Published in final edited form as:
Climacteric. 2012 June ; 15(3): 256–262. doi:10.3109/13697137.2012.660613.

Hormone therapy, dementia, and cognition: the Women's Health Initiative ten years on

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Abstract

Principle findings on dementia from the Women's Health Initiative Memory Study (WHIMS) showed that conjugated equine estrogens plus medroxyprogesterone acetate (CEE/MPA) increase dementia risk in women aged 65 years and above, but not risk of mild cognitive impairment. The dementia finding was unexpected, given consistent observational evidence that associates estrogen-containing hormone therapy use with reduced risk of Alzheimer's disease. It remains controversial whether hormone use by younger postmenopausal women near the time of menopause reduces dementia risk or whether WHIMS findings should be generalized to younger women. Given the challenges of conducting a primary prevention trial to address that question, it is helpful to consider the impact of hormone therapy on cognitive test performance, particularly verbal memory, for its own sake and as a proxy for dementia risk. The WHI Study of Cognitive Aging (WHISCA) showed that CEE/MPA worsened verbal memory, whereas CEE alone had no influence on cognition. These findings have been replicated in several randomized clinical trials. The apparent negative effect of CEE/MPA on verbal memory does not appear to be age-dependent. Additional investigations are needed to understand the impact of other hormonally active compounds on dementia and cognitive outcomes.

Keywords

Alzheimer's disease; cognition; dementia; estrogen; hormone therapy; menopause; memory; progestogen; review; selective estrogen receptor modulator; women's health initiative

Principal findings from the Women's Health Initiative (WHI) were published in 2002 and 2004[1, 2]. Subsequently, two ancillary studies, the Women's Health Initiative Memory Study (WHIMS) and the Women's Health Initiative Study of Cognitive Aging (WHISCA) provided important new information on cognitive aging and dementia. An intervention, such as hormone therapy, has the potential to affect cognition as well as dementia. Although mechanisms and effects might be similar in the two instances, they are not necessarily so. For this reason, the following discussion considers hormone effects on dementia risk and dementia symptoms separately from the effects on cognition and cognitive aging.

Conflict of interest VH has no conflict of interest to declare. PM received consultant fees from Noven Pharmaceuticals for work unrelated to the content of this paper. The authors alone are responsible for the content and writing of the paper.

DEMENTIA

Cognitive skills change across the life span. *Dementia* refers to major cognitive impairment severe enough to affect occupational, avocational, or social function. In most regions of the world, Alzheimer's disease is the most common cause of dementia[3, 4]. The burden of Alzheimer's disease falls heavily on women, and about twice as many women suffer from this disorder as men. This sex difference is due in large part to the fact that life expectancy is longer for women, and there are therefore more women in the oldest age group, where the risk of Alzheimer's disease is greatest. A second contributor is that women may survive longer than men after an initial diagnosis[5]. Some studies,[6, 7] but not all[8], also suggest higher incidence rates for women.

Before the Women's Health Initiative

Apparent gender differences in Alzheimer incidence and prevalence, together with observations that women with Alzheimer's disease may have disproportionate difficulty with cognitive tasks viewed as female-advantaged[9, 10], suggested a possible relation between sex hormones and Alzheimer's disease. Over the past two decades, approximately two dozen observational studies have examined associations between a woman's use of estrogen-containing hormone therapy and her risk of developing Alzheimer's disease[11–14]. Meta-analyses before WHI linked hormone use to reductions in Alzheimer risk of nearly 40 percent[15, 16]. These clinical observations were supported by strong biological plausibility, including neurotrophic and neuroprotective effects of estrogens and effects of estradiol on metabolic and biochemical pathways implicated in Alzheimer's disease pathogenesis. There is clear laboratory evidence that brain effects may differ among progestogens (e.g., medroxyprogesterone acetate [MPA] compared to progesterone), among estrogens (e.g., conjugated equine estrogens compared to estradiol), between an unopposed estrogen and an estrogen opposed by a progestogen, and between cyclic use of a progestogen compared to continuous use[17–19]. As we review below, randomized trials have informed our understanding of the cognitive effects of MPA, but our understanding of other progestins is limited. Physiological differences between oral and transdermal routes of administration might also be important, as might dosage, but we await results from ongoing clinical trials for a direct head-to-head comparison of this issue.

