mg/d (n = 15); or 4) CEE 1.25 mg/d plus MPA 5 mg/d (n = 11). CEE was always given on days 1-25 and MPA or placebo on days 15-25 of each calendar month.

Using the Daily Menopausal Rating Scale, women were instructed to rate their general mood during the past 24 hours on a scale of 0 (“depressed”) to 7 (“contented or happy”). The test was completed daily during the month of pretreatment and during months 3, 6, 9, and 12.

Data in this slide are shown as a function of week. In general, changes in mood scores were greater in the CEE-alone groups than in the CEE/MPA groups regardless of dose. Women who were given CEE 0.625/MPA 5 mg had significantly lower daily mood scores than those given CEE 1.25 plus placebo over the course of treatment ($P < .01$). As seen in the consistent drop in scores with MPA in weeks 3 and 4, particularly noticeable with the higher dose of CEE, cyclic MPA would seem to have a deleterious effect on mood.

Sherwin and Suranyi-Cadotte conducted a double-blind, randomized, placebo-controlled, cross-over study to investigate whether the correlation of mood and estrogen levels in surgically menopausal women may be mediated by an effect of estrogen on the number of tritiated imipramine binding sites available for the active transport of serotonin.

Immediately after surgery, 31 non-depressed women (mean age = 47 years) were randomly assigned to receive an intramuscular injection of estradiol valerate 10 mg or sesame oil (i.e., placebo) 1 ml once every 28 days for 3 months, after which they were crossed over to the opposing treatment for an additional 3 months.

Mood was assessed pre-operatively and after each of the 3-month treatment phases.

No significant differences were found between groups before surgery. Changes in the number of tritiated imipramine binding sites on platelets closely paralleled the changes in estrogen values at various time points in the study. Similarities in the regulation of platelet and brain imipramine binding sites have been demonstrated previously; therefore, these results suggest that similar changes in the number of binding sites occurred in the CNS.

Scores on the Beck Depression Inventory were lower during phases of treatment with estrogen than with placebo ($P < .01$), coincident with increases in estrogen levels and tritiated imipramine binding.

A second study tested whether mood differed in healthy, surgically menopausal women treated over the long term with estrogen alone compared to those treated with an estrogen-androgen combination and those not treated after surgery.

Women had been receiving 1 ml (= 10 mg) of estradiol valerate or 1 ml of an estrogen-plus-androgen (E+A) formulation for 2 years before the study; the same drugs were administered intramuscularly once during the study. Twenty-two women (mean age = 47.2) received the E+A preparation, 11 (mean age = 46.6) received estrogen alone, and 11 (mean age = 47.4) remained untreated. Subjects were not randomly assigned to groups; instead, groups were matched on several variables to ensure homogeneity among them.

On days 2, 4, and 8 after injection, women in the estrogen-alone group were less depressed ($P < .01$) and less tired ($P < .01$) than those in the group receiving no treatment.

On days 2, 4, and 8 after injection, women in the E+A group were less anxious ($P < .01$), less hostile ($P < .01$), less depressed ($P < .01$), less unsure ($P < .01$), less tired ($P < .01$), and more clearheaded ($P < .01$) than those in the control group. Women who received estrogen plus androgen felt more composed, elated, and energetic than those who were only given estrogen.

These findings offer further support for the idea that mood is tied to circulating estrogen levels in generally healthy, postmenopausal women who are not depressed.
• Somatic complaints and anxiety also improved for women receiving estradiol valerate (EV)/dienorgest or unopposed EV versus placebo.

• The list of somatic complaints (which denote subjective impairment associated with physical and general complaints) improved for women receiving EV/dienorgest combination therapy and unopposed EV compared with baseline scores for each group.

• Similarly, mean scores on the State-Trait Anxiety Inventory (STAI) improved for women receiving EV or EV/dienorgest. Mean Trait anxiety scores (shown above) improved significantly after 8 weeks in the EV/dienorgest and unopposed EV groups, compared with baseline scores. Mean State anxiety scores improved ($P < .05$) after 16 weeks for women receiving unopposed EV, compared with the mean score at 8 weeks (data not shown).

Estrogen Alone May Improve Mood in Perimenopausal Women With Depressive Disorders

- Soares et al investigated the use of unopposed estrogen as a treatment for depressive symptoms in perimenopausal women in this double-blind, placebo-controlled study.
- Depressive symptoms were measured by using the Montgomery-Åsberg Depression Rating Scale (MADRS) and menopausal symptoms were measured with the Blatt-Kupperman Menopausal Index (BKMI), which assesses the severity of symptoms such as vasomotor symptoms, joint pain, sleep disturbance, and headache.
- Patients were randomized to receive either estradiol or placebo. Symptoms were assessed at baseline and every 4 weeks during the course of the study. Symptoms were reassessed after a 4-week washout period at the end of the study.
- At baseline, 52% of the participants met the criteria for major depressive disorder, 22% for dysthmic disorder, and 26% for minor depressive disorder.
- At the end of the treatment period, the MADRS scores for the estradiol group were significantly lower ($P < .001$) than those for the placebo group. The decrease from baseline was significantly greater for the estradiol group than for the placebo group. At week 16 (after washout), patients previously treated with estradiol still showed mean MADRS scores significantly lower ($P < .001$) than those obtained at baseline. In contrast, women who discontinued placebo reported mean MADRS scores almost as severe as those reported at baseline, and significantly higher ($P < .001$) than scores for women who discontinued estradiol treatment.
- Women in the estradiol group also had lower BKMI scores than did women in the placebo group at the end of the study, and estradiol-treated women had a significant decrease from their baseline BKMI scores. It is unclear if improvements in the MADRS score were determined by improvements in physical symptoms (eg, sleep).

