

The NEW ENGLAND JOURNAL of MEDICINE

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D., Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D., Christopher H. van Dyck, M.D., and Leon J. Thal, M.D., for the Alzheimer's Disease Cooperative Study Group*

ABSTRACT

BACKGROUND

Mild cognitive impairment is a transitional state between the cognitive changes of normal aging and very early Alzheimer's disease.

METHODS

In a double-blind study, we evaluated subjects with the amnesic subtype of mild cognitive impairment. Subjects were randomly assigned to receive 2000 IU of vitamin E daily, 10 mg of donepezil daily, or placebo for three years. The primary outcome was clinically possible or probable Alzheimer's disease; secondary outcomes were cognition and function.

RESULTS

A total of 769 subjects were enrolled, and possible or probable Alzheimer's disease developed in 212. The overall rate of progression from mild cognitive impairment to Alzheimer's disease was 16 percent per year. As compared with the placebo group, there were no significant differences in the probability of progression to Alzheimer's disease in the vitamin E group (hazard ratio, 1.02; 95 percent confidence interval, 0.74 to 1.41; $P=0.91$) or the donepezil group (hazard ratio, 0.80; 95 percent confidence interval, 0.57 to 1.13; $P=0.42$) during the three years of treatment. Prespecified analyses of the treatment effects at 6-month intervals showed that as compared with the placebo group, the donepezil group had a reduced likelihood of progression to Alzheimer's disease during the first 12 months of the study ($P=0.04$), a finding supported by the secondary outcome measures. Among carriers of one or more apolipoprotein E $\epsilon 4$ alleles, the benefit of donepezil was evident throughout the three-year follow-up. There were no significant differences in the rate of progression to Alzheimer's disease between the vitamin E and placebo groups at any point, either among all patients or among apolipoprotein E $\epsilon 4$ carriers.

CONCLUSIONS

Vitamin E had no benefit in patients with mild cognitive impairment. Although after three years, the rate of progression to Alzheimer's disease was not lower among patients treated with donepezil than among those given placebo, donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first 12 months of treatment.

From the Mayo Clinic College of Medicine, Rochester, Minn. (R.C.P.); University of California, San Diego, San Diego (R.G.T., D.G., S.J., L.J.T.); Elan Pharmaceuticals, San Diego, Calif. (M.G.); Rush University Medical School, Chicago (D.B.); Baylor College of Medicine, Houston (R.D.); New York University, New York (S.F.); Oregon Health and Science University, Portland (J.K.); Emory University, Atlanta (A.L.); University of South Florida, Tampa (E.P.); Mt. Sinai School of Medicine, New York (M.S.); and Yale University, New Haven, Conn. (C.H.D.). Address reprint requests to Dr. Petersen at the Alzheimer's Disease Research Center, Mayo Clinic College of Medicine, 200 First St. SW, Rochester, MN 55905, or at peter8@mayo.edu.

*Members of the Alzheimer's Disease Cooperative Study (ADCS) Group are listed in the Appendix.

N Engl J Med 2005;352.

Copyright © 2005 Massachusetts Medical Society.

MILD COGNITIVE IMPAIRMENT REPRESENTS a transitional state between the cognitive changes of normal aging and the earliest clinical features of Alzheimer's disease.¹ Amnesic mild cognitive impairment refers to the subtype that has a primary memory component, either alone (single domain) or in conjunction with other cognitive-domain impairments (multiple domain), but of insufficient severity to constitute dementia.²⁻⁶ Previous research has shown that the rate of progression to clinically diagnosable Alzheimer's disease is 10 to 15 percent per year among persons who meet the criteria for the amnesic form of mild cognitive impairment, in contrast to a rate of 1 to 2 percent per year among normal elderly persons.⁷ Approximately 80 percent of those who meet the criteria for amnesic mild cognitive impairment will have Alzheimer's disease within six years, and the presence of one or more apolipoprotein (APOE) ϵ 4 alleles is associated with a more rapid rate of progression.^{8,9} Thus, preventing the progression of mild cognitive impairment to Alzheimer's disease is likely to provide substantial benefit.

Oxidative damage accompanies Alzheimer's disease, and cholinesterase inhibitors are recommended for use in mild-to-moderate Alzheimer's disease.¹⁰ The Alzheimer's Disease Cooperative Study (ADCS)¹¹ showed that treatment with the antioxidant vitamin E could delay the time to important milestones in patients with moderately severe Alzheimer's disease. The present study was designed to determine whether treatment with vitamin E or donepezil, the most widely used cholinesterase inhibitor available at the time the study was designed, could delay the clinical diagnosis of Alzheimer's disease in subjects with the amnesic form of mild cognitive impairment.

METHODS

PARTICIPANTS

We enrolled 769 subjects from 69 ADCS sites in the United States and Canada.¹² The criteria for inclusion were amnesic mild cognitive impairment of a degenerative nature (insidious onset and gradual progression),⁷ impaired memory, a Logical Memory delayed-recall score approximately 1.5 to 2 SD below an education-adjusted norm, a Clinical Dementia Rating (CDR) of 0.5, a score of 24 to 30 on the Mini-Mental State Examination (MMSE), and an age of 55 to 90 years. Detailed inclusion and ex-

clusion criteria are presented in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

STUDY DESIGN

In this multicenter, randomized, double-blind, placebo-controlled, parallel-group study which was conducted between March 1999 and January 2004, subjects with amnesic mild cognitive impairment were randomly assigned to receive 2000 IU of vitamin E, placebo donepezil, and a multivitamin daily; 10 mg of donepezil, placebo vitamin E, and a multivitamin daily; or placebo vitamin E, placebo donepezil, and a multivitamin daily. The multivitamin contained 15 IU of vitamin E. The initial dose of donepezil was 5 mg daily, and the dose was increased to 10 mg after six weeks. The initial dose of vitamin E was 1000 IU daily, and the dose was increased to 2000 IU (1000 IU twice daily) after six weeks. If a subject had difficulty tolerating the higher dose of vitamin E or donepezil, the investigator could reduce the dose of either medication temporarily and then rechallenge with the higher dose.

