Effects of Donepezil on Neuropsychiatric Symptoms in Patients With Dementia and Severe Behavioral Disorders

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Objective: *The objective of this study was to conduct exploratory analyses of data pertaining to the efficacy of donepezil treatment of patients with severe behavioral disturbances. Preliminary studies suggest that cholinesterase inhibitors, including donepezil, may reduce behavioral disturbances in patients with Alzheimer disease (AD). Most patients included in clinical trials have had low levels of psychopathology at baseline, and the effect of cholinesterase inhibitors on patients with more severe behavioral disturbances is unknown. The authors report the effects of donepezil on behavioral disturbances in patients with relatively severe psychopathology at baseline.* **Methods:** *This is a hypothesis-driven secondary analysis of a three-phase study involving donepezil and sertraline. In phase 1, psychotropic agents were withdrawn; in phase 2, patients were treated in an open-label fashion with donepezil for 8 weeks; and in phase 3, patients on donepezil were randomized to receive placebo or sertraline for an additional 12 weeks. The data set analyzed is comprised of the patient population treated with donepezil (without sertraline) for 20 weeks. One hundred twenty patients were included in the analyses. Mean age was 76 years, average Mini-Mental State Examination Score was 18, and mean Neuropsychiatric Inventory (NPI) total score was 30. Primary efficacy assessments were the NPI, the Clinical Global Impression–Improvement, and the Clinical Global Impression–Severity scales. Secondary measures included the Behavioral Pathology in Alzheimer's Disease Rating Scale, The Hamilton Depression Rating Scale, and the Alzheimer's Disease Functional Assessment and Change Scale.* **Results:** *Excellent concurrent validity was noted between the NPI and the Behavioral Pathology in Alzheimer's Disease Rating Scale. The total score of the NPI was significantly reduced over the 20 weeks of therapy with donepezil. Sixty-two percent of patients had at least a 30% reduction in the total NPI score (significantly greater than the number with no meaningful response). Likewise, more patients had total or partial resolution of depression and delusions than those who had no meaningful change. Factor analysis of baseline NPI data revealed five factors, including a psychosis factor, an agitation factor, mood factor, frontal lobe function factor, and appetite and eating disorders factor. Clinically meaningful treatment effect sizes were notable for the delusion factor (0.340) and the mood factor (0.39). There were significant correlations between the Clinical Global Impression–Improvement and reductions in mood and agitation scores.* **Conclusion:** *The results of these analyses suggest that donepezil reduces behavioral symptoms, particularly mood disturbances and delusions, in patients with AD with relatively severe psychopathology.* (Am J Geriatr Psychiatry 2006; 14:605–612)

Key Words: Donepezil, behavior, neuropsychiatric inventory, psychosis, depression, clinical trial

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Alzheimer disease (AD) is a progressive neurodegenerative disease manifested by decline in memory and other cognitive abilities, deterioration in activities of daily living, and the emergence of a variety of behavioral disturbances.[1] Neuropsychiatric symptoms associated with AD include agitation; psychosis manifested primarily by delusions; mood abnormalities, including depression, anxiety, and irritability; apathy; and other behavioral alterations, including disinhibition, wandering, pacing, rummaging, and alterations in sleep and appetite.[2–7] Neuropsychiatric symptoms are among the most distressing aspects of AD; they are a common cause of institutionalization, may lead to physical abuse by caregivers, are linked to self-destructive behaviors among nursing home residents, and compromise the quality of life of both patients and caregivers.[8–12]

Standard psychopharmacologic agents have been shown in preliminary studies to be useful in managing depression, agitation, and psychosis in AD.[4,13–16] In addition, antidementia agents that affect brain function in patients with AD also may ameliorate behavioral symptoms. Patients receiving cholinesterase inhibitors (ChE-Is), memantine, and combined alpha tocopherol and selegiline exhibited reduced psychiatric symptoms or a reduction in the emergence of new behavioral disorders compared with patients in placebo control groups.[17–23]

Understanding the behavioral effects of ChE-Is has been hampered by a number of shortcomings in the available data. Open-label studies and case reports are subject to observer bias; small sample sizes have limited the generalizations of data possible from some studies; double-blind, placebo-controlled trials typically have included behavior only as a secondary outcome; patients in most controlled trials were not selected for the presence of specific behavioral disturbances or for behavioral changes that reached a defined level of severity; psychopathology among patients in most trials was mild or moderate in severity; and many trials included patients receiving psychotropic medications.