Effects of Estrogen on Cognition and Mood

Section 5:
Estrogen and Sleep
Effects of Estrogen on Brain Function

Physiological Effects  
Estrogen  
Dementia  
Sleep  
Mood  
Cognition

- This section reviews the effects of estrogen on sleep in postmenopausal women.
Sleep Disturbances Are Associated With Estrogen Loss

Many women report sleep complaints around the time of the menopause\textsuperscript{1,2}

Estrogen alone improves women’s subjective reports of sleep quality, even in women who are free of menopausal symptoms\textsuperscript{3}

Compared with nonusers, estrogen users experience increased time in REM sleep and reduced time awake\textsuperscript{4}

\begin{itemize}
\item Sleep complaints are not uncommon around the time of menopause. Oldenhave et al\textsuperscript{1} surveyed 5,213 women between the ages of 39 and 60 years about menopausal symptoms. Menstrual status varied widely among the women, ranging from some who were still menstruating to those whose last menstrual period was $\geq 10$ years before the survey. The investigators found that 15\% to 22\% of menstruating women reported insomnia, and 23\% to 26\% of nonmenstruating women (last menstrual period $>3$ months) reported insomnia.\textsuperscript{1}
\item Sleep disruptions (awakenings) often involve nocturnal hot flushes, which contribute to overall poor sleep quality for peri- and postmenopausal women. However, menopausal insomnia can occur in conjunction with vasomotor symptoms or independently of them.\textsuperscript{2} In a study by Polo-Kantola et al,\textsuperscript{3} unopposed estrogen users reported improved sleep quality, even among women who were not reporting menopausal symptoms. In addition, estrogen decreased frequency of sleep disruptions and improved sleep in menopausal women with insomnia.\textsuperscript{3}
\item Antonijevic et al\textsuperscript{4} has reported that women taking estrogen spent significantly more time in REM sleep compared with nonusers ($50.0 \pm 4.3$ minutes versus $39.4 \pm 4.5$ minutes; $P < .05$), and estrogen users also spent less time awake ($11.9 \pm 5.4$ minutes versus $20.1 \pm 5.9$ minutes; $P < .05$).
\item Similarly, Scharf et al\textsuperscript{5} reported that unopposed estrogen improved sleep efficiency (percentage of time in bed spent sleeping) and improved overall sleep quality. Women in this study ($n = 7$) were between the ages of 45 and 60 years. Three of the participants were naturally menopausal for at least 2 years, and 4 participants were surgically menopausal for at least 7 years.
\item Thus, it is likely that peri- and postmenopausal sleep disruptions are not necessarily dependent on the occurrence of vasomotor symptoms. Central mediation of these sleep disruptions has been proposed.\textsuperscript{6}
\end{itemize}

Estrogen May Restore Normal Sleep Electroencephalogram (EEG)

Improvements in Sleep EEG Patterns After Open-Label Treatment With Estradiol

<table>
<thead>
<tr>
<th>Sleep Parameter</th>
<th>Baseline (mean ± SD)</th>
<th>With Estrogen (mean ± SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time awake in first 2 cycles (minutes)</td>
<td>20.1 ± 5.9</td>
<td>11.9 ± 5.4</td>
</tr>
<tr>
<td>Time in REM sleep in first 2 cycles (minutes)</td>
<td>39.4 ± 4.5</td>
<td>50.0 ± 4.3</td>
</tr>
</tbody>
</table>

n = 11 postmenopausal women; mean age, 55 years.
*P < .05 for all parameters.

• This study, set in a sleep laboratory, examined EEG patterns of women receiving transdermal estrogen. Participants were women between 46 and 62 years of age who were at least one year postmenopausal (mean duration of menopause, 6.7 ± 1.5 years). Assessments were performed at baseline and following 2 weeks of transdermal estradiol (50 µg/day) on the same group of 11 women.

• Women receiving estrogen reported significantly less time spent awake during sleep cycles, and more time spent in REM sleep.

• Subjectively, 10 of 11 women rated their sleep as “very” or “quite” satisfactory while receiving estrogen. At baseline, 10 of 11 women had reported being dissatisfied with their sleep.

