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Hormone therapy and cognitive function

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BACKGROUND: Clinical trials yield discrepant information about the impact of hormone therapy on verbal memory and executive function. This issue is clinically relevant because declines in verbal memory are the earliest predictor of Alzheimer's disease and declines in executive function are central to some theories of normal, age-related changes in cognition.

METHODS: We conducted a systematic review of randomized clinical trials of hormone therapy (i.e. oral, transdermal, i.m.) and verbal memory, distinguishing studies in younger (i.e. $\leq$65 years of age; $n = 9$) versus older (i.e. >65 years; $n = 7$) women and studies involving estrogen alone versus estrogen plus progestogen. Out of 32 placebo-controlled trials, 17 were included (13 had no verbal memory measures and 2 involved cholinergic manipulations). We also provide a narrative review of 25 studies of executive function (two trials), since there are insufficient clinical trial data for systematic review.

RESULTS: There is some evidence for a beneficial effect of estrogen alone on verbal memory in younger naturally post-menopausal women and more consistent evidence from small-n studies of surgically post-menopausal women. There is stronger evidence of a detrimental effect of conjugated equine estrogen plus medroxyprogesterone acetate on verbal memory in younger and older post-menopausal women. Observational studies and pharmacological models of menopause provide initial evidence of improvements in executive function with hormone therapy.

CONCLUSIONS: Future studies should include measures of executive function and should address pressing clinical questions; including what formulation of combination hormone therapy is cognitively neutral/beneficial, yet effective in treating hot flashes in the early post-menopause.

Key words: menopause / hormone therapy / cognition / estrogen / memory

Introduction

This review is organized in two parts. The first is a systematic review of the effects of hormone therapy on verbal memory, as evidenced exclusively by findings from randomized, placebo-controlled, clinical trials. For reasons discussed in detail below, this systematic review distinguishes trials in younger (i.e. <65 years of age) versus older post-menopausal women (i.e. >65 years of age) and distinguishes trials of estrogen alone versus trials of estrogen plus progestogen. The second part of the article is a narrative review, largely based on

findings from observational studies of hormone therapy and executive functions, a topic that has not been sufficiently investigated in clinical trials. We conclude from the first part of the review that there is some evidence for a beneficial effect of estrogen alone therapy on verbal memory in younger post-menopausal women and more consistent evidence from small-n studies of surgically post-menopausal women. We further conclude that there is strong evidence of a detrimental effect of combined estrogen and progestogen therapy, particularly conjugated equine estrogen plus medroxyprogesterone acetate (CEE/MPA), on verbal memory in older post-menopausal women. There is also evidence of a detrimental effect of combination CEE/MPA on verbal memory in younger women. We conclude from the second part of the review that there is sufficient evidence of improvements in executive function with hormone therapy to justify the routine inclusion of these outcome measures in future clinical trials of hormone therapy.

Part 1: Hormone therapy and verbal memory

Background

The hypothesis that hormone therapy might protect against cognitive aging arose in large part from observational studies demonstrating a lower risk of Alzheimer's disease among women who had been treated with hormone therapy compared with those who had never been treated with hormone therapy. Meta-analyses of these observational studies suggested that a history of hormone therapy use decreased the risk of Alzheimer's disease by 29% (Yaffe et al., 1998) to 34% (LeBlanc et al., 2001). Most of the observational studies (i.e. 10 of 12 studies) were based on samples from the USA. Therefore, it is important to note certain characteristic patterns of hormone therapy use in the USA. The Third National Health and Nutrition Examination Survey indicated that 7% of women who used hormone therapy started therapy before they experienced natural or surgical menopause, 48% started therapy within a year after menopause, 10% started 2–4 years after menopause, and 25% started five or more years after menopause (Brett and Chong, 2001). In 1992, 90% of women who used hormone therapy were age 60 or younger (Wysowski et al., 1995). The most frequent type of hormone therapy used was estrogen only therapy (Wysowski et al., 1995; Brett and Madans, 1997). The most common form of estrogen therapy was CEE (Wysowski et al., 1995). In 1992, 69% of women who had used hormone therapy indicated that they had used estrogen only hormone therapy, although only 31% had also used progestogen (Brett and Madans, 1997). Based on these patterns of usage, it is reasonable to assume that the large majority of women in the observational studies initiated estrogen only therapy (typically CEEs) early in life and stopped using hormone therapy after age 60. Thus, it is reasonable to assume that the hypothesis that hormone therapy protects against Alzheimer's disease was based on use of estrogen alone beginning in early post-menopause and stopping before age 60.

It is impractical to initiate a randomized trial in early post-menopausal women (assuming an average age of menopause of 51.4 years) and follow them prospectively until they reach an age, typically a minimum of 65 years, when they are at increased risk for Alzheimer disease. Such an investigation would require a minimum of a 15-year follow-up. The practical solution to this challenge is to conduct a clinical trial in women, who are currently at increased risk for Alzheimer disease, that is, women who are at minimum 65 years of age. The Women's Health Initiative Memory Study (WHIMS) did exactly that, and specifically investigated the impact of CEE in women with prior hysterectomy over age 65 and the impact of CEE/MPA in naturally post-menopausal women over age 65 (Shumaker et al., 2003, 2004). Each of the two trials was stopped prematurely. Although Alzheimer disease was the a priori primary outcome of interest (Shumaker et al., 1998), all-cause dementia became the default primary outcome because of the lack of a sufficient number of Alzheimer cases. In a sample of 2947 post-menopausal women with prior hysterectomy, there was no evidence that CEE lowered the risk of all-cause dementia; the effects were statistically neutral [Hazard Ratio (HR) = 1.49, 95th percentile confidence interval (95% CI) = 0.83–2.66] (Shumaker et al., 2004). In a sample of 4532 naturally post-menopausal women, CEE/MPA doubled the risk for all-cause dementia [HR = 2.01, 95% CI = 2.05 (1.21–3.48)] (Shumaker et al., 2003). Thus, far from supporting the view that hormone therapy protects against dementia, this study demonstrate that combination CEE/MPA substantially increases the risk for all-cause dementia.

