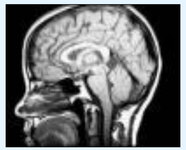

A double-blind, placebo-controlled trial of donepezil for the treatment of menopause related cognitive loss

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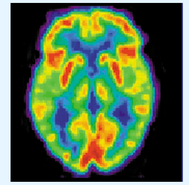


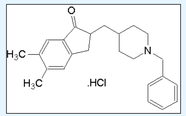
BACKGROUND

The association between menopause and post-menopausal memory and cognitive loss is controversial (1-3). In a survey of community-based women not pre-selected for menopausal symptoms, more peri-menopausal women complained of memory loss than pre-menopausal women (64% vs. 25%), comparable to their complaints of hot flashes (52% vs. 15%) (4). While alternatives to hormone therapy are available for conditions such as hot flashes and sleep dysfunction, no such alternative has been investigated for the cognitive complaints accompanying menopause (5-7).

OBJECTIVE

To investigate the efficacy of the acetylcholinesterase inhibitor donepezil (Aricept ®) in treating the cognitive symptoms associated with menopause. 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.

MORE ON THE INTERVENTION…



Donepezil (Aricept ®) was the second drug approved by the FDA to treat Alzheimer's. It works by raising the level of acetylcholine in the brain, slowing progression of some types of dementias. The dosing is once a day. A common side effect is gastrointestinal discomfort.

METHODS

• Twenty-eight community dwelling women between the ages of 46 and 60 in natural menopause were enrolled in a randomized, double-blind, placebo-controlled study of the drug donepezil.

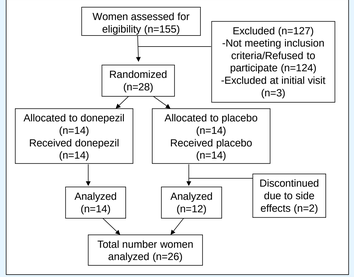
• The Brief Cognitive Rating Scale (BCRS) was used to determine cognitive symptoms to qualify for enrollment and women with depression were excluded.

• Women were randomized to either donepezil or placebo, titrated up to 10 mg per day in six weeks. Treatment was continued for six months.

• The primary outcome measure was the overall change in 1) objective neurocognitive battery tests and 2) subjective rating scales over time (see Table 2). Outcome variables of test scores were analyzed using a Student's t-test and a repeated measures analysis.

PARTICIPANTS

Figure 1: Flow of Women through Study



Women were enrolled and followed in the study from 2002 to 2003 (Figure 1).

RESULTS

Table 1: Participant Demographics

Group	Mean Age (Years)	Education	Race
Placebo (n=12)	53.71 ± 3.56	3 High School; 9 College	2 African American, 10 Caucasian
Drug (n=14)	55.21 ± 3.47	14 Grad/Med/Law	1 African American, 2 Asian, 10 Caucasian, 1 Hispanic

*There were no significant differences in demographics between groups.

Objective Measures of Cognitive Function: On objective measures 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 2). Tests for equality of variance did show a smaller variance within the treated group as compared to the placebo group, but this was not significant.

Subjective Measures of Cognitive Function: On subjective measures (BCRS and 17-Item Hamilton Depression Rating Scale [HAM-D]) there was no significant change in mean scores over time for either group in the initial analysis (Table 1). Both the drug and placebo group, however, did show trends towards improvement on subjective measures. HAM-D scores improved from a mean 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.

Repeated Measures Analysis: 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 in this case, and when only two time points are analyzed.

Table 2: Mean Test Scores and Significance for Placebo and Drug Groups

Test	Placebo (n=12)		Drug (n=14)		p-value
	Time 1 Mean (SD)	Time 2 Mean (SD)	Time 1 Mean (SD)	Time 2 Mean (SD)	
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

*Lower scores signify fewer and/or less severe symptoms.

CONCLUSIONS

In this small study we found that donepezil (Aricept ®) was not more effective than placebo for treating the cognitive symptoms associated with menopause. Women on both drug and placebo rated themselves as cognitively subjectively improved on the BCRS over time. On evaluation of cognitive loss objectively, we found no improvement over time within each group and no observed difference in outcome between the placebo and treatment group.

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