We used an adaptive allocation scheme for the treatment assignment, with the MMSE score, age, and APOE ϵ 4 status as balancing covariates. The study was designed by the mild cognitive impairment protocol committee of the ADCS and was executed and analyzed by the ADCS investigators. Fifty percent of the funding was provided by the National Institute on Aging, with the other 50 percent coming from Pfizer and Eisai. Pfizer and Eisai served in an advisory capacity for the study, but final decisions concerning all phases of the study were made by the ADCS investigators. The study was conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki, and the U.S. Code of Federal Regulations title 21 Part 50 (Protection of Human Subjects) and title 21 Part 56 (Institutional Review Boards). Written informed consent was obtained from all participants and study partners who had knowledge of the participants' functional activities. A data and safety monitoring board reviewed the blinded safety data every three months during the trial.

EFFICACY MEASURES

The primary end point was the time to the development of possible or probable Alzheimer's disease, defined according to the clinical criteria of the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's

Disease and Related Disorders Association.¹³ On verification by a central review committee that a participant met these clinical criteria for Alzheimer's disease, the participant stopped taking donepezil or matching placebo in a blinded fashion and was offered open-label donepezil until he or she completed the study at month 36.

Secondary measures were also assessed, including the scores for the MMSE; the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog); the global CDR; the CDR sum of boxes (the sum of individual CDR domain scores); the ADCS Mild Cognitive Impairment Activities of Daily Living Scale; the Global Deterioration Scale; and a neuropsychological battery consisting of the New York University paragraph-recall test, the Symbol Digit Modalities Test, the category-fluency test, a number-cancellation test, the Boston Naming Test, the digits-backward test, the clock-drawing test, and a maze-tracing task.^{12,14}

STATISTICAL ANALYSIS

The primary analysis was conducted according to the intention-to-treat principle in order to determine whether there was a significant reduction in the time to progression to Alzheimer's disease among subjects treated with either vitamin E or donepezil as compared with those given placebo. The Cox proportional-hazards model was used, and baseline variables (age, the MMSE score, and the APOE genotype) were included in the analysis as covariates. Two primary analyses were conducted, one comparing the vitamin E and placebo groups, and one comparing the donepezil and placebo groups. The Hochberg method¹⁵ was used to adjust the two P values for multiple comparisons. The Schoenfeld residuals test was used to test for nonproportional hazards.¹⁶ A z-test (the difference in the proportions divided by the standard error of the difference) was used to compare estimated survival rates at various points on the Kaplan–Meier curves (at 6, 12, 18, 24, 30, and 36 months). The Hochberg method was used to adjust the six P values for multiple comparisons.

Hazard ratios derived from the Cox analysis were used to compare the risk of progression in the donepezil or vitamin E group with that in the placebo group for the entire cohort and for the subgroup of APOE ϵ 4 carriers. In the 12- and 24-month analyses, data were censored at 388 and 749 days, respectively. The hazard-ratio analyses were secondary, and the resulting P values were not adjust-

ed for multiple comparisons. Baseline characteristics among the three groups were compared with the use of Wilcoxon's rank-sum test or Fisher's exact test, as appropriate. For the statistical evaluation of main effects, a P value of less than 0.05 was considered to indicate statistical significance, and for interaction effects, a P value of less than 0.10 was used.

The secondary outcomes were examined with the use of analysis of covariance for the change in scores without correction for multiple comparisons, and missing values were imputed with the use of a projection method appropriate for assessing responses among subjects with neurodegenerative diseases.¹⁷ As part of the secondary analyses, several cognitive-domain scores for memory (consisting of the ADAS immediate and delayed word-recall scores and the New York University immediate and delayed paragraph-recall scores), executive function (the digits-backward test, Symbol Digit Modalities Test, and number-cancellation test), language (the Boston Naming Test and category-fluency test), and visuospatial skills (the clock-drawing test) were calculated in addition to an overall composite cognitive-function score. The cognitive-domain and overall composite scores were calculated as the weighted sum of the individual standardized test scores. The individual test scores were standardized by dividing each score by the standard deviation of the baseline scores. Weights were calculated as the reciprocal of the sum of the correlation coefficients between the tests in each domain at baseline.

The annual rates of progression to dementia were calculated with the use of a life-table analysis. An analysis based on a logistic-regression model was conducted to determine whether missing data from subjects who were lost to follow-up were missing completely at random¹⁸ and, if so, could be ignored.

RESULTS

STUDY POPULATION

A total of 790 subjects underwent randomization, and 769 completed the baseline assessment. There were no significant differences among the three groups in baseline demographic or psychometric characteristics (Table 1).