This finding came as a surprise to many researchers because prior to WHIMS not a single observational study reported a significant increased risk in dementia with hormone therapy. However, findings from a prospective observational study from Cache County, published before WHIMS, found evidence that prior use of hormone therapy (i.e. typically when initiated early in the menopause) protected against Alzheimer disease, but current use of hormone therapy unless initiated more than 10 years earlier (i.e. on average before age 63) did not protect against Alzheimer's disease. Indeed, the point estimate (HR) for Alzheimer risk among women who were current users of hormone therapy for 3–10 years (i.e. who initiated on average between age 61 and 68) was 2.12, similar to WHIMS, whereas the point estimate was 0.55 among older women who were current users but began at younger ages (Zandi et al., 2002). The authors concluded, 'A new finding in this study is an apparent limited window of time during which sustained hormone replacement therapy (HRT) exposure seems to reduce the risk of AD (p. 2128)'. A subsequent observational study demonstrated that oopherectomy before age 48, but not after age 48, is associated with an increased risk of Alzheimer's disease, and estrogen therapy can prevent this risk (Rocca et al., 2007). A number of articles since the Women's Health Initiative (WHI) have raised the possibility that there is a critical window or period in which hormone therapy exerts cognitive benefits, and this window may be early in the menopausal transition and/or at younger ages (Resnick and Henderson, 2002; Sano et al., 2002; Henderson, 2006; Maki, 2006).

Early basic science studies supported the biological plausibility that estrogen enhanced memory and the function of brain structures and systems subserving memory in young female animals (see McEwen et al. (1997) for a review). Included in these mechanisms of action were changes in the morphology and synaptic plasticity of the hippocampus (Woolley et al., 1990, 1996; McEwen and Woolley, 1994; Woolley and McEwen, 1994), functional interactions with the

cholinergic and serotonergic system (Toran-Allerand et al., 1992; Singh et al., 1994; Bethea et al., 1998; Pan et al., 1999), and enhancements in hippocampal-dependent memory (Gibbs, 1999; Farr et al., 2000). Importantly, the animal model typically used in basic science studies is ovariectomy, a model that best translates to abrupt withdrawal of ovarian steroid hormones following surgical menopause. Also, the model employed younger animals because of the lower cost associated with using younger animals and the lack of appreciation in the basic and clinical field of the potential importance of age.

When basic scientists began to explore the effects of early versus later initiation of hormone therapy on both memory performance and the brain systems that subserve memory, important age effects emerged (see Gibbs and Gabor (2003) and Adams and Morrison (2003) for reviews). For example, early initiation of estrogen alone or estrogen plus progestogen following ovariectomy enhanced performance on a hippocampal-task in female rats, but delaying treatment by 10 months led to no improvements on the task (Gibbs, 2000). In young female rats, estrogen reversed the memory impairment induced by disrupting cholinergic transmission, but in older female rats estrogen does not reverse this memory impairment (Markowska and Savonenko, 2002). A translational study in humans showed similar results: pretreatment with estradiol mitigated against declines in verbal memory following cholinergic suppression in younger, but not older, post-menopausal women (Dumas et al., 2008). The complexity of estrogen actions in the brain is further exemplified by the discovery of non-genomic and synaptic estrogen receptors and the discovery that the brain produces estrogen (see Woolley (2007) for a review). Lastly, the complexity of combination estrogen plus progesterone on brain function is complicated by the discovery that certain forms of progesterone, particularly MPA, but not other progestogens, antagonizes the effects of estrogen on neural structures subserving memory, particularly the hippocampus (Nilsen and Brinton, 2002a, b, 2003). This evidence suggests that progestogen formulation may be an important determinant of the impact of combination therapy on hippocampally mediated functions such as verbal memory. The evidence also provides a rationale for exploring the impact of different estrogen/progestogen combination therapies on verbal memory. Thus, both timing of initiation and type of therapy may be critical determinants of the effects of hormone therapy on cognition and brain function.

Although basic science and clinical studies suggest a need to further investigate the critical window hypothesis, the challenge remains—how do we best test the critical window hypothesis in light of the impracticality of a definitive, 15-year clinical trial? One approach is to investigate the impact of hormone therapy on an outcome variable that predicts dementia later in life. Studies demonstrate that the ability to acquire and recall new verbal information is the best, and possibly the earliest, neuropsychological predictor of who will convert to Alzheimer's disease (Jacobs et al., 1995; Linn et al., 1995; Albert et al., 2001; Tian et al., 2003; Saxton et al., 2004; Tierney et al., 2005; Tabert et al., 2006; Blacker et al., 2007). This ability, commonly called 'verbal memory' in the hormone therapy literature, is labeled as 'episodic memory' in the cognitive literature. Verbal memory is commonly tested with neuropsychological measures including the California Verbal Learning Test. This test that involves the acquisition of a 16-item shopping list over a series of five trials (i.e. Trial 1–5), the immediate recall of the original shopping list after a single exposure to a different and 'distracting' shopping list (i.e. short delay free

recall) and the 20-min delayed recall of the original shopping list (i.e. long-delay free recall) (Delis et al., 2000). Less challenging word list learning tests are sometimes given, including the word list test from the Consortium to Establish a Registry for Alzheimer's Disease, which involves three presentations of a 10-item world list and no distractor word list (Morris et al., 1989). Other verbal memory tests come from the Wechsler Memory Scale Revised (Wechsler, 1987) and involve the immediate and delayed recall of a short story or paragraph from the Logical Memory subtest (hereafter called 'Paragraph Recall') or the immediate and delayed recall of related and unrelated word pairs from the Verbal Paired Associates subtest.

In addition to their utility in predicting who will develop Alzheimer's disease, verbal memory tests are relevant to the study of hormone therapy for other reasons. There is a sex difference in favor of women on this cognitive ability (Kramer et al., 1988, 2003). Moreover, midlife women complain about lapses in verbal memory. In the Seattle Midlife Women's Health Study, of 230 women interviewed (mean age = 47 years), 62% reported an undesirable change in memory (Mitchell and Woods, 2001). Changes included difficulty recalling words or numbers, forgetting events and actions and difficulty concentrating. Women attributed these changes to stress, health and age rather than hormonal changes. In a follow-up analysis, complaints were more frequent in the early and middle transitional stages than in the late transition and post-menopausal stages (Woods et al., 2000). Unfortunately, to date there are no prospective studies of objective memory across the menopausal transition, although results from Gail Greendale and her colleagues from the Study of Women's Health Across the Nation are forthcoming. There are prominent decreases in verbal memory that occur in the absence of pre-clinical or clinical dementia (Zelinski and Burnight, 1997; Davis et al., 2003; Lamar et al., 2003). In the present review, we therefore focus on the impact of hormone therapy on verbal memory not only because verbal memory predicts dementia risk later in life, but also because verbal memory shows an advantage in women compared with men, declines with normal aging, and is the subject of frequent complaint among peri- and post-menopausal women and older individuals.

