The Women's Health Initiative Memory Study: findings and implications for treatment

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Background **The population of the developed world is ageing; consequently there is an increasing prevalence of age-related neuropsychiatric disorders, such as dementia of any cause and Alzheimer's disease (AD), for which few treatments are available. Observational studies suggested that hormone therapy (HT) might protect postmenopausal women against cognitive decline and AD. However, the results of randomised controlled trials in women age 65 years and older were negative. There has been extensive media coverage of these trials and many doctors are asked whether HT improves or worsens brain function in younger women who are prescribed HT for the treatment of menopausal symptoms.**

Recent developments **The Women's Health Inititiative Memory Study (WHIMS) was a multicentre, randomised, double-blind, placebo-controlled clinical trial in which a subgroup of women who participated in the Women's Health Initiative study were assessed for the effects of HT on dementia and mild cognitive impairment. There were two study arms, one involving 4532 postmenopausal women who received continuous combined oestrogen (conjugated equine oestrogens [CEE] plus medroxyprogesterone acetate) or placebo, and the other involving 2947 hysterectomised women randomised to continuous unopposed CEE or placebo. All participants were age 65 years or older. CEE with or without medroxyprogesterone acetate, given to women age 65 years and older, does not protect against dementia or cognitive decline, but substantially increases the risk of dementia of any cause and cognitive decline.**

Where next? **WHIMS answered critically important questions about whether HT can protect against dementia in elderly women who start HT some years after menopause. However, several clinically important questions are unanswered, including questions about the generalisability of WHIMS to groups of women for whom HT is an indication—perimenopausal women and those soon after menopause who have menopausal symptoms—and other methods of treatment delivery and treatment regimens.**

By the year 2050, an estimated 30% of the population in western Europe will be over age 65 years, and up to 10% will have Alzheimer's disease (AD).[1] Furthermore, the prevalence of mild cognitive impairment, thought to be a preclinical stage of AD, is estimated to be between 20% and 30% in elderly people.[2] The social and economic implications of this are greatest among women because their life expectancy and risk of AD are greater than for men.[3] Three prospective observational studies of hormone therapy (HT) and AD each reported that HT reduced the risk of AD by 39–50%.[3–5] Meta-analyses of cohort and prospective case-controlled studies of the potential protective effects of HT against dementia reported risk reductions of up to 34% (RR 0·66; 95% CI 0·53–0·82).[6] However, these studies could be confounded. For example, a high level of education is associated with a decreased risk of AD, particularly for women,[7] and women who receive HT tend be better educated and healthier than those who choose not to receive it (the "healthy-user bias").[8] Furthermore, the results from small randomised controlled studies of the effects of HT on cognition were inconsistent.[6] The possibility that HT protects against age-related cognitive impairment and dementia therefore became a major public-health issue, and large placebo controlled trials of HT in patients with dementia and cognition were needed.

The Women's Health Initiative Memory Study (WHIMS)

The Women's Health Initiative clinical trials assessed the health risks and benefits of HT in postmenopausal women on primary outcomes of breast cancer and cardiovascular disease, as well as secondary outcomes, such as fracture and stroke. WHIMS[9] was an ancillary study to the Women's Health Initiative study, and was designed to assess if, in older women, HT can decrease the risk of dementia. Although WHIMS included one measure of cognitive ability, the mini-mental state examination, age-related changes in memory and other cognitive abilities were studied in The Women's Health Initiative Study of Cognitive Aging.

Study design

A subgroup of 7510 women over age 65 years was studied. Because unopposed oestrogen is associated with endometrial hyperplasia and commonly contraindicated in women with an intact uterus, the participants were randomised according to their uterine status. 4532 women with an intact uterus were randomised to continuous combined oestrogen (0·625 mg conjugated equine oestrogens [CEE] plus 2·5 mg medroxyprogesterone acetate per day) or placebo. 2947 women with a previous hysterectomy were randomised to receive continuous-unopposed oestrogen

