ORIGINAL ARTICLE

Donepezil for the Treatment of Agitation in Alzheimer's Disease

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ABSTRACT

BACKGROUND

Agitation is a common and distressing symptom in patients with Alzheimer's disease. Cholinesterase inhibitors improve cognitive outcomes in such patients, but the benefits of these drugs for behavioral disturbances are unclear.

METHODS

We randomly assigned 272 patients with Alzheimer's disease who had clinically significant agitation and no response to a brief psychosocial treatment program to receive 10 mg of donepezil per day (128 patients) or placebo (131 patients) for 12 weeks. The primary outcome was a change in the score on the Cohen–Mansfield Agitation Inventory (CMAI) (on a scale of 29 to 203, with higher scores indicating more agitation) at 12 weeks.

RESULTS

There was no significant difference between the effects of donepezil and those of placebo on the basis of the change in CMAI scores from baseline to 12 weeks (estimated mean difference in change [the value for donepezil minus that for placebo], −0.06; 95% confidence interval [CI], −4.35 to 4.22). Twenty-two of 108 patients (20.4%) in the placebo group and 22 of 113 (19.5%) in the donepezil group had a reduction of 30% or greater in the CMAI score (the value for donepezil minus that for placebo, −0.9 percentage point; 95% CI, −11.4 to 9.6). There were also no significant differences between the placebo and donepezil groups in scores for the Neuropsychiatric Inventory, the Neuropsychiatric Inventory Caregiver Distress Scale, or the Clinician's Global Impression of Change.

CONCLUSIONS

In this 12-week trial, donepezil was not more effective than placebo in treating agitation in patients with Alzheimer's disease. (ClinicalTrials.gov number, NCT00142324.)

ALZHEIMER'S DISEASE CAUSES A PROGRESsive decline in cognitive and functional ability and distress on the part of both patients and their caregivers. Agitation, a cluster of related symptoms that includes anxiety, irritability, and motor restlessness, leading to behaviors such as pacing, wandering, shouting, and aggression,[1] is seen in 24% of people with Alzheimer's disease who live in the community[2] and in 48% of those living in residential care facilities.[3] Behavioral and psychological symptoms in Alzheimer's disease are distressing to caregivers[4,5] and often precipitate the transition to residential care.[6] Atypical neuroleptic agents remain the mainstay of drug treatment despite only modest short-term efficacy[7,8] and serious side effects, including stroke and death.[9]

Trial data suggest a reduced emergence of behavioral and psychiatric symptoms in patients treated with cholinesterase inhibitors[10]; these data also suggest improvements in scores on the Neuropsychiatric Inventory (NPI)[11] in patients with behavioral disturbances who continue treatment as compared with those in whom treatment is withdrawn.[12] A systematic review and meta-analysis[13] concluded that cholinesterase inhibitors have modest beneficial effects on neuropsychiatric symptoms, with a reduction of 1.72 points (95% confidence interval [CI], 0.087 to 2.57) on the NPI (on a scale of 1 to 144, with lower scores indicating less frequent or severe symptoms). A Cochrane review[14] concluded that treatment was associated with a reduction of 2.44 points (95% CI, 0.76 to 4.12). A post hoc analysis of pooled behavioral data from three large galantamine trials showed modest but significant improvements in the total NPI score and in the subscales for agitation or aggression, anxiety, disinhibition, and aberrant motor behavior.[15] Finally, a small study reported a nonsignificant advantage of rivastigmine over placebo with respect to the score on the Cohen–Mansfield Agitation Inventory (CMAI).[16,17]

Clinical uncertainty persists regarding the efficacy of cholinesterase inhibitors when behavioral disturbance is severe and is the indication for treatment. We conducted a study to assess the effect of 12 weeks of treatment with donepezil (Aricept, Janssen) on clinically significant agitation in patients with Alzheimer's disease. Because best practice involves an initial trial of a non-pharmacologic approach[1] and previous studies have shown a rate of response to placebo in excess of 40%,[18] we enrolled only those patients whose agitation was so severe that it was clinically necessary for them to receive drug treatment and whose agitation failed to respond to a 4-week psychosocial treatment. The primary question was whether donepezil is better than placebo in the management of agitation that is inappropriate for, or has not responded to, a psychosocial treatment.