• Another interesting finding was that sigma EEG activity increased in response to estrogen. The investigators suggested that increased sigma EEG activity (associated with estrogen) may contribute to improved cognitive function in postmenopausal women.

Postmenopausal Women Report Improved Sleep After 3 Months of Estrogen Alone

*Mean Age, 56 Years*

- **Fully Disagree**
- **No Difference**
- **Fully Agree**

- **Sleep Improved†**
- **Fewer Awakenings†**
- **Harder Falling Asleep†**
- **More Tired†**
- **More Morning Tiredness†**
- **More Restless†**

Visual Analog Scale

*Age range, 47 to 65 years; n = 63.
†P < .001 compared with placebo.

- In this study by Polo-Kantola et al, the participants were 63 postmenopausal women between 47 and 65 years of age.
- This was a 7-month prospective, randomized, double-blind, crossover study to evaluate the effects of estrogen on sleep quality.
- Women received 3 months of treatment with either estrogen or placebo, completed a 1-month placebo washout period, then crossed over to the other arm of the study.
- Responses to Visual Analog Scale questions were used to evaluate the effect of estrogen on sleep improvement.
- The subjects reported significant improvement in sleep and fewer awakenings while using unopposed estrogen compared with placebo. They also considered themselves less tired in the morning and during the day.
- Alleviation of climacteric symptoms by unopposed estrogen significantly predicted subjective sleep improvements in this study, but estrogen also improved sleep quality for women who were not experiencing vasomotor symptoms.
Effects of Estrogen on Cognition and Mood

Section 6: HT and Dementia
This section reviews the effects of estrogen on dementia and AD in postmenopausal women.
### Aging, MCI, and Dementia

<table>
<thead>
<tr>
<th>Normal Cognitive Aging&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Mild Cognitive Impairment&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Dementia&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declines in memory or other cognitive domains that are normal for one's age</td>
<td>Memory complaint, preferably corroborated by a confirmed source</td>
<td>Significant decline in memory and at least 1 other cognitive domain</td>
</tr>
<tr>
<td>Declines do not interfere with occupational or social functioning</td>
<td>Objective memory impairment that is greater than that of age peers</td>
<td>Declines interfere with occupational or social functioning</td>
</tr>
<tr>
<td>Normal general cognitive function</td>
<td>Intact activities of daily living</td>
<td></td>
</tr>
<tr>
<td>Not demented</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Time**


- Age-related cognitive decline is defined as an objectively identified decline in cognitive functioning that results from aging, that is within normal limits for a person’s age, and that is not attributable to a specific mental disorder or neurological condition. Such decline may involve problems remembering names or appointments or difficulty solving complicated problems.
- An international group of investigators has defined mild cognitive impairment as the clinical condition between normal aging and AD in which persons experience a loss of memory greater than that expected with aging and less than that with AD. Though not demented, these persons progress to clinically probable AD more quickly than healthy, age-matched individuals. Since their general cognitive function, apart from memory, remains unimpaired, they are able to carry out activities of daily living.
- Dementia is defined by the development of memory impairment together with at least one of the following cognitive disturbances: aphasia (ie, deterioration of language function), apraxia (ie, reduced ability to carry out motor activities in the absence of motor or sensory impairment), agnosia (ie, failure to recognize or identify objects in spite of intact sensory function), or a disturbance in executive functioning. These conditions signal a decline from previous functioning and must be severe enough to impede occupational or social functioning.
- Dementia should be distinguished from the normal decline in cognitive functioning that happens with age.
Alzheimer’s Disease

- A neurodegenerative process of the brain causing a progressive loss of cognitive ability interfering with social and occupational functioning

- US prevalence of AD estimated to be 4.5 million in 2000

- 29% of those 85 years old had AD in 1997, and the size of the older population is increasing

- The rate of AD may be 1.5- to 3-fold higher in women, even after accounting for their longer life span

- Delaying AD nursing home admissions by 1 month could save $1.2 billion annually in the US

• As a result of the general aging of the US population, the prevalence of AD and its economic impact will increase dramatically. If recent trends continue, the number of patients with AD will nearly triple in the next 50 years.

• Being female is a risk factor for AD. In 1997, 68% of the 2.32 million people with AD were women, compared with 32% who were men. The cumulative risk for 65-year-old women to develop AD at the age of 95 years is more than twice that of men.

• Because of the enormous cost of AD, estimated to be as much as $76.3 billion per year, the development of effective treatments is urgent. Delaying the admission of AD patients into health care institutions, specifically nursing homes, by as little as 1 month could save $1.2 billion annually in the United States.

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• The prevalence of AD is expected to rise dramatically as the U.S. population continues to age overall. The impact of HT on AD is thus an urgent issue.

• Hebert et al took estimates of the incidence of AD from a population-based study involving both black and white residents of Chicago, combined them with mortality data from the 2000 U.S. census and the National Center for Health Statistics, and projected the prevalence of AD using projections of population growth from the US Census. Incidence of AD was measured in 3838 persons free of AD at baseline.