Treatment studies of women with dementia due to Alzheimer's disease provided conflicting data. Some observational evidence implied that women with Alzheimer's disease receiving hormone therapy had milder symptoms than women not using hormones[20–22]. Relatively small clinical trials, however, generally failed to show consistent improvement in symptoms of women treated with estrogen compared to placebo[23, 24].

Dementia and mild cognitive impairment in the Women's Health Initiative

The WHI included a large observational cohort and two parallel clinical trials. The trials were stratified by hysterectomy status and used a partial factorial design[25]. There were three randomized interventions: low-fat diet, hormone therapy (conjugated estrogens with or without medroxyprogesterone acetate, depending on hysterectomy status), and calcium plus vitamin D dietary supplements[25]. Participants in the dual trials were relatively healthy community-dwelling postmenopausal women aged 50 to 79 years at baseline (mean age 63 years).

The WHIMS ancillary study was conceptualized as a double-blind controlled trial among women in the WHI hormone therapy trials who were at least 65 years of age. The objective was to determine the incidence of “all-cause dementia” through a four-phase process that included annual cognitive screening. Women who scored below screening cut points

underwent neuropsychological testing and other diagnostic procedures. Mild cognitive impairment was a secondary outcome. WHIMS results were reported in 2003 and 2004[26, 27]. Women, recruited from 39 of 40 WHI centers, included 92% of those potentially eligible. Because the parent WHI trials had been halted prematurely[18,19], there were fewer incident cases of dementia than anticipated and consequently reduced power to address study objectives.

In both WHIMS trials combined there were 108 cases of incident dementia. Exactly half were adjudicated as Alzheimer's disease, but results for Alzheimer's disease were not reported separately. Neither the estrogen-plus-progestogen trial nor the estrogen-alone trial showed the expected reductions in the of all-cause dementia. To the contrary, the dementia rate was increased in women allocated to active treatment. The hazard ratio was approximately doubled for women in the estrogen-plus-progestogen group and increased by about half for women in the estrogen-alone group (Table 1). The difference was significant in the estrogen-plus-progestogen trial but not in the estrogen-alone trial[26, 27]. The absolute risk represents about 12 additional cases of dementia for 1000 women using estrogen plus progestogen for five years, and 6 additional cases per 1000 women using estrogen-alone for five years[26, 27].

Mild cognitive impairment was defined primarily on the basis of a) poor performance (10th percentile or lower) on at least one neuropsychological test from an eight test battery, b) report of some functional impairment from a designated informant, and c) absence of adjudicated dementia[27]. These criteria are similar, but not identical, to other criteria for mild cognitive impairment[28, 29]. The incidence of mild cognitive impairment did not differ between treatment groups (Table 1). Not surprisingly, women who developed dementia were older and had relatively low cognitive performance at the start of the trial.

Dementia: the Women's Health Initiative ten years on

Since these initial WHIMS[26, 27], new research has explored mechanisms by which estrogens may have affected dementia outcomes and has helped clarify WHIMS inferences regarding dementia risk. Other hormonally active compounds may also be relevant to Alzheimer risk.

