A CONTROLLED TRIAL OF SELEGILINE, ALPHA-TOCOPHEROL, OR BOTH AS TREATMENT FOR ALZHEIMER'S DISEASE

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ABSTRACT

Background There is evidence that medications or vitamins that increase the levels of brain catecholamines and protect against oxidative damage may reduce the neuronal damage and slow the progression of Alzheimer's disease.

Methods We conducted a double-blind, placebo-controlled, randomized, multicenter trial in patients with Alzheimer's disease of moderate severity. A total of 341 patients received the selective monoamine oxidase inhibitor selegiline (10 mg a day), alpha-tocopherol (vitamin E, 2000 IU a day), both selegiline and alpha-tocopherol, or placebo for two years. The primary outcome was the time to the occurrence of any of the following: death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia (defined as a Clinical Dementia Rating of 3).

Results Despite random assignment, the base-line score on the Mini–Mental State Examination was higher in the placebo group than in the other three groups, and this variable was highly predictive of the primary outcome ($P<0.001$). In the unadjusted analyses, there was no statistically significant difference in the outcomes among the four groups. In analyses that included the base-line score on the Mini–Mental State Examination as a covariate, there were significant delays in the time to the primary outcome for the patients treated with selegiline (median time, 655 days; $P=0.012$), alpha-tocopherol (670 days, $P=0.001$), or combination therapy (585 days, $P=0.049$), as compared with the placebo group (440 days).

Conclusions In patients with moderately severe impairment from Alzheimer's disease, treatment with selegiline or alpha-tocopherol slows the progression of disease. (N Engl J Med 1997;336:1216-22.)

ALZHEIMER'S disease is a neurodegenerative disorder characterized by loss of memory and other cognitive abilities. Neuropathologically, the disease is characterized by the presence of neurofibrillary tangles and senile plaques, impaired synaptic function, and cell loss.[1] There is a prominent loss of cholinergic, noradrenergic, and dopaminergic neurons in Alzheimer's disease.[2] The pathology of the disorder may involve oxidative stress and the accumulation of free radicals, leading to excessive lipid peroxidation and neuronal degeneration in the brain.[3-6]

Selegiline, a monoamine oxidase inhibitor, and alpha-tocopherol may have beneficial effects in patients with Alzheimer's disease. Selegiline may act as an antioxidant, since it inhibits oxidative deamination, thereby reducing neuronal damage. The drug has been associated with an increased active life span in animals.[7] Studies in patients with Parkinson's disease have demonstrated that selegiline delays the need for dopamine-replacement therapy and significantly prolongs the time during which patients function well enough to work.[8]

Selegiline also increases levels of catecholamines, and adrenergic stimulation may improve the cognitive deficits associated with Alzheimer's disease. In short-term trials of selegiline in patients with Alzheimer's disease, small but significant improvements in cognition[9] and overall ratings of functioning[10] have been reported. A longer study with a small sample yielded a similar but nonsignificant trend.[11]

Alpha-tocopherol (vitamin E) is a lipid-soluble vitamin that interacts with cell membranes, traps free radicals, and interrupts the chain reaction that damages cells.[12] In animal models, alpha-tocopherol reduced the degeneration of hippocampal cells after cerebral ischemia[13] and enhanced the recovery of motor function after spinal cord injury.[14] In hypoxic cultured neurons, alpha-tocopherol inhibited lipid peroxidation[15] and reduced cell death associated with β-amyloid protein.[16] Although no benefit was noted in a study of alpha-tocopherol in patients with Parkinson's disease,[8] there is much interest in a possible role of antioxidants in delaying the onset of Alzheimer's disease.

The primary purpose of the present study was to determine whether selegiline, alpha-tocopherol, or a

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*The members of the Alzheimer's Disease Cooperative Study are listed in the Appendix.

combination of the two agents would slow the clinical deterioration associated with Alzheimer's disease. Although previous trials involving patients with Alzheimer's disease have focused on cognitive deterioration, our study examined functional loss. We sought to determine whether treatment with these agents could delay the time to the occurrence of clinical outcomes that reflect substantial functional deterioration.