Type of dementia	Number (%)					
	CEE arm		CEE + Medroxyprogesterone acetate arm		CEE or CEE + Medroxyprogesterone (n=68)	Matching placebos (n=40)
	CEE alone (n=28)	Placebo (n=19)	CEE + Medroxyprogesterone acetate (n=40)	Placebo (n=21)		
Vascular	2 (7·1)	2 (10·5)	5 (12·5)	1 (4·8)	7 (10·3)	3 (7·5)
Azheimer's disease	13 (46·4)	9 (47·4)	20 (50·0)	12 (57·1)	33 (48·5)	21 (52·5)
Other						
Mixed	5 (17·9)	4 (21·2)	5 (12·5)	3 (14·3)	10 (14·7)	7 (17·5)
Normal-pressure hydrocephalus	0	0	2 (5·0)	0	2 (2·9)	0
Parkinson's	0	0	0	1 (4·8)	0	1 (2·5)
Frontal-lobe	0	0	2 (5·0)	0	2 (2·9)	0
Alcohol-related	0	0	1 (2·5)	0	1 (1·5)	0
Other dementia	2 (7·1)	0	3 (7·5)	2 (9·5)	5 (7·4)	2 (5·0)
Cause unknown	3 (10·7)	3 (15·8)	2 (5·0)	2 (9·5)	5 (7·4)	5 (12·5)
Not classified	3 (10·7)	1 (3·5)	0	0	3 (4·4)	1 (2·5)

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Table: **Treatment assignment of patients with probable dementia**

(0·625 mg CEE) or placebo. CEE was chosen because it was the most widely used HT when the study was designed and the most common drug reported in studies showing a decreased risk of AD. Old (but not young) women were included because a sufficient number of people with dementia were needed to detect a treatment effect over the planned study period. However, the combination treatment arm of the study was stopped in July 2002 (after a mean of 5·2 years of follow-up) because both the number of breast cancers in the active treatment group and an index of the global risk to benefit ratio exceeded a predetermined cut-off. The prevalence of coronary heart disease, stroke, venous thromboembolic disease, and breast cancer was high in the treatment group compared with the placebo group, although the opposite was true of colorectal cancer, hip fracture, and other fractures.[10] In February 2004, the CEE trial was stopped after nearly 7 years of follow-up because of an increased risk for stroke, and little benefit for the primary cardiovascular outcomes or for cancer; hip fracture was reduced in the treatment group compared with the placebo group.

Effect on AD and cognition

61 women with an intact uterus were diagnosed with dementia of any cause; 40 of 2229 women (1·8%) in the combined treatment group and 21 of 2303 women (0·9%) in the placebo group.[11] Thus the proportion of women with dementia of any cause in the group treated with a combination of CEE and medroxyprogesterone acetate was double that of the placebo group (45 *vs* 22 per 10 000 person years; hazard ratio 2·05, 95% CI 1·21–3·48, p=0·01). However, there was no increase in mild cognitive impairment with combination HT.[11] Shumaker and colleagues[12] describe the cognitive test used to assess mild cognitive impairment. The group treated with only CEE did not show a substantial increase in dementia of any cause or mild cognitive impairment.[9] After a mean of 5 years treatment, 47 women were diagnosed with probable dementia of any cause; 28 of 1464 women (1·9%) in the CEE group and 19 of 1483 women (1·3%) in the placebo group (37 *vs* 25 cases of dementia of any cause per 10 000 person years; 1·49, 0·83—2·66, p=0·18). The incidence of AD was not substantially different in either of the HT groups as compared with their respective placebo groups (table).

In both studies, mini-mental state examination scores indicated global cognitive function improved relative to baseline in both the active treatment and placebo groups.[13,14] However, women who took HT were more likely to have mini-mental state examination scores two standard deviations below the average of those who took placebo, suggesting the improvement in cognitive status was smaller with HT than with placebo (figure).

