The Spectrum of Behavioral Responses to Cholinesterase Inhibitor Therapy in Alzheimer Disease

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Background: Behavioral abnormalities are common in Alzheimer disease (AD); cholinergic treatment reduces the behavioral disturbances of some patients with AD. Characterizing the pretreatment profile of patients who are likely to respond to cholinergic therapy will aid the efficient use of clinical resources.

Objective: To determine the baseline behavioral profile for 86 patients with AD treated with the cholinesterase inhibitor donepezil hydrochloride.

Methods: Open-label retrospective study of treatment-related behavioral assessments. Based on previous double-blind placebo-controlled experience using the Neuropsychiatric Inventory (NPI), patients were divided into responder (≥4-point total NPI score decrease, indicating improvement), unchanged (≥3-point total NPI score change), or nonresponder (≥4-point total NPI score increase, indicating worsening) groups. The Mini-Mental State Examination assessed cognitive response.

Results: Behavioral improvement was seen in 35 patients (41%), worsening in 24 (28%), and no change in 27 (31%). Comparison of profiles in behavioral responders vs nonresponders revealed significantly worse delusions ($P = .04$), agitation ($P = .04$), depression ($P = .006$), anxiety ($P = .02$), apathy ($P = .003$), disinhibition ($P = .02$), and irritability ($P < .001$) at baseline in responders. Five behaviors changed significantly from baseline, improving for the responders and worsening for the nonresponders: delusions ($P = .003$ for nonresponders, $P = .004$ for responders), agitation ($P = .01$), anxiety ($P = .006$ for nonresponders, $P = .004$ for responders), disinhibition ($P = .02$ for nonresponders, $P = .05$ for responders), and irritability ($P = .003$ for nonresponders, $P = .001$ for responders). The behavioral changes were dose dependent. Cognition did not change significantly with donepezil treatment within any group.

Conclusions: Donepezil has psychotropic properties, and pretreatment behaviors help predict patients’ responses to treatment.

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ORIGINAL CONTRIBUTION

From the Laboratory of Neuro Imaging (Dr Mega) and Alzheimer’s Disease Research Center (Drs Mega, Masterman, and Cummings, Ms O’Connor, and Mr Barclay), Department of Neurology, and the Department of Psychiatry and Biobehavioral Sciences (Dr Cummings), University of California, Los Angeles, School of Medicine.

CHOLINESTERASE inhibitor therapy in Alzheimer disease (AD) may provide cognitive and behavioral symptomatic improvement for some patients. Not all patients respond to cholinergic therapy; there is a response distribution from marked to no improvement. If significant cognitive response is measured by an improvement of at least 7 points on the cognitive portion of the Alzheimer’s Disease Assessment Scale, then 26% of patients with AD may respond to cholinesterase inhibitor therapy (using donepezil hydrochloride) in 24 weeks of treatment.

Behavioral abnormalities occur in nearly all patients with AD and arguably may have a greater impact on health care resources and caregiver distress than cognitive abnormalities. Several cholinesterase inhibitors have been shown to reduce behavioral and neuropsychiatric changes in AD. A valid and reliable instrument for measuring behavior in AD is the Neuropsychiatric Inventory (NPI), a caregiver-based tool that assesses 10 common behaviors in dementia. When behavioral improvement (as measured by the NPI) is the outcome measure, 60% of a series of patients with AD treated with a cholinesterase inhibitor (metrifonate) show a 30% or greater improvement in apathy from baseline during a 26-week period. Not all patients with AD demonstrated a beneficial behavioral response to cholinesterase inhibitor therapy. Characterizing the baseline clinical profile of those patients who improve or fail to respond to therapy will aid selection of possible treatment responders. Concentrating therapy on patients who have a baseline clinical profile that predicts a treatment response will improve our clinical effectiveness and conserve health care resources.
PATIENTS AND METHODS

