Donepezil Therapy in Clinical Practice

A Randomized Crossover Study

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Objective: To determine the efficacy of donepezil hydrochloride for the treatment of Alzheimer disease in patients drawn from clinical practice.

Design: Two-center, randomized, placebo-controlled, double-masked crossover study.

Setting: Memory disorders units at Massachusetts General and Brigham and Women's hospitals, Boston.

Patients: Sixty individuals (30 men and 30 women; mean ± SD age, 75.0 ± 9.5 years) with probable Alzheimer disease and scores of 20 or less on the information-memory-concentration subscale of the Blessed Dementia Scale.

Interventions: Placebo wash-in, followed in randomized sequence by (1) donepezil hydrochloride therapy, 5 mg/d, for 6 weeks, followed by placebo washout for 6 weeks and (2) placebo treatment for 6 weeks.

Primary Outcome Measure: Change in Alzheimer's Disease Assessment Scale cognitive subscale scores from the beginning to the end of the two 6-week treatment periods.

Results: Among patients completing treatment and testing for both periods (n = 48), subscale scores improved (mean ± SEM) 2.17 ± 0.98 points (95% confidence interval, 0.20-4.10 points) during donepezil therapy relative to placebo therapy (P = .04). Scores returned toward baseline within 3 weeks of drug washout. There was no associated change in caregiver-rated global impression (donepezil vs placebo: proportion improved, 0.24 vs 0.22; proportion worsened, 0.27 vs 0.35; P = .34) or on specific tests of explicit memory or verbal fluency. Contrary to studies with tacrine, the presence of the apolipoprotein E ε4 allele did not predict donepezil treatment failure. Most common adverse events related to donepezil therapy were nausea (5 patients), diarrhea (3 patients), and agitation (3 patients). Serious events possibly related to drug use were seizure, pancreatitis, and syncope (1 patient each).

Conclusion: This independent confirmation of data from phase 3 trials suggests that donepezil therapy modestly improves cognition in patients with Alzheimer disease who are encountered in clinical practice.

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Enhancement of cholinergic transmission has been the mainstay of symptomatic treatment for memory loss and functional impairment in Alzheimer disease (AD). This approach initially derived from evidence linking cholinergic systems to human memory and learning, and from observations of extensive cholinergic damage in AD. Despite the recognized limitations of transmitter enhancement for this disorder, this approach has led to the development of several current or pending treatments for AD.

Donepezil, like the approved medication tacrine, is a centrally active, reversible acetylcholinesterase inhibitor. Used at a dosage of 5 to 10 mg per day, this medication has been reported to improve cognition (measured by a short general cognitive test) and global impression of patient function during 6 to 24 weeks of treatment. It remains unclear from these studies whether donepezil exerts its effect on cognition by specifically enhancing explicit memory, as predicted by the cholinergic hypothesis of memory, or by a more global mechanism such as enhanced attention or executive function.

Questions also remain as to the applicability of the data from phase III trials to clinical practice. One limitation of these studies is they were performed in research populations chosen to exclude many common medical diagnoses (eg, cardiovascular disease and diabetes mellitus) and psychoactive medications (eg,
PATIENTS AND METHODS

Methods of this trial are reported in a format consistent with the recommendations of the Consolidated Standard of Reporting Trials (CONSORT) statement.15

PATIENTS AND ELIGIBILITY

Men and women with a diagnosis of probable AD16 seen at the memory disorders units at Massachusetts General Hospital (MGH) or Brigham and Women's Hospital (BWH), Boston, between March 1, 1997, and December 31, 1997, were considered for this study. In addition to routine diagnostic testing (including determination of patient demographic information and approximate disease duration), patients were also evaluated using the information-memory-concentration subscale of the Dementia Scale17 at their baseline visits and the Mini-Mental State Examination18 3 weeks after study entry (before randomization). A requirement for participation was the ability to undergo cognitive testing, operationally defined as an information-memory-concentration subscale score of 20 or less. Other inclusion criteria were 6 years or more of education, fluency in speaking English, stable doses of any concomitant medication for 4 weeks before enrollment, and the presence of an appropriate caregiver to monitor medication use and attend all follow-up assessments. Patients were medically excluded only if they had specific contraindications to cholinesterase inhibitor use such as a history of sick sinus syndrome or another supraventricular conduction defect, active gastrointestinal tract bleeding, bladder obstruction, asthma or severe obstructive pulmonary disease, or hypersensitivity to cholinesterase inhibitor use. Patients were also excluded if they had taken cholinesterase inhibitors within the previous 3 months.