• The results show that the prevalence of AD is expected almost to triple in the next 50 years, increasing from an estimated 4.5 million persons in 2000 to 13.2 million in 2050. Those aged 85 years and older will suffer the greatest increase: prevalence in this age group is expected to more than quadruple, reaching 8 million in 2050.

Pathology of AD

- Hallmarks are increased neurofibrillary tangles and neuritic plaques
- Hippocampal pathology and volume loss occur early in the disease course
- β-amyloid deposition is an important biochemical feature

![Tangle](Image)
![Plaque](Image)


- Histopathologic diagnosis of AD requires identification of neurofibrillary tangles and neuritic plaques in excess of the amounts expected to occur in age-matched healthy individuals (controls).\(^1\,\,2\)
- Neurofibrillary tangles contain filaments of abnormally phosphorylated tau protein that occupy the cell body and extend into dendrites; plaques consist of a central core of amyloid protein surrounded by astrocytes, microglia, and dystrophic neurites.
- In patients with AD, these plaques and tangles are distributed in specific areas of the cerebral cortex and certain other brain regions. It has been suggested that the higher-order association cortices are the most vulnerable, but there is no apparent association between duration of illness and densities of plaques and tangles.\(^2\)


HT and AD

- HT use is associated with reduced risk or delayed onset of AD in observational studies\(^1-^4\)

- Estrogen reduces production of AD-related \(\beta\)-amyloid protein in laboratory models\(^5\)

- Estrogen probably does not improve AD symptoms or progression\(^6,^7\)


- Kawas et al\(^1\) evaluated the risk of developing AD for HT users and reported an RR of 0.46 (95% CI, 0.209–0.997) for HT users compared with nonusers. This study, however, did not show the effect of dose or duration of HT on risk of AD.
- Paganini-Hill and Henderson\(^2\) reported a 35% decreased risk of AD for users of unopposed estrogen (OR, 0.65; 95% CI, 0.49–0.88). They also assessed the effect of duration of therapy and dose on clinical outcome, and reported that long-term users (\(\geq 15\) years) using 1.25 mg of oral CEE had the lowest observed risk of all groups evaluated (OR, 0.48; 95% CI, 0.19–1.17).
- Tang et al\(^3\) also evaluated the effect of duration of unopposed estrogen on risk of AD, reporting an RR of 0.13 (95% CI, 0.02–0.92; \(P < .01\)) for women who used estrogen for longer than 1 year compared with never-users, and an RR of AD associated with a history of estrogen use of 0.40 (95% CI, 0.22–0.85; \(P = .01\)). Similarly, Zandi et al\(^4\) reported a 41% reduced risk of developing AD (relative hazard [RH], 0.59; 95% CI, 0.36–0.96) for women who used HT at any time, and a 59% reduced risk (RH, 0.41; 95% CI, 0.17–0.86) for women who used HT for 10 years or longer.
- Xu et al\(^5\) found physiologic levels of 17\(\beta\)-estradiol reduced cellular production of \(\beta\)-amyloid in vitro. As \(\beta\)-amyloid deposition is involved in the pathogenesis of AD, these results suggest a mechanism by which estrogen may delay or prevent AD.
- Several small, short-duration studies (eg, Asthana et al\(^6\)) suggested that estrogen might benefit AD symptoms. However, larger studies of longer duration by Henderson et al\(^7\) and Mulnard et al\(^8\) evaluated the effect of unopposed estrogen on cognition in women with mild to moderate dementia and did not show a beneficial effect. Henderson and colleagues administered estrogen for 16 weeks, and Mulnard and coworkers for 1 year. Estrogen did not improve symptoms of AD\(^7,^8\) or slow progression of the disease\(^8\) in these studies.
- Collectively, these observational data suggest that HT may reduce risk of AD if initiated before clinical signs emerge.
Estrogen Reduces β-Amyloid (Aβ) Generation

*P < .05 vs untreated OVX animals.
* * *


- This animal model study evaluated the effects of ovariectomy and 17β-estradiol on brain levels of β-amyloid in guinea pigs. Eight weeks after ovariectomy, ovariectomized guinea pigs were divided into 3 treatment groups (17β-estradiol at dosages of 1 mg/kg or 5 mg/kg, or no treatment) and given estradiol for 10 days (estradiol was administered orally as a powdered food additive). Afterward, brain levels of β-amyloid were compared with levels found in intact female guinea pigs of the same age.

- Ovariectomy was associated with an average 1.5-fold increase in brain β-amyloid levels compared with levels in intact animals (P < .05).

- Both estradiol regimens significantly reduced total brain β-amyloid levels compared with those found in ovariectomized animals (P < .05). Estradiol administered at 1 mg/kg was associated with a mean 18% decrease in total brain β-amyloid compared with pre-treatment levels. Similar findings were reported for the 5 mg/kg treatment group.