PATIENTS

The study group consisted of 86 consecutive outpatients presenting for dementia evaluation to the University of California, Los Angeles, Alzheimer’s Disease Research Center who met all study criteria, had caregivers willing to be interviewed, and agreed to treatment with donepezil hydrochloride, successfully increasing therapy from 5 mg/d for 4 weeks to 10 mg/d for an additional 4 weeks. All patients met National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer’s Disease and Related Disorders Association criteria for probable or possible AD. Diagnosis for all patients included complete medical history, physical and neurologic examination, magnetic resonance imaging or computed tomographic imaging of the brain, electroencephalography, and routine blood tests (including thyroid hormone and vitamin B12 levels and serologic test for syphilis). Exclusion criteria for all patients were delirium, other active systemic or neurologic diseases that could substantially contribute to their cognitive impairment, history of alcohol or substance abuse, history of head trauma with loss of consciousness, and history of psychiatric disorder preceding the onset of symptoms of dementia. In addition, inclusion criteria required that patients have an acquired persistent decline involving at least 3 of the following domains: language, memory, visuospatial skills, cognition (calculation, abstraction, judgment, etc.), and emotion or personality. Diagnosis was assisted using standard neuropsychological testing and the bedside clinical assessment of cognition as previously described. Severity of cognitive deficit was measured in all patients using the Mini-Mental State Examination (MMSE). BEHAVIORAL ASSESSMENT

Caregivers were interviewed with the NPI following procedures previously described in which screening questions for each behavior were first posed. The caregiver was asked if the behavior represented a change from that exhibited by the patient before the onset of the dementia and if it was present during the past month. If a positive response was obtained, then the behavioral domain was explored with scripted questions focusing on specific features of the behavioral disturbance. The caregiver then rated the behaviors. Scores from 1 to 4 were obtained for the frequency and 1 to 3 for the severity of each behavior (a composite score for each domain was the product of the frequency and severity subscores; maximum, 12). The 10 domains assessed using the NPI are delusions, hallucinations, agitation, depression, anxiety, euthymia, apathy, disinhibition, irritability, and abnormal motor output. The MMSE was also administered at the same time as the NPI. We examined the baseline behavioral ratings of all patients treated with donepezil. We divided patients into responders and nonresponders and then determined whether there were differences in baseline NPI scores that distinguished both groups. We also explored the relationships between cognitive and behavioral responses.

A double-blind placebo-controlled study of a cholinesterase inhibitor (mefilonate) demonstrated a significant behavioral response to treatment after 26 weeks, as measured by the NPI. The total score on the NPI improved by nearly 3 points in the treatment group at study end point, while the placebo group showed nearly a 4-point worsening from baseline. Thus, a 4-point improvement was accepted as evidence of a treatment response and a 4-point decrement as evidence of treatment failure. Previous double-blind placebo-controlled studies with the cholinesterase inhibitor donepezil demonstrated, after 8 weeks, a significant separation between the treatment and placebo groups. Thus, our patients underwent evaluation at baseline, week 4 (after 4 weeks at 5 mg of donepezil hydrochloride per day), and week 8 (after 4 weeks at 10 mg of donepezil hydrochloride per day). After 8 weeks of therapy, patients who demonstrated a significant behavioral improvement (≥4-point reduction in total NPI score) were called responders, those who worsened behaviorally (≥4-point increase in total NPI score) were called nonresponders, and those who had no more than a 3-point increase or decrease in total NPI score were called unchanged behaviorally.