The protocol was approved by institutional review boards at MGH and BWH, and was conducted after obtaining written informed consent from patients and family caregivers.

RANDOMIZATION AND TREATMENT INTERVENTIONS

The trial was a 24-week, double-masked, placebo-controlled crossover design. Treatment group status was assigned by a computerized randomization schedule generated by a biostatistician (D.L.H.), and was concealed from all study personnel. Sites were supplied with sealed opaque individual disclosure forms containing each patient’s actual treatment assignment for emergency medical care.

All individuals began with a 6-week, single-blind, placebo wash-in. Patients were then randomized with equal allocation to crossover between double-masked treatment with donepezil hydrochloride (5 mg/d) or placebo in either of 2 sequences (Figure 1, top): (1) 6 weeks each of placebo treatment, donepezil therapy, and placebo washout, or (2) 6 weeks each of donepezil therapy, placebo washout, and placebo treatment. Study medications (donepezil or placebo) were packaged in capsules identical in appearance, taste, and smell. Individuals were instructed to take donepezil or the matching placebo orally once daily in the evening. Dosing compliance was assessed by interview of caregivers and pill counts. Based on pills returned, compliance was estimated as 95.7%.

PATIENT EVALUATIONS

Evaluations were performed at 6, 12, 15, 18, 21, and 24 weeks. This schedule ensured that patients randomized to either schedule would be tested at the beginning and end of their donepezil and placebo treatments, and after 3 weeks of drug washout. Evaluations included (1) cognitive testing and determination of caregiver-rated global impression (see following paragraph), (2) assessment of compliance with study medication use, and (3) interview with the caregiver to verify concurrent medication use and adverse events (including date of onset and cessation, severity, and temporal relation to administration of study medication). Cognitive testing was performed by a psychometrician who was masked to the patient’s treatment status, adverse event profile, concomitant medication use, pill compliance, caregiver-rated global impression of change, and overall study design. A separate set of personnel (also masked to patient information) scored the cognitive tests and entered data into a database. The primary outcome measure was the Alzheimer’s Disease Assessment Scale cognitive subscale (ADAS-cog).19 An 11-item scale testing multiple areas of potential cognitive impairment (memory, language, orientation, reasoning, and praxis); its use in assessing cognitive change in AD has been extensively validated. Maximal impairment on the ADAS-cog is a score of 70, with lower scores indicating less severity.

Secondary outcome measures included explicit verbal recall, verbal fluency, and caregiver-rated global impression of change. Explicit recall was tested by the NYU Stories Test delayed recognition subscale.20 This test is a 7-point scale (7 indicating perfect performance), in which patients answer multiple-choice questions regarding a story heard 10 minutes earlier, with different standardized versions used at each visit. Verbal fluency was tested by having patients generate lists of words beginning with a given letter for 1 minute for each of 3 letters. Choice of first letters varied at each visit to include a standardized range of easy and difficult letters.21 Recall and fluency tests, like the ADAS-cog, were administered at each follow-up visit. In addition, caregivers were asked at 6-week intervals (weeks 6, 12, 18, and 24) to assess the overall change in patient function (caregiver-rated clinical global impression of change) during the previous 6 weeks as mildly to markedly worsened, unchanged, or mildly to markedly improved.

A target sample size of 60 randomized patients was chosen to provide approximately 80% power to detect a 2.5-point improvement in the ADAS-cog score with donepezil therapy relative to placebo therapy, a magnitude similar to that detected in previous studies2,22 of donepezil and tacrine therapy. This calculation assumed a 10% to 20% dropout rate. A total of 64 patients entered the wash-in phase of the study, 60 of whom (51 from MGH and 9 from BWH) were randomized to a crossover sequence (Figure 1, bottom). Scores on the ADAS-cog could not be determined for every randomized patient because of study dropout (9 patients: 7 from MGH and 2 from BWH) or inability to complete ADAS-cog testing at a particular visit. The number of patients able to complete all testing with donepezil and placebo was 48 (41 from MGH and 7 from BWH).