Discussion

The results from WHIMS do not support the use of HT to reduce the risk of AD in women over age 65 years. However, the WHIMS had many shortcomings: most participants (55%) were not compliant with treatment at some time during the study; the number of people who developed dementia was smaller than expected, partly owing to the early termination of the main study; the diagnoses of about 40% of people who had impaired cognitive function and were referred for assessment were not included because they did not comply or the data was incomplete; the finding of an increased risk for dementia but not for mild cognitive impairment is unusual; and many participants in WHIMS had vascular risk factors (40% had hypertension and 9% had diabetes), and hypertension was more prevalent in each of the treatment groups compared with their respective placebo groups (47·3% *vs* 42·3% in the CEE trial, p=0·01; 40·7 *vs* 38·3 in the combined CEE and medroxyprogesterone acetate trial, p=0·03). Group

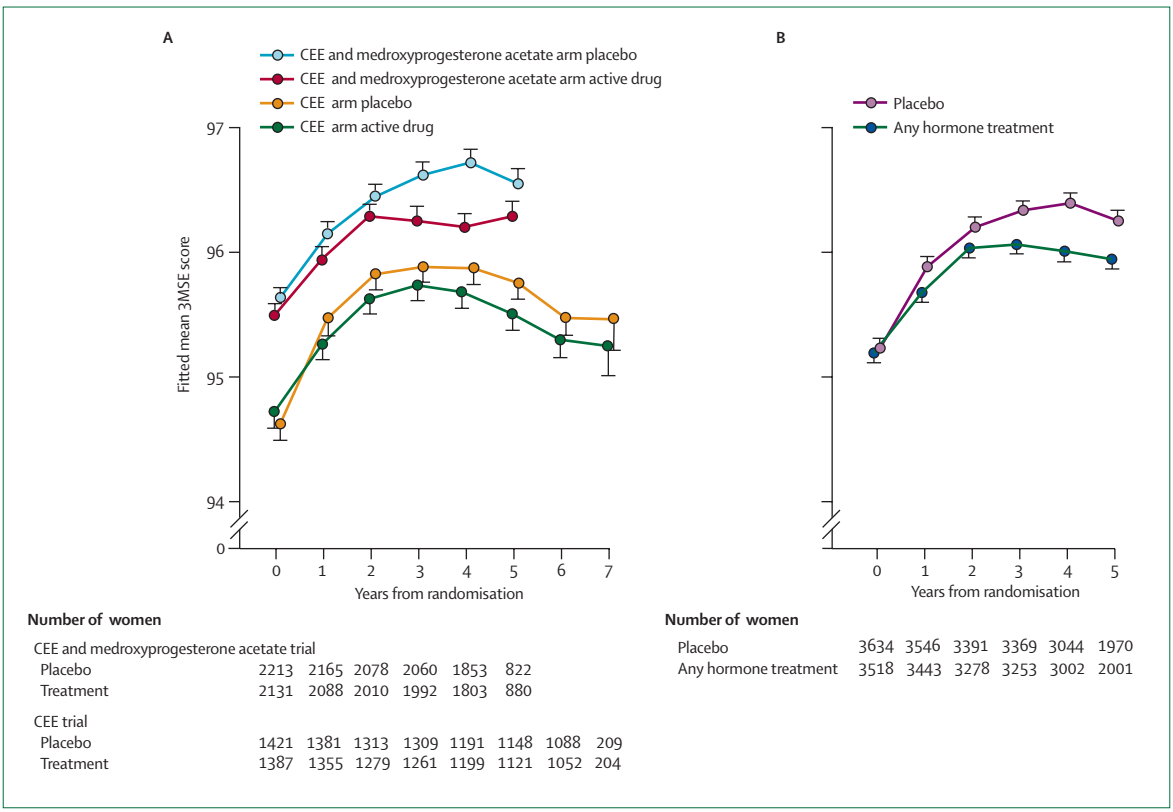

Figure: **Modified mini-mental state examination scores of patients in the WHIMS**
Mean and standard errors of scores on the modified mini mental state examination (3MSE) by years since randomisation, fitted to linear models. (A) Combined CEE and medroxyprogesterone acetate arm and CEE arm. (B) Pooled arms of the trial. Reproduced with permission from the American Medical Association.[14]

differences in these pre-existing risk factors could partly explain the increased rates of adverse vascular effects among women taking HT. Although there was no interaction between HT and individual vascular risk factors for dementia, diabetes and hypertension were associated with higher hazard ratios for the CEE group compared with the placebo group (p=0·06 and p=0·15, respectively). These effects may not have reached significance because of the small number of events in each group (ie, the study was underpowered). In addition, the potential modulatory effect of apolipoprotein E subtype was not measured, although the *APOE* ϵ4 allele is associated with an early age of onset and high risk of AD.[15] Furthermore, reports suggest that oestrogen increases *APOE* expression[16] and oestrogen has been reported to increase cognitive impairment in ϵ4 positive women compared with ϵ4 negative women.[17]