METHODS

The original study was a multicenter, blinded, randomized, parallel-group trial in which patients were assigned to receive risperidone (Rispendal, Eisai), donepezil, or placebo for 12 weeks, after 4 weeks of psychosocial treatment. The target sample size was 285 people with Alzheimer's disease. Recruitment started in November 2003 but was suspended in March 2004, following the recommendation by the United Kingdom Committee for Safety of Medicines that risperidone and olanzapine not be used for the treatment of behavioral symptoms in dementia.[19] The trial was restarted in July 2004 with a two-group design (donepezil and placebo), and recruitment ended in September 2005.

PARTICIPANTS

Patients were recruited at eight clinical centers in England. They were eligible for inclusion if they met the diagnostic criteria of the National Institute of Neurological and Communication Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[20] for probable or possible Alzheimer's disease; had clinical agitation (causing distress to the patient and at least moderate management problems for caregivers on at least 2 days per week for a 2-week period, together with a CMAI[16] score of 39 or more, on a scale from 29 to 203, with higher scores indicating more frequent or severe agitation); were older than 39 years of age; lived in a residential care facility or with a caregiver in the community; were not receiving neuroleptic agents or cholinesterase inhibitors at the time of enrollment, had not received them in the previous 4 weeks, and were not being considered for such treatment for the next 16 weeks; had the capacity and were willing to consent to participation in the study or lacked the capacity and assented to participation; and had a caregiver who was in agreement with the patient's assent to participate.

Written informed consent was obtained from patients when it could be given, and written assent was obtained from all caregivers for the patients' involvement in the trial. Exclusion criteria were a known sensitivity to donepezil; severe, unstable, or uncontrolled medical conditions; delirium; dementia with Lewy bodies[21]; and evidence of poor compliance with prescribed medication.

INTERVENTIONS

Before randomization, patients participated in a psychosocial treatment program for up to 4 weeks, consisting of four sessions (two in person and two conducted by telephone) during which the main caregiver was trained to deliver one of three treatment options — standardized social interaction, personalized music, or removal of triggers for agitated behaviors[22] — selected on the basis of an assessment during the first session. Patients whose CMAI score was 39 or more after the psychosocial treatment were enrolled in the drug-treatment phase of the study and randomly assigned to receive donepezil or placebo daily for 12 weeks. Patients whose agitation was considered sufficiently severe to merit immediate drug treatment could enter the randomized phase immediately, and those who started psychosocial treatment but whose agitation was judged clinically not to have responded could enter the randomized phase before completion of psychosocial treatment.

Trial medication was encapsulated. Clinicians, those administering the trial medication, patients, caregivers, and outcome assessors were all unaware of the treatment assignments. During weeks 1 through 4 of the trial, patients received one capsule (5 mg of donepezil or placebo) daily. During weeks 5 through 12, patients received two capsules (10 mg of donepezil or placebo) daily. At the end of week 12, decisions about treatment of agitation were the responsibility of the referring physician.

OUTCOME MEASURES

The total CMAI score at 12 weeks was designated as the primary outcome. Secondary outcomes included the caregiver's assessments of symptoms with the NPI,[11] either the NPI Nursing Home Version[23] or the NPI Caregiver Distress Scale (depending on whether the patient was living in a nursing home or at home),[24] and cognitive function as measured with the Severe Impairment Battery (SIB),[25] the Standardized Mini–Mental State Examination

(SMMSE),[26] and the Clinician's Global Impression of Change (CGIC).[27]

Outcomes assessors were psychologists or registered nurses who attended a week-long training course designed to familiarize them with the instruments and standardize delivery. To assess the adequacy and consistency of delivery of the psychosocial treatment, 10% of the sessions were videotaped and rated.