- Decreases in estrogen levels associated with menopause may facilitate brain deposition of β-amyloid, initiating changes that lead to development of AD. Postmenopausal estrogen may exert a protective effect by reducing deposition, thereby inhibiting this mechanism.
Estrogen Did Not Improve Function or Cognition in Women With AD

- Participants for this study were recruited from the 1995-1999 Alzheimer’s Disease Cooperative Study (ADCS).
- This study was a randomized, double-blind, placebo-controlled trial involving 120 women who were diagnosed with mild to moderate AD and who were surgically menopausal.
- The primary outcome measure used to assess change from baseline was the Clinical Global Impression of Change (CGIC) scale. The MMSE and the Clinical Dementia Rating Scale were used as secondary outcome measures.
- Participants were randomized to receive CEE (0.625 mg/d or 1.25 mg/d) or placebo for 1 year. Cognitive assessments, including global outcome measures, were evaluated at baseline and at 2, 6, 12, and 15 months.
- As shown by the ADCS version of the CGIC, neither CEE regimen had any effects on the clinical progression of AD in women with mild to moderate AD. At 12 months, mean changes in scores from baseline on the CDR were significantly ($P < .05$) worse with both CEE regimens than with placebo. Although the lower-dose CEE regimen did have a benefit on the change in MMSE score after 2 months ($P = .05$), the benefit did not persist with continued treatment.
- These data suggest that unopposed estrogen may have a deleterious effect on the clinical course of dementia in demented women and stand in contrast to data on estrogen in the primary prevention of dementia in non-demented postmenopausal women.

Several observational studies have assessed the association between HT use and AD risk.1-18 LeBlanc et al19 reviewed the medical literature on use of HT for prevention of cognitive decline and reduction of dementia in healthy postmenopausal women and performed a meta-analysis of observational studies. Women in the studies ranged in age from 45 to 80 years. Naturally and surgically menopausal women were included and both estrogen/progesterone combination therapy and unopposed estrogen were used. Two cohort studies, Tang et al, 199613 and Kawas et al, 1997,14 provided the strongest evidence for an association between AD and HT. These studies reported RRs of 0.5 (95% CI, 0.25–0.9) and 0.46 (95% CI, 0.21–1.0), respectively, for HT users compared with nonusers. The results of these two cohort studies, along with those of 10 case-control studies,1-7,9,11,15,16 were combined by meta-analysis. Results indicated a 34% decreased risk of AD for women using HT (summary RR, 0.66; 95% CI, 0.53–0.82). Although information on dose regimens was not consistently available, an estimated 66% to 95% of the participants used oral CEE. Alzheimer’s disease risk assessments from two other recently published studies17,18 and a meta-analysis20 are also represented above. Zandi et al17 reported a 41% reduced AD risk for HT users (HR, 0.59; 95% CI, 0.36–0.96) compared with nonusers. A meta-analysis by Hogervorst et al20 reported a similar risk assessment (RR, 0.56; 95% CI, 0.46–0.68). In contrast, Seshadri et al18 found that use of HT was not associated with a reduced AD risk (RR, 1.18; 95% CI, 0.59–2.37). However, the mean age of women in this study was 65, which is younger than the usual age for onset of AD symptoms. Larger, double-blind, placebo-controlled trials are needed to provide more information on the effect of HT on AD risk. Also, the mechanism by which estrogen seems to delay onset of AD warrants further scientific investigation.

• Tang et al studied the association between estrogen use and risk of developing AD among 1124 women. The majority of women used oral CEE.

• Results indicated that, after adjustment for other risk factors of AD, age of onset of AD was later for women who used estrogen than for those who had never used it.

• Additionally, the RR of developing AD was reduced for estrogen users compared with nonusers, and women who used estrogen for longer than one year had a greater reduction in risk compared with women who used estrogen for less than one year or never used it at all.

• Investigators concluded that estrogen delayed the onset of AD and reduced the risk of developing AD.
Estrogen receptor 1 (ESR1) polymorphisms may be associated with risk of developing cognitive impairment or AD in older women.

This observational study enrolled 2,625 women ≥65 years of age. Participants completed an 3MSE at baseline and again at 6 to 8 years of follow-up. The ESR1 polymorphisms, PvuII ("P" or "p") and XbaI ("X" or "x"), were coded so that the capital letter signified the absence of the restriction site.

The figure above represents the education-adjusted risk of developing cognitive impairment or AD. Women who developed cognitive impairment were more likely to have a "p" or an "x" allele. Odds ratios [ORs] were 1.35 (95% CI, 1.07–1.72) and 1.32 (95% CI, 1.03–1.68), respectively. Similarly, women with a "pp" or "xx" genotype were almost 3 times more likely to be diagnosed with dementia or AD compared to women with "PP" or "XX" alleles; ORs were 2.68 (95% CI, 1.14–6.31) for the "pp" genotype and 3.06 (95% CI, 1.06–8.83) for the "xx" genotype.

Six percent (n = 166) of the women in this study developed cognitive impairment. More women who developed cognitive impairment had a "p" allele (62% vs. 56%, P = .03) or an "x" allele (70% vs. 64%, P = .03) compared to those who did not. There was no interaction with current estrogen use or with serum estradiol level and ESR1 polymorphisms.