Methods

For the systematic review of clinical trials of hormone therapy and verbal memory, we carried out a literature search from 1966 to October 2008 through the PubMed database http://www.ncbi.nlm.nih.gov/pubmed/. We also consulted previous reviews. We selected only publications in the English language and used key words 'menopause', 'post-menopausal', 'peri-menopausal', 'women', 'hormone therapy', 'HRT', 'estrogen therapy', 'estrogen replacement therapy', 'clinical trial', 'memory' and 'cognition'. Electronic versions of the retrieved documents were printed and reviewed to determine whether the trial met the following inclusion criteria: (a) participants were peri-menopausal and/or post-menopausal women (i.e. no premenopausal women); (b) design was a randomized-controlled clinical trial with placebo as the comparator treatment; (c) outcome measures included an episodic verbal memory measure; and (d) study design did not include any pharmacological manipulation (e.g. leuprolide acetate or scopolamine).

In light of the predominance of the critical window hypothesis in the literature, we present a summary of studies as a function of mean age at randomization to hormone therapy, specifically dichotomizing studies based on whether the mean age is ≤65 years of age or >65 years of age. The justification for this age cut-off is based on the typical cut-off in cognitive studies in older adults, including the WHIMS (Shumaker et al., 2003, 2004). In light of findings that MPA antagonizes the effects of estrogen on the hippocampus, we further separate the studies based on whether the treatment used was estrogen alone or estrogen in combination with progestogen.

Results

A total of 32 articles were identified as placebo-controlled clinical trials of hormone therapy and cognitive function in peri- or post-menopausal women. Thirteen trials were excluded because they did not include a measure of verbal episodic memory (Vanhulle and Demol, 1976; Fedor-Freybergh, 1977; Ditkoff et al., 1991; Goebel et al., 1995; Polo-Kantola et al., 1998; Duka et al., 2000; Janowsky et al., 2000; Saletu et al., 2002; Hays et al., 2003; Krug et al., 2003; Rapp et al., 2003b; Espeland et al., 2004; Viscoli et al., 2005), and two trials were excluded because the comparison of estrogen versus placebo was nested in pharmacological manipulations of scopolamine, mecamylamine and placebo (Dumas et al., 2006, 2008). There were a total of 17 studies included in this systematic review.

Table I presents a summary of seven randomized, placebo-controlled trials of estrogen alone therapy on episodic verbal memory in samples of women with a mean age <65 years (Hackman and Galbraith, 1976; Sherwin, 1988b; Phillips and Sherwin, 1992; Shaywitz et al., 2003; Dunkin et al., 2005; Joffe et al., 2006; LeBlanc et al., 2007). Among the four positive studies, three were conducted in samples of surgically post-menopausal women (Hackman and Galbraith, 1976; Sherwin, 1988a; Phillips and Sherwin, 1992). Although positive, those three studies are limited by sample sizes of 50 women or less and a therefore a lack of replication in larger samples. Certain aspects of trial design may have limited the ability of the neutral studies to detect an effect of estrogen therapy on verbal memory. First, the sample sizes are small, ranging from 17 to 60 women, so the power to detect a significant effect in these studies is low. Second, one of those studies included only one of the standard measures of verbal memory from the California Verbal Learning Test, and omitted short- and long-delay free recall, which are sensitive to hormone effects in other studies (Maki et al., 2001, 2007; Resnick et al., 2006); however, that same study found that hormone therapy improved performance on a measure from the test that not typically reported but is reflective of executive function rather than verbal memory per se (Joffe et al., 2006). As reviewed later in this article, such evidence provides a justification for including similar measures in future clinical trials. Third, a neutral study, the only crossover study, lasted only 21 days per participant, leading to significant practice effects over the short test–retest interval (Shaywitz et al., 2003). To address that bias against detecting a significant estrogen effect, the authors conducted a between-subjects analysis during the first post-treatment session. In that analysis, estrogen was associated with improved verbal memory. Thus, although the study was 'neutral' when examining group differences in change from pre- to

post-treatment, the study was positive when controlling for practice effects. Fourth, one study included three testing sessions within an 8-week period of time (LeBlanc et al., 2007); successive test sessions over such a short interval can increase carry-over (e.g. practice) effects and lessen the likelihood of observing a significant hormone effect (Maki, 2003). In summary, despite small sample sizes and design choices that can minimize the ability to detect a significant effect of estrogen therapy on verbal memory, these studies provide the rationale for the hypothesis that estrogen alone enhances verbal memory in younger women, particularly those who are surgically post-menopausal.

Table II presents a summary of randomized, placebo-controlled trials of combined estrogen plus progestogen therapy on cognitive function in samples of women with a mean age <65 years (Linzmayer et al., 2001; Maki et al., 2007). Only one trial to date directly compared estrogen alone (e.g. estradiol valerate) versus estrogen plus progestogen (e.g. estradiol valerate plus dienogest) versus placebo (Linzmayer et al., 2001). Combined hormone therapy enhanced associative verbal memory compared with both placebo and estradiol. The largest study to date ($n = 180$) of any form of hormone therapy on verbal memory in women younger than age 65 was the Cognitive Complaints in Early Menopause Trial (Maki et al., 2007) and included women (mean age 52) with cognitive complaints at baseline. Results indicated a trend ($P < 0.07$) for CEE/MPA to decrease both short- and long-delay free recall compared with placebo. In summary, these two studies suggest that different forms of progestogen may have different effects on cognitive function, with negative effects of MPA on verbal memory and positive effects of dienogest, a progestin with anti-androgenic effects that is used primarily in Germany.

The top of Table III presents a summary of randomized, placebo-controlled trials of estrogen alone therapy on episodic verbal memory in samples of women with a mean age of more than 65 years (Wolf et al., 1999; Schiff et al., 2005; Almeida et al., 2006; Yaffe et al., 2006). To date, there are four trials, each with a different estradiol formulation. Results from each of these studies show neutral effects. Notably, the largest of these, a study involving 417 women (mean age 66.7 years) showed no negative impact, nor a trend toward a negative impact, of an ultra low-dose transdermal estradiol (0.14 mg/d) over a 2-year treatment interval. Importantly, no negative effects were observed on other cognitive outcomes in any of these four studies. Therefore, these studies suggest that certain formulations of estradiol can be initiated later in life without negative effects to verbal memory or other cognitive functions.