EVALUATIONS

There were four assessment points. Before psychosocial treatment, consent was obtained, and the CMAI, SMMSE, and NPI Caregiver Distress Scale were administered. Before enrollment in the drug trial, the CMAI, NPI, and SMMSE were administered; those patients with CMAI scores of 39 or higher were enrolled in the trial and underwent randomization, and the SIB, CGIC, and NPI Caregiver Distress Scale were administered. At week 4 (the time of dose escalation), the CMAI, NPI, and NPI Caregiver Distress Scale were administered. At week 12 (the end of the trial), the CMAI, NPI, SMMSE, SIB, CGIC, and NPI Caregiver Distress Scale were administered.

Adverse events were reported immediately to local principal investigators, who decided whether the assigned treatment should be revealed or the patient removed from the trial. Written report forms were faxed to the central trial office and submitted monthly to the chair of the Data Monitoring and Ethics Committee.

RANDOMIZATION

Telephone randomization was performed centrally by the Medical Research Council (MRC) Clinical Trials Unit. Assignment of treatment to drug-pack numbers was performed with the use of a random sequence of numbers (fixed blocks of six). The list of treatment assignments was checked and approved by trial statisticians.

The data manager determined treatment assignments using a fully blind minimization algorithm containing an embedded list of pack numbers with corresponding treatment. The first 20 patients were assigned by means of simple randomization with the use of a prepared list. For the rest of the patients, a minimization method was used to balance treatment assignments according to four stratifying factors: participating center, age (40 to 59 years, 60 to 74 years, or ≥75 years),

Figure 1. Enrollment, Group Assignment, Follow-up, and Analysis.
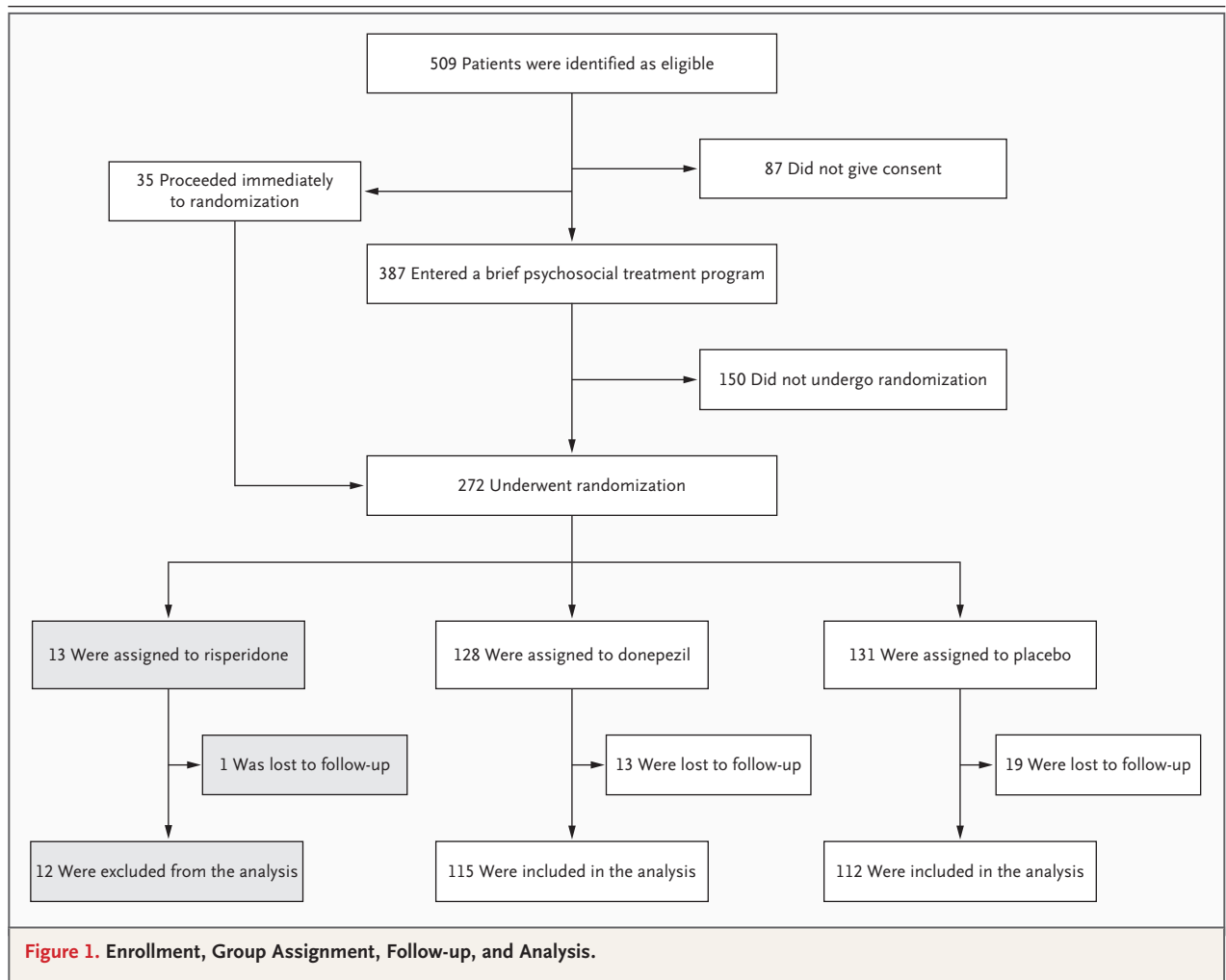
psychosocial treatment (no treatment, incomplete treatment [<4 weeks], or complete treatment [4 weeks]), and place of residence (own or relative's home, residential care facility, or other). The minimization algorithm summed previous treatment assignments across the four strata, matching the new patient and using probability ratios of 0.75 and 0.25 to assign treatment, with the higher ratio (0.75) applied to the treatment with the lower total.

