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COGNITIVE EFFECTS OF SHORT-TERM USE OF RALOXIFENE: A RANDOMIZED CLINICAL TRIAL

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Two questions regarding findings from the Women's Health Initiative are (1) What is the effect of various hormonal regimens including selective estrogen receptor modulators? and (2) Is the negative effect on cognitive functioning related to the older age (65+ years) of the women? This study addresses these two questions in a short-term randomized trial of the effects of raloxifene versus alendronate on cognition. The study found only one significant interaction where the raloxifene and alendronate group changed differently across the two testing occasions. Hence, raloxifene does not have any impact, positive or negative, on short-term cognitive functioning when compared to alendronate.

Keywords cognition, raloxifene, selective estrogen receptor modulators

Perceptions toward the use of postmenopausal hormone therapy have undergone a sea of change since findings from the Women's Health Initiative (WHI) have been published (Anderson et al., 2004; Rossouw et al., 2002). As the contrast between the generally positive conclusions reached from years of observational research and the often negative conclusions supported by this rigorous randomized clinical trial, and the preceding Heart and Estrogen/Progestin Replacement Study (HERS; Hulley et al., 1998, 2002; Grady et al., 2002) it became apparent that healthcare professionals and women face a recondite dilemma in how to reach a decision on whether to use hormone therapy.

The impact of hormonal therapy on cognitive function has been an area of substantial interest to women and clinicians considering such treatment. Estrogen-only therapy was not found to protect against dementia or mild cognitive impairment (Shumaker et al., 2004). In fact, estrogen-only therapy was found to be associated with a significant increased risk. Although the results from the WHI on the use of combined therapy provide compelling evidence that such therapy increases the risk of dementia it does not appear to increase the risk of developing mild cognitive impairment (Schumaker et al., 2003). It also does not appear to be associated with greater cognitive decline although estrogen and progestin may be associated with a small increased risk of clinically meaningful cognitive decline, as measured by the Modified Mini-Mental Status Examination (Rapp et al., 2003). In addition to increasing the risk of dementia, clear results emerged suggesting combined hormonal therapy increased the risk of ischemic stroke (Wassertheil-Smoller et al., 2003). A lingering question regarding the findings from WHI is if the negative effect on cognitive functioning may relate to the older age (65+ years) of the women who were enrolled in WHI.

Although this large scale, randomized trial has dampened enthusiasm for the use of hormone therapy as a factor that may preserve cognition during

aging many questions on the nature of any association between hormone exposure and cognition are unanswered by the WHI. Foremost is the effect of various hormonal regimens including the use of selective estrogen receptor modulators (SERMs). In a study by Nickelsen et al. (1999), no significant differences between the SERM (raloxifene) and placebo groups were found on various measures of cognitive function after 12 months of treatment. There was, however, a significant increase in verbal memory performance (favoring the raloxifene 120 mg/day group) after one month of treatment. Yaffe et al. (2001) researched the effects of raloxifene treatment for three years on overall cognitive functioning in postmenopausal women with osteoporosis. Although no significant effects were found, there was a trend toward a lesser decline in the raloxifene group on the two tests of verbal memory and attention compared to the placebo group.

This study extends research in hormonal therapy and cognition in a short-term randomized trial. This trial among post-menopausal women initiating treatment for osteoporosis began as a trial of estrogen and progestin, the SERM, raloxifene, and alendronate, a biphosphonate highly effective in treating osteoposrosis. When the initial results from WHI were published it was decided that discontinuation of the combined therapy arm was ethically required. This study thus reports results of the effects of raloxifene versus alendronate on cognition over a three-month trial.

METHODS

Participants

Inclusionary/exclusionary criteria are listed in Table 1.

A total of 605 women were identified from the DEXA scans as meeting criteria for a diagnosis of osteoporosis. One hundred sixty-seven women were found to have information on electronic medical review that excluded them from participation, the woman's physician deemed the woman inappropriate for participation in 168 instances and 142 women declined to participate. Contact could not be made with 41 women and 70 women were enrolled in the study.

Ten women had been randomized to the combined estrogen/progestin arm prior to the results from the WHI were released. These women were dropped from the current analysis leaving 32 randomized to the raloxifene group and 28 to the alendronate group. Five women in each group did not complete the three-month testing leaving 27 evaluable participants in the raloxifene group and 23 in the alendronate group.

