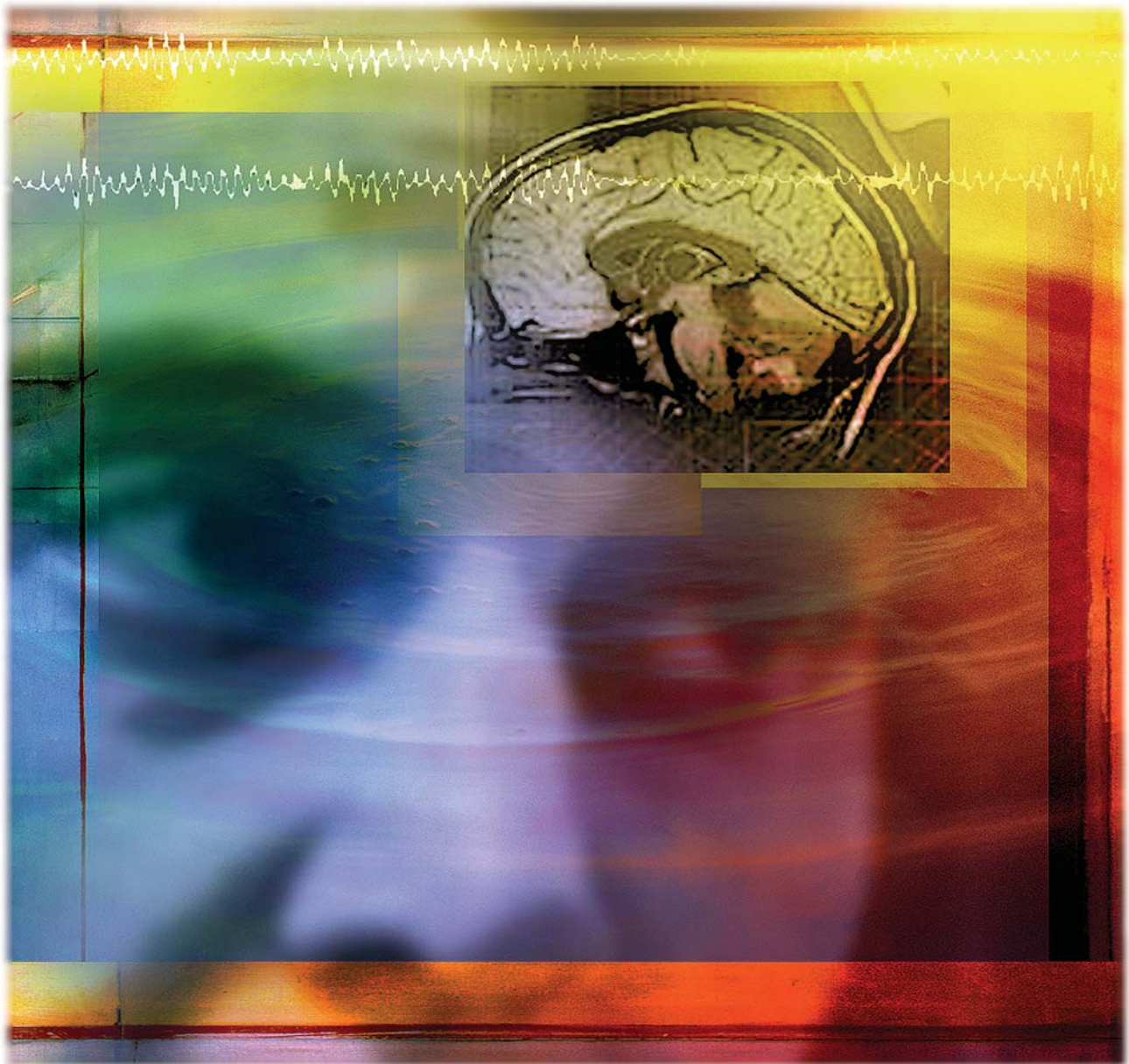

Effects of Hormone Therapy on Cognitive Function: State of the Science Post-WHI

Pauline M. Maki, PhD



Roy Scott

Introduction

Midlife women frequently report memory problems. The majority of women participating in the Seattle Midlife Women's Health Study (62%) report declines in memory function from an earlier period in life.¹ These declines include difficulty recalling words or numbers, forgetting events and actions, and difficulty concentrating. Women attributed declines in memory to stress, health problems and age, rather than hormonal changes or menopausal stage. Women in the early and middle transitional stages are more likely to report these declines than are women in the late transition to postmenopausal stages.² Among women seeking treatment for relief of menopausal symptoms, this rate may be even higher.