We report an hypothesis-driven secondary analysis of the effects of donepezil in patients with severe behavioral disturbances. The available data address some of the shortcomings of past investigations and provide a unique window on the effect of a ChE-I on behavioral disturbances of greater severity than have been present in any past clinical trial. We hypothesized that donepezil would reduce behavioral alterations in this group of patients and that the greatest effects would be on mood alterations and apathy based on previous studies of ChE-Is.[17,22]

METHODS

Study Design

The data used in this study were derived from a three-phase study designed to assess the affect of donepezil and sertraline on behavior changes in AD.[24] In phase 1, patients were withdrawn from psychotrophic medication. In phase 2, patients meeting all study entry criteria were dispensed 5 mg donepezil and were instructed to take one tablet each evening for four weeks. After one month of 5 mg per day and in the absence of dose-limiting side effects, the dose of donepezil was increased to 10 mg (two 5-mg tablets) each evening. If adverse events emerged, the dose was decreased to 5 mg. In phase 3, after the eight-week open-label treatment of donepezil, all patients who continued to meet the inclusion and exclusion criteria of the study were randomly assigned to 12 weeks of double-blind treatment with either sertraline or placebo. Random assignment was computer-generated.

In the current study, we used data from the eight-week open-label period of donepezil treatment and the data from the group assigned to donepezil monotherapy in the double-blind portion of the study. Together, these two phases provided data on 20 weeks of donepezil treatment. References to "baseline" in the data presented pertain to the information collected at the time of entry to the study.

Patient Selection

Patients were male or female outpatients, 50 years of age or older, who met diagnostic criteria for probable or possible AD using the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association.[25] In addition, patients had to have a Neuropsychiatric Inventory (NPI)[3] total score greater than 5 and a severity score of greater than or equal to 2 in at least two domains of the 12-item NPI. Also required for entry into the study were a Mini-

Mental Status Examination (MMSE)[26] score between 8 and 23, a modified Hachinski Ischemia Scale score less than or equal to 4,[27] and a Clinical Dementia Rating scale (CDR) score less than or equal to 2.[28] Patients who had been receiving any psychotropics underwent a washout equivalent to five half-lives of the drug or its pharmacologically active metabolites, whichever was greater. Patients were excluded if they were diagnosed as having dementia resulting from causes other than AD or if they had a history of a seizure disorder, traumatic brain injury, or an unstable medical condition. Patients with a history of a primary psychiatric diagnosis—recurrent depression, bipolar illness, schizophrenia—also were excluded. All patients or surrogates provided informed consent for participation in the trial, and the trial was approved in each participating institution by the authorized Institutional Review Board.

Outcome Measures

There were three primary efficacy assessments: the NPI,[3] the Clinical Global Impression–Improvement (CGI-I), and the Clinical Global Impression–Severity (CGI-S) scales.[29] The NPI is a caregiver-based interview and rating scale assessing 12 behavioral domains, including two neurovegetative symptoms common in patients with dementia. The scale provides ratings for delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavioral disturbances, and eating/appetite changes. The frequency (1–4) and severity (1–3) of each behavior is rated by the caregiver using scripted questions and an anchored rating scale. The score for each domain is the product of the frequency times the severity. There is a total possible score of 144 with higher scores indicating greater psychopathology. The CGI-I and CGI-S scales measure physician-rated global improvement and severity, respectively. Assessments were collected at baseline, at week 8 after four weeks of maximal tolerated treatment with donepezil, and at the end of the trial.