When a patient was to undergo randomization, physicians at the center completed the Patient Entry and Randomization Checklist, obtained the patient's consent to randomization, and then telephoned the data manager at the MRC, who determined the number of the drug pack to be assigned and informed the pharmacist at the participating center. The pharmacist then dispensed the appropriate drug pack to local research staff, ensuring concealment.

STATISTICAL ANALYSIS

We prespecified a clinically important response as a 30% or greater reduction in agitation[18] and anticipated that the rate of response to placebo would be 30% and the rate of response to risperidone or donepezil would be approximately 55%. To detect a difference of 25 percentage points between response rates with active treatment and placebo, with 90% power at the 5% level of significance, 81 participants would be required in each group; with a 15% dropout rate, 95 participants would be required in each group.

We used SPSS for Windows (version 12.0.1) to

Table 1. Baseline Characteristics at Randomization According to Study Group.*

Characteristic	Placebo (N=131)	Donepezil (N=128)	P Value
Age — yr			0.83
Mean	84.4±8.2	84.9±7.3	
Median	85.1	85.1	
Interquartile range	79.9–90.2	80.1–90.4	
Total CMAI score			0.34
Mean	60.7±16.5	62.5±17.5	
Median	57.0	59.5	
Interquartile range	47.0–72.0	50.0–71.5	
CGIC score			0.42
Mean	4.3±1.1	4.2±1.1	
Median	4.0	4.0	
Interquartile range	4.0–5.0	3.0–5.0	
Missing data — no.	7	4	
Total NPI score			0.70
Mean	23.6±16.7	23.7±15.9	
Median	20.0	23.0	
Interquartile range	12.0–33.0	11.0–32.0	
Missing data — no.	7	1	
Total score on NPI Caregiver Distress Scale			0.22
Mean	7.3±7.8	8.0±7.5	
Median	5.0	6.0	
Interquartile range	1.0–10.0	2.0–12.0	
Missing data — no.	7	1	
Total SIB score			0.49
Mean	55.9±34.9	53.8±32.0	
Median	67.5	60.0	
Interquartile range	22.0–88.0	26.0–83.0	
Missing data — no.	45	40	
Total SMMSE score			0.82
Mean	8.2±6.8	8.1±5.9	
Median	8.0	8.0	
Interquartile range	2.0–14.0	3.0–12.0	
Missing data — no.	36	44	

manage data and Stata (version 9.2) for analyses. Demographic and clinical characteristics were summarized by using counts and percentages for categorical variables, means ±SD for normally distributed continuous variables, and medians with interquartile ranges for non-normally distributed continuous variables.