With reports from the Women's Health Initiative (WHI) of an increase in the risk for dementia with hormone therapy (HT),³ clinicians frequently confront the challenge of addressing patients' concerns about perceived cognitive declines and fears of dementia. This is a particular concern among women currently using HT, and among those considering initiating HT for the treatment of menopausal symptoms. The present article addresses how our understanding of HT's effects on cognition has evolved in light of findings from the WHI.

Normal and Abnormal Cognitive Aging

HT studies have focused on three primary areas of cognitive aging: normal, age-related changes in cognition; preclinical dementia; and clinical dementia. Individuals who show a decline in performance on cognitive tests from an earlier period in life, but who perform at levels normal for their age are exhibiting normal, age-related changes in cognitive function. Given the lack of proven interventions to slow normal cognitive declines, an important consideration is whether HT might help to maintain cognitive abilities as a woman ages. A second important question is whether HT alters the risk for pathological changes in cognition, specifical-

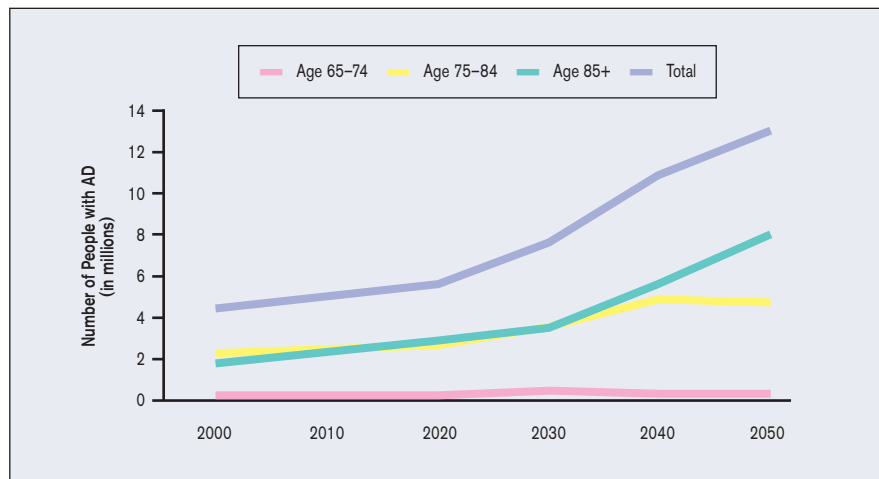


Figure 1. Estimated increase in the prevalence of Alzheimer's disease in the United States.

Adapted from Hebert LE, Scherr PA, Bienias JL, et al. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol* 2003;60:1119-22.

ly preclinical and clinical dementia. Preclinical dementia is observed among individuals who score significantly below their age-peers on cognitive tests, particularly tests of memory, but have minimal, if any, declines in day-to-day function.⁴ This preclinical stage is referred to as "mild cognitive impairment." Clinical dementia sets in when impairment becomes evident in multiple cognitive domains and significantly affects day-to-day functioning.

The most common form of dementia is Alzheimer's disease (AD). In the United States, the number of people diagnosed with AD doubles every 5 years beginning at age 65, and the death rate among women is almost 2½ times higher than that among men.⁵ Estimates suggest that the prevalence of AD will nearly triple by the year 2050 to 13.7 million Americans,⁶ unless treatments are identified that lower disease risk or delay disease onset. With no known primary or secondary treatments to prevent dementia, there is a pressing need for information about factors that might increase or decrease the risk of AD, particularly in women who are at highest risk for the disease (Figure 1).

Hormone Therapy and Dementia Risk

Interest in HT and dementia was heightened with findings from observational studies suggesting a significant

decreased risk for AD among women who had received HT.⁷ Three prospective, observational studies suggested that HT reduced the risk by 39 to 50%.⁸⁻¹⁰ Concerns about treatment bias in the observational studies prompted the Women's Health Initiative Memory Study (WHIMS), a randomized clinical trial in women over age 65.¹¹ WHIMS addressed whether the risk for all-cause dementia (AD, vascular dementia, etc.) is decreased among two groups of women: older hysterectomized women treated with conjugated equine estrogens (CEE); and older, naturally menopausal women treated with CEE plus medroxyprogesterone acetate (MPA; CEE/MPA). The inclusion of older women only was due to the practical need for a sufficient number of dementia cases over the planned 8.5-year study. This need precludes similar studies in younger populations.

