ORIGINAL ARTICLE

Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease

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ABSTRACT

BACKGROUND

Clinical trials have shown the benefits of cholinesterase inhibitors for the treatment of mild-to-moderate Alzheimer's disease. It is not known whether treatment benefits continue after the progression to moderate-to-severe disease.

METHODS

We assigned 295 community-dwelling patients who had been treated with donepezil for at least 3 months and who had moderate or severe Alzheimer's disease (a score of 5 to 13 on the Standardized Mini–Mental State Examination [SMMSE, on which scores range from 0 to 30, with higher scores indicating better cognitive function]) to continue donepezil, discontinue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine. Patients received the study treatment for 52 weeks. The coprimary outcomes were scores on the SMMSE and on the Bristol Activities of Daily Living Scale (BADLS, on which scores range from 0 to 60, with higher scores indicating greater impairment). The minimum clinically important differences were 1.4 points on the SMMSE and 3.5 points on the BADLS.

RESULTS

Patients assigned to continue donepezil, as compared with those assigned to discontinue donepezil, had a score on the SMMSE that was higher by an average of 1.9 points (95% confidence interval [CI], 1.3 to 2.5) and a score on the BADLS that was lower (indicating less impairment) by 3.0 points (95% CI, 1.8 to 4.3) ($P<0.001$ for both comparisons). Patients assigned to receive memantine, as compared with those assigned to receive memantine placebo, had a score on the SMMSE that was an average of 1.2 points higher (95% CI, 0.6 to 1.8; $P<0.001$) and a score on the BADLS that was 1.5 points lower (95% CI, 0.3 to 2.8; $P=0.02$). The efficacy of donepezil and of memantine did not differ significantly in the presence or absence of the other. There were no significant benefits of the combination of donepezil and memantine over donepezil alone.

CONCLUSIONS

In patients with moderate or severe Alzheimer's disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months. (Funded by the U.K. Medical Research Council and the U.K. Alzheimer's Society; Current Controlled Trials number, ISRCTN49545035.)

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Most studies evaluating cholinesterase inhibitors for the treatment of Alzheimer's disease have focused on patients with mild-to-moderate disease. Despite questions about the methods used in the trials[1] and about the clinical significance of reported benefits,[1,2] guidelines advocate treatment with a cholinesterase inhibitor, although some recommend discontinuation when Alzheimer's disease becomes severe.[3] Evidence of the efficacy of memantine has been shown primarily in patients with moderate or severe Alzheimer's disease.[4] The findings of a study showing that combination therapy with memantine and a cholinesterase inhibitor was more effective than treatment with a cholinesterase inhibitor alone[5] have not been replicated.[6] Results from randomized, controlled trials involving patients with moderate-to-severe[7,8] or severe[9-12] Alzheimer's disease suggest that cholinesterase inhibitors are associated with modest improvements in cognition and function, and these drugs are approved by the Food and Drug Administration in the United States for the treatment of severe Alzheimer's disease. All the trials involving patients with severe Alzheimer's disease, however, have involved nursing home residents, and none of the trials focusing on moderate-to-severe or severe Alzheimer's disease have investigated the strategy of continuing treatment with cholinesterase inhibitors in patients already taking those drugs. There is very limited evidence to guide the difficult decision regarding continuation or discontinuation of treatment when the disease progresses, but continued treatment is associated with an increase in adverse outcomes, including syncope, the need for insertion of permanent pacemakers, and hip fractures.[13]

We investigated whether community-living patients with Alzheimer's disease, who have moderate-to-severe disease and are already receiving donepezil, benefit from continuing treatment and whether initiating memantine at this point in the course of the disease is beneficial. We had three objectives: first, to test whether, over a period of 52 weeks, continuation of donepezil, as compared with discontinuation of the drug, would be associated with better cognition and function; second, to test whether memantine treatment, as compared with placebo memantine, would be associated with better cognition and function; and third, to test whether combining donepezil and memantine would provide additive or synergistic benefits.

Methods

Study Design and Participants

The Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO) study was a multicenter, double-blind, placebo-controlled, clinical trial with a two-by-two factorial design. The outcomes were assessed for 52 weeks.[14] We enrolled community residents who had caregivers who either lived with them or visited them at least daily. Eligible participants met standardized clinical criteria[15] for probable or possible moderate or severe Alzheimer's disease, had been prescribed donepezil continuously for at least 3 months and had received a dose of 10 mg for at least the previous 6 weeks, and had a score between 5 and 13 on the Standardized Mini–Mental State Examination (SMMSE, on which scores range from 0 to 30, with higher scores indicating better cognitive function).[16] In addition, each eligible patient's prescribing clinician was considering a change in drug treatment (i.e., stopping donepezil or introducing memantine) on the basis of National Institute for Health and Clinical Excellence (NICE) guidelines[3] at the time, discussions with the patient and caregivers, and the physician's clinical judgment. Agreement in writing to take part in the study was obtained from the participants if they were considered to have the capacity to give informed consent, and the main caregivers gave written informed consent for their own involvement and assent for the patients' involvement.