Comparative analyses were restricted to patients who were assigned to the donepezil and placebo groups. Specifically, patients were analyzed in the groups to which they were assigned. Primary analysis was performed for patients with complete data at both baseline and week 12, including those who did not adhere to the protocol

Table 1. (Continued.)

Characteristic	Placebo (N=131)	Donepezil (N=128)	P Value
Female sex — no. (%)	114 (87.0)	105 (82.0)	0.27
Race — no. (%)†			0.41
White	126 (96.2)	126 (98.4)	
Black	4 (3.1)	1 (0.8)	
Missing data	1 (0.8)	1 (0.8)	
Regular use of stable dose of psychotropic agents at trial entry — no. (%)‡	18 (13.8)	33 (25.8)	0.02
Place of residence — no. (%)			0.68
Own or relative's home	7 (5.3)	4 (3.1)	
Residential care facility	121 (92.4)	121 (94.5)	
Other	3 (2.3)	3 (2.3)	
Brief psychosocial treatment — no. (%)			0.94
None	18 (13.7)	16 (12.5)	
Incomplete (<4 wk)	11 (8.4)	10 (7.8)	
Complete (4 wk)	102 (77.9)	102 (79.7)	
Relationship of informant to patient at randomization — no. (%)§			
Professional caregiver	119 (90.8)	123 (96.1)	0.12
Spouse	1 (0.8)	3 (2.3)	
Child	5 (3.8)	—	
Sibling	1 (0.8)	—	
Other	1 (0.8)	—	
Missing data	4 (3.0)	2 (1.6)	

* Plus–minus values are means ±SD. CMAI denotes Cohen–Mansfield Agitation Inventory, which includes 29 items. Scores range from 29 to 203, with higher scores indicating more frequent or severe agitation. Scores above 40 are usually considered to be clinically significant. CGIC denotes Clinician's Global Impression of Change, which has a single item. Scores range from 1 to 7, with higher scores indicating greater impairment. NPI denotes Neuropsychiatric Inventory, which has 12 domains, including neurovegetative signs (preceding 2 weeks). Scores range from 1 to 144, with lower scores indicating less frequent or severe symptoms and signs. The NPI Caregiver Distress Scale has 12 domains (NPI Nursing Home Version used if the patient lived in a nursing home). Scores range from 0 to 60, with lower scores indicating less distress. SIB denotes Severe Impairment Battery, which includes 51 items. Scores range from 0 to 100, with higher scores indicating better performance. SMMSE denotes Standardized Mini–Mental State Examination, which includes 12 questions. Scores range from 0 to 30, with higher scores indicating better performance.
† Race was reported by physicians.
‡ Psychotropic agents taken included benzodiazepine or other nighttime sedating medication, sedative antidepressant agents, mood-stabilizing medication, and other neuroleptic agents.
§ At 12 weeks, on study completion, the relationship of the informant to the patient was the same in all but two cases (one professional caregiver was replaced by the patient's child, and one sibling was replaced by a professional caregiver).

(e.g., those who never started treatment but for whom we had complete data). For the primary analysis, the change in the CMAI score from baseline to 12 weeks was summarized as the mean (±SD) change among patients with complete data at both baseline and 12 weeks. To establish the magnitude and direction of the treatment effect, the change in the CMAI score from baseline to 12 weeks in the donepezil group was compared with the change in the placebo group by means of analysis of covariance (ANCOVA), and the results were expressed as the difference (plus 95% confidence interval), with adjustment for the baseline value. An additional ANCOVA was performed with adjustment for the four stratification factors, as well as time and the baseline value. Changes in secondary outcomes were summarized and compared in a similar fashion.

