Acetylcholinesterase Inhibitor in Combination With Cognitive Training in Older Adults

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To determine if donepezil, an acetylcholinesterase (AChE) inhibitor, improved the assimilation of cognitive training by older adults with memory complaints, we gave 168 nondemented, community-dwelling volunteers with memory complaints either 5 mg of donepezil (Aricept) or placebo daily for 6 weeks in a randomized, double-blind, placebo-controlled trial. The dosage rose to 10 mg daily for another 6 weeks before a 2-week course of cognitive training and was maintained for the remainder of a year. Cognitive training improved performance; donepezil was well tolerated. However, there were no significant benefits of donepezil compared with placebo. An additional dose-ranging study with a starting dose of 5 mg a day suggests that the high dose was not the reason. Physiological tolerance may occur with chronic donepezil treatment and may increase AChE levels; this may be why short-term studies have shown the benefit of AChE inhibitor use in nondemented participants whereas chronic use has failed to enhance cognition.

Key Words: Acetylcholinesterase inhibitor—Cognitive training—Donepezil.

The purpose of this study was to determine if an acetylcholinesterase inhibitor (AChI) would improve the effectiveness of cognitive training designed to enhance memory performance in nondemented older adults. The use of AChIs is based on the cholinergic hypothesis that the memory deficit seen in patients with Alzheimer’s disease (AD) and the memory decrements associated with normal aging are due to a relative deficit in cholinergic function (Bartus, Dean, Beer, & Lippa, 1982; McGeer & McGeer, 1976). Prior studies support the theory that AChIs can enhance memory function in normal adults (Bentley, Husain, & Dolan, 2004; Bentley, Vuilleumier, Thiel, Driver, & Dolan, 2003; Davis et al., 1978; Freo et al., 2005; Furey, Pietrini, & Haxby, 2000; Furey et al., 1997). Our own research that suggested improved assimilation and retention of a complex aviation task with low-dose (5 mg/day) donepezil treatment also supported the relevance of the cholinergic hypothesis for normal aging (Yesavage et al., 2002).

Cognitive training has been used in attempts to attenuate age-related cognitive deficits. Training programs have succeeded in improving memory and other cognitive functions (Backman, Mantyla, & Herlitz, 1990; Ball et al., 2002; Brooks et al., 1999; Verhaeghen, Marcoen, & Goossens, 1992; Willis, 1987; Willis & Nesselroade, 1990; Willis et al., 2006); however, not all participants benefit from training. Greater improvement has been associated with better initial abilities (Hill, Yesavage, Sheikh, & Friedman, 1989). Some nondemented participants in prior studies might have suffered from mild cognitive impairment (MCI), which is a strong risk factor for AD. Such patients might actually have incipient AD and thus be relatively unresponsive to training.

The main hypothesis of the current study was that pharmacologic treatment would augment cognitive training effects so that the donepezil + cognitive training group would perform better than the placebo + cognitive training group (Hypothesis 1). Primary outcome measures were measures of delayed recall. Exploratory hypotheses proposed the examination of several potential moderators or predictors of treatment response (gain in recall scores), including demographic (age, education), biological (apolipoprotein E, or APOE, status), and baseline cognitive function measures (Hypothesis 2). Finally, this study tested whether changes in performance on cognitive measures were mediated by changes in levels of acetylcholinesterase (AChE) inhibition or changes in working-memory ability (Hypothesis 3).

METHODS

Design

We tested our hypotheses in a randomized controlled trial with two parallel groups: donepezil + cognitive training versus placebo + cognitive training. The pharmacologic treatment lasted 12 months. Twelve weeks after the pharmacologic treatment started, we instituted a 2-week-long cognitive training course. We took measures prior to the initiation of pharmacologic treatment (T1), after 12 weeks from the start of pharmacologic treatment but before the cognitive training (T2), after the cognitive training was completed (Week 14; T3) and 52 weeks from the start of the protocol (T4; see Figure 1).

Participants

The study was open to community-dwelling individuals of either gender, of any race or ethnicity, who were between the ages of 55 and 90 years. We recruited participants from a range of community resources, including senior centers, newspaper advertisements, and press releases.

Inclusion and exclusion criteria allowed entry of the usual spectrum of cognitive abilities found in community-dwelling individuals but excluded participants with various forms of
dementia. Our inclusion–exclusion criteria, enumerated in the following paragraphs, were based on those described by Petersen and associates (2005) to include a broad range of community-dwelling older adults, from those with normal function to those with MCI.