More research is needed to determine the mechanism whereby ESR1 polymorphisms or linked genes influence cognitive function in older women.
As described on slide 34, the Cache County Study was a prospective, observational study that examined the incidence of dementia among a group of older, postmenopausal women in Cache County, Utah. The second part of the study (1998-2000) re-evaluated the cohort of women to determine how many had developed dementia over a 3-year period. Follow-up interviews were conducted for women whose baseline evaluation had indicted no dementia (other exclusions included death, inadequate information, and stroke). This re-analysis was performed on 2,401 women.

Between the initial interview and follow-up procedures (ie, 3 years), significantly fewer men than women developed AD: 35 men (2.6%; n = 1357) vs. 88 women (4.7%; n = 1889). Of women who reported any use of HT, 26 (2.4%; n = 1066) developed AD, significantly fewer than those who had had no use of HT (58 out of 800; 7.3%).

This figure depicts the AD annual hazard for HT users, nonusers, and men.

Women who used HT for 10 years or more had an AD risk similar to that of men. In contrast, HT nonusers had an annual hazard higher than that for women who used HT for 3 to 10 years, or for less than 3 years. The following slide looks at these findings in more detail.
Among Cache County participants, AD was less common among women with a history of HT use compared with nonusers. The figure above illustrates that longer duration of use was associated with additional reductions in AD risk.

Women who used HT at any time had a 41% reduced risk of developing AD (RH, 0.59; 95% CI, 0.36–0.96), and women who used HT for 10 years or longer had a 59% reduced risk of AD (RH, 0.41; 95% CI, 0.17–0.86). Healthy user bias and level of education were controlled for both of these assessments.1

Use of calcium or multivitamins was not associated with reductions in AD risk.

Current HT use was associated with decreased risk only if HT use exceeded 10 years (RH, 0.55; 95% CI, 0.21–1.23), although statistical significance was not reached.

The seeming null effect of current use may not merely be a factor of duration of use. There may be a limited window of time, possibly early in the postmenopause, during which HT is most protective. The end of this period may coincide with onset of the preclinical stage of AD (which may begin 10 or more years before AD can be diagnosed) after which HT is less likely to reduce AD risk.1,2 It has also been suggested that estrogen-responsive neurons may be less responsive after a prolonged period of estrogen depletion,3–5 such that intervention early in the postmenopause may offer more protection. Additional study of these mechanisms is warranted.

Women’s Health Initiative Memory Study (WHIMS)

- Ancillary study to the WHI, a randomized, multicenter study of CEE alone and CEE plus MPA
- Primary outcome measure: probable dementia
- Two studies from WHIMS have been published:
  - Effect of CEE/MPA on probable dementia and mild cognitive impairment¹
  - Effect of CEE/MPA on global cognitive function²


As discussed on slide 41, the WHIMS was an ancillary study to the WHI and enrolled participants from both its estrogen and E+P arms. The WHIMS used the 3MSE to screen for probable dementia, the study’s primary outcome, and mild cognitive impairment, as well as to assess global cognitive function.¹,² Patients who scored below designated cut points on the 3MSE underwent additional clinical evaluation, including a neuropsychological and neurological work-up. Cases were adjudicated by a central adjudication committee (Kappa = .66).

WHIMS: Dementia and Mild Cognitive Impairment

- 4532 postmenopausal women with a uterus and free of probable dementia, aged ≥65 years, were recruited from WHI centers and enrolled in the E+P arm of the WHIMS

- Study drug administration was stopped early
  - Mean time between randomization and last 3MSE in WHIMS was 4.05 years

- The ending of the CEE-only component of WHI and WHIMS ~1 year before its planned completion was announced by the NIH on March 2, 2004


• 4532 postmenopausal women aged 65 years or older without probable dementia were recruited from 39 of 40 WHI centers and enrolled in the CEE/MPA arm of the WHIMS.

• On July 8, 2002, CEE/MPA was discontinued because of increased health risks in women receiving combined HT. The mean time between the date of randomization into WHI and the last 3MSE for all WHIMS participants was 4.05 (SD, 1.19) years. ¹

• On March 2, 2004, the NIH announced it was ending the CEE-only component of the WHI trial, and thus of the WHIMS, approximately 1 year before its planned completion.² According to the NIH, preliminary data suggested that there was a trend toward an increased risk of probable dementia and/or mild cognitive impairment in women given unopposed estrogen when compared to those given placebo. Publication of the results from the estrogen arm of both the WHI and WHIMS is forthcoming.


Overall, the number of women diagnosed with probable dementia or mild cognitive impairment was small. Of the 4532 patients enrolled in the study, 61 participants from 31 of the 39 study centers were diagnosed with probable dementia. Forty of these cases were in the CEE/MPA group, and 21 were in the placebo group. The HR for probable dementia among women receiving CEE/MPA compared with those given placebo was 2.05 (95% CI, 1.21–3.48; \( P = .01 \)).