Patients were excluded if they had severe or unstable medical conditions, were receiving memantine, or were considered to be unlikely to adhere to the study regimens. Details of the design have been published previously.[14]

Study Oversight

The study was overseen by King's College London and was funded by the U.K. Medical Research Council (MRC) and the Alzheimer's Society. Full ethical approval was received from the Scotland A Multicenter Research Ethics Committee. Pfizer-Eisai and Lundbeck donated supplies of the drugs and placebo but had no involvement in the design or conduct of the study or the analysis or reporting of the data. The study protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. The first author vouches for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

STUDY PROCEDURES

Participants were randomly assigned to one of four treatments: continuation of donepezil (at a dose of 10 mg per day, with placebo memantine, starting in week 1); discontinuation of donepezil (administration of donepezil at a dose of 5 mg during weeks 1 through 4 and placebo donepezil starting in week 5, plus placebo memantine starting in week 1); discontinuation of donepezil and initiation of treatment with memantine (administration of donepezil at a dose of 5 mg during weeks 1 through 4, with placebo donepezil starting in week 5, and initiation of memantine at a dose of 5 mg in week 1, with the dose increased in 5-mg increments weekly to a dose of 20 mg from week 4 on); or continuation of donepezil and initiation of memantine (continuation of donepezil at a dose of 10 mg and initiation of memantine at a dose of 5 mg in week 1, with the dose increased in 5-mg increments weekly to a dose of 20 mg from week 4 on). Treatment assignments were made (by telephone) by the U.K. Medical Research Council Clinical Trials Unit with the use of randomized minimization[17] (for full details, see the Supplementary Appendix, available at NEJM.org). The procedure involved stratifying groups according to center (among the 15 participating centers), duration of donepezil treatment before entry (3 to 6 months vs. >6 months), baseline SMMSE score (5 to 9, indicating severe disease, vs. 10 to 13, indicating moderate disease), and age (<60 years, 60 to 74 years, or ≥75 years). In addition, to maintain concealment of the treatment assignments, the first 80 participants were assigned with the use of a prepared list of simple randomized assignments.[17] Donepezil (in 5-mg tablets), memantine (in 5-mg and 10-mg tablets), and matched placebo tablets were provided by the manufacturers; patients, caregivers, clinicians, outcome assessors, and investigators were unaware of the treatment assignments. Efficacy and safety data were reviewed by an independent data monitoring and ethics committee every 6 months during the course of the trial.

OUTCOME MEASURES

The coprimary outcomes were scores on the SMMSE and on the caregiver-rated Bristol Activities of Daily Living Scale (BADLS, on which scores range from 0 to 60, with higher scores indicating greater impairment).[18] Secondary outcomes were scores on the Neuropsychiatric Inventory[19] (NPI, on which scores range from 0 to 144, with higher scores indicating increased behavioral and psychological symptoms), scores on the DEMQOL-Proxy[20] (on which scores range from 31 to 134, with higher scores indicating better patient health-related quality of life), and caregiver health status, as assessed with the use of the General Health Questionnaire 12[21] (GHQ-12, on which scores range from 0 to 12, with higher scores indicating increased psychological symptoms in nonprofessional caregivers).

STATISTICAL ANALYSIS

A sample size of 800 was planned originally, but the size was adjusted to 430 on the basis of reduced standard deviations for the outcomes from a blinded analysis of accrued data. With a sample size of 430, we estimated that the study would have 95% power to detect a 1.0-point difference between the donepezil and placebo groups or between the memantine and placebo groups in SMMSE scores and 90% power to detect a 2.0-point difference between the donepezil and placebo groups or between the memantine and placebo groups in BADLS scores at any one assessment point (objectives 1 and 2), assuming an expected rate of 20% for missed visits, at a two-sided significance level of 5%. With this sample size, we estimated that the study would also have 96% power to detect a 1.5-point difference in SMMSE scores and 80% power to detect a 2.5-point difference in BADLS scores between the combination-therapy and monotherapy groups at any one assessment point (objective 3).

Unless otherwise specified, we performed the analyses on data from all patients who underwent randomization and who received at least one dose of study drug, applying the principle of intention to treat as much as was practically possible, given any missing data. Data from participants were analyzed according to the groups to which they had been assigned, irrespective of withdrawal from the assigned study drug or initiation of open-label treatment. An analysis of variance was used to identify significant differences in continuous baseline characteristics across the four study groups, and Fisher's exact test was used to identify differences in categorical baseline characteristics.