Secondary efficacy assessments included the Behavioral Pathology in Alzheimer's Disease Rating Scale[30] (Behave-AD), a 25-item scale assessing paranoid and delusional ideation, hallucinations, changes in activity patterns, aggressiveness, diurnal rhythm disturbances, affective disturbance, and anxieties and phobias. The Behave-AD is completed by a clinician based on an interview with the caregiver. The Behave-AD also includes a global (0–3) rating scale based on the degree of disruptiveness of the behaviors exhibited. The Alzheimer's Disease Assessment Scale–Cognitive portion (ADAS-Cog)[31] and Cohen-Mansfield Agitation Inventory–Community (CMAI-C)[32] also were included as secondary outcomes.[33]

Statistical Analysis

The donepezil monotherapy cohort was defined as patients who received at least one dose of donepezil at baseline and who were maintained on donepezil (only) during the 20-week study period. Those who had a baseline evaluation and at least one postbaseline efficacy assessment were included in the intent-to-treat (ITT) population for analyses of efficacy. Within the ITT population, analyses of both observed cases (OC) and end point (defined as the last observation carried forward [LOCF]) were conducted. For this short-term study with a low dropout rate, LOCF was the only approach to account for missing data performed. This analytic strategy is currently the standard for U.S. Food and Drug Administration (FDA)-oriented analyses and has limited risk of introducing bias when attrition is limited. For all continuous efficacy variables, a pairwise t-test was used to compare baseline versus postbaseline assessments. All statistical tests were two-sided at the 0.05 level. Subjects were included in safety analyses if they were known to have taken at least one postbaseline dose of donepezil or had at least one postbaseline safety assessment.

The Pearson chi-squared statistic was applied to assess the correlation between NPI and the Behave-AD scale and other parameters. McNemar's test was used in responder analyses[34] assessing NPI item scores and total score. Logistic regression analysis was performed to predict NPI total score response by baseline covariates, including age, gender, and baseline MMSE, NPI, CGI-S, and Behave-AD global rating. Factor analysis was applied to the 12 items of the NPI[34] to identify behavioral domain factors. The SAS procedure PROC FACTOR was applied with option MINEIGEN = 1 and PROMAX rotation. The initial factor step is a principal component analysis conducted to reduce the items and to decide the number of factors; this is followed by factor

analysis for factor classification (assigning each item to the proper factor). The reason for using the PROMAX rotation is to accommodate possible correlations among the items. Hoteling's statistic was used to test overall significance of factors derived from factor analysis.

RESULTS

A total of 275 patients participated in the first eight weeks of open-label donepezil treatment with 245 (85%) completing the eight-week trial. Table 1 summarizes the demographic features of the study sample. Those beginning the open-label phase had a mean age of 76.3 years (standard deviation [SD]: 7.5); 61% were women; average MMSE score was 17.8 (SD: 4.6); and baseline NPI total scores were 30.8 (SD: 17.2). Behave-AD mean total scores were 10 (SD: 7), and Hamilton Depression Rating Scale total scores averaged 6.9 (SD: 5.0). For those continuing on donepezil only (donepezil plus placebo after randomization to placebo or sertraline) in the blinded phase of the study (N = 120), mean age was 76.9 years (SD: 7.4); 57% were women; average MMSE score was 17.9 (SD: 5.2); and baseline NPI total scores were 30.5 (SD: 17.3). Behave-AD mean total score was 9.3 (SD: 6.7) and mean Hamilton Depression Rating Scale total score was 6.5 (SD: 5.2).

Concurrent Validity

Confidence in the results of behavioral outcome measures is strengthened by concurrent validity when multiple behavioral measures are included. Excellent concurrent validity was demonstrated in this study between Behave-AD measures of delusions, hallucinations, activity disturbances, aggressiveness, affective disturbances, and anxieties and phobias and the corresponding scores (delusions, hallucinations, aberrant motor behavior, agitation, depression, and anxiety) of the NPI measured by frequency, severity, and product of frequency times severity (correlation coefficient ranges: 0.44–0.79, df = 118, all $p < 0.0001$). The four CMAI-C domains likewise were strongly correlated with the total NPI score (ranges: 0.50–0.59, df = 118, $p < 0.0001$). The CGI-S score correlated with the NPI total ($r = 0.4$, df = 118, $p < 0.0001$) and the CGI-I score correlated with the NPI score change ($r = 0.37$, df = 118, $p < 0.001$). The correlation between the ADAS-Cog and the NPI total was not significant ($r = 0.01$, df = 118, $p = 0.88$).