Table 1. Criteria used for assessing suitability for study

Inclusionary/Exclusionary criteria
• Between 60 and 75 years of age
• At least 10 years of education
• Fluent speaker of Standard American English, with English as the primary language
• Good physical health established by medical history and physical examination
• No history of, or examination evidence for, any major physical illness including current insulin-dependent diabetes, uncontrolled hypertension, heart disease, or cancer
• No history of, or examination evidence for, any neurological condition that would impact cognitive functioning including epilepsy, multiple sclerosis, HIV, Parkinson's disease, dementia, stroke, or other focal lesion
• No DSM-IV criteria for an Axis I psychiatric disorder within the past year; no use of psychotropic medication for at least three months prior to enrollment in the study
• No use of hormonal treatment or drugs known to affect neurotransmitter function for at least one month prior to enrollment in the study
• No use of dietary supplements thought to affect cognition or mood, including gingko biloba, ginseng, and St. John's Wort, for at least three months prior to enrollment in the study
• No known allergies to medications
• Postmenopausal, as established by the lack of a menstrual period for at least six months

Procedures

This protocol was approved by the Institutional Review Board for the Southern California Permanente Medical Group.

All women who received a Dual Energy X-ray Absorptiometry (DEXA) scan that resulted in a diagnosis of osteoporosis or osteopenia were considered for recruitment into this protocol. The radiology department that services most of Orange County Kaiser members notified the patient's physician when newly diagnosed osteoporosis was identified. The program coordinator for this study was also notified. Electronic medical records were accessed to see if any exclusionary criteria were noted. If not and if the woman's physician planned to initiate treatment and agreed that participation in this randomized trial was appropriate, the woman was contacted by her physician. The woman was informed by her physician that she had been diagnosed with osteoporosis or osteopenia and with verbal assent she was informed that she would be contacted by study personnel who would describe the study in detail.

When a potential participant was contacted by study personnel, eligibility criteria were confirmed and the study was described in detail. If verbal agreement to participate was given, a time to conduct the in-person

neuropsychological testing was scheduled either at a Kaiser facility or at the participant's residence. Prior to actual medication assignment and participation in testing, they completed written informed consents approved by the Southern California Permanente Medical Group Institutional Review Board. After the baseline neuropsychological testing was conducted, the participant was randomly assigned to receive study medication. The Kaiser pharmacy closest to the participant's residence was notified of the randomized medication. The pharmacy prepared the prescription with all usage instructions without identifying the medication. Women assigned to the raloxifene group were instructed to take 60 mg one time per day and those in the alendronate group 10 mg one time per day. The participant's physician was notified of the medication to which the participant was randomized to allow for appropriate treatment should complications arise. All participants were contacted within a week after the pharmacy filled the prescription to assure they received their medication. Medications were mailed to participants who preferred not to go to the pharmacy.

Participants were contacted after four weeks to encourage compliance and to check for side effects. If side effects were reported the participant was encouraged to schedule an appointment with her physician. A similar call was made after ten weeks that included scheduling a time to see the patient for the second testing. All testings were scheduled as close to three months after the baseline testing as possible. None were scheduled beyond four months.

Cognitive Tests

Participants were administered a battery of widely used, well-standardized tests. All examiners were Bachelor's level Research Assistants with over 20 hours of supervised training in test administration. The examiners were blinded to medication group.

The battery selected for this study assesses a broad range of cognitive functions with emphasis on domains likely affected by estrogen. Studies by Kampen and Sherwin (1994), Phillips and Sherwin (1992), and Henderson et al. (1996) suggest that estrogen has clear effects on measures of verbal memory and semantic memory, thus the battery emphasizes tests that evaluate these functions.

Episodic verbal memory, tested with verbal list learning, is reported to be sensitive to ERT (Kampen and Sherwin, 1994; Robinson et al, 1994; Sherwin, 1988). The California Verbal Learning Test is widely used as a measure of episodic memory. There are five learning trials, an immediate recall, delayed

recall, and delayed recognition trials. Paragraph prose recall was assessed with two paragraphs from the Wechsler Memory Scale–III: Logical Memory I and II subtest, each providing 46 bits of information for immediate recall.

Confrontational naming was assessed with the widely used Boston Naming Test. Semantic fluency was assessed with the sixty second naming task in which participants were instructed to name as many animals as possible. This fluency task appears to be more sensitive to estrogen than phonemic fluency (e.g., FAS). Memory for nonverbally presented information was assessed with the Faces I and II subtests from the Wechsler Memory Scale–III.