The treatment response was assessed by calculating the difference between groups in the

Table 2. Changes from Baseline at 12 Weeks.*

Assessment	Mean Change from Baseline†		Estimated Difference in Change (95% CI)‡		P Value	
	Placebo	Donepezil	Adjusted for Baseline Value	Adjusted for Baseline Value and Stratification Factors	Adjusted for Baseline Value	Adjusted for Baseline Value and Stratification Factors
CMAI (all 29 items)						
No. of patients (%)	108 (82)	113 (88)				
Score	4.99±18.98	6.34±20.35	–0.064 (–4.35 to 4.22)	0.18 (–4.22 to 4.59)	0.98	0.94
NPI (all 12 items)						
No. of patients (%)	97 (74)	104 (81)				
Score	3.78±17.75	3.56±17.73	–0.13 (–4.06 to 3.80)	0.10 (–3.79 to 3.99)	0.95	0.96
NPI Caregiver Distress Scale (all 12 items)						
No. of patients (%)	95 (73)	105 (82)				
Score	1.29±7.65	1.53±7.44	–0.20 (–1.86 to 1.47)	–0.45 (–2.06 to 1.15)	0.82	0.58
SIB (all 51 items)						
No. of patients (%)	33 (25)	27 (21)				
Score	–4.82±8.80	1.93±11.14	6.45 (1.07 to 11.83)	7.26 (1.27 to 13.26)	0.02	0.02
SMMSE (all 20 items)						
No. of patients (%)	57 (44)	56 (44)				
Score	–0.96±3.86	0.54±3.47	1.55 (0.23 to 2.88)	1.49 (0.14 to 2.84)	0.02	0.03

* Plus–minus values are means ±SD. Analysis of covariance (ANCOVA) was adjusted for baseline measurement. Stratification factors were center (8 categories), age (continuous variable), participation in psychosocial treatment (none, incomplete [<4 weeks], or complete [4 weeks]), and place of residence (own or relative's home, residential care facility, or other), plus number of study groups at time of enrollment (three or two). CMAI denotes Cohen–Mansfield Agitation Inventory, which includes 29 items. Scores range from 29 to 203, with higher scores indicating more frequent or severe agitation. Scores above 40 are usually considered to be clinically significant. NPI denotes Neuropsychiatric Inventory, which has 12 domains, including neurovegetative signs (preceding 2 weeks). Scores range from 1 to 144, with lower scores indicating less frequent or severe symptoms and signs. The NPI Caregiver Distress Scale has 12 domains. Scores range from 0 to 60, with lower scores indicating less distress. SIB denotes Severe Impairment Battery, which includes 51 items. Scores range from 0 to 100, with higher scores indicating better performance. SMMSE denotes Standardized Mini–Mental State Examination, which includes 12 questions. Scores range from 0 to 30, with higher scores indicating better performance.
† Positive change represents improvement.
‡ Placebo is the reference group; a positive difference favors donepezil.

proportion of patients with more than a 30% reduction in agitation (95% confidence interval). Sensitivity analyses were carried out to examine the robustness of the results with different assumptions about departures from randomization policies, depending on the availability of data and the particular set of circumstances (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

The authors designed the study, site investigators gathered the data, trial statisticians carried out the analyses, and the authors wrote the manuscript and vouch for the completeness and accuracy of the data and analyses. The companies that donated the medications had no role in the trial design, data accrual, data analysis, or preparation of the manuscript.

RESULTS

Between November 2003 and December 2005, a total of 509 patients were identified as eligible; 87 (17.1%) did not give consent for inclusion. Thirty-five patients proceeded immediately to randomization. Of the 387 patients who entered the psychosocial-treatment phase, 53 (13.7%) had improvement to the degree that their CMAI score fell below the threshold required to proceed to randomization. Video and written records showed that 93% of psychosocial treatment sessions followed the procedures as demonstrated during training.

Of the 272 patients who underwent randomization between November 2003 and December 2005, a total of 262 (96.3%) received a drug or placebo (12 received risperidone, 124 donepezil, and 126

placebo) (Fig. 1). Among the 250 patients assigned to receive donepezil or placebo, CMAI assessments were completed for 100% at baseline and for 90.8% (227 of 250) at 12 weeks, with all four CMAI assessments completed for 221 of 227 patients (113 in the donepezil group and 108 in the placebo group).

Demographic characteristics and the stage of dementia were similar in the two groups (Table 1); the groups were slightly imbalanced in terms of the proportion of patients regularly taking any stable dose of psychotropic agents at trial entry, but the treatment effect was similar in patients who were taking such agents at baseline and those who were not (P=0.51 for the test of an interaction).