PRIMARY OUTCOME MEASURES

A total of 214 participants had progression to dementia, with 212 being classified as having possi-

Table 1. Baseline Characteristics of the Subjects.*

Variable	Placebo Group (N=259)	Donepezil Group (N=253)	Vitamin E Group (N=257)	All Subjects (N=769)
Age — yr	72.9±7.6	73.1±7.1	72.8±7.3	72.9±7.3
Female sex — no. (%)	121 (47)	112 (44)	119 (46)	352 (46)
APOE ε4 carrier — no. (%)	136 (53)	147 (58)	141 (55)	424 (55)
ADAS-Cog score				
Original	11.03±4.2	11.28±4.5	11.48±4.4	11.26±4.4
Modified	17.40±6.0	17.72±6.2	18.04±6.0	17.72±6.1
MMSE score	27.35±1.8	27.25±1.8	27.20±1.9	27.27±1.8
CDR sum-of-boxes score	1.87±0.8	1.80±0.8	1.78±0.8	1.82±0.8
Score on Global Deterioration Scale	2.72±0.6	2.66±0.6	2.64±0.6	2.67±0.6
Score on Activities of Daily Living Scale	45.87±5.2	46.49±4.3	45.82±4.6	46.06±4.7

* Plus-minus values are means ±SD. A total of 2264 subjects were screened. The primary reason for exclusion was failure to meet cutoff scores for the Logical Memory paragraph. Scores for the original cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) can range from 0 to 70, and scores for the modified ADAS-Cog can range from 0 to 85, with higher scores indicating poorer function. Scores for the Mini-Mental State Examination (MMSE) can range from 0 to 30, with higher scores indicating better function. Scores for the Clinical Dementia Rating (CDR) sum of boxes can range from 0 to 18, with lower scores indicating better performance. Scores for the Global Deterioration Scale can range from 1 to 7, with higher scores indicating poorer function. Scores for the Activities of Daily Living Scale can range from 0 to 53, with higher scores indicating better function.

ble or probable Alzheimer's disease, 1 as having mixed dementia, and 1 as having primary progressive aphasia. The overall rate of progression to Alzheimer's disease was 16 percent per year.

During the three years of the trial, there were no significant differences in the probability of progression from mild cognitive impairment to Alzheimer's disease on the basis of the Cox analysis between the vitamin E group and the placebo group (hazard ratio, 1.02; 95 percent confidence interval, 0.74 to 1.41; $P=0.91$) or the donepezil group and the placebo group (hazard ratio, 0.80; 95 percent confidence interval, 0.57 to 1.13; $P=0.42$) (Fig. 1A). The Schoenfeld residuals global test of nonproportional hazards was significant ($P=0.001$ for the comparison of the donepezil group with the placebo group and $P=0.01$ for the comparison of the vitamin E group with the placebo group), indicating that the proportional-hazards assumption for the Cox model was not met. The 36-month analysis was therefore followed by a prespecified assessment of the treatment effects at each six-month evaluation point. This analysis showed that there were

no significant differences between the vitamin E and placebo groups at any time during the trial.

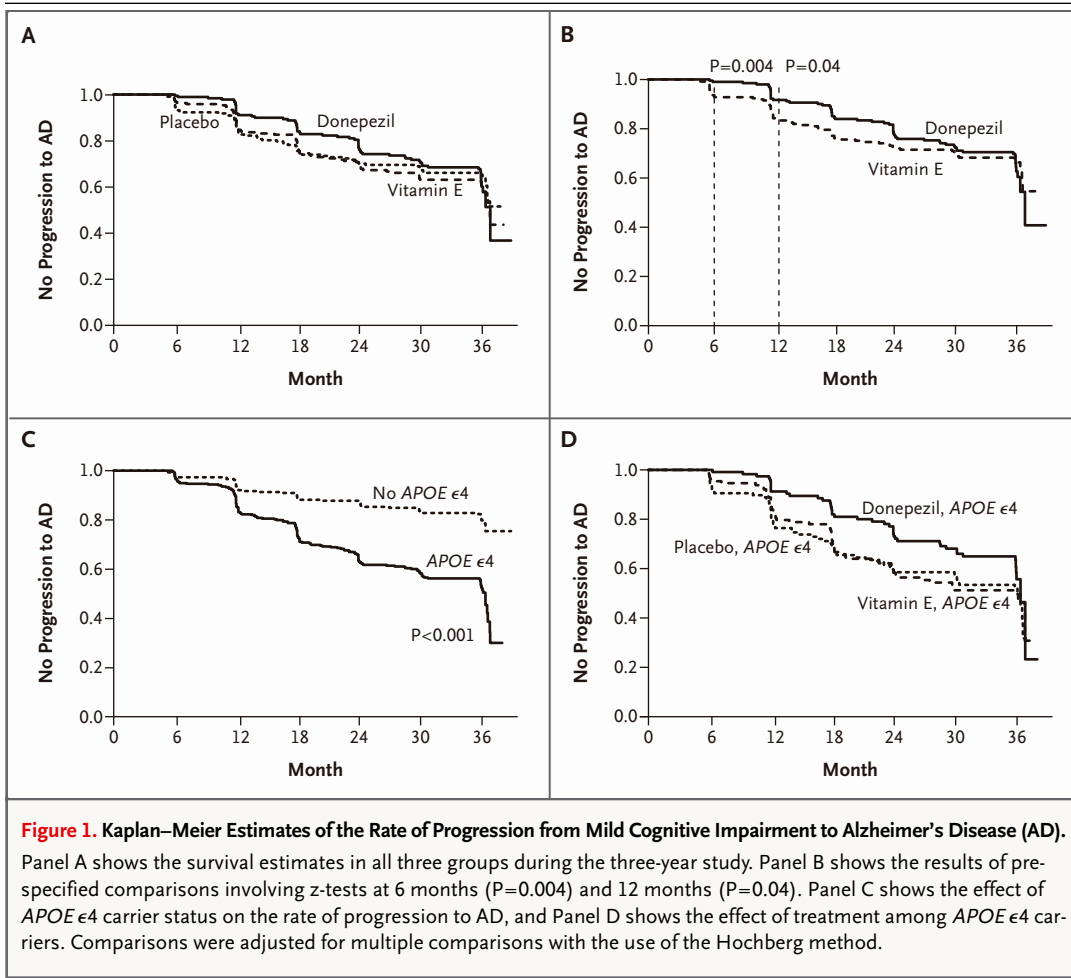
The risk of progression to Alzheimer's disease was lower in the donepezil group than in the placebo group for the first 12 months of the trial ($P=0.004$ at 6 months and $P=0.04$ at 12 months by a z -test adjusted for comparisons at multiple points) (Fig. 1B). A total of 38 subjects in the placebo group had progression to Alzheimer's disease in the first 12 months, as compared with 33 in the vitamin E group and 16 in the donepezil group. By 36 months, however, the numbers of subjects with progression to Alzheimer's disease did not differ significantly among the three groups: 73 in the placebo group, 76 in the vitamin E group, and 63 in the donepezil group. For the comparison that included all subjects, the hazard ratios for progression to Alzheimer's disease were lower in the donepezil group than the placebo group during year 1 ($P=0.004$) and during years 1 and 2 ($P=0.03$), but not during the entire three years of the study ($P=0.21$; P values not adjusted for comparisons at multiple points).