Inclusion criteria.—Participants had to be in good general health—they could have no additional diseases that we expected would interfere with the study. They had to have normal B12 levels, resting blood pressure levels, and thyroid function tests or be without any clinically significant abnormalities that would interfere with the study. They had to have normal general clinical chemistry results and complete blood count results. They could have self-reported memory complaints, but they had to score between 24 and 30 on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). They had to have a sufficiently preserved general cognition level to function in the community.

We included both individuals with MCI and individuals with normal age-adjusted scores on the Logical Memory II subscale of the revised Wechsler Memory Scale (Wechsler, 1987). Following criteria presented in Petersen and colleagues (2005), we considered scores below an education-adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) to be indicative of MCI. The cutoff was as follows: with a maximum score of 25 (Part A), the cutoff was ≤8 for ≥16 years of education, ≤4 for 8 to 15 years of education, and ≤2 for 0 to 7 years of education. Participants could have no significant cerebrovascular disease (modified Hachinski score of ≤4), and they had to have visual and auditory acuity that would be adequate for neuropsychological testing and benefit from cognitive training. On the 17-item Hamilton Depression Scale, they had to have a score of ≤12. We did permit participants to take some medications: they could take estrogen replacement therapy; or they could take ginkgo biloba.

Exclusion criteria.—We excluded participants if they had significant neurologic disease (other than suspected incipient AD), such as Parkinson’s disease, multi-infarct dementia, Huntington’s disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or a history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities. To determine this, a senior staff physician reviewed the medical history, list of current medications, and lab test data collected for each participant and conducted a physical examination that included testing basic neurological signs. Using criteria set from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994), we also excluded participants if they had a history of alcohol or substance abuse or dependence in the past 2 years, major depression in the past 2 years, or significant systemic illness or an unstable medical condition that which could lead to difficulty in complying with the protocol.

The protocol received approval by the Institutional Review Board of Stanford University. Participants gave informed, written consent and were compensated $200 for their participation at completion of the year-long study. Compensation was prorated for participants who did not complete the protocol.

Pharmacologic Treatment

Drug administration and dosage.—Participants meeting study criteria received, in a randomized double-blind fashion, either donepezil or placebo (kindly provided by Eisai Inc., Woodcliff Lake, New Jersey) for 52 weeks. All participants started at 5 mg/day for 6 weeks before moving to 10 mg/day (schedule recommended by Doody, 1999). The 10-mg dose was provided as two 5-mg pills. However, if patients could not tolerate 10 mg of donepezil or placebo, they were allowed (in consultation with the monitoring physician) to continue with 5 mg. Participants were encouraged to take the medication before noon but were allowed to take the medication at their preferred time, if consistent. Personal contact was maintained by a blinded research assistant who issued medication, inquired about possible side effects, and conducted pill counts. Participants were seen 14 times over the year: once every 3 weeks for the initial 12 weeks and then monthly after the start of cognitive training. If a participant missed three or more consecutive doses in any 1-month period, we withdrew the participant as a treatment failure but included the participant in our random regression (intent-to-treat) analyses.

Adverse events.—We recorded adverse events throughout the year until 1 week after medication discontinuation. A physician monitored reported side effects.

Withdrawal of participants.—We withdrew participants from the study if it was medically necessary, if they wished to withdraw, or if they did not comply with study protocol (e.g., used prohibited medication).

Blinding.—All participants and research staff were blinded. We accomplished the medication blinding by using identical donepezil and placebo tablets. Randomization and allocation to treatment was performed by the pharmacy through the use of random-number-generated codes. Pharmacy staff was not aware of any other participant data.

Cognitive Training

For 2 weeks, that is, during Weeks 13 and 14, the participants had 2 hours of cognitive training every morning. Monday
through Friday. The training for all classes was conducted by
the same experienced teacher and took place in a classroom
adjacent to our laboratory. The training followed the format
of a “comprehensive extended” training developed in earlier
work (Brooks, Friedman, Pearman, Gray, & Yesavage, 1999).
This consisted of supplemental nonmnemonic “pretraining,”
including visualization techniques, combined with mnemonic
training. This program has been shown in controlled trials to be
effective in improving list learning and name–face recall in
nondemented older adults. The list-learning task made use of
visual associations of to-be-remembered items to a permanent
list of locations or loci (usually locations in each participant’s
living room). The name–face recall technique similarly used
visual associations between a facial feature and a transforma-
tion of the person’s name to an image placed on the feature
(Brooks et al.; Hill, Sheikh, & Yesavage, 1988; Yesavage,
1983, 1985; Yesavage & Rose, 1984). Primary outcome mea-
sures were readministered prior to training on Day 1 of the
cognitive training program (T2). Pretraining started on Day 2
and lasted through Day 4. Mnemonic training started on Day 5
and lasted through Day 9. A test was administered on Day 10
at the end of the second training week (i.e., Week 14, or T3; see Figure 2).