All participants in the WHIMS were without probable dementia at the time of their enrollment in the WHI. Dementia evaluations took place in four phases. In Phase I, the modified Mini-Mental State Examination (3MSE) was used to screen WHIMS participants for probable dementia and mild cognitive impairment (MCI)—the preclinical phase of dementia—and to assess global cognitive function. Patients who scored

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below designated cut points on the 3MSE underwent additional clinical evaluation in Phase II, including a neuropsychological evaluation and interviews with the patient and an informant. Phase III involved a clinical dementia evaluation that yielded a determination of no dementia, MCI or probable dementia. Phase IV involved the use of laboratory and imaging studies to aid in diagnosis of the specific dementia subtype (eg, AD, vascular). Central adjudication by three experts was carried out to reach consensus on diagnosis. Across all arms of the study combined, about half of referrals (51%) underwent adjudication and the rest either refused further testing (15%), had incomplete data (14%), died (< 1%) or were not adjudicated (19%).³

The study population for the HT arm of the WHIMS was comprised of 4,532 postmenopausal women age 65 years and older who were enrolled in the CEE/MPA arm of the WHI (Table 1).¹¹ After an average of 4 years of follow-up, 40 cases of probable dementia occurred in the 2,229 women randomly assigned to CEE/MPA, compared with 21 cases in the 2,303 women randomly assigned to placebo. The hazard ratio (HR) for probable

dementia was 2.05, indicating a doubling of the risk for dementia. The HR for MCI was 1.07, which was not statistically significant (95% CI, 0.74-1.55; *P* = .72). In a secondary analysis of cognitive function as measured by the 3MSE, mean total scores in both groups increased slightly over time, presumably due to improvement with practice, but the increases in the CEE/MPA group were smaller compared with the placebo group (*P* < .05).¹² WHIMS investigators considered these differences to be “not clinically important.” However, a potentially meaningful decline (> 2 SDs) in 3MSE total scores was observed more frequently in the CEE/MPA group (6.7%) compared with the placebo group (4.8%; *P* = .008).

The estrogen therapy (ET) alone arm of the WHI included 2,947 hysterectomized women age 65 years and older who were randomly assigned to CEE only.³ After an average of 5.2 years of follow-up, 28 cases of probable dementia occurred in the 1,464 CEE users compared with 19 cases in the 1,483 women randomly assigned to placebo. This difference was not statistically significant (HR = 1.49; 95% CI, 0.83-2.66; *P* = .18). Similarly, the risk for MCI did not differ between the two groups, with 76 cases in the CEE arm compared to 58 in the placebo arm (HR = 1.34; 95% CI, .95-1.89). Importantly,

however, there was no indication of a risk reduction in either AD or MCI with CEE alone.

As per the protocol, WHIMS investigators evaluated the effects of HT on risk for dementia across the two arms combined, and the analysis indicated a significant risk for dementia.³ Sixty-eight of the 3,693 women randomized to active treatment received a dementia diagnosis compared to 40 of 3,786 women randomized to placebo, for an HR of 1.76 (95% CI, 1.19-2.60). Although the risk for dementia in the CEE-alone arm did not reach significance, the incidence rates for probable dementia and hazard ratios did not differ significantly between the CEE/MPA and CEE-alone arms. One must be cautious in comparing the two arms and, in particular, in attributing less risk to CEE alone, because compared with women in the CEE/MPA arm, those in the CEE-alone arm had used HT more frequently in the past, were more ethnically diverse, were more likely to have had a previous stroke or coronary heart disease, had lower educational attainment and had lower 3MSE scores (Table 1).

HT and Risk for Dementia: A Vascular Effect?

