Down Syndrome and Alzheimer Disease

Response to Donepezil

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Background: Individuals with Down syndrome who develop Alzheimer disease may show an improvement in cognitive functioning after treatment with acetylcholinesterase inhibitors.

Objective: To determine whether individuals with Down syndrome and Alzheimer disease will show improvement after institution of donepezil treatment.

Design: A nonrandomized controlled trial using donepezil in a pilot study format.

Setting: Academic medical center.

Patients: Convenience sample of 6 treated patients with Down syndrome and 9 closely matched historical control subjects.

Intervention: Oral administration of donepezil for a 5-month period.

Primary Outcome Measure: The Down Syndrome Dementia Scale.

Results: Significant improvement in dementia scores for the treated group during a 3- to 5-month period (P = .03).

Conclusions: Acetylcholinesterase inhibitors may be helpful in reversing the symptoms of dementia during early and middle stages of cognitive decline. These findings support the rationale for a more extensive study of the efficacy of acetylcholinesterase inhibitors in Down syndrome dementia.

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People with Down syndrome (DS) are at risk of developing the dementia associated with Alzheimer disease (AD). After age 35 years, virtually all individuals with DS have developed the neuropathologic characteristics of the disorder, although a smaller percentage undergo symptoms of cognitive decline. The topography of cell loss secondary to AD in DS parallels the changes seen in AD in the general population and involves neurons responsible for cholinergic neurotransmission. In both AD and DS, a similar cholinergic deficit has been implicated in the progressive impairment of cognitive, language, and behavioral functioning.

To date, the most successful clinical strategy to enhance cholinergic neurotransmission in AD has been through use of acetylcholinesterase inhibitor drugs. The acetylcholinesterase inhibitor donepezil has been shown to improve language production, comprehension, word finding, and the ability to follow commands in patients with AD in the general population. Despite widespread use of donepezil for AD in the general population, there are few, if any, controlled studies of this drug to treat dementia in DS. We present the results of an open-label pilot study of donepezil to treat symptoms of dementia in DS.

RESULTS

Nine patients with DS were treated with donepezil for a mean (SD) of 127.7 (33.9) days (range, 83-182 days; SEM, 11 days). Patients received an initial daily dose of 5 mg for a mean (SD) of 50.9 (46.6) days and were then increased to a daily dose of 10 mg for 78.2 (59.5) days.

Treated and control subjects were comparable with respect to initial level of dementia, length of follow-up, and age. At their pretreatment assessment, the patients treated with donepezil averaged 52.3 (SEM, 1.4) years of age compared with an average age of 52.5 (SEM, 2.6) years for the comparison group (Mann-Whitney test for difference, P = .86). Treated patients were followed up for a mean of 136.0 days.

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SUBJECTS AND METHODS

From a database containing data on 46 patients, the study included 9 who were treated with donepezil and 6 who served as nontreated controls. All subjects in this study lived within community residences. The 9 treated subjects with DS and dementia received donepezil for up to 6.25 months. Dementia was assessed before treatment and after a minimum follow-up of 3 months by means of the Down Syndrome Dementia Scale (DSDS). The DSDS is an informant-based measure in which information is gathered on changes in cognitive and daily living skills. Sixty questions are divided equally under 3 categories indicating early, middle, and late stages of dementia. All subjects met middle-stage criteria for dementia according to the DSDS before initiation of treatment. Specific criteria met by all study subjects and control subjects included a cognitive cutoff score on the DSDS of 3 or greater and an early- and a middle-stage tally (EMT) of 17 or greater. Data available included descriptive age, sex, assessment of dementia at multiple time points, months of follow-up between assessments, and dose and duration of treatment with donepezil.

A comparable group of patients with DS and dementia who had not been treated with donepezil was selected from the database for comparison. Eligible control subjects were required to meet middle-stage criteria for dementia according to the DSDS (as described above), to have had at least 2 assessments for dementia by means of the DSDS, and to have had no previous or concurrent treatment with donepezil or other psychotropic medications. The comparison group consisted of 6 subjects who had been studied during a 12-month period before the approval of donepezil use for treating AD by the Food and Drug Administration.

The remainder of the patients in the database pool were excluded from the study for the following reasons: (1) Twelve were excluded because they had only 1 assessment with the DSDS (mean DSDS EMT at only assessment, 4.00; SD, 4.75), and this assessment did not meet the criteria for middle-stage dementia. (2) An additional 14 subjects were excluded because, although they were tested at multiple time points, none met the middle-stage criteria for dementia at any of the assessments. In these patients, the mean EMT at baseline and after an average of 12 months of follow-up was 4.14 (SD, 4.52) and 4.07 (SD, 4.65), respectively. These figures reflected an average change of –0.08 points per month of follow-up. (3) Three subjects were excluded because of use of tacrine (pre- and post-DSDS EMTs, 17.67 and 16.33, respectively, after an average follow-up of 11.3 months). (4) Two patients were excluded because of pseudodementia secondary to other psychotropic medication (pre- and post-DSDS average EMTs of 7.50 and 3.00, respectively, after 15 months of follow-up).