The bottom portion of Table III presents a summary of randomized, placebo-controlled trials of combined estrogen plus progestogen therapy on cognitive function in samples of women with a mean age older than 65 years (Binder et al., 2001; Grady et al., 2002; Resnick et al., 2006; Pefanco et al., 2007). Three of these four trials showed either a negative effect (Resnick et al., 2006; Pefanco et al., 2007) or a trend ($P < 0.06$) for a negative effect of hormone therapy on verbal memory (Grady et al., 2002). Two of these trials, Heart and Estrogen/progestin Replacement Study and WHI Study of Cognitive Aging (WHISCA), involved large sample sizes (e.g. 1328 and 1416), a similar dose of hormone therapy (e.g. 0.625 mg CEE plus 2.5 mg MPA) and a follow-up of more than 1 year (Grady et al., 2002; Resnick et al., 2006), and both found a negative impact on memory

Table I Randomized, placebo-controlled, clinical trials of estrogen alone and verbal memory in younger women

Author (Year)	N (All) Final ET/Pl	Mean Age (SD or span)	Prior HT Use (%)	Menopausal Status/ menopausal symptoms/ years since menopause	Design	Dur	ET	Dose	Test	Results
Hackman and Galbraith (1976)	(?) 18 9/9	(29–68)	?	Eight surgically menopausal patients/10 patients with symptoms (4 mild and 1 moderate in ET group)/Unknown yrs since menopause	Parallel (2 grps)	6 m	Cyclic Oral piperazine El	3 mg/d for 21 d (1.5 mg bid); 7 days off	Total Score on the Guild Memory Test (Paragraph Recall, Paired Associates, Digits Forward and Backward, DSST)	ET > Pl on total memory score
Sherwin (1988a, b)	(53) 50	45.4	Likely none	All surgical menopausal (BSO/ TAH)/Likely symptomatic from hysterectomy following baseline assessment/No delay in intervention after surgical menopause	Crossover (4 grps)[a]	3 m	Monthly injections of E (IM E2/d), E-A (TE, E2 dienanthate, and E2 benzoate), A (TE)	E2 IM (10 mg); TE (150 mg), E2 (7.5 mg), E2 benzoate (1 mg); TE (200 mg)	Paragraph Recall	HT > Pl
Phillips and Sherwin (1992)	(31) 19 10/9	48 (5)	Likely none	All surgical menopausal (BSO/ TAH)/Likely symptomatic from hysterectomy following baseline assessment/No time delay in intervention after surgical menopause	Parallel (2 grps)	2 m	Monthly injections of E2	10 mg/m	Paragraph recall; Paired Associates	ET > Pl Immediate Paragraph recall; Immediate and Delayed Paired Associates
Shaywitz et al. (2003)	(60) 60 29/31	51.2 (32–64)	27%	Post-menopausal/80% had menopausal symptoms/Est. 3 yrs post-menopausal	Crossover	21 d	Continuous Oral CEE	1.25 mg/d,	Paragraph Recall; Paired Associates	ET = Pl[b]
Dunkin et al. (2005)	(26) 17 9/8	57.0 (7.2)	6%	Post-menopausal, 13% surgically menopausal/Menopause symptoms unknown/ Approximately 8 years since menopause	Parallel (2 grps)	10 wk	Transdermal E2	0.1 mg E2/d	California Verbal Learning Test (Trials 1–5 total, short- and long-delay free recall, recognition); Paragraph Recall; Paired Associates	ET = Pl[c]
Joffe et al. (2006)	(52) 50 26/24	51.0 (3.8)	18%	18% Early Transition, 38% Late Transition, 40% Early Postmenopause, and 4% Hysterectomy without oopherectomy/62% with symptoms (30% mild, 14% moderate, 18% severe)/n/a	Parallel (2 grps)	3 m	Transdermal E2	0.05 mg/d	California Verbal Learning Test (Trials 1–5, perseverative errors during verbal recall, proactive interference during verbal recall, verbal learning, retroactive memory)[d]; Wechsler Memory Scale Verbal Memory[e]	ET > Pl perseverative errors; Trend proactive interference (P < 0.07)[f]

Continued

Table I *Continued*

Author (Year)	N (All) Final ET/ PI	Mean Age (SD or span)	Prior HT Use (%)	Menopausal Status/ menopausal symptoms/ years since menopause	Design	Dur	ET	Dose	Test	Results
LeBlanc et al. (2007)	(37) 32 14/18	52.6 (0.64)	?	last menstrual period between 3 and 36 months before enrollment/Average 4 daily hot flashes/n/a	Parallel (2 grps)	2 m	Oral tablet	2 mg/d	Paragraph Recall; Paired Associates[g]	ET = PI

Abbreviations: a = androgen, BSO = bilateral salpingo oopherectomy, CEE = Conjugated Equine Estrogen, d = day, DSST = digit symbol substitution test, Dur = duration, E = estrogen, E-A = Estrogen and androgen, Est. = estimated, ET = Estrogen Therapy, E1 = estrone, E2 = estradiol, E3 = estriol, grps = groups, HT = Hormone Therapy, IM = intramuscular, m = months, mg = milligrams, n/a = not applicable for perimenopausal women, PI = Placebo, SD = Standard Deviation, TAH = total abdominal hysterectomy, TE = testosterone enanthate, wk = week, yr = years.

Note: If mean years since menopause was not provided in article, value was estimated as difference between current age and average age of menopause = 51.

[a]Fifty-three subjects were originally recruited, nine dropped out, and six additional women were recruited into study. Here all three active treatment groups are combined in results, because they did not differ from one another.

[b]To examine effect of treatment independent of practice effects, secondary analyses focused on between-groups differences during first post-treatment testing session. That analysis revealed a benefit of hormone therapy over placebo.

[c]Trend toward heavier women benefiting more than lighter women from estrogen in terms of verbal memory processes.

[d]Standard California Verbal Learning Test outcomes (e.g. short delay recall, long delay recall) were not included in results.

[e]Immediate and delayed logical memory and paired associates from the Wechsler Memory Scale—Revised were not provided; instead summary indices were provided including Wechsler Verbal Memory (i.e. Logical Memory I × 2) and Delayed Recall (which combined visual and verbal memory). Thus, results are not comparable to other studies where individual test results are presented.

[f]Results interpreted as evidence of executive function enhancement rather than verbal memory enhancement.

[g]Testing three times over a 2-month period: baseline, 4 weeks, and 8 weeks.

Table II Randomized, placebo-controlled, clinical trials of estrogen plus progestins and verbal memory in younger women

Author (Year)	N (All)/Final HT/Pl	Age (SD or span)	Prior use of HT	Menopausal status/menopausal symptoms/years since menopause[a]	Design	Dur	HT	Dose	Test	Results
Linzmayer et al. (2001)	(?) 49 16/ 17/16[a]	57 (46–67)	?	Post-menopausal at least 1 yr/ Insomnia sleep disorder and moderate to severe menopausal symptoms on Kupperman Index (>15)/Est. 6 yrs	Parallel (3 grps)	2 m	Arm 1=Oral EV + dienogest; Arm 2 = EV alone	2 mg + 3 mg/d; 2 mg/d	Common, Associative and Total Verbal memory (Grunberger)	HT > Pl = ET associative verbal memory
Maki et al. (2007)	(180) 158 78/80	52 (3.4)	14 m on average	Post-menopausal at least 1 yr/50% symptomatic/21 m since last period	Parallel (2 grps)	4 m	Oral CEE + MPA	0.625 mg+2.5 mg/ d	California verbal learning test (trials 1–5, short- and long-delay free recall, recognition); paragraph recall	HT=Pl; Trend HT<Pl (P < 0.07) short and long-delay free recall

Abbreviations: CEE = Conjugated Equine Estrogen, d = day, Dur = duration, Est. = estimated, EV = estradiol valerate, grp = group, HT = Hormone Therapy, m = months, mg = milligram, MPA = Medroxyprogesterone Acetate, Pl = Placebo, SD = Standard Deviation, yr = year.