The primary analyses of the primary outcomes and the continuous secondary outcomes were conducted with the use of multilevel modeling repeated-measures regression,[22] adjusted for baseline scores and for the four minimization factors

(center, duration of donepezil treatment before entry, baseline SMMSE score, and age). All available scores at every visit, regardless of whether the patient was still taking the trial medication or had switched to open-label treatment, were included in the primary analysis, and there was no imputation of missing scores. The scheduled, rather than the actual, visit week was used in the model. For each outcome, two models were fitted — one with the interaction of donepezil with memantine, to estimate the additional benefit of combination therapy (objective 3) and to test for the interaction, and one without the interaction, to estimate the difference between the active drug (donepezil or memantine) and placebo (objectives 1 and 2). Different random-effects structures were compared with the use of Akaike's information criterion.[23] The chosen model included random effects for each visit with an unstructured covariance matrix; full details are provided in the Supplementary Appendix.

The length of time that participants in the four groups took the study drugs was compared with the use of the log-rank test for equality of survivor functions and a Cox proportional-hazards model to quantify differences among the groups. The incidence of serious adverse events was compared among the groups by means of Poisson regression. Sensitivity analyses were performed to determine the effect of missing data and of discontinuation of treatment; details are provided in the Supplementary Appendix. The analyses were conducted with the use of Stata software, version 11.2.[24] Since the primary objectives were well defined and ordered, adjustment for multiple testing was not indicated in the analysis.[25] For secondary outcome measures and outcomes at assessment points other than those during the 52-week study-treatment period, we defined statistical significance at the 99% confidence interval level to compensate for multiple comparisons.

Before commencing the data analysis, we published values for minimum clinically important differences for the SMMSE (1.4 points), the BADLS (3.5 points), and the NPI (8 points); these values were based on 0.4 SD of the change from baseline in the first 127 participants who completed the DOMINO trial.[26]

RESULTS

PARTICIPANTS

During the period from February 2008 to March 2010, a total of 295 participants were enrolled. Recruitment was slower than anticipated, and it was not possible to extend the recruitment period, since the public funder of the study (MRC) believed that the disadvantages of a delay in reporting results outweighed the benefits of increasing the power of the study. The baseline characteristics of the participants in the four treatment groups were broadly similar (Table 1). Figure 1 shows the numbers of patients who were enrolled, were assigned to a study group, and completed follow-up. Figure 2 shows the number of participants in each group who were still receiving the study drug at each study visit and the cumulative probability of discontinuation of the study drug. The probability of withdrawal from the study drug among patients assigned to continue donepezil was half that among patients assigned to discontinue donepezil (hazard ratio for withdrawal among patients assigned to continued donepezil treatment, 0.51; 95% confidence interval [CI], 0.36 to 0.72; P<0.001). Patients assigned to memantine also had a lower probability of treatment withdrawal than did those assigned to placebo memantine (hazard ratio, 0.66; 95% CI, 0.47 to 0.93; P=0.02).

PRIMARY OUTCOME MEASURES

The mean scores on the SMMSE and the BADLS in all study groups and at all visits are shown in Figure 3. The between-group differences in primary outcome measures at all trial visits are shown in Table 2. Patients who were assigned to continue taking donepezil, as compared with those assigned to discontinue donepezil, had scores on the SMMSE that were higher (indicating better cognitive function) by an average of 1.9 points (95% CI, 1.3 to 2.5; P<0.001) and scores on the BADLS that were lower (indicating less functional impairment) by an average of 3.0 points (95% CI, 1.8 to 4.3; P<0.001). For both these outcomes, there was significant heterogeneity in treatment efficacy over time (P=0.002 and P=0.004, respectively), with less benefit apparent at the 6-week assessment than at later time points. From 6 weeks onward, the differences between the treatment groups were roughly parallel, and we therefore report average effects.

Patients who were assigned to receive memantine, as compared with those who were assigned to receive placebo memantine, had scores on the SMMSE that were higher by an average of 1.2 points (95% CI, 0.6 to 1.8; P<0.001) and scores on the BADLS that were lower by an average of 1.5 points (95% CI, 0.3 to 2.8; P=0.02); both these values were smaller than the minimum

Table 1. Baseline Characteristics of the Participants, According to Treatment Group.*