Change in Neuropsychiatric Inventory Scores

Both the total 10-item (excluding the two neurovegetative symptoms) and the total 12-item NPI score changed significantly (improved) over the course of the 20 weeks of treatment with donepezil (Table 2).

Changes in Other Instrumental Scores

Changes in other instrument scores after introduction of donepezil generally paralleled those reported in more detail for the NPI. Statistically significant improvement was seen on the physically nonaggressive and verbally nonaggressive factor of the CMAI-C at week 20 (Table 2).

Behave-AD scores improved significantly from

TABLE 1. Baseline Demographic and Clinical Characteristics

	Open-Label Baseline Donepezil + Placebo (N = 120)	Double-Blind Randomization (week 8) Donepezil + Placebo (N = 120)
Age, yrs, mean ± SD	76.9 ± 7.4 years	Same as open-label baseline
Female (%)	57	Same as open-label baseline
NPI-12 total score, mean ± SD	31.4 ± 15.9	30.5 ± 17.3
BEHAVE-AD total score, mean ± SD	9.9 ± 7.0	9.3 ± 6.7
HAM-D total score, mean ± SD	6.5 ± 5.0	6.5 ± 5.2
MMSE, mean ± SD	17.6 ± 4.6	17.9 ± 5.2

SD: standard deviation; NPI: Neuropsychiatric Inventory; BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale; HAM-D: Hamilton Depression Rating Scale; MMSE: Mini-Mental Status Examination.

TABLE 2. Change Scores on Instruments Used in the Study (mean; standard deviation)

	Baseline	Number at Baseline	Week 8	Week 20	Week 20 LOCF
NPI-10	26.7 (14.2)	119	−0.7 (12.6)	−7.2 (12.8)[a]	6.6 (13.2)[a]
NPI-12	31.4 (15.9	119	−.08 (13.1)	−8.2 (13.3)[a]	−7.4 (13.7)[a]
CMAI-C					
Physically nonaggressive	15.1 (9.7)	118	−1.2 (6.8)	−2.8 (6.9)[a]	−2.4 (7.0)[a]
Physically aggressive	1.6 (4.2)	118	0.1 (2.5)	0.0 (−2.6)	0.1 (2.5)
Verbally nonaggressive	8.0 (5.6)	118	−0.2 (5.0)	−1.1 (4.9)[b]	−0.9 (4.8)[b]
Verbally aggressive	4.5 (4.6)	118	0.6 (3.8)	−0.1 (3.5)	0.1 (3.7)

[a]$p < 0.001$ versus baseline value.
[b]$p < 0.05$ versus baseline value.
LOCF: last observation carried forward; NPI: Neuropsychiatric Inventory; CMAI-C: Cohen-Mansfield Agitation Inventory–Community.

baseline to week 20 in the ITT-OC analysis (mean changes: −1.1, $p < 0.005$) (Table 2).

Similarly, CGI scores were significantly reduced (improved) at week 20 on both OC ($p < 0.001$) and LOCF analyses ($p < 0.01$).

Time Course of the Behavioral Changes

Behavioral measures showed similar response trajectories. Numeric trends for improvement were evident at week 12 and were statistically significant by week 20 (Table 2).

Responder Analysis

To explore the pattern of response to treatment with donepezil, we identified patients with total resolution (patients exhibited the symptom at baseline and not at study completion for any domain), partial resolution (fewer symptoms present at completion than baseline), or other. For the total NPI score, 62% of patients exhibited either total or partial resolutions in all 12 domains (compared with those with no meaningful response; McNemar's test = 6.1, df = 1, $p = 0.0137$). Analysis of NPI domains revealed that many more patients with depression had total (44.9%) or partial (26.1%) resolution compared with those who had no meaningful response (McNemar's test = 11.4, df = 1, $p = 0.007$). Likewise, more patients had total (41.2%) or partial (23.5%) resolution of delusions compared with those who had no meaningful response (McNemar test = 3.8, df = 1, $p = 0.049$).