The oral HT used in WHIMS was either unopposed CEE or continuous combined CEE and medroxyprogesterone acetate. Previous reports suggest that medroxyprogesterone acetate counteracts the beneficial effects of oestrogen.[18–20] CEE, which is composed of a heterogeneous group of at least ten oestrogens[21] may also contain oestrogens with negative effects on cognition.[22] Countering this viewpoint, however, is the preponderance of CEE use among women included in observational studies who had a low risk of dementia. Factors such as the type of oestrogen, route of delivery (eg, transdermal or intramuscular), and dose could alter the effect of HT on cognition and dementia.

Despite possible limitations, WHIMS addressed a critically important clinical issue and found no support for the use of HT (either CEE in combination with medroxyprogesterone acetate, or CEE alone) to reduce the risk of dementia in postmenopausal women older than 65 years. The biological explanation for the increase in dementia is unknown, but might include acute vascular events. These data are strong evidence against the use of HT for cognitive benefit in women older than 65 years. In WHIMS, 54% of women were over age 70 years and 18% were over age 75 years at baseline, but in clinical practice, women of this age are rarely (if ever) prescribed HT for the first time. Also, current treatment guidelines recommend HT for symptomatic menopausal women. Hence, an important question is to what extent the WHIMS data apply to this group of women. Given the findings of WHIMS, what should clinicians advise symptomatic menopausal women about the effects of HT on the brain?

Search strategy and selection criteria

The WHIMS papers were reviewed. A MEDLINE search for the terms "estrogen", "oestrogen", "progestagen", "hormone replacement therapy", "memory", "dementia", and "Alzheimer's disease" between 1969 and 2004 was done. From this search, only papers published in English were reviewed. Papers that were original and relevant to the review topic were included in the final reference list.

The research does not allow a definitive answer to the question of possible benefits of HT to the brains of younger women. A "critical period" shortly after menopause has been suggested; this "window" could be when HT needs to be prescribed to protect cognitive function.[23] The notion of a critical window has been viewed as a desperate last attempt to find a reason to continue recommending HT to patients. What then is the evidence that may support this position?

The practicalities of long-term follow-up preclude a dementia-prevention study in younger women and the best data come from prospective observational studies. For example, in a sample of older women (mean age 74 years) enrolled in the Cache County Study, previous use of HT was associated with a decreased risk of AD, but current use was only protective if begun at least 10 years earlier.[4] Randomised clinical trials in younger women suggest cognitive benefits with early hormone use, although these studies are small in size and short in duration. Impairment in memory after ovarian suppression or oophorectomy can be prevented with early initiation of oestrogen treatment.[24,25] Furthermore, experimental psychopharmacological study of people supports the biological plausibility for neuroprotection with early HT;[26] neuronal membrane turnover[27] and serotoninergic,[28] cholinergic,[29] and dopaminergic[30] responsivity is modulated by use of HT started around the time of menopause. Other insights into the potential of HT to exert neuroprotection come from randomised clinical trials of cognitive outcomes, particularly verbal memory. Two small randomised trials assessed the cognitive effects of HT in women age 50–65 years[31,32] and found beneficial effects on verbal memory and reading. In contrast to the findings of these trials, earlier randomised trials of combined oestrogen plus progesterone in older women show no benefit to verbal memory.[33,34] Both studies differed in the age of the women studied, the type of HT they were given, and sample size. Together, the results of these studies could suggest that early initiation of HT may be beneficial but later use is detrimental.

Conclusion

CEE should not be prescribed to women over age 65 years to enhance cognition or prevent dementia. It is unclear whether the findings of WHIMS can be generalised to women younger than 65 years who are menopausal. We recommend cautioning patients who are young and menopausal about the WHIMS findings but recognise that the absolute risk of dementia in these women is very low and that the clinical benefits may outweigh the risk. Many women will continue to use HT to treat the symptoms of menopause; further research is needed on the neurobiological effects of oestrogen in this group.

Authors' contributions

All authors contributed to the writing of this review.

Conflicts of interest

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