Characteristic	Donepezil Tapered and Discontinued		Donepezil Continued		Total (N=295)
	Placebo Memantine Added (N=73)	Active Memantine Added (N=76)	Placebo Memantine Added (N=73)	Active Memantine Added (N=73)	
Age — yr	77.7±8.0	76.2±8.9	77.2±7.5	77.5±9.0	77.1±8.4
Sex — no. (%)					
Male	26 (36)	30 (39)	22 (30)	24 (33)	102 (35)
Female	47 (64)	46 (61)	51 (70)	49 (67)	193 (65)
Race — no. (%)†					
White	71 (97)	73 (96)	69 (95)	67 (92)	280 (95)
Black	2 (3)	2 (3)	1 (1)	4 (5)	9 (3)
Other	0	1 (1)	3 (4)	2 (3)	6 (2)
Previous duration of donepezil therapy — no. (%)					
3 to <6 mo	3 (4)	4 (5)	3 (4)	4 (5)	14 (5)
6 to <12 mo	8 (11)	4 (5)	9 (12)	3 (4)	24 (8)
12 to <24 mo	15 (21)	17 (22)	14 (19)	16 (22)	62 (21)
24 to <36 mo	19 (26)	17 (22)	18 (25)	8 (11)	62 (21)
36 to <60 mo	19 (26)	20 (26)	21 (29)	31 (42)	91 (31)
≥60 mo	9 (12)	14 (18)	8 (11)	11 (15)	42 (14)
SMMSE score‡					
Mean	9.1±2.4	9.2±2.5	9.0±2.8	9.1±2.6	9.1±2.6
Distribution — no. (%)					
5–9, indicating severe Alzheimer's disease	39 (53)	39 (51)	38 (52)	38 (52)	154 (52)
10–13, indicating moderate Alzheimer's disease	34 (47)	37 (49)	35 (48)	35 (48)	141 (48)
BADLS score§	28.6±8.9	27.1±9.0	28.2±9.0	26.9±9.8	27.7±9.2
NPI score¶	22.9±17.0	23.1±16.2	22.3±16.7	20.3±14.4	22.2±16.1
DEMQOL-Proxy score‖	101.4±11.7	96.5±15.3	98.3±13.5	100.9±12.9	99.3±13.5
GHQ-12 score**	2.8±3.1	3.1±3.1	2.3±2.3	1.8±2.3	2.5±2.8

* Plus–minus values are means ±SD. Apart from two missing General Health Questionnaire 12 (GHQ-12) scores (one for a caregiver of a patient who discontinued donepezil and received placebo memantine and one for a caregiver of a patient who discontinued donepezil and received active memantine), scores were available for all 295 enrolled patients at baseline. There were no significant differences among the groups for any of the baseline characteristics, with the exception of the total GHQ-12 score (P=0.03).
† Race was determined by the investigator.
‡ Scores on the Standardized Mini–Mental State Examination (SMMSE) range from 0 to 30, with higher scores indicating better cognitive function. Because of eligibility criteria, the scores for patients in this trial were between 5 and 13.
§ Scores on the Bristol Activities of Daily Living Scale (BADLS) range from 0 to 60, with higher scores indicating greater functional impairment.
¶ Scores on the Neuropsychiatric Inventory (NPI) range from 0 to 144, with higher scores indicating increased behavioral and psychological symptoms.
‖ Scores on the DEMQOL-Proxy range from 31 to 134, with higher scores indicating better patient health-related quality of life.
** Scores on the GHQ-12, which measures caregiver health status, range from 0 to 12, with higher scores indicating increased psychological symptoms in informal caregivers.

clinically important difference. This reflects the average effect among patients assigned to continue donepezil as well as among those assigned to discontinue donepezil. The interactions of memantine therapy with visit were not significant. For both donepezil and memantine, the benefits with respect to scores on the SMMSE and the BADLS appeared to be larger in the absence of the other agent than in the presence of the other agent (Table S4 in the Supplementary Appendix), but these differences were not significant (P=0.14 and P=0.09, respectively, for the tests for interac-