Measures: Hypothesis 1 (Efficacy)

Primary outcome measures.—The following measures,
administered before the test (Week 13) and after it (Week
14), have reliably reflected training results (Yesavage, 1985).

Word list recall.—Participants received individual copies of
a list of 16 words; they had 4 minutes to memorize the words in
order. We tested short-term recall after a 5-minute distracter
task, and we tested delayed recall after 30 minutes. At recall,
participants were asked to write as many words as they could
remember in the order they were presented. Equivalent alternate
lists of words were used and counterbalanced.

Name–face recall.—We had pictures of faces projected one
at a time onto a screen with the associated name (first and last)
read aloud and presented underneath the face. Participants
studied the name–face pair for 1 minute. Immediately after the
12 name–face pairs were presented, the same set of faces was
presented again without the names, one per minute, in
a different random order. Participants were asked to write
down both names associated with each face.

Secondary outcome measures.—We used the core subset of
the Medical Outcomes Study Functioning and Well-Being
Profile (Stewart, 1992) to measure quality of life. We used the
Everyday Problems Test (Willis & Marsiske, 1993) to measure
functional capacities.

Measures: Hypothesis 2 (Moderators)

We selected the following measures to test whether
demographic, baseline cognitive, and biological (APOE)
characteristics of participants would predict treatment response.

Demographics.—We tested specific hypotheses regarding
basic demographic variables (age and education) as relevant
predictors of differential treatment response (McKitrick et al.,
1999).

Cognitive measures.—We used a battery of widely used
cognitive measures to test baseline cognitive functions that
were likely to moderate response to the intervention (Table 1).

Biological measure: APOE genotype.—Using the method of
Lahiri and Nurnberger (Nurnberger et al., 2000), we extracted
genomic DNA from frozen whole blood samples. We per-
formed APOE genotyping according to the restriction isotyping

Measures: Hypothesis 3 (Mediators)

We hypothesized and measured two potential mediators of
drug response: change in an index of working memory and
change in red blood cell (RBC) AChE activity.

Table 1. Means and Standard Deviations of Basic Demographic,
Cognitive, and Biological Characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Donepezil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.0 (7.4)</td>
<td>64.3 (8.0)</td>
</tr>
<tr>
<td>Gender: female/male</td>
<td>44/39</td>
<td>44/41</td>
</tr>
<tr>
<td>Education</td>
<td>16.0 (2.3)</td>
<td>16.6 (2.3)</td>
</tr>
<tr>
<td>MMSE score</td>
<td>28.6 (1.4)</td>
<td>28.6 (1.2)</td>
</tr>
<tr>
<td>MCI: %</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>MCI APOE e4 carriers: %</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Non-MCI: %</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Non-MCI APOE e4 carriers: %</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>Paired Associates I score</td>
<td>16.3 (3.9)</td>
<td>15.7 (4.5)</td>
</tr>
<tr>
<td>Paired Associates II score</td>
<td>6.5 (1.5)</td>
<td>6.5 (1.7)</td>
</tr>
<tr>
<td>Benton score</td>
<td>7.1 (1.5)</td>
<td>6.9 (1.6)</td>
</tr>
<tr>
<td>Logical Memory I score</td>
<td>25.6 (7.3)</td>
<td>24.4 (8.3)</td>
</tr>
<tr>
<td>Logical Memory II score</td>
<td>20.5 (7.7)</td>
<td>19.7 (9.2)</td>
</tr>
</tbody>
</table>

Note: Numbers for the table are as follows: donepezil, n = 83; placebo, n = 85. Standard deviations are shown in parentheses. MMSE = Mini-Mental State Examination; MCI = mild cognitive impairment; APOE = apolipoprotein E. The MMSE is from Folstein et al. (1975); the Paired Associates and Logical Memory tests are from Wechsler (1987); and the Benton test is from Sivan (1992).
Working memory.—We used change scores of the Digit Span (Wechsler, 1987) and the Symbol Digit modalities (Smith, 1991) as indicators of working memory and mediators of drug response. We computed change scores both from baseline to Week 13 and from baseline to Week 52.