Structural brain imaging after WHIMS completion—At the conclusion of the WHIMS trials, an MRI brain imaging study was implemented at 14 WHIMS clinical centers. All former participants were eligible except those with specific contraindications to the procedure (e.g., cardiac pacemaker). 1403 women provided structural MRI data, obtained on average eight years after randomization and three years (estrogen-plus-progestogen trial) or 1.4 years (estrogen-alone trial) after WHIMS ended[30]. The primary outcome was ischemic lesion volume on structural brain images. Mean differences between women who had received on-trial hormone therapy and those who had received placebo were not significant. Secondary MRI outcomes included total and regional brain volumes assessed on T1 gradient echo images. Here, small but significant differences favored women originally assigned to placebo for frontal lobe volume (2.4 ml difference) and hippocampal volume (0.1 ml difference)[31]. Results were similar for CEE and CEE/MPA. One caveat is that fewer than half (49%) of WHIMS volunteers at participating clinical centers provided MRI data[32], leading to selection bias that undermined validity of the original randomized design.

Follow-up analyses focused on 53 women with incident dementia or mild cognitive impairment[33]. For women originally assigned to hormone therapy, cognitive impairment was significantly associated with smaller mean volumes for total brain (20.7 ml difference) and hippocampus (1.0 ml difference) compared to women without cognitive impairment. There was no difference in the volume of ischemic lesions. The interpretation of these

results is not straightforward, as increased hippocampal volume is reported for younger postmenopausal women using hormone therapy[34] and smaller brain volumes were not observed for cognitive impaired women in the placebo groups[33]. Study investigators concluded that cognitive impairment in women who received conjugated estrogens is mediated though brain atrophy[33] and not through subclinical ischemic disease[30, 33].

Critical window in relation to Alzheimer's disease risk—As recognized even before WHIMS outcomes were reported[35], WHIMS results would not necessarily be applicable to hormone therapy prescribed to younger postmenopausal women. Women in this age group were ineligible for WHIMS. The critical window, or timing, hypothesis proposes that effects of exogenous estrogens on dementia risk are modified by a woman's age or temporal proximity to menopause. Thus, hormone use by younger postmenopausal women might reduce dementia risk, but later use might not. This hypothesis is supported by observational research that links hormone therapy use to reduced Alzheimer risk[15, 16]. Most observational studies compared ever-users to never-users. Because most women who used hormone therapy did so for a limited time close to menopause[36], reported associations in these studies primarily reflected past hormone use by relatively younger women.

Several observational studies have specifically considered whether reported associations might vary according to past use versus current use or might vary by age. Shortly before WHIMS results were published, Cache County, Utah investigators showed that past hormone therapy use was associated with a reduction in Alzheimer risk (hazard ratio [HR] 0.3, 95% CI 0.2 to 0.7) but current use was not (HR 1.1, 95% CI 0.6 to 1.9)[14]. After WHIMS, findings from the Multi-Institutional Research in Alzheimer Genetic Epidemiology case control study demonstrated for the first time a significant interaction between a woman's age and effects of hormone therapy on Alzheimer risk[37]. When examined by age tertile, younger postmenopausal women (aged 50 to 63 years) who used hormone therapy were at reduced risk for Alzheimer's disease (odds ratio [OR] 0.35, 95% CI 0.2 to 0.7). For women in the two oldest tertiles, associations were not significant (ORs of 0.9 [0.5 to 1.5) and 1.0 [0.6 to 1.6])[37]. Because use of hormone therapy by younger women was necessarily at a younger age closer to the time of menopause, one interpretation of the age interaction is that the results are consistent with the critical window hypothesis. Preliminary analyses of past hormone use by WHIMS participants[38] are congruent with Cache County results. Women reporting hormone use prior to the WHIMS trial — independent of the effects of on-trial treatment — were less likely to develop Alzheimer's disease during the WHIMS clinical trial (HR 0.35, 95% 0.2 to 0.9). This protective association contrasts with deleterious effects of conjugated estrogens during the clinical trial itself (Table 1) but does not detract from the on-trial results[27]. More recently, investigators from a large managed care organization in northern California examined dementia diagnoses in relation to hormone therapy during midlife and late life. The first assessment was based on self-reported current use, when the mean age was 49 years. The second, three decades later, was based on pharmacy records. Over 1500 women were diagnosed with dementia. Compared to women never on hormone therapy, those reporting hormone use only at midlife showed reduced risk (HR 0.7, 95% 0.6 to 0.9), whereas women receiving hormone therapy only in late life were at increased risk (HR 1.5, 95% CI 1.1 to 2.0)[39].