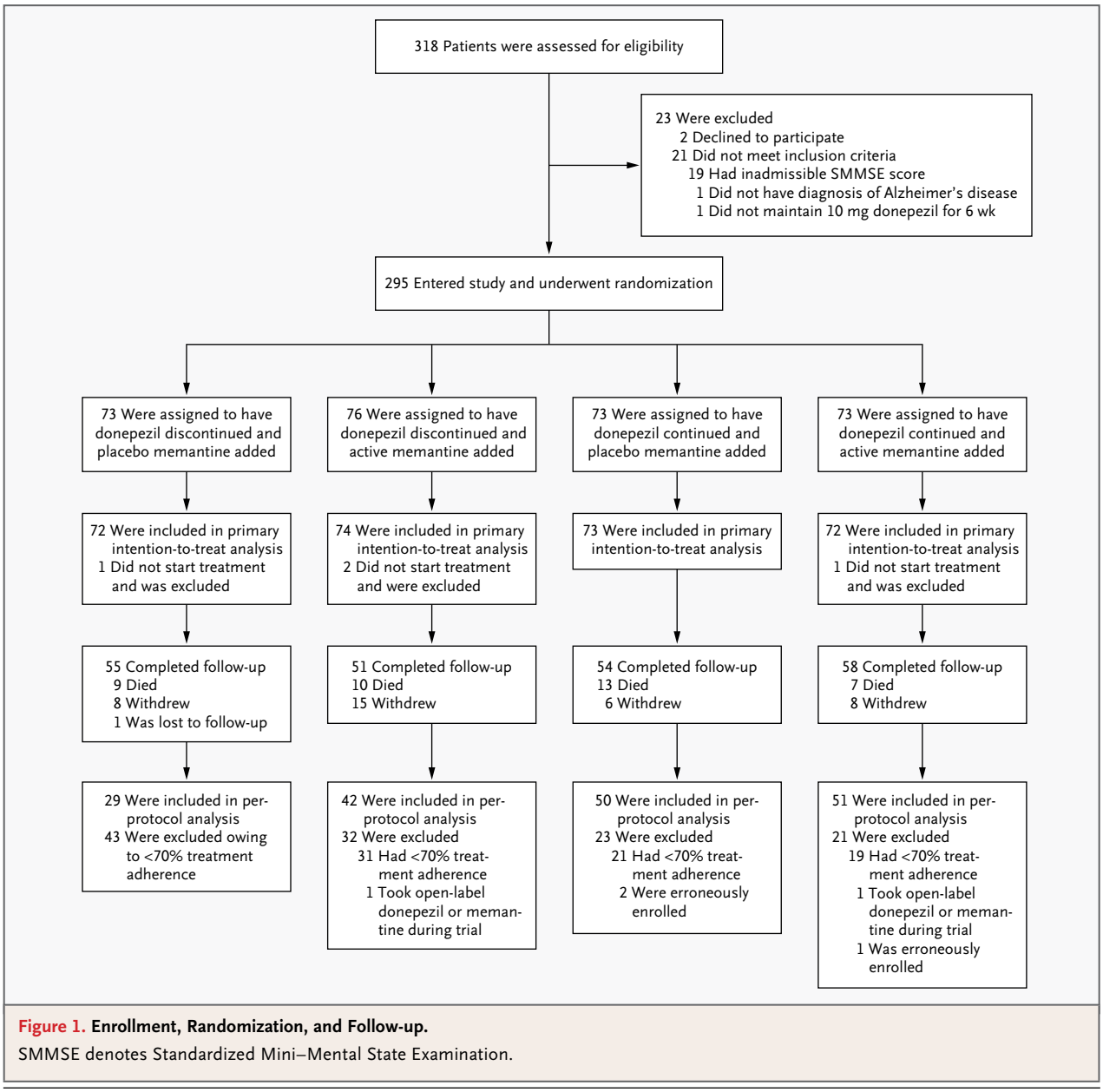
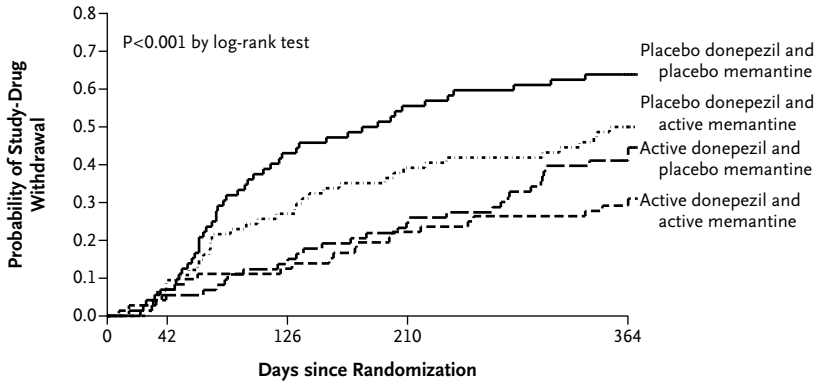


Figure 1. Enrollment, Randomization, and Follow-up.
SMMSE denotes Standardized Mini–Mental State Examination.

tion). There was no significant benefit of adding memantine to donepezil, with respect to scores on the SMMSE (0.8 points higher with memantine than with placebo; 95% CI, −0.1 to 1.6; P=0.07) or with respect to scores on the BADLS (0.5 points lower with memantine than with placebo; 95% CI, −2.2 to 1.2; P=0.57).