SECONDARY OUTCOME MEASURES

There were few significant differences in cognitive function from baseline between the vitamin E and placebo groups. The exceptions were in the scores for the executive, language, and overall cognitive scores, and these were confined to the first 18 months of the study. There were more differences in the change from baseline scores between the donepezil group and the placebo group, as shown in Table 2; they included the scores for the MMSE, CDR sum of boxes, Global Deterioration Scale, and modified ADAS-Cog, as well as memory, language, and overall cognitive scores, but with one exception, they were also confined to the first 18 months of the study.

APOE ε4 CARRIERS

Possession of the APOE ε4 allele was a major predictor of progression to Alzheimer's disease in all three groups, with 76 percent of the cases of progression to Alzheimer's disease occurring among APOE ε4 carriers ($P<0.001$) (Fig. 1C). There were 136 carriers in the placebo group, 147 in the donepezil group, and 141 in the vitamin E group (Table 1). The curves for the vitamin E and placebo groups separated slightly during the first year, then merged again ($P=0.77$) (Fig. 1D). In this secondary analysis, it was observed that the curves for the donepezil and placebo groups had separated by



six months and remained apart during the remainder of the trial ($P=0.04$), with donepezil treatment reducing the risk of progression to Alzheimer's disease by approximately one third at year 3 among subjects with one or more *APOE* $\epsilon 4$ alleles (Table 3).

OUTCOMES AND ADVERSE EVENTS

Adverse events in the donepezil group included muscle cramps, gastrointestinal symptoms, and sleep disturbances (Table 4). Twenty-three deaths occurred during the study (17 during the double-blind phase and 6 during the open-label phase), and all were judged to be unrelated to treatment. During the double-blind phase, seven subjects died in the donepezil group and five subjects died in each of the other two groups ($P=0.79$).

A total of 230 subjects discontinued treatment during the double-blind phase: 92 in the donepezil group, 72 in the vitamin E group, and 66 in the pla-

cebo group ($P=0.90$). Among the leading reasons for discontinuation besides death were adverse events in the case of 47 subjects and withdrawal of consent in the case of 105 subjects.

EFFECT OF MISSING DATA

To assess the effect of missing data, we compared the baseline values between the 230 subjects who withdrew during the double-blind phase and the 539 subjects who progressed to open-label treatment or completed the double-blind phase. There were no significant differences in demographic characteristics or neuropsychological measures. A contingency-table analysis of the number of subjects according to the treatment group and period of withdrawal indicated a trend toward more early dropouts (at the three- and six-month visits) in the donepezil group than in the placebo group ($P=0.07$). The results of an evaluation of the assumption that the missing data were missing com-

Table 2. Changes from Baseline in Cognitive and Functional Measures.*

Test	Change in Score from Baseline					
	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo
Cognitive and functional measures						
MMSE						
Donepezil	0.06±2.03†	-0.31±2.25‡	-0.52±2.46‡	-0.98±2.54‡	-1.47±3.04	-2.31±3.72
Vitamin E	-0.53±2.28	-0.54±2.28	-0.96±2.61	-1.21±2.78	-1.75±3.09	-2.20±3.64
Placebo	-0.36±2.02	-0.80±2.34	-1.02±2.61	-1.49±2.90	-1.77±3.24	-2.75±4.04
Activities of Daily Living Scale						
Donepezil	-0.21±3.43	-1.41±4.48	-1.78±5.02	-3.09±6.24	-4.44±7.39	-6.26±8.67
Vitamin E	-0.34±4.29	-1.08±4.90	-2.13±5.76	-2.84±6.16	-4.16±7.46	-5.63±8.75
Placebo	-1.06±4.54	-1.44±5.00	-2.34±6.02	-3.43±6.73	-5.00±8.05	-6.39±8.99
CDR sum of boxes						
Donepezil	0.05±0.66	0.25±0.92‡	0.51±1.18‡	0.87±1.55	1.19±1.69	1.60±2.09
Vitamin E	0.17±0.70	0.51±1.21	0.75±1.44	1.02±1.76	1.26±1.89	1.67±2.18
Placebo	0.14±0.86	0.40±1.28	0.72±1.55	0.97±1.76	1.26±2.15	1.64±2.55
Global Deterioration Scale						
Donepezil	-0.01±0.52†	0.11±0.57	0.19±0.66‡	0.32±0.73	0.45±0.78	0.59±0.89
Vitamin E	0.11±0.49	0.21±0.61	0.27±0.73	0.42±0.80	0.51±0.85	0.64±0.96
Placebo	0.07±0.53	0.15±0.65	0.27±0.73	0.38±0.81	0.48±0.87	0.56±0.99
ADAS-Cog (original)						
Donepezil	-0.61±3.79	0.17±3.73	1.08±4.37	1.22±4.79	2.71±5.21	3.68±5.95
Vitamin E	-0.16±4.19	0.91±4.21	1.19±4.32	1.93±5.13	3.01±5.57	4.59±6.54
Placebo	-0.13±3.34	0.61±4.10	1.29±4.71	1.49±5.07	2.98±5.62	3.74±6.97
ADAS-Cog (modified)						
Donepezil	-1.23±4.74†	-0.55±5.20‡	0.03±5.64‡	0.35±6.23	2.05±6.74	3.12±7.39
Vitamin E	-0.47±5.06	0.27±5.20	0.49±5.42	1.15±6.37	2.48±6.68	3.98±7.56
Placebo	-0.09±4.38	0.60±4.96	0.99±6.07	1.02±6.27	2.65±7.02	3.72±8.54