Together, these observational results are consistent with the critical window hypothesis as applied to Alzheimer's disease risk. Nevertheless, it remains controversial whether results from WHIMS for women aged 65 years and older generalize to younger postmenopausal women, or whether inferences from observational studies are valid in implying reduced Alzheimer risk for younger hormone users[40]. A persistent concern is that observational findings could be flawed by unrecognized confounding, particularly by factors associated with better health and healthier life style practices (the healthy user bias). If the increased

relative risk of dementia for older women in WHIMS is generalized to women below age 60, where dementia incidence is rare[41], the absolute risk of dementia would itself be rare, representing about one additional case of dementia among 1000 women using hormone therapy for five years.

Other compounds that interact with estrogen receptors—Other drugs with the ability to interact with estrogen receptors have the potential to affect dementia risk. Raloxifene, a nonsteroidal selective estrogen receptor modulator, can be prescribed to postmenopausal women to treat and prevent osteoporosis and to reduce risk of invasive breast cancer in women with osteoporosis. Some brain effects differ from those of estradiol. In a multinational clinical trial of postmenopausal women (mean age 66 years) with osteoporosis[42], high-dose raloxifene (120 mg/d) was associated with a trend toward lower risk of dementia or mild cognitive impairment compared to placebo (HR 0.7, 95% CI 0.5 to 1.01) (see Table 1).

Few data address dementia outcomes with other selective estrogen receptor modulators (tamoxifen, bazodoxifene, lasofoxifene, others); phytoestrogens such as soy isoflavones, which also act as selective estrogen receptor modulators; or tibolone, a progestogenic steroid characterized as a selective tissue estrogenic activity regulator and having multiple hormonal effects.

COGNITIVE AGING

Cognitive Aging in the Women's Health Initiative

As an ancillary study to WHI, WHISCA was the largest trial of the impact of hormone therapy on standardized tests of memory and other cognitive functions[43]. Results from 1416 participants (mean age = 74 years) in the estrogen-plus-progestogen arm were published in 2006[44], and results from 886 participants (mean age 74 years) in the estrogen-alone arm were published in 2009[45]. One considerable limitation of WHISCA is that the cognitive outcomes were first measured three years after treatment randomization in WHI. The trial therefore addressed change in cognitive performance from an on-treatment baseline. The primary outcomes in WHISCA were longitudinal changes in memory for word lists and geometric figures, respectively called verbal and figural memory.

Over 1.35 years of follow-up, verbal learning declined significantly in the active treatment versus placebo arm ($p = .009$), with trends for declines in short ($p = .016$) and long ($p = .015$) free delay recall[44]. In contrast, results on the figural memory test showed a trend for improved performance over time ($p = .012$). Overall, these results suggested that the effects of estrogen-plus-progestogen therapy depended on the type of memory tested. The finding that estrogen-plus-progestogen treatment negatively impacted verbal memory replicated previous findings[46]. These results are interesting in light of the finding that estrogen-plus-progestogen also increased dementia risk in WHIMS[24] and that deficits in verbal memory are the earliest neuropsychological predictor of Alzheimer's disease[47, 48].

Findings from the estrogen-alone arm of WHISCA contrasted with those from the estrogen-plus-progestogen arm[45]. After an average follow-up of 2.7 years, there were no significant differences or trends between groups on verbal or figural memory. Secondary analyses revealed worse performance in the estrogen group on a test of visuospatial abilities at the initial WHISCA assessment three years post-randomization. This difference did not remain significant over the duration of the study. Overall, these results indicated that estrogen-alone did not have any enduring positive or negative impact on cognitive function in older women without a uterus.