The increased risk of dementia with HT in the WHI was hypothesized to be due primarily to an increase in vascular-relat-

Table 1. Incidence of Probable Dementia by Treatment Assignment in all Arms of the Women’s Health Initiative Hormone Therapy Intervention Trial.*

	Estrogen-Alone Trial			Estrogen + Progestin Trial			Estrogen Alone or Estrogen + Progestin Trial		
	Treatment Placebo (n = 1464)	(n = 1483)	HR (95% CI)	Treatment Placebo (n = 2229)	(n = 2303)	HR (95% CI)	Matching Treatment Placebos (n = 3693)	(n = 3786)	HR (95% CI)
Probable dementia No. (%)	28 (1.9)	19 (1.3)		40 (1.8)	21 (0.9)		68 (1.8)	40 (1.1)	
Follow-up mean (SD), y	5.16 (1.77)	5.20 (1.71)		4.01 (1.21)	4.06 (1.18)		4.47 (1.56)	4.51 (1.52)	
Rate per 10,000 person-years	37	25	1.49 (0.83-2.66)	45	22	2.05 (1.21-3.48)	41	23	1.76 (1.19-2.60)

*Reprinted with permission from Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women’s Health Initiative Memory Study. *JAMA* 2004;291:2947-58. Copyrighted © 2004, American Medical Association. All rights reserved. CI indicates confidence interval; and HR, hazard ratio.

ed dementia. The risk of ischemic stroke was significantly higher among women randomized to active treatment in both the CEE/MPA arm (HR = 1.44; 95% CI, 1.09–1.90)¹³ and the CEE-alone arm (HR = 1.39; 95% CI, 1.10–1.77).¹⁴ In recent years there has been an increased appreciation for the relationship between dementia and silent ischemic events; ie, those ischemic events that are not clinically manifest but are evident at autopsy or on imaging scans. Several studies report increased risk of dementia in individuals showing infarcts. For example, a higher prevalence of dementia and lower cognitive outcomes are found among those with postmortem evidence of infarcts plus Alzheimer’s pathology compared to those with Alzheimer’s pathology alone.¹⁵ These findings suggest that ischemic events lead to a worse clinical outcome in AD. Notably, women with AD appear to have a higher incidence of infarctions at autopsy compared to men.¹⁶ To further explore the impact of HT on ischemia and cognition in the WHI, WHIMS participants are now undergoing structural magnetic resonance imaging brain scans as part of a new study to determine whether the risk for ischemic events differed between active treatment and placebo groups.

Do the WHIMS Results Generalize to Younger Women?

An important and unanswered question is whether the WHIMS dementia findings in women 65 years and older generalize to the typical HT user who initiates therapy earlier in life for the treatment of menopausal symptoms. Prospective, observational studies suggesting that HT reduces the risk of AD are based on women with typical patterns of HT use earlier in the menopause. Thus, the prospective and randomized studies differ not only in terms of whether treatment was randomized but also in terms of the timing of initiation of therapy. Recent studies suggest that age of initiation of therapy may be an important determinant for whether HT is harmful or beneficial to brain function.

Some observational studies provide support for the view that early initiation of HT might protect against AD whereas later use may increase the risk. For example, data from a prospective observational study from Cache County Utah revealed an increased risk for AD in older women who initiated HT on average after age 64, and a decreased risk for dementia in older women who initiated HT on average before age 64 (Figure 2).¹⁰ These observational findings predicted the WHIMS findings of increased dementia in women initiating HT after age 65. The findings also led to the “critical period hypothesis”,¹⁷ which proposes that HT confers optimal neuroprotection when initiated close in time to the menopausal transition.

Additional evidence in favor of the critical period hypothesis was found in a recent case-control study of women participating in the Multi-Institutional Research in Alzheimer Genetic Epidemiology (MIRAGE) study (Table 2).¹⁸ The sample included 971 postmenopausal women, and the large number of AD cases (n = 426) provided sufficient power to examine whether age modulated the effect of HT on AD risk. Hormone users included women who used either standard HT or oral contraceptives after age 35 for at least 6 months (n = 279). Across all age groups combined, the risk of AD

was significantly lower among HT users (OR = 0.70; 95% CI, 0.51–0.95). In analyses stratified by age tertiles, only the youngest age group (aged 50–63) showed a significant risk reduction (OR = 0.35; 95% CI, 0.19–0.66). One interpretation of these findings is that early initiation protects against AD; those in the youngest age group necessarily initiated HT at a younger age, but those in the older age groups could have initiated HT at any age. The variability in age of initiation in the older groups may also account for the wider confidence intervals observed in those groups.