The severity of dementia at entry significantly influenced the effect of donepezil on SMMSE scores, with larger benefits observed in patients with moderate disease (SMMSE score, 10 to 13) than in those with severe disease (SMMSE score, 5 to 9). The average difference in scores between the groups assigned to continue donepezil and the groups assigned to discontinue donepezil was 2.6 points (95% CI, 1.5 to 3.7) among patients with moderate disease (P<0.001) and 1.3 points (95% CI, 0.2 to 2.4) among patients with severe disease (P=0.02). Because we undertook several tests for interaction, this difference according to the severity of dementia, which was only moderately significant, may have arisen by chance and needs to be confirmed, particularly since the severity of dementia did not have a significant effect on the difference in the BADLS score that was observed with continued, as compared with dis-



No. of Patients Still Receiving Study Drug					
Placebo donepezil and placebo memantine	72	67	41	32	20
Placebo donepezil and active memantine	74	67	54	45	27
Active donepezil and placebo memantine	73	69	63	55	34
Active donepezil and active memantine	72	68	63	56	38

Figure 2. Kaplan–Meier Actuarial Plot of the Cumulative Probability of Withdrawal from the Assigned Study Drug.
The table below the graph shows the number of patients still receiving the study drug at each time point (corresponding to the usual visit dates).

continued, donepezil therapy or on the differences in SMMSE or BADLS scores observed with memantine therapy, as compared with placebo.

SECONDARY OUTCOME MEASURES

Patients who received memantine, as compared with those who received placebo memantine, had scores on the NPI that were lower (indicating fewer behavioral and psychological symptoms) by an average of 4.0 points (99% CI, 0.6 to 7.4; P=0.002), representing a smaller benefit than the minimum clinically important difference. We did not observe a significant difference in scores on the NPI with the continuation, as compared with the discontinuation, of donepezil therapy (2.3 points lower with continuation; 95% CI, −1.1 to 5.7; P=0.08). The addition of memantine to donepezil, as compared with the addition of placebo memantine to donepezil, resulted in a decrease in the NPI score that was greater by 5.1 points (99% CI, 0.3 to 9.8; P=0.006). In contrast with results on the SMMSE and BADLS, for both donepezil and memantine, the benefits with respect to the NPI score appeared to be larger in the presence of the other agent than in the absence of the other agent (Table S4 in the Supplementary Appendix), but these differences were not significant (P=0.42). Both continuation of donepezil therapy, as compared with discontinuation, and memantine therapy, as compared with placebo, resulted in larger average decreases (indicating fewer psychological symptoms) across trial visits in GHQ-12 scores for caregiver health status (a 0.5-point larger decrease with continuation vs. discontinuation of donepezil; 99% CI, −0.01 to 1.0; P=0.01; and a 0.5-point larger decrease with memantine vs. placebo; 95% CI, −0.1 to 0.9; P=0.03); however, the differences did not reach significance, which was defined at P<0.01 to allow for multiple secondary outcome measures.

SENSITIVITY ANALYSES

Patients who withdrew from treatment after the 18-week visit or after the 30-week visit had a lower score on the SMMSE and a higher score on the BADLS at their last visit before withdrawal than did those who continued treatment (Table S3 in the Supplementary Appendix). Patients who withdrew at any point during the study had lower SMMSE scores and higher BADLS scores after withdrawal than did those who continued to receive treatment. Of the 137 patients who withdrew from treatment before the end of the trial, 64 (47%) attended the 52-week visit (with 1 patient missing the SMMSE assessment). A number of sensitivity