Note: Years since menopause was estimated as difference between age at testing and average age of menopause = 51.

[a]Study included an estrogen plus progestogen, estrogen alone, and placebo group. Sample sizes are given in that order. Study also included an open-label arm after the RCT, but results are presented for blinded arm only.

for word lists. Notably, WHISCA participants were a subset of women in WHIMS, the large clinical trial that showed a doubling of the risk of dementia with CEE/MPA (Shumaker *et al*., 2003). Women with dementia were excluded from WHISCA, but the data nonetheless support the view that verbal memory measures may be a valid proxy when considering the effects of hormone therapy on dementia risk. A fourth study found a deleterious effect of micronized estradiol and progesterone on Paragraph Recall but not Paired Associates (Pefanco *et al*., 2007). Effects of this preparation on word list recall were not assessed. The only neutral trial in this group included only Paired Associates, so a negative impact on other, more sensitive verbal memory measures, cannot be ruled out (Binder *et al*., 2001). In summary, these data suggest a consistent detrimental effect of combination estrogen plus progesterone on word list memory and Paragraph Recall.

Conclusions

In conclusion, a review of clinical trials of hormone therapy and verbal memory indicates modest support for a beneficial effect of estrogen alone therapy in women younger than age 65 and a detrimental effect of combination estrogen plus progestogen therapy in women older than age 65. There is also evidence of a detrimental effect of combination CEE/MPA on verbal memory in younger women. There is no evidence of a benefit or a risk to verbal memory with estrogen alone therapy in older women. This review suggests that the effects of hormone therapy on verbal memory appear to depend on the age at initiation and the use of progestogens. Thus, if one combines users of estrogen alone with users of estrogen plus progestogen into one general category, a true beneficial effect of estrogen alone on verbal memory may be missed.

Two large, ongoing clinical trials promise to shed important new insights into the effects of hormone therapy on cognitive function in younger and older post-menopausal women. The Kronos Early Estrogen Prevention Study (KEEPS) is a 5-year, multicenter clinical trial that will enroll 720 women aged 42–58 years who are within 36 months of their final menstrual period to yield three treatment groups of 150 completers each (total of 450 women). KEEPS participants will be randomized to receive: (1) oral CEE (0.45 mg daily) plus micronized progesterone (200 mg); (2) transdermal estradiol (50 mg per day) plus micronized progesterone; or (3) placebo (Harman *et al*., 2005). The second ongoing trial is the Early Versus Late Intervention Trial with Estradiol (ELITE) led by Howard Hodis of the University of California at Los Angeles. ELITE is a single-site clinical trial that will enroll a total of 504 post-menopausal women who are <6 years from menopause (early) versus 10 years or more from menopause (late) to receive either oral estradiol (1 mg daily) or a placebo. Women with a uterus will also use vaginal progesterone gel 4% (or a placebo gel) the last ten days of each month. Both KEEPS and ELITE examine verbal memory as a primary outcome, so both studies will shed new light on the effects of hormone therapy on verbal memory. Importantly, both studies focus on naturally menopausal women, so both studies will lend insights into the issue of whether the beneficial effects of estrogen on cognitive function observed in surgically menopausal women extend also to naturally menopausal women.

Table III Randomized, placebo-controlled, clinical trials of hormone therapy and verbal memory in older post-menopausal women

Author (Year)	N (All) Final ET/Pl	Age (SD or span)	Prior HT Use (%)	Menopausal status/menopausal symptoms/years since menopause	Design	Dur	HT	Dose	Test	Results
Estrogen alone										
Wolf et al. (1999)	(40) 38 21/17	68.7 (1)	?	13 Hysterectomy (8 with BSO)/Unknown symptoms but presumably mostly asymptomatic/17.4 yrs since menopause	Parallel (2 grps)	2 wk	Transdermal E2	0.1 mg/d	Word pair recall	ET = Pl
Almeida et al. (2006)	(115) 86 47/39	73.7 (3.8)	38%	All post-menopausal/?/29 yrs since menopause	Parallel (2 grps)	20 wk	Oral E2	2 mg/d	California Verbal Learning Test (Trials 1−5 and long-delay recall)	ET = Pl
Yaffe et al. (2006)	(417) 376 191/185	60−80 66.7 (5.0)	?	Intact uterus/16% with symptoms/15.4 yrs since menopause	Parallel (2 grps)	2 yrs	Transdermal E2	0.014 mg/d	Paragraph Recall; Word List Memory	ET = Pl
Estrogen and progestogen										
Binder et al. (2001)	(67) 52 34/18	81 (75−91)	33%	48% Hysterectomy/Presumably asymptomatic, no depression/34 yr since menopause	Parallel (3 grps)	9 m	CEE alone in 59%; CEE + cyclic MPA in 41%[a]	0.625 mg/d; 0.625 mg/d + 5 mg/d for 13 d at m 2, 5 and 8	Paired Associates	No effect
Grady et al. (2002)	(1328) 1163 517/546	66.8[b] (44−79)	24%	Intact uterus/Hot flushes in 15%, all had coronary disease/18 yr since menopause	Parallel (2 grps)	4.2 yr	CEE + MPA	0.625 mg/d + 2.5 mg/d	CERAD Word List Memory; Word List Recall	Trend HT < Pl (P < 0.06) for Word List Memory; HT = PL for other measure
Resnick et al. (2006)	(1416) 1320 690/726	73.8 (65+)	22%	All naturally menopausal/Moderate to severe hot flushes in 5%/Est. 22 yrs since menopause	Parallel (2 grps)	3 yr[c]	CEE + MPA	0.625 mg/d + 2.5 mg/d	California Verbal Learning Test (Trials 1−5 total, short- and long-delay free recall, recognition)	HT < PL for Trials 1−5, short and long-delay free recall
Pefanco et al. (2007)[d]	(57) 45 32/25	75.5 (5.5)	?	32% Hysterectomy/?/24.5 yr	Parallel (2 grps)	3 yr	Micronized E2; micronized P	0.25 mg/d; 100 mg/d for 2 wks every 6 m	Paired Associates; Paragraph Recall	HT < PL for immediate Paragraph Recall[d]; HT = PL for other measures

Abbreviations: BSO = bilateral salpingo oopherectomy, CEE = Conjugated Equine Estrogen, CERAD = Consortium to Establish a Registry of Alzheimer's Disease, d = day, Dur = duration, Est. = estimated, ET = estrogen therapy, E2 = estradiol, grp = group, HT = Hormone Therapy, m = months, mg = milligram MPA = Medroxyprogesterone Acetate, P = progesterone, Pl = Placebo, SD = Standard Deviation, wk = week, yr = year.