Apolipoprotein E genotype was available from 35 patients who completed the study and participated in

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concurrent genetic research studies. Genotype was determined by polymerase chain reaction and digestion with HhaI, as described elsewhere. The subset of patients with available APOE genotype had essentially the same mean age, Mini-Mental State Examination score, and duration of disease as the full study cohort (data not shown).

STATISTICAL ANALYSIS

The primary unit of analysis was the difference between ADAS-cog scores at the beginning and end of a 6-week treatment period, with negative changes indicating improvement during the interval. Significance testing for this result was performed using analysis of variance for repeated measures with drug treatment (donepezil or placebo) as the independent variable. The analysis of variance model was also used to analyze the effect of drug-placebo sequence, age, sex, level of education, disease duration, center of enrollment (MGH or BWH), and severity of dementia at baseline (Blessed Dementia Scale or Mini-Mental State Examination score). Changes in ADAS-cog scores were also analyzed by dividing responses into improvement (negative change) vs no improvement, with significance testing for the within-subject comparison of donepezil and placebo therapy performed using the McNemar test. Secondary measures of memory and fluency were similarly analyzed according to the difference in performance at the beginning and end of donepezil or placebo treatment. Differences in caregiver-rated impressions of global change (categorized as worsened, no change, or improved) between the 2 periods were compared using a 2-sample Wilcoxon test with treatment sequence as the independent variable. All analyses were 2-sided, and P<.05 was required for statistical significance.

Results of some studies suggest that genetic markers might predict responsiveness to cholinergic treatment. The apolipoprotein E (APOE) ε4 allele in particular, noted for its association with risk for AD, has been reported to predict a lack of response to tacrine therapy; this effect may apply specifically to women. Apolipoprotein E ε4 has been suggested to mark a greater extent of cholinergic damage in these patients and thus, more limited capacity for improvement with cholinesterase inhibition. Identification of predictors of response to therapy would be a significant advance for clinical practice and our biological understanding of AD.

We undertook the present study to address the following questions: (1) Can the beneficial effects of donepezil therapy on cognition be replicated in patients drawn from clinical practice? (2) Does donepezil therapy exert its effect on cognition by improving explicit memory? (3) Do certain patient characteristics such as APOE genotype predict response to donepezil therapy?

RESULTS

After placebo wash-in, 60 patients with probable AD were randomized to crossover from 6 weeks of treatment with donepezil hydrochloride, 5 mg/d, and 6 weeks of washout to placebo therapy or from placebo to donepezil therapy (Figure 1, top). Although the study was open to patients with AD who had almost any medical or psychiatric disorder (see the “Comments” section), the requirement that patients be cognitively testable restricted the study population largely to those with mild to moderate dementia (Table 1). Fifty-one patients completed the donepezil and placebo treatment periods (Figure 1, bottom), 48 of whom were able to undergo ADAS-cog testing after both treatments.

Performance on the ADAS-cog significantly improved during treatment with donepezil, and slightly
worsened during placebo therapy (Table 2). Combining within-individual changes during drug and placebo use, ADAS-cog scores showed a 2.17-point (95% confidence interval, 0.20-4.10 points) net improvement in response to donepezil administration. Categorized according to whether ADAS-cog scores increased (worsened) or decreased (improved), 21 (44%) of 48 patients demonstrated improvement during donepezil but not placebo treatment, compared with only 9 (19%) of 48 patients who improved during placebo but not donepezil therapy (P = .03). The benefit of donepezil therapy largely abated within 3 weeks of placebo washout (Figure 2). Response to donepezil use was similar, regardless of treatment sequence, without evidence of a drug carryover effect. There was also no effect on response to donepezil therapy associated with patient age, sex, level of education, disease duration, center of enrollment (MGH or BWH), or severity of dementia at baseline (measured as Blessed Dementia Scale or Mini–Mental State Examination score).

To examine the effect of donepezil use on specific cognitive domains, we examined the performance on tests of explicit verbal memory and verbal fluency. Mean scores on these tests were not improved with donepezil use relative to placebo therapy (Table 3). We also used a caregiver-rated impression of global change scale to assess the caregiver’s impression of change in patient function during treatment. Although there was slightly more frequent improvement and less frequent worsening during donepezil than placebo therapy (Table 3), these results did not approach statistical significance (P = .34).

