Brief Report

A Double-Blind, Placebo-Controlled Trial of Donepezil for the Treatment of Menopause-Related Cognitive Loss

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ABSTRACT

Background: Perimenopausal and menopausal women are more likely to complain of memory loss than are premenopausal women, although the association between menopause and cognitive loss remains controversial. Recently published studies on the risks of hormone therapy have left many women and their physicians seeking effective nonhormonal treatments for menopausal symptoms, including cognitive loss.

Objective: This study investigated the efficacy of the cholinesterase agent donepezil in the treatment of menopause-related cognitive loss.

Methods: Community-dwelling women in natural menopause were recruited for a randomized, double-blind, placebo-controlled study of donepezil. To qualify for enrollment, the Brief Cognitive Rating Scale was used to determine cognitive symptoms, and women with depression were excluded. Subjects were randomized to receive either donepezil, commencing at 5 mg/d, or placebo. At week 6 of randomization, the dosage of donepezil was increased to 10 mg/d. Treatment continued throughout the 26-week study. The primary outcome measure was the overall change in neurocognitive test results over time. Outcome variables of test scores were analyzed before and after receipt of donepezil or placebo.

Results: A total of 28 women aged 46 to 60 years were enrolled. Fourteen women were randomized to receive active drug, 14 to placebo. Two women dropped out of the placebo group. There were no statistically significant differences between treatment groups in post-/pre-dose mean score ratios. No interactions were statistically significant. The *P* values for tests of equal variances did not reveal a difference in the means. Subjective measures did show some trends toward improvement in memory and cognition.

Conclusion: Donepezil was no more effective than placebo in treating the symptoms of menopause-related memory and cognitive loss. (*Gend Med*. 2007;4:352–358) Copyright © 2007 Excerpta Medica, Inc.

Key words: cognitive loss, donepezil, menopause, randomized control trial.

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INTRODUCTION

The association between menopause and postmenopausal memory and cognitive loss is controversial. Whereas some studies have found menopause to be associated with cognitive decline, others have found no such effect.[1–3]

Sherwin[4] postulated a role for estrogen in memory, finding a decline in verbal memory among women experiencing surgical menopause after hysterectomies. Subsequent studies have found estrogen to play a crucial role in various aspects of cognition throughout a woman's life.[5] In a survey of community-based women not preselected for menopausal symptoms, perimenopausal women were significantly more likely to complain of memory loss than were premenopausal women (64% vs 25%, respectively; $P < 0.02$), comparable to their complaints of hot flashes (52% vs 15%, respectively; $P < 0.01$).[6]

In a meta-analysis, Hogervorst et al[1] found variable results for the effects of hormone therapy (HT) on cognitive function in postmenopausal women. The authors concluded that HT was beneficial for verbal memory, abstract reasoning, and informational processing, and that these effects were independent of both mood and symptom alleviation but were diminished when controlled for socioeconomic status. They found that conjugated equine estrogen, the most widely used form of estrogen therapy, was least associated with such effects. The authors suggested that HT may be of benefit in the prevention and treatment of Alzheimer's disease, although this contention has been disputed.[7,8]

In another meta-analysis, Yaffe et al[9] found that estrogen therapy improves cognitive performance in recently menopausal women with symptoms but not in asymptomatic postmenopausal women. The investigators also noted that a lower baseline concentration of estrogen was associated with more cognitive impairment.[10] Alternatively, a longitudinal population-based study found that higher estrogen levels did not improve cognitive performance.[11]

In an interesting study, Elsabagh et al[12] examined 189 postmenopausal women, staging their time from menopause. The authors found no association with memory but did find an age-independent decline in executive function in the late postmenopausal stage. Such findings have led to the development of the "critical period" hypothesis, which postulates that early initiation of HT after natural or surgical menopause is more beneficial than later treatment.[5,13]

Given the level of ongoing controversy regarding the risks and benefits of estrogen and HT, it is not surprising that the number of women choosing HT for alleviation of symptoms continues to fall.[14] The search for effective nonhormonal treatments for menopausal symptoms has led to the use of agents such as venlafaxine, clonidine, and melatonin for the treatment of hot flashes and sleep disturbances.[15–17] However, no such alternative is available for treating the cognitive complaints accompanying menopause.