Note: If mean years since menopause was not provided in article, value was estimated as difference between current age and average age of menopause = 51.

[a]Note that 63% of women received estradiol alone, while 37% also received cyclic progesterone.

[b]Age at randomization; age at testing 71 ± 6 yrs.

[c]Testing began on average 3 years after randomization, and women were followed for a mean of 1.5 years.

[d]Both treatment groups increased after 3 months and decreased at 36 months, but the HT group performed lower than at baseline at 36 months.

Part 2: Hormone therapy and executive functions

Background

Earlier in this review, we described the rich array of translational research studies demonstrating that estrogen enhances the function and synaptic plasticity of the hippocampus. It is clear from functional neuroimaging studies in humans that performance on verbal memory tests depends on the integrity of the hippocampus (Nyberg et al., 1996; Schacter and Wagner, 1999; Schacter et al., 1999). Neuroimaging studies in post-menopausal women demonstrate that estrogen therapy enhances hippocampal function during performance of word list tasks (Resnick et al., 1998; Maki and Resnick, 2000). The hippocampus shows the earliest neuropathology of Alzheimer's disease and appears decades before disease onset (Sandberg et al., 2001). The critical window hypothesis would suggest that intervention with hormone therapy decades before disease onset prevents declines in verbal memory and lowers risk of Alzheimer's disease, but intervening later has no effect. These findings strongly implicate the hippocampus as a critical structure in any effects of early intervention with estrogen on the prevention of Alzheimer's disease and declines in verbal memory.

Next we review evidence from observational studies and pharmacological models of menopause in young women to underscore the need to look for estrogen effects beyond the hippocampus in order to fully understand how estrogen might impact verbal memory and other cognitive functions. This evidence suggests that estrogen appears to enhance memory in part through executive functions mediated by the prefrontal cortex. Executive functions encompass cognitive processes such as set-shifting, response inhibition, working memory, problem-solving, reasoning and behavioral monitoring (Baddeley, 1986; Miller and Cummings, 1999). Executive functions that aid encoding and retrieval in memory tasks involve the strategic implementation of complex encoding strategies and mnemonic devices and the strategic placement of stimuli into spatial and temporal contexts (Wheeler et al., 1995; Stuss et al., 1996). For example, on list learning tasks such as the California Verbal Learning Task, one of the strategies that enhances acquisition and recall of verbal items is to cluster items according to category (e.g. recalling all of the fruit items and then all of the items of clothing). Notably, females use this strategy more than males (Kramer et al., 1988), and hormone therapy enhances clustering during word retrieval (Maki et al., 2001). Unfortunately, with the exception of a few clinical trials, there is insufficient clinical trial data to evaluate the effects of hormone therapy on tests of executive function. For that reason, we will present a brief overview of the observational and experimental literature to justify the inclusion of a broader array of executive functions in future clinical trials.

Studies in humans and animals provide support for the biological plausibility that estrogen enhances function of the prefrontal cortex. Neuroimaging studies demonstrate enhancement not only of hippocampal function but also of prefrontal function during retrieval of words from memory (Resnick et al., 1998; Maki and Resnick, 2001). The prefrontal cortex is one of the highest estrogen binding sites in the female brain, with estradiol concentrations in the prefrontal cortex being approximately two times higher compared with the temporal lobe and seven times higher compared with the hippocampus (Bixo et al., 1995). In female monkeys, estrogen increases spinophilin-immunoreactive spine number in the prefrontal cortex (Tang et al., 2004). Ovariectomy decreases spine density in the prefrontal cortex of female rats (Wallace et al., 2006). Cyclic estrogen therapy reduced the age-related decline observed on a test of spatial working memory that is mediated by the frontal lobes in female monkeys (Rapp et al., 2003a). This estrogen-induced benefit was observed independent of delay and therefore was unrelated to the memory demands of the task, suggesting to the authors that estrogen was exerting beneficial effects on processes such as 'susceptibility to proactive interference and distractibility' (p. 5712) (Rapp et al., 2003a). Neuroimaging studies in humans demonstrate a double dissociation between executive control processes (subserved by prefrontal cortex) and mnemonic processes (subserved by posterior brain regions) contributing to working memory performance (Postle et al., 1999). Given the primacy of executive processes on tests of working memory and the reliance of such tests on prefrontal cortex, we include studies of working memory in our narrative review.

Narrative review

Evidence that estrogen decreases errors of executive function on verbal memory tests

Use of hormone therapy has been associated with a decrease in false positive and perseverative errors, two types of errors in executive function that are common in patients with lesions in the frontal cortex (Miller and Cummings, 1999; Ramage et al., 1999). False positive errors refer to the endorsement of non-target items (e.g. saying that you heard a word that was not previously presented), and perseverative errors reflect deficient response inhibition (e.g. a tendency to make the same error over time). An observational study in 19 'menopausal women' (mean age ≈53; methods do not specify peri- or post-menopausal status) found significantly lower rates of false positive and perseverative errors on the California Verbal Learning Test in a group of hormone therapy users compared with non-users, but no difference in Paragraph Recall (Keenan et al., 2001). Similarly, surgically post-menopausal women (mean age ≈65) who had used long-term estrogen therapy showed fewer perseverative errors on the California Verbal Learning Test compared with controls (Norbury et al., 2007). As shown in Table I, in a randomized clinical trial involving 52 peri- or post-menopausal women (mean age = 51), those randomized to receive placebo for 12 weeks made more perseverative errors on the California Verbal Learning Test compared with those women who were randomized to receive estradiol (Joffe et al., 2006).

Evidence that estrogen improves source memory

Results from another observational study suggested that estrogen may help to mitigate against age-related cognitive decline by maintaining cognitive functions mediated by the frontal lobes (Wegesin and Stern, 2007). That study focused on the frontal lobe hypothesis of aging, which suggests that normal age-related cognitive decline—as distinct from prodromal Alzheimer's disease—reflects changes in executive function that are mediated by the frontal lobes (Albert and Kaplan, 1980; Craik and Jennings, 1992; Dempster, 1992; Moscovitch and Winocur, 1992; Stuss et al., 1996; West, 1996). The specific hypothesis under investigation was that aging and

estrogen effects would be greater for source memory (i.e. an executive function involving the recollection of the context in which an item was presented) compared with item memory (i.e. a hippocampal function involving memory for a specific item). Young, regularly cycling women (mean age ≈21.5) performed better on source and item memory compared with older, post-menopausal women (mean age = 69). Post-menopausal women treated with estrogen demonstrated better source memory scores compared with those not treated with estrogen, whereas no differences existed between groups in item memory performance. Results were interpreted as suggesting that estrogen enhanced prefrontal, but not hippocampal, function in these older women.