pletely at random demonstrated that cognitive scores for the MMSE and the ADAS-Cog and total score for the CDR sum of boxes at each visit were predictive of withdrawal before the next visit, indicating that the missing observations cannot be ignored. To assess the z-test results, we conducted a sensitivity analysis consisting of simulations in which the subjects in the donepezil group who dropped out in the first 12 months were randomly divided into two groups: a group of 40 to match the number of dropouts in the placebo group during this period and a group of 24 excess dropouts. A proportion of the 24 excess dropouts was then selected at random and assumed to have had progression to Alzheimer's disease. That proportion was set at the conservative level of double the rate in the group of subjects who completed the study. This analysis included six excess progression events.

In these analyses, the 6- and 12-month z-test results remained significant in favor of the donepezil group over the placebo group. The results at all other times were nonsignificant. Similar analyses were performed for the vitamin E and placebo groups, and the results were uniformly nonsignificant.

DISCUSSION

Over the three years of the study, there were no significant differences in the probability of progression to Alzheimer's disease between either the vitamin E or the donepezil group and the placebo group. However, since the effect of treatments varied during the three years of the trial and assumptions for the primary-analysis model were not met, prespecified group comparisons were carried out at each of the six-month evaluations. These analy-

Table 2. (Continued.)*

Test	Change in Score from Baseline					
	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo
Cognitive domains §						
Memory						
Donepezil	0.01±0.51†	0.00±0.57	-0.03±0.57‡	-0.07±0.59	-0.32±0.60	-0.26±0.60
Vitamin E	-0.10±0.48	-0.08±0.49	-0.12±0.55	-0.12±0.57	-0.43±0.55	-0.31±0.59
Placebo	-0.17±0.47	-0.10±0.51	-0.15±0.52	-0.11±0.55	-0.34±0.55	-0.28±0.62
Executive						
Donepezil	0.09±0.36	0.11±0.40	0.03±0.42	-0.01±0.45	-0.06±0.46	-0.16±0.48
Vitamin E	0.11±0.41‡	0.04±0.41	0.00±0.42	0.03±0.45	0.00±0.47	-0.19±0.48
Placebo	0.04±0.42	0.05±0.44	-0.02±0.45	0.01±0.48	-0.08±0.51	-0.19±0.53
Language						
Donepezil	0.09±0.24†	0.04±0.22‡	0.04±0.24†	-0.03±0.25	-0.06±0.29	-0.11±0.32
Vitamin E	0.07±0.23‡	0.05±0.26‡	0.02±0.28‡	-0.03±0.31	-0.05±0.33	-0.10±0.35
Placebo	0.03±0.23	0.00±0.24	-0.03±0.24	0.00±0.27	-0.04±0.28	-0.08±0.33
Visuospatial						
Donepezil	0.00±0.32	0.00±0.32	-0.05±0.32	-0.06±0.35	-0.14±0.35	-0.14±0.34
Vitamin E	0.03±0.34	-0.01±0.35	-0.02±0.33	-0.04±0.34	-0.07±0.36	-0.12±0.37
Placebo	-0.01±0.34	0.02±0.32	-0.04±0.36	-0.06±0.39	-0.09±0.39	-0.11±0.39
Overall						
Donepezil	0.18±0.82†	0.15±0.92‡	0.01±0.96†	-0.16±1.03	-0.59±1.18	-0.67±1.24
Vitamin E	0.10±0.81†	0.00±0.90	-0.13±0.94	-0.16±1.07	-0.54±1.14	-0.70±1.21
Placebo	-0.12±0.80	-0.03±0.86	-0.24±0.96	-0.15±1.09	-0.53±1.17	-0.65±1.35

* Scores for the Mini-Mental State Examination (MMSE) can range from 0 to 30, with higher scores indicating better function. Scores for the Activities of Daily Living Scale can range from 0 to 53, with higher scores indicating better function. Scores for the Clinical Dementia Rating (CDR) sum of boxes can range from 0 to 18, with lower scores indicating better performance. Scores for the Global Deterioration Scale can range from 1 to 7, with higher scores indicating poorer function. Scores for the original cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) can range from 0 to 70, and scores for the modified ADAS-Cog can range from 0 to 85, with higher scores indicating poorer function.

† P<0.01 for the comparison with the baseline value.

‡ P<0.05 for the comparison with the baseline value.