Cognitive Aging Studies Following the Women's Health Initiative

Several randomized trials published after WHIMS concluded that estrogen-alone had no significant impact on cognitive function in older postmenopausal women. This finding was evident regardless of preparation and dose, and included trials of ultra low-dose transdermal estradiol (0.014 mg/day; n = 417)[49], oral estradiol (1 mg/day; n=460)[50], oral estradiol (2 mg/day; n = 115)[51], and low dose transdermal estradiol (0.25 mg/day; n = 57)[52]. Whether estrogen-alone affects memory in younger postmenopausal women is unclear. Small clinical trials in younger surgically menopausal women suggested benefits to verbal memory[53, 54]. Consistent with emerging evidence of possible benefits of estrogen to prefrontal functions[55], a placebo-controlled study of transdermal estradiol (0.05 mg/day) found benefits to certain CVLT outcomes that are sensitive to prefrontal outcomes, but not to verbal learning[56].

The Cognitive Complaints in Early Menopause Trial (COGENT) addressed the critical question[57] of whether the deleterious effects of CEE/MPA on verbal memory might be due to the advanced age of the study participants. With a sample size of 180 women, COGENT represents the largest randomized, placebo-controlled trial of estrogen-plus-progestogen in younger postmenopausal women aged 45–55 years of age. Based on a cognitive test battery similar to that in WHISCA, the primary finding of interest from COGENT was a trend toward a negative impact of estrogen-plus-progestogen on short and long-delay verbal memory ($p = .054$ and $p = .066$, respectively). These results indicated that the negative impact of CEE/MPA on memory is evident in younger postmenopausal women, and there appears to be no critical window for the impact of CEE/MPA on verbal memory. That finding was replicated in a randomized clinical trial of women with moderate-to-severe hot flashes study who were randomized to 12 months of treatment with either CEE/MPA, black cohosh, red clover or placebo[58]. In contrast to findings that CEE/MPA decreased memory in COGENT and WHISCA, a small clinical trial using CEE alone (n=7) as the control group found that CEE/micronized progesterone (n=8) decreased delayed verbal memory and improved working memory, but CEE/MPA (n = 9) had no effect on either measure.

The Kronos Early Estrogen Prevention Study (KEEPS) will address whether micronized progesterone and a lower dose of MPA affect memory. KEEPS is a multicenter, 5-year randomized, placebo-controlled clinical trial designed to evaluate the effectiveness of 0.45 mg of conjugated equine estrogens, 50 microg weekly transdermal estradiol, each in combination with cyclic oral, micronized progesterone, 200 mg for 12 days each month on cardiovascular and cognitive outcomes in women aged 42–58 years who were within 36 months of their final menstrual period. Results are expected in 2012.

In light of findings of a decreased risk of MCI with 120 mg/d of raloxifene (Table 1), it is interesting to consider cognitive findings from randomized trials of raloxifene and other SERMS. Analysis of cognitive outcomes in the raloxifene/MCI study revealed a trend toward less decline with raloxifene on verbal memory and attention[59]. Similarly. raloxifene (60 mg/d) significantly improved verbal memory over a 12-month period in a randomized, placebo-controlled trial involving 213 women aged 70 and older[60]. Consistent with limited neuroimaging data[61, 62], the finding that SERMS influence verbal memory suggests an estrogen-like action in the hippocampus. The relative effects of SERMS and CEE on cognition have not been directly compared in a head-to-head trial. Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) assessed cognitive outcomes with the same cognitive test battery used in WHISCA[63]. The study included 1498 women aged 65 and older who were randomly assigned to receive raloxifene (60 mg/d) or tamoxifen (20 mg/d). Findings revealed greater benefits with raloxifene compared to tamoxifen on one of four verbal memory measures, suggesting minimal cognitive differences between the two SERMs. One considerable limitation of Co-STAR was that like WHISCA, the first assessment of cognitive outcomes began after randomization. Another limitation is the lack of a placebo

arm. Similarities between the Co-STAR and WHISCA cohorts and methods provided an opportunity to compare the cognitive effects of the two SERMS, CEE and placebo[64]. CEE and the SERMs produced deficits in global cognitive function, particularly among women with poor baseline cognitive function. This finding added to a growing body of evidence[65, 66] that estrogenic agents confer harm when given to women with poor baseline cognitive function, and may suggest a healthy cell bias of estrogen[67].