Logistic regression analysis was conducted to determine what demographic factors contributed significantly to behavior change defined as total or partial response of NPI-12 score. Baseline NPI score, MMSE, Behave-AD global rating, and CGI-S were fitted into the model separately with adjustment for age and gender. Only baseline NPI score (Wald chi-square test = 4.2, df = 1, $p = 0.04$) and baseline Behave-AD global rating (Wald chi-square test = 3.9, df = 1, $p = 0.047$) were statistically significant, whereas baseline MMSE, baseline CGI-S, gender, and age did not assist in predicting the outcome. Patients with more severe disturbances at baseline were more likely to exhibit responses than those with lower levels of neuropsychiatric symptomatology.

Factor Analysis

Factor analysis of the baseline NPI-12 data revealed an optimal five-factor solution based on eigenvalue criteria. All items were loaded on the factor with maximum loading values. Factor 1 encompassed delusions, hallucinations, and sleep abnormalities; factor 2 included agitation, irritability, and aberrant motor behavior; factor 3 comprised depression, anxiety, and apathy; factor 4 included euphoria and disinhibition; and factor 5 included appetite and eating disorders. Factor 1 had a 27% reduction from baseline to final assessment (effect size 0.34) (effect size: mean change from baseline/SD of mean change); factor 2 had a 17% reduction (effect size 0.34); factor 3 evidenced a 27% reduction (effect size 0.39); factor 4 had a 27% reduction (effect size 0.20); and factor 5 had a 19% reduction (effect size 0.16).

These changes were overall statistically significant (Hotelling T^2 test = 12.45, $F[4,115] = 10.06$, $p = 0.02$), indicating the changes are not randomly distributed. Relatively large effect sizes were evident for the psychosis factor and the mood factor.

Changes in NPI factors revealed significant correlations between the CGI-I and the mood factor (Pearson $r = 0.26$, $df = 118$, $p = 0.004$) and the agitation factor (Pearson $r = 0.30$, $df = 118$, $p = 0.007$).

DISCUSSION

This patient sample exhibited uniquely severe behavioral disturbances compared with other trials in which the NPI has been used as the behavioral measure (Table 3). The sample also was unique in being free of psychotropic medication at the time of entry, and patients were maintained with many fewer psychotropic treatments throughout the course of the trial. These features afforded the opportunity to investigate the behavioral effects of donepezil in patients with relatively severe psychopathology. Inclusion of multiple measures of psychopathology facilitated demonstration of concurrent validity of the measures. Factor analysis resulted in identification of five clinically plausible factors and demonstrated 27% reductions in the delusion factor and mood factor during the treatment trial. These had corresponding effects sized of 0.34 and 0.39, respectively, within the range observed in many trials of psychotropic agents. Together, the analyses suggest that donepezil reduced delusions and depression in patients with AD, and the effects were most evident in those with more severe behavioral disturbances at baseline.

The severity of behavioral changes at baseline in this study is greater that any previously reported trial of cholinesterase inhibitors (Table 3). The total NPI score of 30 is somewhat lower than baseline scores in trials of atypical antipsychotic medications in which NPI scores ranged from 30–60.[35–40] The effect of donepezil in patients with behavioral disturbances of this level of severity remains to be tested.

Beneficial effects on mood and anxiety have previously been reported with ChE-Is. A detailed analysis of the study of Feldman and colleagues[22] by Gauthier et al.[41] showed significant drug–placebo differences in favor of donepezil on the depression and anxiety items of the NPI. Similarly, an analysis of a double-blind, placebo-controlled trial of galantamine[42] revealed that patients who were symptomatic at baseline had significant reductions of anxiety when treated with galanthamine compared with those receiving placebo.[19] Rosler and coworkers observed a reduction of baseline mood disorders in patients treated with rivastigmine.[43]

Antipsychotic effects of ChE-Is have been observed less consistently across studies and were not predicted in the current analysis. The 27% reduction in the psychosis factor was comparable in effect size (0.34) on the changes in mood (27% reduction; effect size 0.39). Reduced hallucinations have been reported after treatment with rivastigmine,[43] and effects on both delusions and hallucinations were observed in a study of the effects of rivastigmine on patients resident in nursing homes.[44]

Although the effect sizes of changes in mood and psychotic symptoms were substantial, some patients with severe behavioral disturbances may need psychotropic medications for more complete symptom control. Further studies are required to determine if the efficacy of psychotropic drug treatment is enhanced or the required duration of therapy reduced in patients receiving ChE-Is.