§ The values for the cognitive-domain measures (memory, executive, language, and visuospatial) are standardized composite z scores, with positive numbers indicating improvement. The overall cognitive score was based on the four domain scores and computed as explained in the Methods section.

ses demonstrated that vitamin E had no significant effect during the trial with respect to the development of Alzheimer's disease at any time. The analysis for donepezil, however, demonstrated a reduced likelihood of progression to Alzheimer's disease in the donepezil group, as compared with the placebo group, for the first 12 months of the trial.

These results suggest that donepezil treatment may delay clinical progression to Alzheimer's disease but do not address the question of the underlying mechanism. As shown in Table 2, the overall cognitive function of the subjects with mild cognitive impairment in the donepezil group did not decline on most of the measures during the first

6 to 18 months of the study and thereafter declined at about the same rate as in the placebo group. As a result, the size of the donepezil-placebo treatment effect on the MMSE score was about 0.5 point throughout the 36-month trial. This delay in cognitive decline probably contributed to the slower rate of progression to Alzheimer's disease in the donepezil group. The observed relative reduction in the risk of progression to Alzheimer's disease of 58 percent at one year and 36 percent at two years in the entire cohort is likely to be clinically significant. Although our findings do not provide support for a clear recommendation for the use of donepezil in persons with mild cognitive impairment, they

Table 3. Hazard Ratios for the Risk of Progression to Alzheimer's Disease in the Donepezil and Vitamin E Groups as Compared with the Placebo Group.*

Interval	All Subjects		APOE ϵ 4 Carriers	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Donepezil vs. placebo				
First 12 mo	0.42 (0.24–0.76)	0.004	0.34 (0.16–0.69)	0.003
First 24 mo	0.64 (0.44–0.95)	0.03	0.54 (0.35–0.86)	0.009
All 36 mo	0.80 (0.57–1.13)	0.21	0.66 (0.44–0.98)	0.04
Vitamin E vs. placebo				
First 12 mo	0.83 (0.52–1.32)	0.43	0.78 (0.46–1.34)	0.37
First 24 mo	0.95 (0.67–1.36)	0.79	0.95 (0.64–1.41)	0.79
All 36 mo	1.02 (0.74–1.41)	0.91	0.95 (0.66–1.36)	0.77

* CI denotes confidence interval. P values were not adjusted for multiple comparisons. In the donepezil group, when corrected for multiple comparisons, the P value at 24 months for all subjects became nonsignificant (P=0.052), and the P value at 36 months for APOE ϵ 4 carriers also became nonsignificant (P=0.078).

could prompt a discussion between the clinician and the patient about this possibility.

We also found that amnesic mild cognitive impairment and the presence of one or more APOE ϵ 4 alleles were highly predictive of progression to Alzheimer's disease. Of the 214 diagnoses of dementia, 212 were possible or probable Alzheimer's disease, with 76 percent of the cases of progression to Alzheimer's disease occurring among APOE ϵ 4 carriers. The results show that the enrollment criteria for amnesic mild cognitive impairment were highly specific. Furthermore, this study replicated observational studies demonstrating a rate of progression from mild cognitive impairment to Alzheimer's disease of 10 to 15 percent per year.^{5,7}

Treatment with vitamin E and donepezil did not produce any unexpected side effects. No episodes of bleeding occurred in the vitamin E group. There were more discontinuations in the donepezil group than in the other two groups, as would be expected from its known side-effect profile.^{10,19} Most discontinuations were related to gastrointestinal side effects, sleep disturbances, and muscle cramps. There were slightly more deaths in the donepezil group, but the number was not out of proportion to the number expected among subjects in this age group and was not significantly different from the numbers in the vitamin E and placebo groups.

We used numerous secondary measures, and in general, they appeared to corroborate the overall outcome data concerning the rate and risk of progression from mild cognitive impairment to Alzheimer's disease. Results for language and the

overall composite measure showed some effect of vitamin E therapy, but they were of insufficient magnitude to affect the overall performance of the group. In the donepezil group, the results for memory, language, the overall composite measure, and global measures of cognition, disease severity, and stage of dementia paralleled the overall treatment effect of the drug on the risk of progression to Alzheimer's disease.

Table 4. Adverse Events.*

Adverse Event	Donepezil Group	Vitamin E Group	Placebo Group
	<i>percent</i>		
Diarrhea	16.7†	10.2	6.6
Muscle cramps	16.3†	1.2	1.9
Insomnia	10.8†	3.1	1.9
Nausea	8.4†	1.2	1.9
Abnormal dreams	6.8†	0.4	1.6
Bronchitis	6.4	2.4	3.1
Loose stools	6.0‡	2.7	1.6
Vomiting	6.0‡	2.7	1.9
Arthritis	5.2‡	2.0	1.6
Cataract extraction	4.8	5.9	2.7

* The rates are for adverse events that occurred in at least 5 percent of subjects in the donepezil or vitamin E group and at least two times in the placebo group during the double-blind phase.

† P<0.01 for the comparison with the placebo group.

‡ P<0.05 for the comparison with the placebo group.

A major modifying effect of the comparison of donepezil with placebo was the *APOE* ϵ 4 carrier status. Most of the treatment effect of donepezil occurred among the *APOE* ϵ 4 carriers. In secondary analyses, we observed that when the analysis was confined to the *APOE* ϵ 4 carriers, the effect of donepezil was significant at 12, 24, and 36 months. However, there are insufficient data to warrant recommending *APOE* genotyping in persons with mild cognitive impairment, and our results cannot be used to make this recommendation, since the study was not statistically powered to determine the effects of treatment in separate groups of *APOE* ϵ 4 carriers and noncarriers.