The group of excluded patients did not differ from the treated or untreated cohort with respect to age, sex, or concomitant medical conditions, including seizures. The 3 patients with dementia who were receiving tacrine did not differ from the study sample in regard to magnetic resonance imaging findings or pathologic reflexes.

Data were compared by means of nonparametric tests for comparison of 2 groups. Differences between groups for continuous variables were tested with the Mann-Whitney test. For categorical data, differences were tested by the Fisher exact test (2-tailed).

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Table 1. DSDS Scores for Treated and Nontreated Patients*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Donepezil (n = 9)</th>
<th>Control Subjects (n = 6)</th>
<th>Mann-Whitney P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSDS score (early + middle), mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 0</td>
<td>30.4</td>
<td>29.0</td>
<td>.72</td>
</tr>
<tr>
<td>Time 1</td>
<td>24.3</td>
<td>30.7</td>
<td>.29</td>
</tr>
<tr>
<td>Difference (time 0 – time 1)</td>
<td>6.1</td>
<td>–1.7</td>
<td>.93</td>
</tr>
<tr>
<td>Paired difference, P</td>
<td>.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>52.3</td>
<td>52.5</td>
<td>.86</td>
</tr>
<tr>
<td>Follow-up, mean, d</td>
<td>136.0</td>
<td>147.2</td>
<td>.41</td>
</tr>
</tbody>
</table>

*DSDS indicates Down Syndrome Dementia Scale; ellipses, not applicable.

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(1134 days before reassessment, whereas control subjects were followed up for 147.2 (SEM, 8.6) days (Mann-Whitney test for difference, P = .41). At baseline, patients who were subsequently treated with donepezil received an averaged assessment for early plus middle dementia of 30.4 (SEM, 2.3) on the DSDS compared with an initial level of dementia of 29.0 (SEM, 2.6) (Mann-Whitney test for difference, P = .72).

Subjects were reassessed by means of the DSDS after an average time interval of 5 months (Table 1). Patients treated with donepezil improved in terms of dementia test scores (mean, 24.3; SEM, 4.0) relative to control subjects, who failed to demonstrate a significant change in scores over time (mean, 30.7; SEM, 3.0). When the change in DSDS over time was compared between donepezil-treated patients and control subjects, the difference was statistically significant (P = .03).

Results of independent clinical evaluation of the entire sample generally confirmed the results of the DSDS assessment. Six of 8 patients were judged to have improved by clinical impression of the neurologist (I.T.L.), who was blind to the DSDS results. None of the 4 patients examined in the comparison group was judged as improved. Clinical evaluations were not available on all patients; hence, numbers were small and the difference was of borderline statistical significance (Fisher exact test, P = .06).

As part of our ongoing assessment of dementia in DS, many of the subjects included in this study had been assessed by means of the DSDS questionnaire at additional time points before the beginning of the treatment period. A dementia assessment was completed an average of 4.1 times (range, 0-9) from 1 to 18 months before baseline study assessment (time 0). Because of the variable length of time between early measurements and start date for the study, all past measurements on the DSDS were averaged to give 1 presurvey composite score of dementia for each patient. As reflected in Table 2, the level of dementia increased in both groups during the period...
preceding the initiation of medication and increased at the same rate during this period. The mean change from prestudy to baseline for the donepezil-treated group was 7.19 (SEM, 1.45) during an average of 11.9 months, or 0.61 points per month. By contrast, the mean level of dementia scores in the control group increased by 3.65 (SEM, 0.96) during an average of 5.8 months (0.62 points per month) (P = .89 for difference between groups in rate of increase). In the approximately 5 months after the study start date, the level of dementia in the subjects treated with donepezil improved, reflected in an average decline of 1.36 points per month of follow-up, while the control group continued to demonstrate higher measures of dementia over time (an increase of 0.32 point on the DSDS per month; P = .04 for the difference in rate between the treated and control groups).