RBC AChE activity.—We tested RBC AChE inhibition as a mediator variable (Rogers, Doody, Mohs, & Friedhoff, 1998; Rogers & Friedhoff, 1996). To determine AChE activity in RBC membranes, we collected a 5-ml venous blood sample at baseline, Week 13, and Week 52. We analyzed the blood with a specific radioenzyme assay, applying the methods used by Rogers (Hulse, Rogers, Friedhoff, Sukovaty, & Pedersen, 1992; Rogers & Friedhoff).

RESULTS

Participants

There were no statistically significant differences between groups on background variables, including basic demographics and baseline cognitive measures (Table 2). The two groups also had very similar gender and APOE ε4 carrier distributions, although, by chance, 50% of placebo MCI participants were APOE ε4 carriers, versus 30% of the drug group. Dropout rates and several side effects were significantly higher in the drug group than in the placebo (Table 2). These side-effect data (the 10 mg/day dosage caused more side effects) are similar to those of a controlled trial with 468 patients that examined both 5- and 10-mg dosages (Rogers et al., 1998). In our study, dose reductions occurred in 14 of 83 donepezil participants (16.9%) and 4 of 85 placebo participants (4.7%).

Class attendance was excellent (89% of the participants attended all 10 sessions; fewer than 1% of them missed more than one session). Participants were tested on their knowledge of the list of loci they developed for using the list-learning mnemonic, and 86% remembered either all 15 or 16 of the 16 loci on their lists.

At the end of Week 14, participants were asked several questions about the mnemonic test they had just completed. They scored an average of 6.32 (1.23) on a 7-point scale (ranging from 1, not at all, to 7, very much) in response to a question asking if, during the test, they employed the list-learning technique they were taught. When asked whether they understood the list-learning technique, they scored an average of 6.45 (1.10); and on a question asking whether they would apply the mnemonic techniques to their everyday lives, they scored 6.20 (1.33).

Statistical Analysis

Hypothesis 1: Efficacy.—The primary analysis compared gain in list learning and name–face recall from baseline to after cognitive training (Week 14). We also examined gain in list learning and name–face recall from baseline to after the 12 weeks of pharmacologic treatment alone and retention of list learning and name–face recall skills from end of cognitive training to follow-up (Week 52). Although the overall effects of cognitive training were uncontrolled, they were similar to those reported in prior controlled trials. In other words, i.e., gain scores improved in a manner similar to that in our prior controlled trials (Yesavage, 1985); there were no significant effects associated with donepezil treatment at any measurement point either alone or as an augmentation of the effects of cognitive training (Table 3a). Similarly, there were no differences between treatments on measures of quality of life (Medical Outcomes Study Functioning and Well-Being Profile) or functional capacity (Everyday Problems Test; see Table 3b).

Table 2. Drop Outs, Dose Reductions, and Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Donepezil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drop out for any reason in first 12 weeks*</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Dose reductions from 10 to 5 mg/day*</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle cramps***</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia*</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Pain (other locations)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Frequent urination</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: Numbers for the table are as follows: donepezil, n = 83; placebo, n = 85.
*p < .05; ***p < .001 by chi square.

Table 3a. Primary Outcome Measures

<table>
<thead>
<tr>
<th>Group</th>
<th>Measure</th>
<th>Week 0: Baseline</th>
<th>Week 13: Pretest</th>
<th>Week 14: Post-Test</th>
<th>Week 52: Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Name–face</td>
<td>3.0 (2.9)</td>
<td>3.2 (3.2)</td>
<td>3.5 (2.9)</td>
<td>4.3 (3.9)</td>
</tr>
<tr>
<td></td>
<td>Change from baseline</td>
<td>0.2 (2.4)</td>
<td>0.4 (2.1)</td>
<td>1.2 (2.7)</td>
<td>1.2 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Word list</td>
<td>6.8 (3.9)</td>
<td>7.0 (4.1)</td>
<td>9.3 (4.3)</td>
<td>11.3 (4.5)</td>
</tr>
<tr>
<td></td>
<td>Change from baseline</td>
<td>0.3 (2.9)</td>
<td>2.5 (4.6)</td>
<td>4.5 (4.0)</td>
<td>4.5 (4.0)</td>
</tr>
<tr>
<td>Placebo</td>
<td>Name–face</td>
<td>3.1 (3.0)</td>
<td>3.0 (3.2)</td>
<td>4.3 (3.6)</td>
<td>5.2 (3.6)</td>
</tr>
<tr>
<td></td>
<td>Change from baseline</td>
<td>-0.1 (2.5)</td>
<td>1.1 (2.7)</td>
<td>1.6 (2.7)</td>
<td>1.6 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Word list</td>
<td>6.6 (4.2)</td>
<td>7.8 (4.3)</td>
<td>9.9 (4.6)</td>
<td>11.5 (4.5)</td>
</tr>
<tr>
<td></td>
<td>Change from baseline</td>
<td>1.3 (3.4)</td>
<td>3.2 (4.4)</td>
<td>4.3 (4.2)</td>
<td>4.3 (4.2)</td>
</tr>
</tbody>
</table>