We therefore chose to investigate the efficacy of the acetylcholinesterase inhibitor donepezil in treating the cognitive symptoms associated with menopause. The rationale for using a cholinergic agent includes evidence for estrogen's beneficial effects on cholinergic neuron viability, with declining estrogen ultimately leading to a reduction of brain acetylcholine levels, a critical neurotransmitter for memory function.[18] We hypothesized that donepezil, which raises brain acetylcholine levels, would be well tolerated and more effective than placebo in the treatment of menopause-related memory and cognitive loss.

METHODS

The study was approved by the Lenox Hill Hospital Institutional Review Board in 2002. All participants were community-dwelling postmenopausal women, with menopause defined as the cessation of periods for 1 year. Women were recruited from 2002 to 2003 through advertisements in the local paper and through fliers placed throughout New York City in physicians' offices, churches, and other local community organizations. Only women who had undergone natural menopause were considered eligible for the study. All women were screened

over the telephone and administered the Brief Cognitive Rating Scale (BCRS) and the 17-item Hamilton Depression Rating Scale (HAM-D). Women were invited for a baseline visit if they scored 2 on at least 3 items or 3 on any 1 item of the BCRS and scored <12 on the HAM-D.[19,20] Women were excluded if they had taken HT or any memory- or mood-enhancing supplements (including over-the-counter products) in the preceding 6 months. At the baseline visit, all women underwent a structured neurologic and psychiatric evaluation, and those with chronic psychiatric or neurologic conditions were excluded.

After giving informed consent, eligible women underwent a structured neurocognitive battery, measuring their cognitive ability and memory function. The tests used were selected based on their prior effectiveness in assessing cognitive and memory functions in menopausal women.[1,21] These tests included the vocabulary section of the Wechsler Adult Intelligence Scale-III; logical and working memory from the Wechsler Memory Scale-III; list learning from the Buschke Selective Reminding Test; the naming section of the Boston Diagnostic Aphasia Examination; and the Controlled Oral Word Association Test of verbal fluency.

After baseline testing, women were randomized to receive donepezil, 5 mg daily, or placebo and followed for 26 weeks. The length of the study was determined based on available data on the use of donepezil in treating other cognitive disorders, such as dementia.[22] An interim visit at the end of week 6 was used to assess tolerability and to titrate donepezil up to 10 mg daily, based on patient drug tolerability and the physician's discretion. The final visit took place at the end of the sixth month of randomization, when the women again underwent a structured neurologic and psychiatric examination, and were readministered the BCRS and HAM-D.

The primary outcome measure used was the overall change in cognition as measured on the neurocognitive battery over the 6-month period. Secondary outcomes included subjective measures of cognitive function and change on the BCRS and HAM-D. For each variable, a ratio was calculated for final versus baseline visit (post/pre). A ratio was used because it incorporates the baseline value and adjusts for baseline variability. The mean and standard error were calculated for each ratio per treatment group. The differences in mean ratios between treatment groups were compared using a *t* test. Demographic variables (age and years of education) were analyzed using analysis of variance and subsequently controlled for. An additional repeated-measures analysis was also performed using the general linearized model function of SPSS 11.0 for Windows (SPSS Inc., Chicago, Illinois). Last, a power analysis was performed to determine the range and highest power of the individual tests.

RESULTS

From a total of 155 women initially recruited, 28 women who met the inclusion criteria and agreed to participate were enrolled and followed in the study from 2002 to 2003 (**Figure**). There was no significant difference in mean (SD) age (placebo group, 53.71 [3.56] years vs drug group, 55.21 [3.47] years; $P > 0.2$; range, 46–60 years) or years of education between groups, with 24 of the women having graduated from college. Three women were African American, 2 were Asian, 1 was Hispanic, and all others were white.

Two women dropped out of the study for personal reasons, and both women were later found to be taking placebo. Three women complained of vivid dreams but opted to stay in the study and were later found to be receiving active drug. There were no other adverse effects.

In the objective measures of cognitive function, there were no significant differences between treatment groups in post-/pre-dose mean ratios, and there were no significant interactions in the initial analysis (**Table**). Tests for equality of variance did show a smaller variance within the treated group compared with the placebo group, but this was nonsignificant.