Results of previous studies11-14 suggest that patients with AD carrying the APOE ε4 allele may be less responsive to cholinergic treatment than noncarriers. We did not see this effect: of 35 patients with APOE genotype determination who completed donepezil and placebo treatment, carriers of APOE ε4 saw this effect: of 35 patients with APOE genotype determination who completed donepezil and placebo treatment, carriers of APOE ε4 had somewhat greater improvement with donepezil use than did patients without APOE ε4 (Table 4). Scores on the ADAS-cog improved with donepezil therapy in male and female carriers of APOE ε4, although the small numbers in each group preclude definitive analysis (data not shown).

Of 9 withdrawals from the study after randomization, 2 were due to serious adverse events judged to be possibly related to donepezil therapy: syncope and generalized seizure (1 patient each). An additional patient was diagnosed as having mild pancreatitis at the end of donepezil treatment. None of these complications recurred after discontinuation of donepezil use. Donepezil therapy was otherwise well tolerated. The remainder of withdrawals were due to unrelated adverse events (rash

Table 1. Characteristics of Study Patients‡

<table>
<thead>
<tr>
<th>Group A: Placebo/Donepezil (n = 30)</th>
<th>Group B: Donepezil/Placebo (n = 30)</th>
<th>Total (N = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>18/12</td>
<td>30/30</td>
</tr>
<tr>
<td>Age, y</td>
<td>74.9 ± 10.1</td>
<td>75.1 ± 9.0</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>4.1 ± 2.8</td>
<td>3.5 ± 2.1</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.2 ± 3.5</td>
<td>14.2 ± 3.5</td>
</tr>
<tr>
<td>MMSE score</td>
<td>21.6 ± 3.5</td>
<td>21.9 ± 4.0</td>
</tr>
<tr>
<td>BDS score</td>
<td>11.1 ± 4.1</td>
<td>10.0 ± 4.4</td>
</tr>
<tr>
<td>ADAS-cog score</td>
<td>18.7 ± 7.4</td>
<td>18.3 ± 8.2</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD. MMSE indicates Mini–Mental State Examination; BDS, Blessed Dementia Scale information-memory-concentration subscale; and ADAS-cog, Alzheimer’s Disease Assessment Scale cognitive subscale. Donepezil was given as donepezil hydrochloride.

Table 2. Cognitive Response to Donepezil Treatment*

<table>
<thead>
<tr>
<th>Treatment/Placebo/Change in ADAS-cog Score</th>
<th>Patients Completing Testing, No.</th>
<th>Placebo</th>
<th>Donepezil</th>
<th>Donepezil-placebo‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>52</td>
<td>+0.62 ± 0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil</td>
<td>51</td>
<td>-1.50 ± 0.58†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil-placebo‡</td>
<td>48</td>
<td>-2.17 ± 0.98†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are given as mean ± SEM. ADAS-cog indicates Alzheimer’s Disease Assessment Scale cognitive subscale. Donepezil was given as donepezil hydrochloride.

†Difference between changes in ADAS-cog scores during donepezil and placebo treatment (negative score indicates improvement).

Table 3. Lack of Effect on Secondary Outcome Measures

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Donepezil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiver-rated global impression, No. (%)</td>
<td>12/53 (23)</td>
<td>12/51 (24)</td>
</tr>
<tr>
<td>Improved/total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened/total</td>
<td>15/53 (28)</td>
<td>14/51 (27)</td>
</tr>
<tr>
<td>Explicit verbal memory score, mean ± SEM*</td>
<td>+0.23 ± 0.29</td>
<td>-0.32 ± 0.28</td>
</tr>
<tr>
<td>Verbal fluency score, mean ± SEM*</td>
<td>-0.27 ± 0.31</td>
<td>-0.71 ± 0.34</td>
</tr>
</tbody>
</table>

*Differences between the beginning and end of treatment (positive score indicates improvement). Donepezil was given as donepezil hydrochloride.
The results of our study show a modest beneficial effect of donepezil therapy on cognitive function, as measured by the ADAS-cog in a population with AD drawn from clinical practice. This result represents an independent confirmation of data from phase III trials performed in highly selected study populations. The beneficial effect largely washed out within 3 weeks of discontinuation of drug use, supporting a symptomatic mechanism of action. With the exception of the few potentially serious events described, no adverse effect of donepezil therapy was severe enough to cause patients to discontinue treatment.