Note: Numbers for the drugs are as follows. Donepezil: For Weeks 0, 13, 14, and 52, n = 83, 68, 67, and 55, respectively. Placebo: For Weeks 0, 13, 14, and 52, n = 85, 79, 75, and 65, respectively. Standard deviations are shown in parentheses.
**Table 3b. Secondary Outcome Measures**

<table>
<thead>
<tr>
<th>Group</th>
<th>Measure</th>
<th>Week 0: Baseline</th>
<th>Week 13: Pretest</th>
<th>Week 52: Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donepezil</strong></td>
<td>Quality of life (MOS)</td>
<td>65.3 (11.1)</td>
<td>NT</td>
<td>60.3 (10.3)</td>
</tr>
<tr>
<td></td>
<td>Functional capacity (EPT)</td>
<td>35.2 (4.7)</td>
<td>35.2 (5.3)</td>
<td>36.0 (5.1)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>Quality of life (MOS)</td>
<td>66.0 (12.2)</td>
<td>NT</td>
<td>64.1 (11.7)</td>
</tr>
<tr>
<td></td>
<td>Functional capacity (EPT)</td>
<td>36.2 (3.9)</td>
<td>35.7 (4.7)</td>
<td>36.5 (4.0)</td>
</tr>
</tbody>
</table>

*Note: Numbers for the drugs are as follows. Donepezil: For Weeks 0, 13, and 52, n = 83, 67, and 55, respectively. Placebo: For Weeks 0, 13, and 52, n = 85, 79, and 65, respectively. MOS = Medical Outcomes Study Functioning and Well-Being Profile; EPT = Everyday Problems Test; NT = not tested. Standard deviations are shown in parentheses.*

**Hypothesis 2: Moderators—Demographic, baseline cognitive, and APOE.**—We examined demographic (age and education), baseline cognitive, and genetic measures (Table 2) as moderators of treatment effect by using random effects regression models for Moderator × Time × Condition interactions. Thus, the data were analyzed to determine if selected moderators differentially affected outcome from the pharmacologic treatment over time. There were no significant interactions between time and condition and demographic, baseline cognitive, or genetic measures.

**Hypothesis 3: Mediators—Change in working memory and change in AChE inhibition under the initial 12 weeks of donepezil therapy.**—The first step in a mediator analysis is to demonstrate that the potential mediator changes during treatment. If the change is statistically significant, then the second step is to demonstrate that the change in the mediator explains some portion of the treatment effect on clinical outcome measures. There were no significant changes with donepezil versus placebo on the working-memory mediator measures (i.e., Symbol Digit Substitution and Digit Span; see Table 4). Thus, the “drug response” was absent and we could not perform the first step in the mediational analyses. However, increased levels of AChE inhibition would be expected in the active treatment versus control. We performed a set of correlations to determine if the level of AChE inhibition was related to gain on memory scores. After 12 weeks, the level of RBC AChE inhibition, 69% at 5 mg/day and 70% at 10 mg/day, was similar to that found by Rogers (1998) and there were no significant correlations between AChE inhibition levels and memory performance gain scores. Those participants who had their dosage reduced to 5 mg had similar levels of AChE inhibition as those who could tolerate 10 mg.