PRIMARY OUTCOME

The estimated mean reduction in the CMAI score from baseline to 12 weeks did not differ significantly between the placebo and donepezil groups (Table 2 and Fig. 2); the average change in the score was 4.99±18.98 points in the placebo group and 6.34±20.35 points in the donepezil group. With adjustment for the baseline value, the estimated difference in the reduction from baseline (the value for donepezil minus that for placebo) was −0.06 (95% CI, −4.35 to 4.22).

The proportion of patients with a response to treatment (defined as a 30% or greater reduction in the total CMAI score from baseline to 12 weeks) was similar in the two groups — 22 of 108 patients (20.4%) in the placebo group and 22 of 113 (19.5%) in the donepezil group (difference in treatment response [the value for donepezil minus that for placebo], −0.9 percentage point; 95% CI, −11.4 to 9.6).

SECONDARY OUTCOMES

The reduction in the NPI score from baseline to 12 weeks did not differ significantly between the placebo and donepezil groups (Table 2); the mean reduction was 3.78±17.75 points for the placebo group and 3.56±17.73 points for the donepezil group. With adjustment for the baseline value, the estimated difference in reduction between the two groups was −0.13 (95% CI, −4.06 to 3.80). Similarly, scores on the NPI Caregiver Distress Scale (which range from 0 to 60, with lower scores indicating less distress) improved in both groups, with a mean reduction of 1.29±7.65 points in the placebo group and 1.53±7.44 points in the donepezil group. With adjustment for the baseline value, the esti-
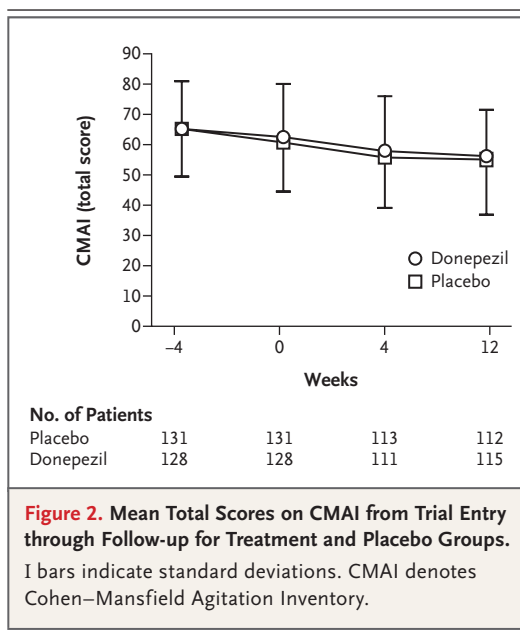
Figure 2. Mean Total Scores on CMAI from Trial Entry through Follow-up for Treatment and Placebo Groups.

I bars indicate standard deviations. CMAI denotes Cohen–Mansfield Agitation Inventory.

mated difference in reduction between the groups was −0.20 (95% CI, −1.86 to 1.47).

Mean follow-up values for the CGIC (on which scores range from 1 to 7, with higher scores indicating greater impairment) were 3.93±1.08 for the placebo group and 3.87±1.25 for the donepezil group. With adjustment for the baseline CGIC score, the estimated mean difference in the change from baseline between the two groups was −0.06 (95% CI, −0.37 to 0.25) in favor of the placebo group.

For the SIB (scores range from 0 to 100, with higher scores indicating better performance), patients receiving donepezil increased their score by 1.93±11.14 points as compared with a decrease in the placebo group of 4.82±8.80 points. With adjustment for the baseline value, the estimated mean difference between groups in the change from baseline was 6.45 (95% CI, 1.07 to 11.83), indicating greater cognitive deterioration in the placebo group (P=0.02). However, the proportion of patients fully able to complete the SIB was 25% in the placebo group and only 21% in the donepezil group.

Similarly, patients receiving donepezil had an estimated mean increase in the SMMSE score (scores range from 0 to 30, with higher scores indicating better performance) from baseline to 12 weeks of 0.54±3.47 points as compared with a mean decrease of 0.96±3.86 points in the placebo group. With adjustment for the baseline value, the estimated difference in the change from baseline

Table 3. Adverse Events.