The Judgment of Line Orientation test assessed visual perception independent of motor output. There are suggestions that estrogen may have a negative impact on this measure (Drake, et al., 2000). Working memory was assessed with the Digit Span Forward (DSF) and the Digit Span Backward (DSB) from the revised Wechsler Memory Scale. The Trail Making Test (Parts A and B) (in the public domain) is a complex visual scanning graphomotor task often used to assess executive control processes.

The Geriatric Depression Scale (GDS) was also administered to determine if symptoms of depression confounded any cognitive effects.

Analytic Strategy

The goal of this study was to determine if women randomized to raloxifene showed a different pattern of change in cognitive performance than did women randomized to alendronate. This was analyzed by testing the significance of the interaction term in a split-plot, repeated measures analysis of variance. A significant interaction term would indicate that one group changed from baseline to three month testing differently from the other group.

RESULTS

The women in the raloxifene group had an average age of 66.7 (SD = 4.3) and those in the alendronate group 67.8 (SD = 4.4) years ($p = .38$). Education levels did not differ between groups ($p = .66$). In the raloxifene group 7.4% ($n = 2$) had less than a high school education, 25.9% ($n = 7$) had a high school education, 33.3% ($n = 9$) had some college education and 33.3% ($n = 9$) had at least a Bachelor's degree. In the alendronate group, 17.4% ($n = 4$) had less than a high school education, 17.4% ($n = 4$) had a high school education, 30.4% ($n = 7$) had some college education, and 34.8% ($n = 8$) had at least a Bachelor's

degree. On the baseline testing there were no significant differences between groups on any of the neuropsychological tests.

All descriptive statistics for both the baseline and three-month neuropsychological tests are provided in Table 2. Only one interaction term was statistically significant; that for Logical Memory II: Thematic Recall ($p = .02$). The raloxifene group showed improved performance whereas the alendronate group declined slightly. No other cognitive interactions were significant. There was also no significant interaction when using scores on the GDS as dependent variables ($p > .9$).

DISCUSSION

The study found only one interaction, out of 23 tested, showing a significant interaction where the raloxifene and alendronate groups changed differently from before treatment to three months post-treatment. The finding that raloxifene tended to reduce the risk of a decline in thematic paragraph prose recall after a delay is consistent with the expected rate of Type I errors and most likely reflects chance, because multiple comparisons were performed. It is thus concluded that raloxifene does not have any impact, positive or negative, on short-term cognitive functioning when compared to alendronate.

It is important to note that the current study was originally designed to compare the impact of postmenopausal hormone therapy and raloxifene on the risk of dementia (primary outcome) or mild cognitive impairment (secondary outcome) in healthy women aged 60 to 75 years. When the initial results from WHI were published it was decided that discontinuation of the combined therapy arm was ethically required. This article thus reports results of the effects of raloxifene versus alendronate on cognition over a three-month trial.

Per questions resulting from the WHI findings, a negative effect was not found on cognitive functioning in the older age (65+ years) cohort of the women enrolled in the study. These findings are consistent with those reported by Nickelsen et al. (1999) who found no cognitive or mood changes among women randomized to placebo, 60 mg or 120 mg raloxifene for one year. Nickelsen's study had found a short-term (one month) improvement in the raloxifene group. The only significant difference found was a small increase in performance favoring the raloxifene 120 mg/day group in an assessment of verbal memory after one month of treatment. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial women received a brief cognitive screening battery at baseline, six months, one, two, and three years. Women in