Despite evidence of oxidative stress in patients with Alzheimer's disease and mild cognitive impairment and observational studies suggesting that supplementation with antioxidant vitamins may decrease the risk of Alzheimer's disease, we did not find that vitamin E significantly affected the risk of progression.²⁰⁻²² Furthermore, this therapy had only minimal effects on secondary measures.

In summary, this study provides evidence that treatment may delay the clinical diagnosis of Alzheimer's disease. Specifically, the likelihood of Alzheimer's disease was reduced for only the initial

12 months of the study among patients treated with donepezil, as compared with those who received placebo; however, in secondary analyses, it was observed that the effect was more prominent among *APOE* ϵ 4 carriers, with a reduction in risk apparent throughout the 36 months of the study. The results of the secondary analyses of cognitive and global measures supported the primary-outcome results.

Our findings suggest that the design of our study and the enrollment criteria are practical and can be used to demonstrate the effects of a given intervention in subjects with amnesic mild cognitive impairment. Other therapeutic agents under development, particularly those designed to prevent Alzheimer's disease or progression to Alzheimer's disease, may be particularly beneficial in subjects with mild cognitive impairment.

Supported by a grant from the National Institute on Aging (UO1 AG10483), and by Pfizer and Eisai. DSM Nutritional Products donated the vitamin E.

Dr. Grundman is an employee of Elan Pharmaceuticals. Dr. Doody reports having received consulting fees, speakers' fees, and grant support from Pfizer and Eisai; Drs. Ferris and Sano, consulting fees from Pfizer; Drs. Levey and van Dyck, speakers' fees from Pfizer; Drs. Ferris, van Dyck, and Thal (through the University of California, San Diego, for this study), grant support from Pfizer; and Drs. Pfeiffer, van Dyck, and Thal (through the University of California, San Diego, for this study), grant support from Eisai.

APPENDIX

The following institutions and persons participated in the ADCS: Affiliated Research Institute: C.H. Merideth, T.A. Milbrand, S. Mende; Arizona Health Sciences Center: G. Ahern, C. Kells, K. Burton; Barrow Neurology Clinic: A. Schwartz, C. Echols, M. Zomok, L. Dawson; Bauml-Eisner Boca Raton: B. Bauml, J. Crasto, R. Radzivil; Bauml-Eisner Fort Lauderdale: L. Eisner, J. Riveros, A. Johnson; Bauml-Eisner Miami Beach: B. Bauml, J. Crasto, D. Alonso, A. Torres; Baylor College of Medicine: R. Smith Doody, J. Sims, N. Robinson; Brown University: B. Ott, M. Clemens, J. Grace; Burke Medical Research Institute, White Plains: J. Blass, R. Cirio; Cedars-Sinai Medical Center: A. Schneider; Clinical Insights: L. Adler; Clinical Research Systems: R. Margolin, D. Kent; ClinSearch: M. Roffman, I. Marritt; Cognitive Neurology, St. Joseph's Health Center: A. Kertesz, D. Morlog; Columbia University: M. Sano, E. Dominguez, A. Raganuth, R. Santiago, C. Weber; Cornell Medical Center: B. Meyers; Duke University Medical Center: J. Burke, S. Vann Wyne, M. McCart; E. Bruyere Memory Disorder Research: D.A. Guzman, C. Gravelle, I. Bedirian; Emory University: A. Levey, J. Cellar, N. Gauchman, S. Valia; Fletcher Allen Health Care: P.A. Newhouse, E. Gay; Georgetown University Medical Center: P. Aisen, M.A. Cechola, K. Johnson, B. Reynolds; Geriatric and Adult Psychiatry: A. Siegal; Geriatric Medical Research Group: S. Darvesh, J. Cross, G. Sherwood; Glenrose Rehabilitation Hospital: P. McCracken, S. Aloisio, S. Duban, C. McKelvey; Indiana University: M. Farlow, P. Nurnberger, K. Fleming, N. Jessup, J. Pearson, E. Riley; Jewish Hospital Memory Clinic: H. Chertkow, C. Hosein; Johns Hopkins University: J. Brandt, C. Munro, S. Kilada, S. O'Donnell; Kansas University, Kansas City: G.J. Lopez, P. Switzer; Maimonides Medical Center: A. Miller, T. La Rocca, S. Freimark; Massachusetts General: J. Growdon, M. Tennis; Mayo Clinic, Jacksonville: N. Graff-Radford, F. Parfitt, L.M. Makarov; Mayo Clinic, Rochester: D.S. Knopman, B. Boeve, N. Haukom, M. Mandarino, D. Mullinax, R. Petersen; McGill Centre for Studies in Aging: S. Gauthier, D. Amyot; MCP Hahnemann University: C. Lippa, A.M. Wilson, R. Petrucci; Medical University of South Carolina: D. Bagwell, J.E. Mintzer, M. Stuckey; Memorial Veterans Hospital, Boston University: R.C. Green; Memory Disorders Institute: J. Shua-Haim, V. Shua-Haim, S. Wall, A. Hovick; Mt. Sinai School of Medicine: K. Davis, R.C. Mohs, K. Swedish, M. Casadiego, L. Negroni, K. Knox; Nathan Kline Institute for Psychiatric Research: N. Pomara, C. de la Pena; Neurobehavioral Research: R. Brenner; New York University Medical Center: S. Ferris, M. Vlassopoulos, J. Kastelan, J. Lam; Northwestern University: M.M. Mesulam, L. Herzog; Oregon Health Sciences University: J. Kaye, J. Lear, S. Berman, K. Wild; Pacific Research Network: S. Thein, Jr.; Palm Beach Neurological: D. Cipriani, C. Sadowsky, Y. Ramirez-Rojas; Princeton Biomedical Research: A.A. Sugerman, J.P. Cole-Kady, K. Alvarez, R. Soika; Quantum Labs: J. DeLaGandara; Rush-Presbyterian-St. Luke's Medical Center: N. Aggarwal, D. Bennett, R.M. Ferraro, C. Aldridge, M. Li, R.M. Nance; Southern Illinois University: S. Vicari, F. Schaefer; Southwestern Vermont Medical Center: P. Solomon, B.J. Hathaway, L. Crowe, M. Robinson; Saint Louis University: G. Grossberg; Stanford-Veterans Affairs Aging Clinical Research Center: J.A. Yesavage; Staten Island University Hospital: M. Levy; Sun Health: M. Sabbagh, K. Hatton; Sunnybrook Health Sciences: S. Black, J. Lawrence, M. Evans; SUNY Stony Brook: L. Krupp, D.M. Madigan; Sutter Institute for Medical Research: W.J. Au, D.N. Poff, M. Mulligan, I. Orengo; U.B.C. Clinic for Alzheimer's Disease: H. Feldman, V. O'Neill, K. Gilchrist; University of Calgary Cognitive Assessment Clinic: D. Hogan, P. Mueller; University Hospitals of Cleveland: D. Geldmacher, C. Santillan, P. Talea, M. Sanders; University of California, Davis: C. DeCarli, J. Coleman; University of California, Irvine: C. Cotman, R. Mulnard, C. McAdams-Ortiz, H. Kim; University of California, Los Angeles: J. Cummings, D.L. Masterman, M.F. Carter, N. Bennett, L. Berndt; University of California, San Diego: M. Grund-