Evidence that estrogen improves working memory and set-shifting
In some observational studies, hormone therapy has been shown to enhance performance on certain tests of working memory and cognitive set-shifting. Working memory and cognitive set-shifting underlie many higher-order cognitive operations and rely on the integrity of dorsolateral prefrontal cortex (Berman *et al.*, 1997; D'Esposito *et al.*, 1999; Cabeza and Nyberg, 2000; Manoach *et al.*, 2003; Veltman *et al.*, 2003). An observational study of 73 younger post-menopausal women (mean age = 56) found evidence that hormone therapy enhanced performance on tests of working memory, but not Paragraph Recall (Duff and Hampson, 2000). Beneficial effects of estrogen have also been reported on the N-back, a widely used measure of working memory, and Trails B, a cognitive set-shifting measure in younger post-menopausal women (mean age = 53) (Keenan *et al.*, 2001). In a pharmacological model of menopause, estrogen suppression induced by leuprolide acetate was associated with a decrease in performance on the N-back and the Letter-Number Sequencing Task (a measure of working memory), but not the California Verbal Learning Test, in a sample of 25 premenopausal women (mean age = 36) compared with healthy controls (Grigorova *et al.*, 2006). There is also evidence that hormone therapy is associated with improved performance on the Wisconsin Card Sort Task, a test requiring abstract reasoning, problem solving, working memory, strategizing and mental shifting (Erickson *et al.*, 2007; Wegesin and Stern, 2007). These effects have been found in older women who had used short-term (<10 years) hormone therapy (mean age = 70) (Erickson *et al.*, 2007) and older women (mean age = 69) who had used estrogen therapy for a variable length of treatment (Wegesin and Stern, 2007). These results suggest an influence of estrogen on executive functions mediated by dorsolateral prefrontal cortex.

Neuroimaging evidence that estrogen improves frontal lobe function
Neuroimaging studies demonstrate that estrogen enhances function of the frontal lobe in women during cognitive challenges. Compared with six women randomized to receive placebo for 12 weeks, five women randomized to receive estradiol for 12 weeks showed greater frontal lobe activity during verbal and spatial working memory tasks (Joffe *et al.*, 2006). In a double-blind, randomized, placebo-controlled, crossover trial of 46 younger post-menopausal women (mean age = 50.8), estrogen therapy for 21 days enhanced left-hemisphere activation during verbal encoding and increased activity in the right superior frontal gyrus during verbal retrieval (Shaywitz *et al.*, 1999). This pattern of brain activation represents enhancement of the hemisphere

encoding/retrieval asymmetry effect, a pattern of frontal lobe activity typically observed in younger, but not older, adults during memory tasks. Each of these neurobiological differences between hormone therapy users and non-users was evident despite a lack of behavioral differences in performance, suggesting that neuroimaging techniques may detect effects of estrogen on the frontal lobes that are not yet apparent by behavioral measures.

A series of neuroimaging investigations demonstrated a clear relationship between estradiol and activation in the frontal cortex during successful verbal encoding in healthy premenopausal women undergoing pharmacological ovarian hormone suppression with leuprolide acetate (Craig *et al.*, 2007, 2008a, b). Hormone suppression led to decreased activation in left prefrontal cortex, anterior cingulate and medial frontal gyrus (Craig *et al.*, 2007). A subsequent investigation demonstrated that this effect was reversed when estradiol levels returned to normal, higher levels (Craig *et al.*, 2008a). Suppressing cholinergic function with the drug scopolamine led to a similar reduction in activation in left inferior frontal gyrus during verbal encoding, and the combination of estrogen suppression and cholinergic suppression led to dramatic decreases in activity in this area (Craig *et al.*, 2008b). The left inferior frontal gyrus is involved in semantic processes—that is, deep processing of the meaning of verbal material—suggesting that estrogen aids in the encoding of verbal information into memory.

Few studies have investigated the impact of estrogen plus progestogens versus estrogen alone on executive functions. In an early positron emission tomography study in premenopausal women, ovarian hormone suppression with leuprolide acetate attenuated the typical pattern of neural activity—activation in dorsolateral prefrontal cortex, inferior parietal cortex and inferior temporal cortex—during a modified version of the Wisconsin Card Sorting Task. 'Add-back' treatment with estrogen or progesterone reversed this effect. Estrogen add-back led to greater left hippocampal activation compared with progesterone add-back. An observational study (*n* = 65) of older post-menopausal women (mean age = 65) compared performance on tests of verbal memory and executive function among women using estrogen only, women using estrogen plus progesterone and women using neither (Grigorova and Sherwin, 2006). There were no clinically meaningful differences between groups on any measure, except a minor increase in response time on the N-back test in the estrogen plus progesterone group, suggesting that progesterone delays processing time without influencing response accuracy. In the observational study described above where hormone therapy was associated with enhanced performance on tests of working memory and set shifting, but not Paragraph Recall, there were no differences in performance between women receiving estrogen alone and those receiving estrogen plus progesterone (Duff and Hampson, 2000). A similar finding was evident in the study examining the frontal lobe hypothesis of aging, such that hormone therapy was associated with enhanced executive function regardless of whether a woman was receiving estrogen alone or estrogen plus progestogen (Wegesin and Stern, 2007).

Discussion

In summary, evidence from pharmacological models of menopause in premenopausal women, observational studies in post-menopausal

women, and a couple of randomized trials suggest a beneficial effect of estrogen on executive functions. These beneficial effects are evident on measures of verbal memory that reflect the implementation of executive strategies such as semantic encoding or semantic organization, as well as on errors of response inhibition and perseveration. Benefits are also evident on tests of executive function, including tests of working memory (e.g. N-back, letter number sequencing), problem solving (e.g. Wisconsin Card Sorting) and source memory. The observation that these effects occur in the absence of effects on verbal memory in some studies, indicates that in some circumstances the effects of estrogen on executive function are evident even when there are no effects on hippocampally mediated tasks. The centrality of declines in executive function to some theories of cognitive aging underscores the importance of broadening our understanding of hormone effects beyond the hippocampus and verbal memory.