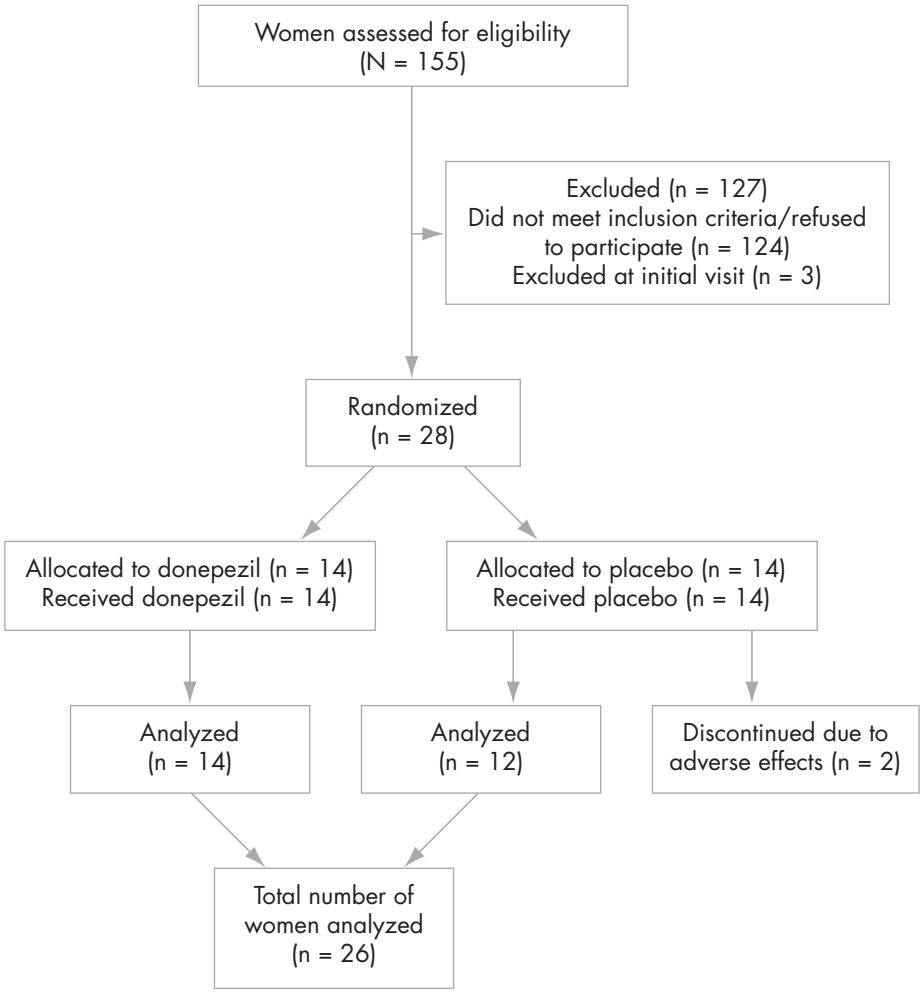

Figure. Flow of women through the study.

In the subjective measures of cognitive function (BCRS and HAM-D), there was no significant change in mean scores over time for either group in the initial analysis (**Table**). Both the drug and placebo groups, however, did show trends toward improvement on subjective measures. HAM-D scores improved from a mean (SD) score of 4.21 (2.887) to 2.21 (2.547) in the drug group, and from 4.83 (2.443) to 3.75 (5.396) in the placebo group. The repeated-measures analysis showed more significance between groups and over time on test scores, with BCRS scores showing the most significant improvement over time ($P < 0.001$), favoring the drug group. However, this method of analysis is not optimal when the sample size is small, as it was in this case, and when only 2 time points are analyzed.

As a result of the small sample size, statistical power was also relatively low for this study. The range on individual tests was 7% to 53%.

DISCUSSION

In this small study, we found that donepezil was not more effective than placebo for treating the cognitive symptoms associated with menopause. Although we found that women rated themselves as cognitively improved on the BCRS over time, there was no difference between the drug and placebo groups using paired *t* tests. Our repeated-measures analysis showed a sta-

Table. Mean (SD) test scores and significance for placebo and donepezil groups.