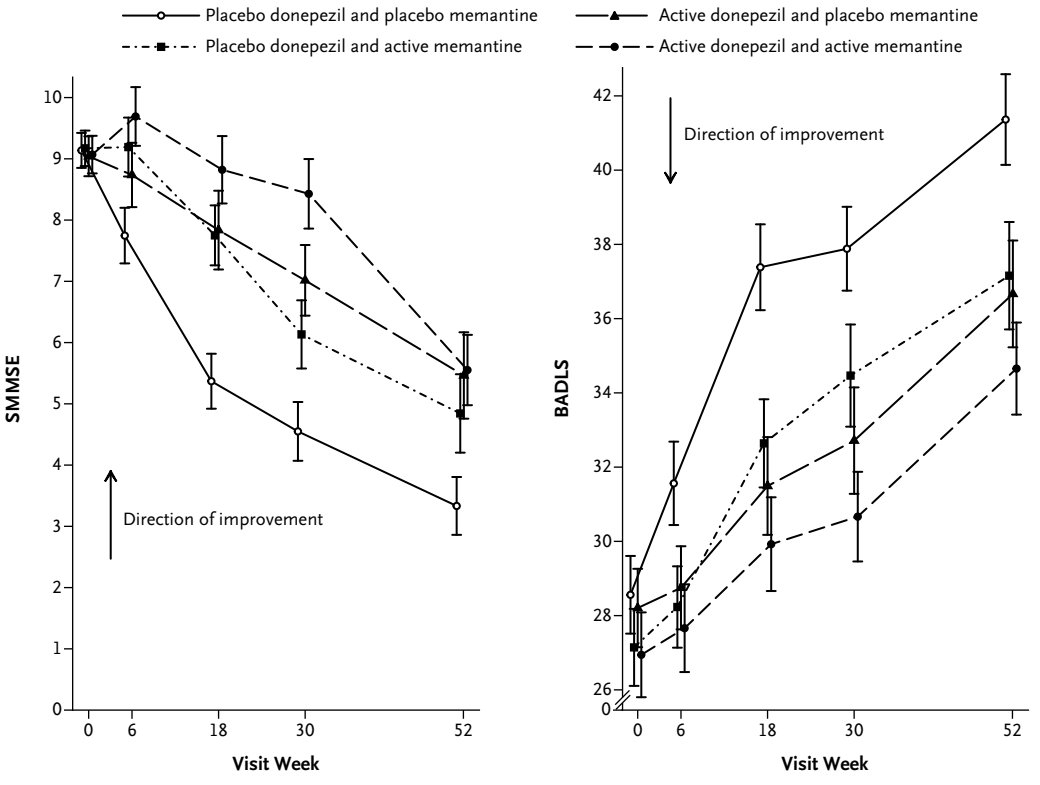


Figure 3. Mean Scores on the Standardized Mini–Mental State Examination (SMMSE) and the Bristol Activities of Daily Living Scale (BADLS), According to Visit Week and Treatment Group.

Scores on the SMMSE range from 0 to 30, with higher scores indicating better cognitive function; scores on the BADLS range from 0 to 60, with higher scores indicating greater impairment. Shown are raw estimates of the mean score at each visit. I bars denote the standard error.

analyses were conducted to assess the effect of treatment withdrawal and missing outcome assessments on the results. The results of the sensitivity analyses were broadly similar to those of the primary analysis (see Table S3 in the Supplementary Appendix).

SAFETY

A total of 188 serious adverse events were reported, of which 6 (2 in the group receiving placebo donepezil and placebo memantine, 2 in the group receiving memantine and placebo donepezil, and 2 in the group receiving donepezil and memantine) were considered to be possibly related to the study drugs. None were considered to be unexpected serious adverse reactions. There was no evidence that the incidence of serious adverse events or death differed according to treatment group (P=0.77). Details of the serious adverse events and deaths in all treatment groups are provided in Table S5 in the Supplementary Appendix.

DISCUSSION

This double-blind, placebo-controlled trial involving community-living patients with moderate or severe Alzheimer's disease who were already receiving treatment with a cholinesterase inhibitor showed that there were modest cognitive and functional benefits of continuing donepezil over the course of 12 months. The difference in scores on the SMMSE between those who continued donepezil and those who discontinued it exceeded the prespecified minimum clinically important difference of 1.4 points, but the difference in scores on the BADLS was less than the minimum clinically important difference of 3.5 points. The initiation of memantine therapy was also associated with sig-

Table 2. Estimate of Treatment Differences in Primary and Secondary Outcome Measures.*

Outcome	Overall Difference (95% or 99% CI)	P Value for Interaction		Difference at Each Assessment (99% CI)			
		Between Donepezil and Memantine	With Visit Week	Week 6	Week 18	Week 30	Week 52
SMMSE		0.14					
No. of patients with scores				284	263	246	217
Continued vs. discontinued donepezil	1.9 (1.3 to 2.5)		0.002	1.0 (0.1 to 2.0)	2.0 (1.0 to 3.1)	2.6 (1.6 to 3.7)	1.9 (0.7 to 3.1)
Active vs. placebo memantine	1.2 (0.6 to 1.8)		0.24	1.0 (0.1 to 1.9)	1.5 (0.5 to 2.5)	1.5 (0.5 to 2.6)	0.7 (–0.5 to 2.0)
BADLS		0.09					
No. of patients with scores				284	263	246	218
Continued vs. discontinued donepezil	–3.0 (–4.3 to –1.8)		0.004	–1.4 (–3.0 to 0.2)	–4.0 (–6.2 to –1.9)	–3.9 (–6.3 to –1.5)	–2.9 (–5.6 to –0.1)
Active vs. placebo memantine	–1.5 (–2.8 to –0.3)		0.28	–0.6 (–2.3 to 1.0)	–2.0 (–4.2 to 0.1)	–1.9 (–4.3 to 0.5)	–2.0 (–4.7 to 0.8)
NPI		0.42					
No. of patients with scores				283	262	246	217
Continued vs. discontinued donepezil	–2.3 (–5.7 to 1.1)		0.08	–2.3 (–5.8 to 1.1)	–4.9 (–9.8 to 0.1)	–2.7 (–7.4 to 2.0)	0.3 (–5.8 to 6.3)
Active vs. placebo memantine	–4.0 (–7.4 to –0.6)		0.14	–2.9 (–6.4 to 0.5)	–1.9 (–6.9 to 3.1)	–5.6 (–10.3 to –0.9)	–5.7 (–11.8 to 0.4)
DEMQOL-Proxy		0.54					
No. of patients with scores					263		218
Continued vs. discontinued donepezil	–1.6 (–4.7 to 1.4)		0.39	Not assessed	–1.1 (–4.6 to 2.4)	Not assessed	–2.4 (–6.4 to 1.6)
Active vs. placebo memantine	1.3 (–1.8 to 4.3)		0.33	Not assessed	1.9 (–1.6 to 5.4)	Not assessed	0.5 (–3.6 to 4.5)
GHQ-12		0.94					
No. of patients with scores				282		236	197
Continued vs. discontinued donepezil	–0.5 (–1.0 to 0.01)		0.89	–0.5 (–1.2 to 0.1)	Not assessed	–0.5 (–1.3 to 0.4)	–0.7 (–1.7 to 0.3)
Active vs. placebo memantine	–0.5 (–0.9 to 0.1)		0.35	–0.3 (–1.0 to 0.4)	Not assessed	–0.8 (–1.6 to 0.0)	–0.3 (–1.3 to 0.7)