### Table 2. DSDS Scores Over Time*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Treated/Control Subjects</th>
<th>Donepezil, Mean</th>
<th>Control Subjects, Mean</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSDS score (early + middle)</td>
<td>7/6</td>
<td>23.81</td>
<td>25.35</td>
<td>.77</td>
</tr>
<tr>
<td>Pre-T0</td>
<td>9/6</td>
<td>30.44</td>
<td>29.00</td>
<td>.72</td>
</tr>
<tr>
<td>T0</td>
<td>9/6</td>
<td>24.33</td>
<td>30.67</td>
<td>.29</td>
</tr>
<tr>
<td>T1</td>
<td>9/6</td>
<td>–6.11</td>
<td>1.67</td>
<td>.03</td>
</tr>
<tr>
<td>Difference (T1 – T0)</td>
<td>9/6</td>
<td>.05</td>
<td>.13</td>
<td>. .</td>
</tr>
<tr>
<td>Paired difference, T0 – T1 (Wilcoxon Signed rank test), P</td>
<td>9/6</td>
<td>4.53</td>
<td>4.91</td>
<td>. .</td>
</tr>
<tr>
<td>Average FU, mo</td>
<td>9/6</td>
<td>–1.36</td>
<td>0.32</td>
<td>.04</td>
</tr>
<tr>
<td>Difference per month of FU</td>
<td>7/6</td>
<td>7.19</td>
<td>3.65</td>
<td>.12</td>
</tr>
<tr>
<td>Difference (T0 – Pre-T0)</td>
<td>7/6</td>
<td>.02</td>
<td>.03</td>
<td>. .</td>
</tr>
<tr>
<td>Paired difference, T0 – T1 (Wilcoxon Signed rank test), P</td>
<td>7/6</td>
<td>.61</td>
<td>.62</td>
<td>.89</td>
</tr>
<tr>
<td>Difference per month of FU</td>
<td>7/6</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
</tbody>
</table>

*DSDS indicates Down Syndrome Dementia Scale; T0 and T1, time 0 and time 1, respectively; FU, follow-up; and ellipses, not applicable.
†Mann-Whitney test.

Results showed that, in a small sample of individuals with DS, the use of donepezil in an open-label pilot trial was associated with a significant improvement in cognitive functioning, as reflected by lower scores on the DSDS, compared with a closely matched control group. All subjects met the criteria for middle-stage dementia on the DSDS, indicating that the disease was moderately advanced. This improvement held not only at the 5-month time points but also when composite scores of test results before the use of donepezil were compared between the 2 groups. There was no evidence that the treated and control patients differed in their rate of decline before treatment was begun. Improvement in patient status was also demonstrated by the results of clinical neuropsychological examination by global impression of the neurologist.

Our clinical and psychological assessment of dementia in DS addressed the International Classification of Diseases, 10th Revision, criteria for the diagnosis of AD in DS as reviewed by Aylward et al. The DSDS was chosen as an informant-based measure to document the degree of dementia and possible changes within the time span of the study. This scale has been used to identify cognitive decline in DS during a period of 6 months to 3 years. In a comparison of a clinician’s diagnosis of dementia in DS and the DSDS, a specificity of 0.89 and a sensitivity of 0.85 were found for a group of 62 adults with DS, 26 of whom were demented. In this study, a good correlation was found between the DSDS and other observer scales for dementia in DS.

After the use of donepezil, Kishnani et al reported an improvement in physician’s global impression, diaries of caregivers, and the Vineland Adaptive Behavioral Scale in 2 patients with DS who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for dementia. In keeping with Kishnani and coworkers’ observations, no adverse events related to cholinergic side effects were observed with the medication in our treatment group. Specifically, we did not observe adverse effects of peripheral cholinergic overstimulation that were described by Hemingway-Eltomey and Lerner in 3 patients with DS treated with donepezil.

The purpose of the present study was to observe the short-term efficacy of donepezil for treating symptoms of dementia in DS. In a study of 282 patients in the general population with AD, Evans et al found improved cognitive functioning in more than 65% of patients with AD reaching 3 months or more of treatment with donepezil. Kishnani et al noted that most improvement in 2 patients with Down syndrome and dementia occurred in the first 3 months.

In a cohort of patients from the general population with moderate to severe AD, Feldman et al found that the donepezil-treated group was significantly improved compared with control subjects at least up to week 24. Doody et al reported that donepezil showed efficacy during at least the first year of therapy. It is not yet clear whether the more sustained cognitive improvement noted in patients with AD but no Down syndrome will be seen in DS.

The drawbacks of this study included small sample size, nonblinded observations of the raters, criteriabased selection of subjects from a larger database, and historical controls. However, based on the initial response of this cohort of patients with DS, further placebo-controlled trials of donepezil are indicated for the treatment of dementia in DS.
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Author contributions: Study concept and design (Dr Lott); acquisition of data (Drs Lott and Nelson and Mr Doran); analysis and interpretation of data (Drs Lott and Osann and Mr Doran); drafting of the manuscript (Drs Lott, Osann, and Nelson); critical revision of the manuscript for important intellectual content (Drs Lott and Osann and Mr Doran); statistical expertise (Dr Osann); obtaining funding (Drs Lott and Nelson); administrative, technical, or material support (Drs Lott and Nelson); study supervision (Dr Lott).

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REFERENCES