Test	Placebo (n = 12)		Donepezil (n = 14)		
	Time 1 (predose) Mean	Time 2 (postdose) Mean	Time 1 (predose) Mean	Time 2 (postdose) Mean	*P*
Vocabulary	14.08 (2.843)	14.67 (2.425)	14.29 (1.939)	14.36 (2.341)	0.2107
Logical memory	13.17 (3.010)	14.08 (2.678)	12.79 (2.082)	13.86 (2.507)	0.9498
Auditory working memory	13.08 (3.088)	13.17 (3.243)	12.36 (3.177)	12.93 (3.562)	0.7187
Visual working memory	10.58 (3.370)	11.25 (3.334)	10.64 (2.499)	11.57 (2.652)	0.6886
List learning	54.67 (8.553)	55.00 (7.286)	56.43 (7.891)	55.29 (6.293)	0.5334
Naming	56.08 (4.379)	57.08 (4.944)	55.29 (4.046)	55.50 (4.433)	0.3999
Verbal fluency	51.92 (15.541)	53.92 (15.900)	45.79 (10.154)	48.07 (9.856)	0.6924
BCRS*	10.67 (2.570)	7.75 (2.137)	10.00 (1.881)	6.86 (1.834)	0.5971
HAM-D*	4.83 (2.443)	3.75 (5.396)	4.21 (2.887)	2.21 (2.547)	0.9977

BCRS = Brief Cognitive Rating Scale; HAM-D = Hamilton Depression Rating Scale.
*Lower scores signify fewer and/or less-severe symptoms.

tistically significant improvement in BCRS scores among women receiving donepezil, but we believe this test to be a less rigorous measure, given the small sample size and the lack of multiple time points. On objective assessment of cognitive loss, we found no improvement over time within each group and no observed difference in outcome between the placebo and treatment groups. Several factors may have contributed to these results.

We enrolled women in our study based on performance on a subjective cognitive rating test, the BCRS. The use of such subjective measures is not uncommon for enrollment in clinical trials of menopausal symptoms such as hot flashes, depression, and reduced libido. Studies have shown that memory complaints correlate with objective measures of cognitive loss in demented patients and in patients with mild cognitive impairment.[23,24] Furthermore, because extensive neurocognitive batteries are not feasible for most women because of time and financial constraints, treating patients based on subjective cognitive symptoms may be more relevant in a clinical setting. Whereas subjective cognitive measures improved for both drug and placebo groups, there was no such improvement on the objective neurocognitive battery. One explanation may be that our cognitive battery may not have been extensive enough to discern improvement, especially given that our women were, in general, highly educated. Using objective measures of cognitive function as inclusion criteria in our study may have elicited different results.

HT benefits at least some women with menopausal cognitive symptoms, but recent data regarding the risks and benefits of such use have left both women and their physicians in a quandary.[1] The Women's Health Initiative and the Women's Health Initiative Memory Study found an increased risk of coronary events, stroke, breast cancer, dementia, and pulmonary embolism in women taking conjugated equine estrogen.[25–27] Although these studies assessed women aged ≥65 years, the results have left their younger menopausal peers in a dilemma.

Acetylcholinesterase inhibitors such as donepezil, which is approved for the treatment of Alzheimer's-related cognitive loss, have improved the cognitive function of healthy subjects as well as those with cognitive loss from disparate causes such as head trauma and multiple sclerosis.[28,29] In healthy subjects, donepezil improved new

learning and memory for complex tasks, working memory, speed of information processing, and sustained and divided attention.[30–34] This implies that regardless of the etiology of cognitive loss, acetylcholinesterase inhibitors may help by increasing the selectivity of perceptual processes during memory encoding and by altering cerebral glucose utilization.[32]

These studies suggest that there may be a sound biological rationale for the use of medications such as donepezil in treating menopause-related cognitive complaints. One may speculate that the use of acetylcholinesterase inhibitors in conjunction with low-dose HT may also be beneficial in the treatment of menopause-related cognitive loss, although there are no data available to support this contention. Continued research in this area would be helpful in allowing women and their physicians to choose either appropriate alternatives to HT or supplements for treating menopause-related memory and cognitive complaints.

In our study, women in both the drug and placebo groups had improvement on subjective cognitive measures. Although there were trends for improvement in objective cognitive measures among women in the active drug group, we were unable to establish statistical significance, given our small group size and the resulting low power of the study. Future research should include a larger number of women to overcome this limitation.

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