STATISTICAL ANALYSIS

A histogram of NPI data reveals that composite scores do not generate a normal distribution. Multiplying the frequency (1-4) by the severity subscores (1-3) will not produce a composite score of 5, 7, or 11. The nonnormal distribution of the NPI data precludes traditional parametric analysis; thus, a bootstrap method was used. Briefly, the bootstrap method combines the raw composite scores for any given behavior of the entire data set and randomly samples a number of these scores equal to the number making up the groups constituting the data set. A mean difference composite score is then calculated from the random samples. This is then repeated 1000 times on the data set, producing a distribution of possible mean difference composite scores. The observed mean differences can then be compared with this distribution of the possible mean difference composite scores between 2 groups for each NPI behavior. The probability of finding the observed mean difference based on the mean difference generated by resampling is then recorded. This process was repeated 10 times for each of the 10 NPI behaviors to arrive at an average probability value resulting from 1000 resampling combinations for each comparison. If the observed difference is greater than 95% of the differences expected from random resampling in the bootstrap method, the observed difference was judged to be statistically significant at the .05 level. Although the bootstrap method is not universally accepted as the criterion standard in statistical methods, we believe it is the most appropriate for analysis of NPI data. All other comparisons were made with a 2-tailed t test. Unless otherwise indicated, data are given as mean ± SEM.

Table 1 shows the demographic makeup of the 3 groups based on their treatment response to donepezil after 8 weeks of therapy. Thirty-five (41%) of the 86 patients showed a
behavioral response to donepezil, whereas 24 (28%) worsened and 27 (31%) showed no behavioral change.

Cognition (as measured by the MMSE) did not significantly improve (P = .70 for nonresponders, P = .80 for responders, and P = .40 for unchanged patients) with donepezil treatment within any group. The baseline MMSE of the behaviorally unchanged group was 20.04 ± 1.21; 21.29 ± 1.02 while receiving 5 mg of donepezil hydrochloride per day; and 21.6 ± 1.26 while receiving 10 mg of donepezil hydrochloride per day. The baseline MMSE of the nonresponder group was 15.95 ± 1.69; 15.26 ± 1.66 while receiving 5 mg of donepezil hydrochloride per day; and 14.90 ± 1.77 while receiving 10 mg of donepezil hydrochloride per day. The baseline MMSE of the responder group was 18.45 ± 1.30; 18.76 ± 1.28 while receiving 5 mg of donepezil hydrochloride per day; and 18.85 ± 1.27 while receiving 10 mg of donepezil hydrochloride per day. The percentage change (baseline and 10-mg/d treatment assessment) of MMSE scores below 20 for the 3 groups were 58%/63% for the nonresponders, 49%/46% for the responders, and 33%/26% for the unchanged group. There were no significant differences, with treatment or between groups, for MMSE measures.

When only the MMSE change from baseline was evaluated with treatment or between groups, for MMSE measures.

Table 2. Behavioral Profile of Treatment Responders and Nonresponders

**Table 1. Demographics of the Total Patient Group Separated by Baseline Neuropsychiatric Inventory Scores**

<table>
<thead>
<tr>
<th>Unchanged</th>
<th>Nonresponders</th>
<th>Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>27 (31)</td>
<td>24 (28)</td>
</tr>
<tr>
<td>Mean age (SEM), y</td>
<td>75.0 (1.1)</td>
<td>78.0 (1.5)</td>
</tr>
<tr>
<td>Sex, No. F/M</td>
<td>16:11</td>
<td>16:8</td>
</tr>
<tr>
<td>Mean education (SEM), y</td>
<td>13.3 (0.7)</td>
<td>13.5 (0.9)</td>
</tr>
<tr>
<td>Baseline MMSE &lt;20, No. (%)</td>
<td>9 (33)</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Week-8 MMSE &lt;20, No. (%)</td>
<td>7 (26)</td>
<td>15 (63)</td>
</tr>
</tbody>
</table>

*Groups are described in the “Behavioral Assessment” subsection of the “Patients and Methods” section. MMSE indicates Mini-Mental State Examination.*