WRAP UP

Although basis science studies indicate that the effects of hormone therapy on brain function might depend on use and type of progestogen, with the exception of MPA, the clinical relevance of these seemingly important differences remains to be established for dementia and for cognitive aging. Continued investigation of the potential cognitive benefit of SERMs is warranted given clinical trial data demonstrating reductions in mild cognitive impairment and improvements in verbal memory. Findings from clinical trials of cognitive outcomes will not answer long-term questions regarding the risk of Alzheimer's disease, and one cannot conclude from available evidence that hormone therapy should be prescribed at any age to reduce dementia risk. If the relative risk of dementia seen in WHIMS can be validly applied to midlife women who take hormone therapy for treatment of vasomotor symptoms, the absolute risk would be rare (Table 2).

Acknowledgments

Source of funding PM was supported in part by NIH grant R01-MH083782-01A1. V.W.H. was supported in part by National Institutes of Health grant R01-AG023038.

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Table 1

Incident dementia and mild cognitive impairment in the Women's Health Initiative Memory Study and the Multiple Outcomes of Raloxifene Evaluation trial

Trial / clinical outcome	Number contributing to analysis	Active intervention	Mean follow-up	Number of events in active group	Number of events in placebo group	Hazard ratio (95% confidence interval)
WHIMS / all-cause dementia						
Uterus[26]	4532	CE+MPA	4.1 y	40	21	2.1 (1.2 to 3.5)
No uterus[27]	2947	CE	5.2 y	28	19	1.5 (0.8 to 2.7)
Both combined[27]	7471	–	–	68	40	1.8 (1.2 to 2.6)
WHIMS / mild cognitive impairment						
Uterus[26]	4532	CE+MPA	4.0 y	56	55	1.1 (0.7 to 1.6)
No uterus[27]	2947	CE	5.1 y	76	58	1.3 (0.95 to 1.9)
Both combined[27]	7471	–	–	132	103	1.3 (0.97 to 1.6)
MORE / all-cause dementia [42]	3525	Raloxifene[a]	3.0 y	17	18	0.9 (0.5 to 1.8)
MORE / Alzheimer's disease [42]				8	15	0.5 (0.2 to 1.2)
MORE /mild cognitive impairment [42]				44	63	0.7 (0.5 to 0.98)

CE = conjugated estrogens, 0.625 mg/d; MORE = Multiple Outcomes of Raloxifene Evaluation; MPA = medroxyprogesterone acetate, 2.5 mg/d; WHIMS = Women's Health Initiative Memory Study.

[a]Raloxifene 120 mg/d; for standard dose raloxifene (60 mg/d), cognitive outcomes did not differ significantly from placebo (results not shown).

Table 2

Key points: hormone therapy, dementia, and cognition

- Estrogen-plus-progestin therapy initiated at age 65 or older increases dementia risk[a].
- Observational evidence, based largely on short-term use by younger women close to the time of menopause, associates hormone therapy with lower risk of Alzheimer's disease risk.
- If increased risk from WHIMS is extrapolated to postmenopausal women aged 50 to 59 years, the absolute risk of dementia from standard dose hormone therapy would be rare, representing about one additional case among 1000 women using hormone therapy for five years.
- For healthy young and old postmenopausal women, standard dose CEE/MPA therapy has a small, but significant adverse impact on verbal memory.[a]
- For healthy older healthy postmenopausal women, standard dose estrogen therapy does not have a clinically important effect on cognition.[a]

Evidence for other key points is of lower quality.

[a]High quality of evidence based on consistent findings from well-performed randomized trials.