* The scores on the SMMSE and BADLS were primary outcome measures, and the scores on the NPI, DEMQOL-Proxy, and GHQ-12 were secondary outcome measures. The overall difference across all visits is shown with 95% confidence intervals for the primary outcomes only; all other differences (overall for the secondary outcomes and at individual assessments for all outcomes) are at the 99% level. Data for continuation of donepezil as compared with discontinuation are average values across patients who received active memantine and those who received placebo memantine. Data for active memantine as compared with placebo are average values across patients who continued donepezil and those who discontinued donepezil.

nificantly better cognition and function, although the magnitude of the benefit was smaller than it was with donepezil and the differences between patients who received memantine and those who received placebo were smaller than the predefined minimum clinically important difference. Memantine, as compared with placebo, was associated with the emergence of fewer behavioral symptoms as measured by the NPI, but the difference did not reach the minimum clinically important difference. Combined treatment with donepezil and memantine was not significantly superior to treatment with donepezil alone with respect to any of the primary or secondary outcomes.

The improvements in cognition and function associated with donepezil and memantine were small relative to the overall size of the decline in cognitive and functional status that was seen in all patients. Although the cognitive benefit associated with donepezil therapy exceeded a distribution-based minimum clinically important difference,[26,27] the cognitive benefits associated with memantine treatment were smaller and did not reach the minimum clinically important difference. The cognitive benefit associated with continuing donepezil was equivalent to 32%, and that associated with starting memantine was equivalent to 20%, of the total deterioration (a decrease of 5.8 SMMSE points) over the course of 12 months[28,29] that was seen in the group discontinuing donepezil and receiving placebo memantine. The functional benefits of continuing donepezil were equivalent to 23%, and those of starting memantine were equivalent to 11%, of the deterioration (an increase of 12.8 BADLS points) seen over the course of 12 months in the group discontinuing donepezil and receiving placebo memantine (Fig. 3). Memantine treatment was associated with a significantly smaller worsening of NPI scores, an observation that is consistent with the findings in another study,[30] with a benefit that was equivalent to 83% of the 12-month deterioration (4.8 NPI points) seen in the group discontinuing donepezil and receiving placebo memantine.

In this study, patients who discontinued donepezil did not have abrupt withdrawal phenomena,[31] but withdrawal from the study drug was significantly more common among participants assigned to discontinue donepezil and receive placebo donepezil than among those assigned to continue donepezil, with the majority of withdrawals occurring between week 6 and week 18 (Fig. 2). Modest reductions in caregivers' psychological symptoms that were seen with donepezil or memantine did not reach statistical significance but, considered together with lower rates of withdrawal, suggest the possibility that caregivers who live with patients perceived treatment benefits.

Participants were recruited from National Health Service clinics across England and Scotland and were representative of patients with Alzheimer's disease who were treated with cholinesterase inhibitors. Despite difficulties with recruitment, we detected significant benefits of continued donepezil therapy with respect to cognitive and functional outcomes ($P<0.001$), which was the first objective of our study. With respect to our second objective, the benefits of starting memantine were smaller than the benefits of continuing donepezil, but they were significant at the $P<0.05$ level. With respect to our third objective, determining whether the combination of donepezil and memantine treatment showed additive benefits, we did not find significant heterogeneity in the efficacy of donepezil or memantine in the presence or absence of the other drug. Subgroup analyses, however, failed to show significant benefits of adding memantine to donepezil treatment.

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