The baseline behavioral profile of patients who responded to cholinesterase inhibitor therapy is shown in Table 2. The patient group responding to donepezil treatment had a higher percentage of behavioral abnormalities across all NPI domains evaluated except hallucinations. Patients who declined behaviorally (nonresponders) showed a lower percentage of all behaviors except hallucinations. Four behaviors are particularly noteworthy in that their change in percentage of occurrence within the 2 groups was equally marked but in opposite directions; ie, irritability, anxiety, delusions, and depression all showed the greatest changes in occurrence at end of study compared with baseline for the responders and nonresponders. The unchanged group was omitted from this evaluation because they had the fewest behavioral abnormalities at baseline as revealed in Figure 1. The behavioral abnormalities at baseline for those patients who later responded to donepezil therapy were significantly worse (difference in NPI total score, 16.7; P < .001) than for those who did not respond to the cholinesterase inhibitor (Figure 1). Furthermore, this behavioral response was significantly (P < .001) dose dependent for the responders (baseline total NPI, 26.8; while receiving 5 mg of donepezil hydrochloride per day, 17.7; and while receiving 10 mg of donepezil hydrochloride per day, 9.4). The nonresponders’ behaviors tended to worsen across dosages as well (baseline total NPI score, 10.2; compared with score while receiving 5 mg of donepezil hydrochloride per day, 22.8 [P = .003]; with a trend to score increase while receiving 10 mg of donepezil hydrochloride per day, 27.5).

Concomitant psychotropic medications may influence the behavioral response to a cholinesterase inhibitor, and a description of other behaviorally relevant medications is required in any study of AD treatment. We recorded the use of antipsychotics, antidepressants, anxiolytics, anticholinergics, estrogens, vitamin E, and anti-inflammatory agents. No significant differences among the groups were found for psychotropics or neuroprotective agents across the 8 weeks of treatment.
We calculated the cumulative percentage of all patients’ treatment responses reflected by the change in total NPI score from baseline (Figure 2, A). The percentage of patients exhibiting specific behaviors before and after treatment was compared between groups. Among responders, all behaviors became less frequent (the percentage of patients exhibiting the behaviors declined) (Table 2). In contrast, all behaviors except euphoria were manifest in more patients after treatment among the nonresponders. When the mean scores of only the nonresponders with symptoms present at baseline were examined (25% of the nonresponders had no behavioral symptoms at baseline), a significant worsening from baseline to 10 mg of donepezil hydrochloride per day, was still found for delusions (P = .02), agitation (P = .02), depression (P = .003), anxiety (P = .03), disinhibition (P = .04), and irritability (P = .005).

The main purpose of our study was to examine the profile of behaviors at baseline in the responders and nonresponders to determine whether a profile that predicted a beneficial behavioral response could be identified. The mean and SEM for the composite (frequency × severity) NPI scores for nonresponders and responders across the baseline and 5- and 10-mg examinations are shown in Figure 2 (B and C). Results of the analysis of significance using the bootstrap method, comparing baseline and 10-mg examinations within the nonresponders and responders and between groups are shown in Table 3. Comparing the baseline behavioral profiles of the nonresponders vs the responders revealed significantly worse delusions, agitation, depression, anxiety, apathy, disinhibition, and irritability in responders to cholinesterase inhibitor therapy. Five common behaviors—delusions, agitation, anxiety, disinhibition, and irritability—had robust changes from baseline, worsening for the nonresponders and improving for the responders. Depression also significantly worsened for the nonresponders (P = .001), and did not change in responders (P = .08); apathy and abnormal motor behavior significantly improved for responders and showed no change in nonresponders. After 8 weeks of donepezil therapy, all behaviors except euphoria, apathy, and disinhibition were significantly worse in the nonresponders compared with the responders. When the mean scores of only the nonresponders with symptoms present at baseline were examined, responders still had significantly worse depression (P = .02), apathy (P = .03), disinhibition (P = .05), and irritability (P = .005) than nonresponders.

Our results suggest that patients with AD most likely to exhibit a beneficial behavioral response to treatment with donepezil can be identified before therapy. Specifically, those with more marked delusions, agitation, depression, anxiety, apathy, disinhibition, and irritability are most likely to improve when treated with donepezil. These results indicate that donepezil has important psychotropic effects and that these effects are independent of changes in cognition.