We believe that the patients who participated in this trial, although primarily white and well educated, were nonetheless more representative of actual clinical practice than those previously described. We estimate, eg, that at least 23 (38%) of our 60 randomized patients would have been excluded from the phase III donepezil trials, based on concomitant use of psychoactive medications (12 patients: 10 taking antidepressants, 4 taking sedatives, and 2 taking both) or the presence of significant cardiovascular disease (15 patients, 4 also taking psychoactive medications). Patients within these subgroups responded to donepezil therapy approximately as well as other members of the cohort (data not shown), supporting the applicability of the results to a wider range of patients. In addition, our patients were somewhat older (and thus closer to the general population with AD) than those who participated in the phase III trials of donepezil and older than the median age of patients in 11 of 12 studies of tacrine therapy.

Although cognitive scores improved, the magnitude of improvement was small and apparently escaped the notice of the patients' caregivers (Table 3). The absence of global improvement in function differs from results of previous studies. This negative result might reflect insufficient sample size because our study was not primarily designed to assess this question. Indeed, based on data from a recent meta-analysis of tacrine therapy, we estimate needing approximately 400 patients to detect a comparable effect of donepezil therapy on global impression of function. The data, however, highlight the relatively small effect of donepezil therapy on global functioning in AD and the likelihood that many caregivers will be unable to detect improvement related to use of the medication.

There are several potential weaknesses to consider in interpreting our results. Crossover studies of AD have been criticized because of variability in the disease's rate of decline. The short period of drug treatment in the present study, however, makes decline during treatment a relatively small factor. Indeed, baseline ADAS-cog scores remained stable from the first to the second treatment periods in our study (data not shown). Another concern is the possibility of underestimating the true effect of donepezil therapy by our use of a 5-mg daily dose, rather than the highest approved dose of 10 mg. We do not believe this choice had a large effect on the magnitude of response. Although 5 mg was the highest published dose as of the beginning of our trial, subsequent studies of 10-mg doses showed no significant advantage in ADAS-cog scores (and a somewhat higher rate of adverse events). Finally, the mildness of dementia in our population (Table 1) relative to those previously studied might also have limited the magnitude of the effect of donepezil therapy.

The neuropsychologic mechanism for the beneficial effect of donepezil therapy on cognition remains elusive. We could not confirm the prediction that cholinesterase inhibition would specifically improve explicit memory, despite a greater than 90% power to detect a 1-point improvement on the 7-point delayed recognition task that we used. It thus remains to be determined whether donepezil therapy affects another specific cognitive domain or enhances cognitive performance via a general effect on attention or concentration.

We also could not confirm an association between the APOE e4 allele and the lack of response to donepezil therapy. Pharmacogenetic investigations in AD have sought to define genetic subgroups with distinct responses to medication, the ultimate goal being to optimize treatment for individual subtypes of AD. Apolipoprotein E e4 has been postulated to identify 1 such subgroup: patients with more extensive cholinergic damage and thus, diminished ability to respond to administration of cholinesterase inhibitors. It is therefore noteworthy that the trend in our data actually ran counter to the previously reported association between APOE genotype and response to tacrine therapy. This discrepancy might reflect differences between the biological mechanisms of tacrine and donepezil, although this seems unlikely from our understanding of these agents. The data point to the need for further study of this phenomenon.

In summary, our results demonstrate a small beneficial effect of donepezil therapy on cognitive performance without evidence for improved global function. Our results support the use of donepezil in clinical practice but also highlight the need for new and more effective treatments for AD.

### Table 4. Effect of APOE e4 on Response to Donepezil Therapy

<table>
<thead>
<tr>
<th>APOE e4</th>
<th>Patients, No.</th>
<th>ADAS-cog Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncarrier</td>
<td>11</td>
<td>−0.70 ± 1.16</td>
</tr>
<tr>
<td>Carrier</td>
<td>24</td>
<td>−3.63 ± 1.69</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SEM. APOE indicates apolipoprotein E; ADAS-cog, Alzheimer's Disease Assessment Scale cognitive subscale. Donepezil was given as donepezil hydrochloride.*
REFERENCES


2. Drachman DA. Memory and cognitive function in man: does the cholinergic system have a specific role? Neurology. 1977;27:783-790.