Adverse Event	Psychosocial Treatment (N=422)	Donepezil (N=128)	Placebo (N=131)
	number (percent)		
Nausea, vomiting, or anorexia	0	3 (2.3)	1 (0.8)
Diarrhea	0	2 (1.6)	0
Gastrointestinal bleeding	0	0	0
Rash	0	2 (1.6)	1 (0.8)
Increased agitation	2 (0.5)	2 (1.6)	3 (2.3)
Postural hypotension	0	0	1 (0.8)
Fall	1 (0.2)	2 (1.6)	2 (1.5)
Femoral fracture	1 (0.2)	2 (1.6)	0
Stroke	1 (0.2)	1 (0.8)	0
Myocardial infarction	0	1 (0.8)	0
Urinary tract infection	0	2 (1.6)	3 (2.3)
Chest infection	0	1 (0.8)	1 (0.8)
Seizure	0	2 (1.6)	3 (2.3)
Death	4 (0.9)	3 (2.3)	4 (3.1)

was 1.55 (95% CI, 0.23 to 2.88), indicating greater cognitive deterioration in the placebo group (P=0.02). As with the SIB, the proportion of patients fully able to complete the examination was low (44% in both groups).

SENSITIVITY ANALYSES

Results for the CMAI, NPI, NPI Caregiver Distress Scale, SIB, and SMMSE proved robust with different assumptions about departures from randomization policies and various other ways of handling missing data (see the Supplementary Appendix). For the CMAI, the results of the repeated-measures model (a linear mixed-effect model incorporating data from all four assessment points) were slightly in favor of the donepezil group (0.29; 95% CI, −3.66 to 4.23) but were consistent with the results of the adjusted ANCOVA model (Table 2).

ADVERSE EVENTS

Adverse events were similar in the donepezil and placebo groups. Details of all reported adverse events are shown in Table 3.

DISCUSSION

This 12-week trial examined the effectiveness of donepezil for the treatment of clinically significant agitation in patients with Alzheimer's disease.

No significant treatment advantage was shown for donepezil as compared with placebo. The primary analysis, which was adjusted for baseline symptom severity, showed an estimated difference in the change from baseline of less than 0.1 point on the CMAI between the placebo and intervention groups. The confidence interval for the difference suggests that the study excluded a benefit of 4.5 points or more on a scale ranging from 29 to 203.

Although previous trials have indicated that cholinesterase-inhibitor therapy results in modest but significant improvement in the overall severity of neuropsychiatric symptoms in patients with mild levels of behavioral disturbance, this may be explained by improvements in symptoms other than agitation. For example, a study that examined individual items on the NPI in patients with Alzheimer's disease showed significant benefits for mood-related symptoms but not for agitation.[28] Furthermore, in a trial in which rivastigmine was shown to have efficacy in the treatment of apathy, delusions, and hallucinations in patients who had dementia with Lewy bodies, there was no effect on the NPI measure for agitation.[29]

Like other studies examining the use of donepezil in the treatment of patients with severe Alzheimer's disease,[30,31] our trial showed that on cognitive measures assessed by the SIB and SMMSE, there was a modest benefit from donepezil as compared with placebo.

The trial was conducted in a pragmatic manner, and the inclusion criteria were broad. Most of the patients in the study were nursing home residents with severe dementia and were thus representative of patients who present with difficult-to-manage behaviors, such as agitation. We chose agitation measured by the CMAI as the primary outcome because we believe this measure captures those behaviors that are most likely to lead to requests for drug treatment. However, agitation may not represent a homogenous clinical phenomenon, and this is a potential limitation of the trial. The generalizability of our findings is limited by the high proportion of women in our study and by the 35% of participants who did not proceed to randomization for a number of reasons, including successful completion of psychosocial treatment.

The effectiveness of second-generation antipsychotic drugs, which have become the mainstay of treatment for psychosis, agitation, and aggression in Alzheimer's disease, has been seriously questioned on the basis of the results of the Clinical

Antipsychotic Trials of Intervention Effectiveness trial, which showed no significant advantage of these drugs over placebo.[32] The results of our trial suggest that the cholinesterase inhibitors do not represent an effective alternative treatment for clinically significant agitation in patients with Alzheimer's disease.

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