Three important methodological issues must be considered with regard to our study. First, patients who do not exhibit symptoms at baseline cannot improve with therapy, and the nonresponder group in this study manifested fewer baseline abnormal behaviors than the responders. However, when those patients in the nonresponder group with baseline symptoms were separately analyzed, responders still had significantly worse baseline depression, apathy, disinhibition, and irritability; and donepezil treatment still considerably worsened many behaviors in the nonresponders. These effects cannot be attributed to differences in baseline behaviors or in cognitive function; there was no significant difference in the pretreatment and posttreatment MMSE scores in both groups. The MMSE response for all patients in our study is similar to that of previous studies with cholinesterase inhibitors—26% improved at least 3 points. This finding reflects the independence of behavior as measured by the NPI and cognition as measured by the MMSE. Second, there was no placebo control group in this open-label study; therefore, improvement in patients with more abnormal behaviors, and worsening in patients with fewer abnormal behaviors, may reflect a regression to the mean. This potential flaw is mitigated partially by the design choice in which all patients were treated with an identical strategy and group assignment was based on outcome (to which clinicians and family members were blinded at baseline). Third, this design cannot distinguish between drug-related worsening of behaviors and emergence of new behaviors as part of the natural history of AD in the nonresponder group. Behaviors worsen in the course of AD,17 and without a placebo group matched for the baseline behaviors with the nonresponder group, it is impossible to discriminate both competing hypotheses. Similarly, we cannot confirm that donepezil improved behaviors without a control group. Future studies might attempt a withdrawal of drug in nonresponders to determine if behaviors return to baseline and if treatment responders decline.

Characterizing the pretreatment profile of patients who respond to an intervention improves the clinician’s ability to target the subgroup most likely to benefit from a medication. In our study, donepezil therapy was associated with a significant improvement from baseline in irritability, agitation, anxiety, disinhibition, and delusions in 41% of pa-
Patients with AD and may have significantly increased these same behaviors in 28% of patients; a placebo arm would be necessary to confirm these findings. No significant change from baseline on the MMSE occurred in any group with treatment, although 26% of the total cohort improved at least 3 points on the MMSE. Although the MMSE is a limited test of cognition, it is used to assess the cognitive function of patients with AD in the clinical setting. Thus, a decrease in cognition, measurable by the MMSE, cannot explain the behavioral worsening with treatment.

Figure 2. The change from baseline of the total Neuropsychiatric Inventory (NPI) score for all study patients (n = 86) at week 4 (while receiving 5 mg of donepezil hydrochloride per day) and at week 8 of therapy (while receiving 10 mg of donepezil hydrochloride per day). Patients with at least a 4-point decrease in total NPI score are responders, whereas those with at least a 4-point increase are nonresponders (A). Also shown are mean and SEM data for the composite (frequency × severity) NPI scores for the nonresponders (n = 24) (B) and responders (n = 35) (C) to donepezil therapy at baseline, week 4, and week 8.
The neurochemical and neurofunctional patterns associated with the spectrum of behavioral responses to cholinesterase inhibitor therapy in AD are unknown. Preliminary data suggest that patients with AD who respond behaviorally to cholinesterase inhibitor therapy may have significantly lower perfusion in the orbitofrontal cortex at baseline compared with nonresponders. Behavioral improvement in patients with AD, particularly a resolution of apathy associated with anterior cingulate hyperperfusion, occurs with cholinesterase inhibitor therapy. Physostigmine salicylate, a short-acting cholinesterase inhibitor, may increase frontal perfusion and thalamic metabolism in AD. The facilitation of frontal-subcortical function may be the mechanism of response to cholinesterase inhibitor therapy in AD. Insights from future studies await results of prospective functional imaging and behavioral assessment with cholinesterase inhibitor therapy in AD.