Therefore, for every 10,000 women aged 65 years or older with risk-factor profiles similar to those of WHIMS participants, an additional 23 cases of probable dementia might be observed among women taking CEE/MPA compared with women taking placebo.

There was no statistically significant difference in the risk of being diagnosed with mild cognitive impairment among women receiving CEE/MPA compared with those receiving placebo (HR, 1.07; 95% CI, 0.74–1.55; \( P = .72 \)).

Among the 56 women in the CEE/MPA group and the 55 women in the placebo group initially diagnosed with mild cognitive impairment, 11 women in the CEE/MPA group and 10 women in the placebo group were eventually diagnosed with probable dementia.

Since early postmenopausal women were not included in the study, it is unclear whether these results can be applied to early postmenopausal women taking HT for symptom relief.
• The risk of a diagnosis of mild cognitive impairment in the CEE/MPA group was similar to the risk reported in the placebo group (HR, 1.07; 95% CI, 0.74–1.55). The differences between groups in cumulative hazards for a diagnosis of mild cognitive impairment were minimal throughout the 5-year study.

• The number of diagnoses of mild cognitive impairment per year ranged from 4 at year 5 in the CEE/MPA group to 18 at year 3 in the placebo group and at year 2 and 3 in the CEE/MPA group.

Although the numbers of patients diagnosed with probable dementia each year were small, cumulative HRs indicate that the risk of being diagnosed with probable dementia began to increase among patients taking CEE/MPA compared with those taking placebo 1 year after randomization. These differences continued through the 5-year study, at least through year 4.

Overall, the rate of a diagnosis of probable dementia in the CEE/MPA group compared with that observed in the placebo group was 2.05 (95% CI, 1.21–3.48).

As shown in the preceding slides, WHIMS demonstrated no influence of CEE/MPA on mild cognitive impairment (the preclinical stage of AD) and a significant increase in the probability of dementia (ie, all-cause dementia).

As a complement to the graphs of hazard ratios on the preceding slides, this slide shows the incidence of mild cognitive impairment and dementia by years of follow-up. Although there was no significant increase in the overall risk of mild cognitive impairment, a significant rise in the incidence in patients on E+P did occur at year 2. In the case of probable dementia, the data showed an increase in years 2, 3, and 4 especially.
### Classification of Probable Dementia Cases by Treatment Assignment

<table>
<thead>
<tr>
<th>Dementia Type</th>
<th>Number (%) of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEE/MPA (n = 40)</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>20 (50.0)</td>
</tr>
<tr>
<td>Other dementia types</td>
<td></td>
</tr>
<tr>
<td>Mixed type</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Normal pressure hydrocephalus</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Parkinson</td>
<td>0</td>
</tr>
<tr>
<td>Frontal lobe type</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Alcohol related</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Other dementia</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Etiology unknown</td>
<td>2 (5.0)</td>
</tr>
</tbody>
</table>


- There were too few cases to examine the effects of CEE/MPA on specific subtypes of dementia, including AD, in the WHIMS.
- AD was the most common classification of probable dementia cases, with 20 cases (50.0%) in the CEE/MPA group and 12 cases (57.1%) in the placebo group. Other dementia classifications reported in both groups included vascular dementia and mixed-type dementia. Five patients taking CEE/MPA were classified as having vascular dementia, compared with 1 patient receiving placebo.
- Among patients taking CEE/MPA, 2 cases of probable dementia were classified as normal pressure hydrocephalus and 2 were classified as frontal lobe type. One case of probable dementia in the placebo group was classified as a Parkinson type dementia. The etiology was unknown in 2 cases in each group.
- Although 75 participants had a stroke during the follow-up period (39 in the CEE/MPA group and 36 in the placebo group), only 1 patient diagnosed with probable dementia had a stroke during the study before her diagnosis. Two others diagnosed with probable dementia in the CEE/MPA group had a history of stroke.
- Investigators hypothesized that the increased risk of stroke observed with CEE/MPA may contribute to the increased risk of probable dementia. Although the risk of probable dementia was increased in WHIMS participants without a history of stroke, it is possible that these patients may have experienced small, undetected cerebrovascular events, which could increase the risk of probable dementia.2
- Recent studies suggest that the pathophysiological mechanisms and clinical symptoms of AD and vascular dementia may overlap,1 and standard clinical diagnostic methods tend to favor a classification of AD over vascular dementia when both may be present.3

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Patient Adherence in WHIMS

- 2534 participants (55.9%) were nonadherent at some point during the trial
- Nonadherent patients stopped study medication, took less than 80% of pills, or started HT outside of the trial
- When nonadherent participants were censored 6 months after first becoming nonadherent, the number of probable dementia cases that occurred before censoring was reduced from 41 to 21 in the E+P group and from 20 to 6 in the placebo group (HR, 3.22; 95% CI, 1.25–8.29; P = .02)

At some time during the trial, 2,534 participants (55.9%) were nonadherent. A patient who was nonadherent either:
- Stopped study medication by her own decision or for protocol-based safety reasons
- Took less than 80% of her pills between dispensing and collection
- Started prescribed postmenopausal HT outside of WHI

The earliest date of nonadherence was selected, and follow-up data were censored 6 months later for secondary analyses examining the impact of nonadherence on the effects of HT.