Other data suggest that timing of HT initiation may influence cognitive aging. For example, prospective observational data from the Melbourne Midlife Women’s Health Study revealed better verbal memory among women who initiated HT before the final menstrual period compared with women who initiated HT sometime after menopause.¹⁹ These findings are consistent with findings from randomized clinical trials showing beneficial effects of HT on verbal memory in women initiating HT immediately after surgical menopause.^{20,21} The findings also agree with those of two recent randomized clinical trials showing enhanced verbal memory in women aged 50 to 65 randomized to receive HT,^{22,23} but no benefit

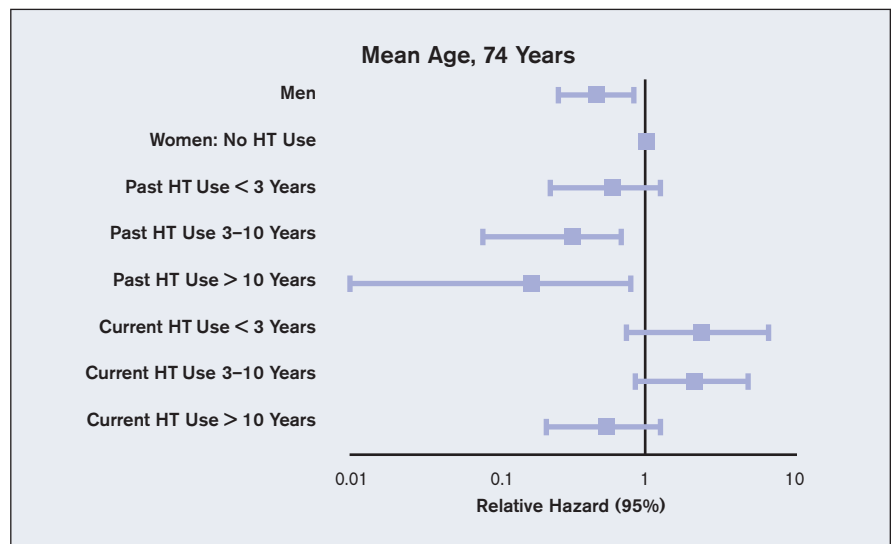


Figure 2. Risk of incident AD in the Cache County Study: the effect of timing and duration of HT use. Reprinted with permission from Zandi PP, Carlson MC, Plassman BL, et al. Hormone replacement therapy and incidence of Alzheimer’s disease in older women: The Cache County Study. *JAMA* 2002;288:2123-9. Copyrighted © 2002, American Medical Association. All rights reserved.

Table 2.
Risk for Alzheimer's Disease by Age and Hormone Therapy Use in the MIRAGE study*

	Number of Alzheimer cases	Number of controls without dementia	Crude OR (95% CI)	Adjusted OR (95% CI) [†]
Entire sample (ages 50-99)				
No HT	339	353	Reference	Reference
HT	87	192	(0.35-0.63)	(0.51-0.95)
First age tertile (50-63 years)				
No HT	58	135	Reference	Reference
HT	17	112	0.35 (0.19-0.64)	0.35 (0.19-0.66)
Second age tertile (64-71 years)				
No HT	105	127	Reference	Reference
HT	28	52	0.65 (0.39-1.1)	0.86 (0.50-1.5)
Third age tertile (72-99 years)				
No HT	176	91	Reference	Reference
HT	42	28	0.78 (0.47-1.3)	0.97 (0.57-1.6)

*Reproduced with permission from the BMJ Publishing Group. Henderson VW, Benke KS, Green R, et al. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. *J Neurol Neurosurg Psychiatry* 2005;76:103-5.

CI indicates confidence interval; and HT, estrogen-containing hormone therapy.

[†]Adjusted for age, education, and ethnicity.

or a trend toward worse verbal memory in women who were, on average, age 71 or 82 at randomization.^{24,25} Variations in age at initiation might also explain the inconsistency in findings regarding HT and cognitive function. Additional randomized clinical studies are needed to understand whether the discrepancy between findings from the prospective observational studies and the WHIMS reflect the critical issue of study design (randomized versus observational), timing of initiation of HT in relation to the menopause (early versus late) or some other factor.