Our investigation of the baseline profile of patients with AD who demonstrated a significant behavioral response to treatment with a cholinesterase inhibitor revealed that responders suffer greater pretreatment behavioral disturbances, as measured by the caregiver-based NPI, than do nonresponders. Most of the behaviors that were significantly reduced in responders (delusions, agitation, depression, anxiety, disinhibition, and irritability) were also significantly increased from baseline levels in nonresponders to cholinergic therapy. Using a behavioral measure such as the NPI to evaluate response to treatment with cholinesterase inhibitors in AD will add another clinically relevant dimension in judging the efficacy of these agents rather than using cognitive measures alone.

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Table 3. Results of Bootstrap Method of Composite Neuropsychiatric Inventory Scores

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Nonresponders vs Responders at Baseline</th>
<th>Nonresponders vs Responders at 8-Week Assessment</th>
<th>Nonresponders at Baseline vs 8-Week Assessment</th>
<th>Responders at Baseline vs 8-Week Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>.04</td>
<td>.001</td>
<td>.003</td>
<td>.004</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>.67</td>
<td>.003</td>
<td>.13</td>
<td>.07</td>
</tr>
<tr>
<td>Agitation</td>
<td>.04</td>
<td>.002</td>
<td>.009</td>
<td>.01</td>
</tr>
<tr>
<td>Depression</td>
<td>.007</td>
<td>.007</td>
<td>.001</td>
<td>.08</td>
</tr>
<tr>
<td>Anxiety</td>
<td>.02</td>
<td>.001</td>
<td>.006</td>
<td>.004</td>
</tr>
<tr>
<td>Euphoria</td>
<td>.10</td>
<td>.91</td>
<td>&gt;.99</td>
<td>.06</td>
</tr>
<tr>
<td>Apathy</td>
<td>.003</td>
<td>.87</td>
<td>.60</td>
<td>.004</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>.02</td>
<td>.06</td>
<td>.02</td>
<td>.049</td>
</tr>
<tr>
<td>Irritability</td>
<td>.001</td>
<td>.003</td>
<td>.003</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abnormal motor</td>
<td>.25</td>
<td>.001</td>
<td>.07</td>
<td>.003</td>
</tr>
</tbody>
</table>

*Groups are described in the “Behavioral Assessment” subsection of the “Patients and Methods” section; the bootstrap method, in the “Statistical Analysis” subsection. Eight-week assessment indicates assessment while receiving donepezil hydrochloride, 10 mg/d. Data are given as probability values.

Conclusions

REFERENCES

tensive damage, much of which cannot be pictured on a single magnetic resonance imaging section. There is not a consistent attempt to show available images of the brain for all the cases. However, other figures and the tables are of excellent quality.

I found some case reports and clinical sections to be particularly interesting, such as cases of pure amnesia, which is a relatively rare condition. The case report of progressive cognitive decline in a patient with myotonic dystrophy is likewise of interest given the paucity of these types of case reports in the literature, but as a case used to illustrate progressive cognitive decline, I question its general applicability. In contrast, no cases of more common neurological conditions, such as Alzheimer disease and frontotemporal dementia, are included.

This book can be readily appreciated by neurologists, psychologists, therapists, and physiatrists but will probably be of greatest use to those professionals who work most directly in the challenging field of neuropsychological rehabilitation.

Richard J. Caselli, MD
Scottsdale, Ariz

Prose: ★★★★
Figures, Tables, and Illustrations: ★★★
Science: ★★★★★
Usefulness: ★★★★★

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Correction

Error in Figure. In the Original Contribution by Mega et al titled “The Spectrum of Behavioral Responses to Cholinesterase Inhibitor Therapy in Alzheimer Disease,” published in the November issue of the Archives (1999;56:1388-1393), the wrong line graph was presented on page 1392 in Figure 2, part A. Figure 2, part A, is reprinted correctly here.

Figure 2. The change from baseline of the total Neuropsychiatric Inventory (NPI) score for all study patients (n = 86) at week 4 (while receiving 5 mg of donepezil hydrochloride per day) and at week 8 of therapy (while receiving 10 mg of donepezil hydrochloride per day). Patients with at least a 4-point decrease in total NPI score are responders, whereas those with at least a 4-point increase are nonresponders (A).