When nonadherent patients were censored, the number of probable dementia cases that occurred before censoring was 21 in the CEE/MPA group and 6 in the placebo group.

In the analysis including only compliant patients, the HR for a diagnosis of probable dementia with CEE/MPA compared with placebo was 3.22 (95% CI, 1.25–8.29; P = .02). The specific diagnoses for compliant patients were not presented.
• In the WHI, the Kaplan-Meier cumulative hazard of all stroke types began to diverge between 1 and 2 years after randomization.

• Cumulative hazards within age groups (50–59, 60–69, 70–79 years) for normotensive and hypertensive women, and within low, medium, and high stroke-risk tertiles (as determined by Framingham equations) indicated that CEE/MPA was associated with an increase in stroke risk in each group; however, this effect was delayed in the low-risk tertile compared with the middle- or highest-risk tertiles and in normotensive compared with hypertensive women.
One of the hypotheses for the increase in all-cause dementia in the HT group reported in the WHIMS is that it reflects the increase in the risk of stroke or silent ischemic disease reported in the estrogen-plus-progestin arm of the WHI.

This slide shows the number of cases of stroke per 10,000 person-years as a function of year of follow-up and as a function of whether the women were randomized to receive E+P or estrogen alone. The combined HT group had an increased incidence of stroke at years 2, 3, and 4 that tended to reverse at year 6. These data parallel those on dementia shown on slide 76, which demonstrated an increase in probable all-cause dementia in years 2, 3, and 4. Thus the incidence of dementia seems to follow that of stroke, supporting the idea that the E+P might have increased dementia by exacerbating ischemic stroke, even if silent.

The Women’s Health Initiative Study on Cognitive Aging (WHISCA) is an ancillary study to the WHIMS. The design is similar in that women are evaluated annually for 6 years. WHISCA will evaluate whether HT reduces age-related cognitive and memory decline, and will also look at the rate of change in memory/cognitive function for HT users compared with nonusers, and whether the addition of a progestin to an estrogen-alone regimen modifies the effect of estrogen on cognitive abilities.
What WHIMS and WHISCA Cannot Address

- Whether there is a critical period of initiation of HT for prevention of
  - Cognitive aging
  - AD
- Whether dose, types of HT, or duration of treatment may have different effects

WHIMS and WHISCA were designed to evaluate the effects of HT on cognitive aging and AD. However, questions about the existence of a critical period for initiation of HT and about different dose regimens and formulations of HT are not likely to be answered by these trials.
### Observational vs Randomized Studies

#### HT and AD

<table>
<thead>
<tr>
<th>Observational Prospective Studies</th>
<th>Women’s Health Initiative Memory Study (WHIMS)</th>
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<tbody>
<tr>
<td>- Typical patterns of HT use (age, treatment)</td>
<td>- Only women ≥65 years of age</td>
</tr>
<tr>
<td>- Mostly estrogen only</td>
<td>- CEE + MPA</td>
</tr>
<tr>
<td>- ↓ Risk for AD</td>
<td>- ↑ Risk of all-cause dementia</td>
</tr>
</tbody>
</table>

- This summary slide delineates the differences between observational, prospective studies on HT and AD and the WHIMS. The two differ not only in method but also in types of women studied.
- The observational trials involve the typical patterns of use of HT (ie, early initiation). In contrast, the WHIMS studied only women aged 65 years and older. Older women had to be included because they had a probability of developing dementia within the short time frame of the study.
- A second difference is that, in the observational studies, women were taking mostly unopposed estrogen, since it was not known at the time that nonhysterectomized women should be taking a progestin to protect their uteri.
- A final difference between the observational studies and the WHIMS is the outcome measure: the former focused on a decreased risk of AD, whereas the latter focused on an increased risk of all-cause dementia, including vascular dementia. It remains unknown whether there was an increase in the risk of AD in the WHIMS, since the statistical power was insufficient to address that question.
Effects of Estrogen on Cognition and Mood

Section 7:
Summary and Conclusions
Summary: Estrogen, Cognition, and Mood in Postmenopausal Women

- Estrogen has myriad effects on the brain that have the potential to affect cognition and mood.
- In some studies, early HT use is associated with better memory in healthy postmenopausal women.
- In some studies, estrogen use is associated with improvements in mood and sleep.
Summary: Estrogen, Cognition, and Mood in Postmenopausal Women

continued

- Estrogen probably does not slow AD progression or improve AD symptoms
- Observational studies suggest a role for estrogen in delaying the onset of AD
- Randomized trial data in women over age 65 years suggest an increased risk of all-cause dementia with E+P
- There is no FDA approval for HT in the treatment or prevention of cognitive decline, AD, or depression