Table 2. HRT group and cognitive performance

	Baseline				3-Months				
	Raloxifene		Alendronate		Raloxifene		Alendronate		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p* value
Faces immediate	35.6	4.1	34.7	4.2	39.5	4.6	37.3	5.2	0.32
Faces delayed	35.4	6.5	35.3	4.7	40.3	4.3	39.2	4.3	0.79
Logical memory 1	39.5	10.8	39.1	9.5	42.4	9.0	42.4	12.5	0.87
Logical memory 1 Thematic recall	15.9	3.4	17.0	3.5	18.0	3.1	17.9	3.3	0.17
Logical memory 2	25.1	8.6	24.7	7.8	27.7	7.1	27.5	8.0	0.94
Logical memory 2 Thematic recall	10.7	2.5	11.9	3.1	12.0	2.0	11.6	2.3	0.02
Logical memory recognition	26.0	2.6	26.1	2.7	26.0	3.0	25.3	3.2	0.26
CVLT trials 1–5	51.0	9.0	46.5	8.2	54.7	10.7	51.6	9.8	0.56
CVLT trial 1	7.0	1.7	6.1	1.9	8.1	2.7	7.1	1.8	0.79
CVLT Trial 5	12.0	2.0	11.3	2.5	12.3	2.2	12.5	2.6	0.14
CVLT SDFR	10.5	2.5	9.0	3.8	11.0	2.8	10.6	3.0	0.09
CVLT SDCR	11.3	2.6	10.9	2.9	11.6	2.5	11.7	2.5	0.47
CVLT LDFR	10.7	2.8	9.7	3.7	11.4	2.5	10.7	3.2	0.78
CVLT LDCR	11.6	2.5	10.7	3.1	12.1	2.1	11.3	2.9	0.87
Letter number sequencing	9.1	2.8	8.7	2.2	9.8	2.0	9.0	2.2	0.73
Digits forward	10.1	2.5	9.3	2.3	9.7	2.1	9.7	2.6	0.27
Digits backward	6.2	1.5	5.6	2.1	6.7	2.0	6.0	2.1	0.94
Trail making Part A	35.7	11.4	43.3	20.7	38.3	17.2	44.8	27.3	0.76
Trails making Part B	95.2	41.0	121.3	65.6	95.7	66.4	106.9	61.6	0.36
JLO	22.4	3.6	21.1	6.3	21.3	7.5	21.0	6.7	0.50
Boston Naming Test	54.2	5.3	51.4	7.0	55.4	4.1	53.5	5.9	0.27
Animal naming	19.0	4.2	19.0	6.1	19.1	5.9	19.2	6.6	0.94
COWAT	38.9	13.5	34.0	11.0	40.6	15.1	39.5	14.9	0.28

COWAT = Controlled Oral Word Association Test; CVLT = California Verbal Learning Test; SDFR = Short Delay Free Recall; SDCR = Short Delay Cued Recall; LDFR = Long Delay; Free Recall; LDCR = Long Delay Cued Recall; JLO = Judgment of Line Orientation; Digits Forward = Digit Span Forward; Digits Backward = Digit Span Backward. p-values represent significance of the interaction term in a split-plot, repeated measures analysis of variance.

this large study ($n = 7705$) were also randomized to placebo, 60 mg or 120 mg of raloxifene. After three years of follow-up there was no significant difference between treatment groups on cognitive performance although it is noted that women assigned to raloxifene had a slightly lower risk of decline in measures of verbal memory and verbal attention.

In addition to the preponderance of generally small clinical trials, much of the initial enthusiasm for estrogen as a potential protective agent against cognitive decline stemmed from compelling basic science. Estrogen has been shown to have unequivocal evidence of positive neuronal effects including neurotrophic and neuroprotrotective effects (Diaz et al., 2000) and enhancement of several neurotransmitters including the cholinergic system (Gibbs, 2000), serotonin (Osterlund et al., 2000), and dopamine (Leranth et al., 2000). Studies of ovariectomized rats have revealed SERM influence on the hippocampus (Bryant et al., 1997). Although such findings may suggest a possible role in SERM mediation of memory circuits in rats, its effect on human brains is less unclear. Alternatively, studies have suggested that raloxifene's influence may be understood as impacting antiestrogenic activity in the hypothalamic-pituitary axis of the rat brain (Clemens et al., 1983; Shughrue et al., 1997). Consequently, raloxifene's effects on the human brain are likely complex.

Continuing to understand raloxifene remains important. Although current understanding is incomplete, raloxifene has been shown to have a favorable risk-benefit safety profile. Further, raloxifene holds promise for both the prevention of osteoporosis, and for a host of other disorders impacting the health of post-menopausal women (Francucci et al., 2005). There is mounting evidence documenting clinical benefits and adverse effects of raloxifene from large, randomized, placebo-controlled trials. Further, increased understanding of the ways in which diverse ligands modulate the estrogen receptor will likely enlarge the number of other SERMs designed and targeted to selective clinical applications.

An important limitation of this study is the small sample size. As mentioned earlier, following the initial results from WHI it was decided that discontinuation of the combined therapy arm was ethically required. The results are thus limited to the effects of raloxifene versus alendronate on cognition over a three-month trial. The smaller sample size decreased the statistical power to detect a defined level of risk reduction. Nevertheless, the results of this study remain compelling given the fact that the study included the use of a broad and inclusive standardized neurocognitive battery that was administered by thoroughly trained testers.

In summary, this study in combination with the two trials of raloxifene cited earlier appears to present a more coherent picture of raloxifene's impact on cognition in the short term. It is concluded that raloxifene does not have any impact, positive or negative, on short-term cognitive functioning when compared to alendronate.

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