General discussion

Although ongoing clinical trials such as KEEPS and ELITE will contribute to our understanding of estrogen effects on verbal memory, substantial gaps in knowledge will remain. These gaps are a barrier to effective clinical practice. First, clinicians should aim to prescribe a formulation of combination estrogen plus progestogen therapy that is effective for hot flashes but neutral or beneficial to cognitive function. To date, there is no strong support that any estrogen plus progestogen combination that is widely used in clinical practice is neutral to verbal memory; rather, evidence suggests harm. The need for a direct comparison of estrogen plus various progestogens on cognitive function in early post-menopausal women is great. Like MPA, micronized progesterone, the progesterone formulation used in KEEPS, was associated with declines in verbal memory in older women (Pefanco *et al.*, 2007). MPA was also associated with declines in verbal memory in younger post-menopausal women (Maki *et al.*, 2007), suggesting that the negative impact of progestogen may be evident regardless of age at initiation. Second, clinicians face the reality that there is no clear definition of 'early intervention'. How early must intervention with estrogen be to confer benefits to verbal memory (as evidenced in four of seven clinical trials in women younger than age 65), and possibly to Alzheimer's disease? New evidence of a substantial risk for Alzheimer's disease among women who underwent oopherectomy before age 48 but not after that age (Rocca *et al.*, 2007) suggests that the critical window might begin in the perimenopause. Another related issue is whether the benefits to verbal memory observed in surgically menopausal women extend to naturally menopausal women, particularly asymptomatic women. There is evidence that objective (but not subjective) hot flashes relate to verbal memory dysfunction (Maki *et al.*, 2008), so some of the cognitive benefit derived from hormone therapy may relate to treatment of hot flashes. Third, how long must hormone therapy be used to confer benefits? The treatment length among the four positive clinical trials was 2–4 months. It is unknown how long any benefit might last following discontinuation. Observational data suggest that past use of hormone therapy for 3–10 years delays the onset of Alzheimer' disease (Zandi *et al.*, 2002). Fourth, clinicians must weigh the cognitive consequences of continuing hormone therapy in women who were early initiators. Can a woman who initiates early remain on therapy

without experiencing cognitive declines, or perhaps even experiencing cognitive benefits with continued use? None of the ongoing clinical trials will address the question of whether initiating hormone therapy early in the menopause and continuing therapy until after age 65 yields a positive or negative impact on verbal memory, Alzheimer's disease, or other critical cognitive functions. There is some evidence that the greatest risk reduction from Alzheimer's disease comes with longer duration of treatment (Tang *et al.*, 1996; Zandi *et al.*, 2002), but a clinical trial to address this issue is not feasible. The 'good' news is that Alzheimer's disease is very rare in women aged 50–60, so there is little evidence of an immediate negative impact of hormone therapy on risk for Alzheimer's disease.

It is important to emphasize that neither estrogen alone therapy nor estrogen plus progestogen therapy is indicated for the prevention or treatment of cognitive function. The focus on cognitive function is therefore relevant to women who use hormone therapy for other indications, primarily the treatment of menopausal symptoms. For this reason, any discussion of hormone therapy and cognitive function should take into account the possible medical risks of hormone therapy. Given that the focus in the present review is on the critical window hypothesis and women who initiated therapy closer to the menopause, it is helpful to review the medical risks associated with hormone therapy in this group and in particular in women less than 60 years of age (see van de Weijer (2008) for a review). Although clinical trial findings suggest that CEE/MPA is harmful to cognitive function, arguably the most comprehensive data on the medical risks of combined hormone therapy come from the WHI, so we will refer to those findings when discussing medical risks. A recent analysis of the risks of hormone therapy as a function of age in WHI found no cardiovascular risk with CEE alone or CEE/MPA in women younger than age 60; in fact, women who initiated hormone therapy closer to menopause (i.e. within 10 years) had reduced cardiovascular risk compared with the increase in coronary heart disease risk among women more distant from menopause ($P < 0.02$) (Rossouw *et al.*, 2007). The effects of hormone therapy on overall mortality also tended to differ by age ($P = 0.06$), with a significant reduction in overall mortality among women aged 50–59 (HR = 0.70, 95% CI = 0.51–0.96). Stroke was significantly increased among women who initiated hormone therapy closer to menopause (i.e. within 10 years), (HR = 1.77, 95% CI, 1.05–2.98), but after exclusion of women with prior cardiovascular disease the HR was 1.23 (non-significant). Breast cancer is a significant concern associated with HT therapy, but the HR associated with HT in the WHI among women aged 50–59 was non-significant (HR = 1.19, 95% CI, 0.84–1.70) (Rossouw *et al.*, 2007).

From a research point of view, the study of hormones and cognition faces several challenges. There is little evidence that estrogen enhances cognition; rather, in the four of seven positive trials estrogen was seen to maintain one's level of cognitive function. For example, in both surgical menopause and pharmacological models of menopause, estrogen suppression leads to deficits in verbal memory, and performance returns to baseline levels—not higher—following add-back estrogen (Sherwin, 1988b; Sherwin and Tulandi, 1996). The view of estrogen as a memory maintainer or protector rather than as a memory enhancer has important implications for research. First, the magnitude of normal, age-related declines in verbal memory in women in their 50s is very minimal. Second, the magnitude of the

practice effect, the amount of improvement from the first test session to the next, is substantial. Thus practice effects are likely to mask any more subtle effect of estrogen on cognitive function. For these two reasons, it is very challenging to detect a signal for estrogen benefits in peri-menopausal or early post-menopausal women. Two experimental approaches have been shown to be useful in overcoming these limitations. First, pharmacological models of memory declines induced by suppressing ovarian hormones and/or acetylcholine have been shown to be very sensitive to the effects of estrogen on cognition. Second, neuroimaging studies focusing on brain regions subserving memory function have been shown to be sensitive to estrogen effects even in the absence of behavioral change. If neuropsychological studies are to be conducted to test this hypothesis, then large samples sizes are needed to ensure sufficient power.

Continued research is necessary to fully evaluate the impact of hormone therapy on cognitive function and risk for Alzheimer's disease. In light of the issues described above, arguably the most important priority is for a randomized clinical trial directly comparing the effects of different estrogen/progestogen combination therapies on verbal memory and executive function in peri-menopausal/early menopausal women (i.e. within 5 years of the final menstrual period), with a minimum follow-up period of 3 months. Such a study is needed to determine which type of hormone therapy is most cognitively neutral/beneficial in naturally menopausal women who are likely to seek hormone therapy for the treatment of menopausal symptoms. Optimally, such a study would examine cognitive benefits in relation to improvements in hot flash symptoms, since objective hot flashes (i.e. measured with ambulatory skin conductance monitors) have been shown to relate to impairments in verbal memory (Maki *et al.*, 2008).

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