Two of the primary mechanisms by which HT is thought to exert neuroprotection appear to be age-dependent; namely, effects on the hippocampus and interactions with the cholinergic system. Early studies show that estrogen exerts direct effects on the morphology and connectivity of the hippocampus, a brain area critical to memory functioning. Dendritic

spine density in the hippocampus fluctuates with circulating estradiol over the estrous cycle²⁶ and increases with estradiol treatment²⁷ in female rats. The mechanisms by which estradiol induces increases in hippocampal spine density are age-dependent, with younger, but not older, female rats showing the increase.²⁸ Estrogen interacts with the cholinergic system to reverse memory deficits in younger rats,²⁹ but not in older rats.³⁰ These studies suggest two mechanisms by which HT might confer protection to the hippocampus and memory in younger, but not older animals.

Limitations on the Critical Period Hypothesis

The critical period hypothesis may apply only to certain cognitive domains affected by normal aging, and to certain HT regimens. For example, older rhesus monkeys given cyclic estrogen without a progestin

show improvement on a spatial working memory task.³¹ Similarly, older women initiating HT show preservation of figural memory as they age compared to controls matched for age, education, and performance prior to HT initiation.³² Finally, elderly women with osteoporosis enrolled in the Multiple Outcomes of Raloxifene Evaluation and randomized to raloxifene treatment demonstrated improved verbal memory and psychomotor speed over a 3-year interval compared to women randomized to placebo.³³

Critical Period for Cardioprotection and Neuroprotection

A similar critical period has been proposed for HT and cardioprotection.³⁴ For example, although the WHI was underpowered to detect benefit for cardioprotection in the CEE-alone arm, the data suggested a trend toward benefit (HR = .50; 95% CI, .53-1.03). Recent longitudinal studies suggest that cardiovascular risk factors, including hypercholesterolemia and hypertension, increase the risk for AD, and that statins may lower the risk for AD.^{35,36} The parallel between potential early benefit of HT on the cardiovascular system and brain raise interesting questions about possible common mechanisms of benefit and risk. Results from the CEE-alone arm of the WHI suggest that the hormone effects on cardiovascular and other outcomes may be age-dependent.¹⁴ There was a trend toward an effect of age on the Global Index ($P < .10$), a composite score reflecting the impact of treatment across multiple health outcomes, including breast cancer, fractures, cardiovascular disease and stroke. Although the study was underpowered to detect an age effect, the pattern of effects on the Index suggested a tendency to favor CEE among the youngest group and placebo among the oldest group. Questions concerning the impact of HT on cognition and cardiovascular health are the focus of the Kronos Early Estrogen Prevention Study, a 5-year, randomized, placebo-controlled trial examining the effects of transdermal

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and oral HT on cardiovascular risk factors and cognitive test performance over time in 900 younger (ie, perimenopausal and early postmenopausal) women.

Summary and Conclusions

Basic science studies, observational studies, and randomized clinical studies suggest that women in the earlier stages of the menopausal transition might gain cognitive benefits from HT. These data support the critical period hypothesis, but not definitively. Indeed, it is not likely that a definitive study supporting the critical period hypothesis will be carried out any time in the near future. This is due in part to the impracticality of performing a randomized clinical study in midlife for a dementia outcome after age 65. The limitations of carrying out a primary prevention study in midlife are a concern not only for HT, but for statins and other agents that might optimally alter the course of cognitive aging when given before the disease process is evident. Given those limitations, there is a critical need for clinical studies with cognitive test endpoints examining the effects of various menopausal therapies (selective estrogen-receptor modulators, various progestins, estrogens, routes of delivery, phytoestrogens), particularly among symptomatic women and women with premature ovarian failure. With the increase in the number of elderly women worldwide and the lack of proven approaches to preventing dementia, a better understanding of the impact of HT on cognitive function is critically important.

How is a clinician to counsel women about the risks of HT and dementia? Cognitive complaints are not an indication for HT. Therefore, consideration of cognitive effects applies to women who initiate HT for menopausal symptoms or other complaints. In the absence of firm data to the contrary, it seems clinically prudent to caution women initiating HT early in life about

the WHIMS findings, recognizing that the absolute risk of dementia in those women is very low. ■

Pauline M. Maki, PhD, is Associate Professor of Psychiatry and Psychology, Departments of Psychiatry and Psychology, University of Illinois at Chicago.

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