The primary limitation of this study is that the analyses, although hypothesis-driven, were post hoc.

TABLE 3. Neuropsychiatric Inventory (NPI; 10-item or 12-item*) Baseline Score in Major Trials of Cholinesterase Inhibitors and Memantine

Trial/Agent	Baseline NPI
Tariot et al.[20]	
Memantine	13.4 (SE: 1.07)
Placebo	13.4 (SE: 1.08)
Reisberg et al.[45]	
Memantine	21.4 (SD: NR)
Placebo	19.5 (SD: NR)
Feldman et al.[22]	
Donepezil	19.5 (SE: 1.48)
Placebo	19.3 (SE: 1.45)
Winblad et al.[46*]	
Donepezil	13.1 (SD: 13.76)
Placebo	11.8 (SD: 12.23)
Tariot et al.[47]	
Donepezil	21.0 (SD: 14.5)
Placebo	20.5 (SD: 14.7)
Tariot et al.[42]	
Galantamine	12.9 (SE: 1.2)
Placebo	11.0 (SE: 0.7)
Holmes et al.[23]	
Donepezil	
Placebo	14.3 (SE 1.4)
Current Study	15.1 (SE 1.8)
Donepezil (baseline)	30.8 (SD: 17.2)
Donepezil + placebo (week 8)	30.5 (SD: 17.3)

SD: standard deviation; SE: standard error of measurement; NR: not reported.

The initial period of treatment was unblended; the blinding in the second portion of the study may have diminished observer bias. This study has three unique strengths: 1) patients were recruited to the study because of behavioral disturbances of a defined severity; 2) the patients included had behavioral alterations more severe than any previously reported trial; and 3) patients free of psychotrophics at baseline.

In summary, this analysis of the effects of donepezil in patients with relatively severe behavioral disturbances at baseline and uncompensated by treatment with psychotropic agents indicates that donepezil has significant behavioral effect reducing mood disturbances and psychotic symptoms.

This project was supported by a grant from the National Institute on Aging for the UCLA Alzheimer's Disease Research Center (P50 16570), the Alzheimer's Research Center of California, the Sidell-Kagan Foundation, and the Deane F. Johnson Alzheimer's Research Foundation.

The following investigators participated in the current study: George Alexopoulos, M.D.; William Bondareff, Ph.D., M.D.; William J. Burke, M.D.; Jeffrey L. Cummings, M.D.; P. Murali Doraiswamy, M.D.; Maurice Dysken, M.D.; Sanford I. Finkel, M.D.; George Grossberg, M.D.; Gregory Haefner, M.D.; Jon F. Heiser, M.D.; Lawrence Jenkyn, M.D.; Rita Jewett, Ph.D., K. Ranga Rama Krishnan, M.D.; Vinod Kumar, M.D.; Joseph Kwentus, M.D.; William J. McEntee, M.D.; Donna Masterman, M.D.; Jacobo E. Mintzer, M.D.; Arnaldo Negron, M.D.; Paul Newhouse, M.D.; Margarita Nunez, M.D.; Raymond Ownby, M.D., Ph.D.; William Pendlebury, M.D.; Elaine Peskind, M.D.; Murray Raskind, M.D.; Barry Reisberg, M.D.; Donald Royall, M.D.; Steven Sevush, M.D.; Paul R. Solomon, Ph.D.; Pierre Tariot, M.D.; and Larry Tune, M.D.

Dr. Cummings has provided consultation or performed research for Pfizer, Inc.; Drs. McRae and Zhang are employees of Pfizer, Inc.

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