**Table 4. Mediator Measures**

<table>
<thead>
<tr>
<th>Group</th>
<th>Measure</th>
<th>Week 0: Baseline</th>
<th>Week 13: Pretest</th>
<th>Week 52: Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donepezil</strong></td>
<td>Symbol digit</td>
<td>50.9 (8.9)</td>
<td>49.1 (8.2)</td>
<td>51.9 (8.7)</td>
</tr>
<tr>
<td></td>
<td>Digit span</td>
<td>16.5 (3.9)</td>
<td>16.6 (4.0)</td>
<td>17.6 (4.1)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>Symbol digit</td>
<td>50.0 (9.2)</td>
<td>49.7 (9.3)</td>
<td>52.2 (9.0)</td>
</tr>
<tr>
<td></td>
<td>Digit span</td>
<td>15.7 (3.1)</td>
<td>15.5 (3.4)</td>
<td>16.8 (3.2)</td>
</tr>
</tbody>
</table>

*Note: Numbers for the drugs are as follows. Donepezil: For Weeks 0, 13, and 52, n = 83, 70, and 52, respectively. Placebo: For Weeks 0, 13, and 52, n = 85, 79, and 63, respectively. Standard deviations are shown in parentheses.*

**DISCUSSION**

The fact that there is no index of central cholinergic function, combined with the wide range of interindividual AChE inhibition, makes it challenging to determine the proper dosage of donepezil in nondemented individuals. Nondemented individuals, including those with MCI and incipient dementia, are likely to have wide variations in levels of baseline cortical AChE inhibition as well as differing levels of cholinergic receptors. Thus, it is unlikely that a fixed dosage of an AChE inhibitor will be effective for all individuals.

A possible solution to identifying the optimal dosage for each individual was suggested by the original studies of phystostigmine, conducted about 30 years ago. Davis and his collaborators (Davis, Hollister, Overall, Johnson, & Train, 1976; Davis et al., 1978) performed a series of experiments that defined an individual’s “optimal” dosage not in terms of milligrams or measures of cholinergic inhibition but by using a proxy measure of central cholinergic function: improvement of performance on a memory task. In an attempt to determine whether or not dosage was a factor, we studied an additional cohort of 30 participants dosage was adjusted to 2.5 mg, 5.0 mg, or 7.5 mg on the basis of their optimal list-learning test performance. An analysis of gain in cognitive scores after cognitive training while receiving these “optimally” adjusted dosages showed no advantage from dose optimization. These results as well as results for the participants in the main experiment who did not advance beyond 5 mg provided no evidence that dosage was a factor that could be adjusted to improve outcome. This is consistent with the finding that the level of RBC AChE inhibition on 5-mg and 10-mg dosages was virtually identical in the main study.

Physiological tolerance to the effects of donepezil is another factor that may affect the benefit from donepezil that an individual receives. In other words, AChE levels may increase with chronic treatment, thereby reducing the potential for long-term clinical benefit. Although the literature is not consistent, this might explain why some short-term studies have shown the benefit of AChIs in nondemented populations whereas chronic administration to similar populations has failed to enhance cognition. For example, some researchers found cerebrospinal fluid levels of AChE to be significantly elevated after participants received donepezil treatment for 6 months (Davidsson et al., 2001; Parnetti et al., 2002). In contrast, using positron emission tomography techniques, other researchers showed
cortical AChE activity to be reduced after participants received 12 weeks of treatment (Bohnen et al., 2005). A study using rats also showed decreased cortical AChE activity that was unchanged in magnitude after 14 days of treatment (Haug, Bogen, Osmundsen, Walaas, & Fonnum, 2005). Thus, although some studies suggest that physiological tolerance to the effects of donepezil may occur, the literature is not consistent and does not provide a convincing explanation for the lack of effects of donepezil found in the experiment reported herein.

Davis and Sadik (2006) offered the disruption of circadian rhythms as another explanation for the lack of effect of donepezil on chronically treated nondemented patients. They argued that several studies have suggested that the chronic dosing of an AChE inhibitor around the clock will have adverse effects on sleep and other circadian parameters that interfere with consolidation of memory. Their proposed solution is more frequent treatment with AChE inhibitors having a short half-life that thus do not carry their inhibitory effects over into sleep periods, instead of treatment with donepezil, which has a long half-life.

In conclusion, the results of this study of 168 community-dwelling older adults with memory complaints suggest that a 10-mg treatment of donepezil will not improve the cognitive function of most of these individuals, with or without adjunctive cognitive training. Despite considerable rationale that such agents may work in the short term, successful long-term treatment in nondemented populations remains elusive. Problems include establishing the proper dosage, the potential for the development of physiological tolerance, and interference with circadian rhythms with an associated disruption of the process of memory consolidation. Until these challenges are met, the use of donepezil as an augmentation of memory in nondemented populations is not warranted.

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REFERENCES


and after treatment with different AChE inhibitors. *Neurological Sciences*, 23, S95–S96.


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