man, J.M. Olichney, S.M. Johnson, C.W. Jenkins; University of California, San Francisco: K. Yaffe, R. Gearhart, V. Smith; University of Kentucky, Lexington: F. Schmitt, J. Cox, S. Anderson, C. Sowards Dearth; University of Miami, Gulf Coast Education and Research: J. Rivero, R. Ownby, J. Williams; University of Michigan, Ann Arbor: N. Foster, J. Lord, N. Johnson; University of Minnesota, Minneapolis: A. Hochhalter; University of Nevada, School of Medicine: C. Bernick, G. Vranesh, D. Munic, P. LeBlanc; University of New Mexico: J. Adair, S. McClelland; University of Pennsylvania: C. Clark, K. Gravanda, V. Cotter, J. Nuñez, E. Ryan-Ripp; University of Pittsburgh: S. DeKosky, L. Smith-Macedonia, T. Baumgartner, A.L. Kane; University of Rochester Medical Center: P. Tariot, B. Goldstein, L. Terwilliger; University of South Florida, Tampa: E. Pfeiffer, B. Luhn, D. Baxter, J. Hunter; University of Southern California: L. Schneider, N. Taggart, K. Stevens-Dagerman; University of Texas Southwestern Medical Center: M. Weiner, K. Martin-Cook, T. Ninman, S. Pierce; University of Washington: E. Peskind, M. Raskind, R. Wood, N. Brown, J. O'Connell, N. Pham; Veterans Affairs Medical Center, Augusta: M.E. Nichols, C. Bailie, D. Hillesland; Vanderbilt University: R. Margolin, D. Kent, L. McFarland; Washington University School of Medicine: J.C. Morris, S. Stiening, A. Dromerick, C. Dyer; Wien Center: R. Duara, P.D. Roberts; Yale University School of Medicine: C. Van Dyck, M. MacAvoy, L. Cretella, T. Rightmer, L. Zeiser.

REFERENCES

- Petersen RC. Conceptual overview. In: Petersen RC, ed. *Mild cognitive impairment: aging to Alzheimer's disease*. New York: Oxford University Press, 2003:1-14.
- Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Early detection of dementia: mild cognitive impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;56:1133-42.
- Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol* 2001;58:1985-92.
- Lopez OL, Jagust WJ, DeKosky ST, et al. Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study. *Arch Neurol* 2003;60:1385-9.
- Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256:183-94.
- Ganguli M, Dodge HH, Shen C, DeKosky ST. Mild cognitive impairment, amnesic type: an epidemiologic study. *Neurology* 2004;63:115-21.
- Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303-8. [Erratum, *Arch Neurol* 1999;56:760.]
- Petersen RC, Smith GE, Ivnik RJ, et al. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. *JAMA* 1995;273:1274-8. [Erratum, *JAMA* 1995;274:538.]
- Tierney MC, Szalaj JP, Snow WG, et al. A prospective study of the clinical utility of ApoE genotype in the prediction of outcome in patients with memory impairment. *Neurology* 1996;46:149-54.
- Doody RS, Stevens JC, Beck C, et al. Management of dementia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;56:1154-66.
- Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 1997;336:1216-22.
- Grundman M, Petersen RC, Ferris SH, et al. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Arch Neurol* 2004;61:59-66.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939-44.
- Bennett DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in older persons. *Neurology* 2002;59:198-205.
- Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 1988;75:800-2.
- Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982;69:239-41.
- Aisen PS, Schafer KA, Grundman M, et al. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. *JAMA* 2003;289:2819-26.
- Ridout MS. Testing for random dropouts in repeated measurement data. *Biometrics* 1991;47:1617-9.
- Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998;50:136-45.
- Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. *Arch Neurol* 2004;61:82-8.
- Morris MC, Evans DA, Bienias JL, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA* 2002;287:3230-7.
- Morris MC, Evans DA, Bienias JL, Tangney CC, Wilson RS. Vitamin E and cognitive decline in older persons. *Arch Neurol* 2002;59:1125-32.

Copyright © 2005 Massachusetts Medical Society.