METHODS

Patients were recruited from 23 centers participating in the Alzheimer's Disease Cooperative Study (see the Appendix). A total of 341 patients with probable Alzheimer's disease of moderate severity, as measured by a Clinical Dementia Rating of 2,[17] were enrolled. Informed consent was obtained from each patient or a family member. At the time of enrollment, the patients were free of other central nervous system diseases, were not taking psychoactive medications, and were residing either at home or in a supervised setting with a care giver but not in a skilled-nursing facility. The study population has been described in detail previously.[18]

The patients were randomly assigned (after stratification according to center with the use of a permuted-block procedure) to receive selegiline, alpha-tocopherol, selegiline and alpha-tocopherol, or placebo. Selegiline (Eldepryl, Somerset Pharmaceuticals, Tampa, Fla.) was given in a dose of 5 mg twice a day, and a racemic mixture of *dl*-alpha-tocopherol (vitamin E, Hoffmann–LaRoche, Nutley, N.J.) was given in a dose of 1000 IU twice a day; both agents were given in the morning and in the afternoon.

Primary Outcome Measure

The primary outcome measure was the time to the occurrence of any one of the following end points: death; institutionalization; loss of the ability to perform at least two of three basic activities of daily living (i.e., eating, grooming, using the toilet), as measured by part 2 of the Blessed Dementia Scale[19]; and severe dementia, defined as a Clinical Dementia Rating of 3.[17] The date of death or institutionalization was used to calculate the time to either of these end points; if that date was not available, the date of the next follow-up visit was used. To calculate the time to the loss of the ability to perform activities of daily living or the occurrence of severe dementia, we used the date of the follow-up visit during which the end point was documented.[18]

Secondary outcome measures included measures of cognition, function, behavior, and the presence or absence of extrapyramidal signs. Cognition was assessed with the cognitive portion of the Alzheimer's Disease Assessment Scale[20] and the Mini–Mental State Examination.[21] Function was assessed with the total score on the Blessed Dementia Scale. This scale has two sections: instrumental activities of daily living (e.g., remembering lists and handling small sums of money) and basic activities of daily living (e.g., eating, using the toilet, and grooming). Function was also assessed with the Dependence Scale, a seven-point scale that rates the need for supervision and care.[22] The Equivalent Institutional Service, a subsection of the Dependence Scale, rates the level of care received as follows: 1, limited home care; 2, care equivalent to that received in an adult care facility; and 3, care equivalent to that received in a skilled-nursing facility. Behavioral disturbance was assessed with the Behavior Rating Scale for Dementia.[23] Extrapyramidal signs were assessed with a modification of the motor part of the Unified Parkinson's Disease Rating Scale.[24] A score of 2 or higher on any item was considered to indicate the presence of extrapyramidal signs.

Safety

To assess the safety of treatment, routine blood and urine analyses were performed and vital signs and weight were checked at all clinic visits. Medical events that occurred during the treatment period were reported as adverse events. These events were categorized on the basis of the description provided.

Follow-up

Assessments were conducted one month after enrollment and at three-month intervals for the remainder of the two-year study period. At each interval, every effort was made to assess primary and secondary outcomes, regardless of whether an end point had been reached or the medication had been discontinued.

Drug-Level Monitoring

The level of alpha-tocopherol was monitored by measuring serum tocopherol concentrations, and the level of selegiline was monitored by measuring amphetamine, its major metabolite, in urine. Tests for selegiline were considered positive if the presence of amphetamine was detected in 75 percent of the urine samples obtained from a given patient. Tests for alpha-tocopherol were considered positive if serum tocopherol levels were 2.0 mg per deciliter (46 μmol per liter) or higher in 75 percent of the blood samples obtained from a given patient.

Statistical Analysis

Base-line differences in predetermined potential covariates among the four groups were examined with the use of either analysis of variance or chi-square analyses, as appropriate. The variables examined included demographic characteristics (age, duration of illness, education, and sex) and clinical characteristics (scores on the Mini–Mental State Examination and Blessed Dementia Scale and the presence or absence of extrapyramidal signs). The variables that differed significantly among the groups at the 0.1 level were examined as predictors of the primary outcome, and the significant predictors were included in the analysis of the treatment effect.

The primary intention-to-treat analysis of treatment efficacy compared each treatment with placebo with the use of a Kaplan–Meier estimation[25] and log-rank testing for the unadjusted analysis and the Cox proportional-hazards model to control for any imbalance in the predetermined covariates among the four groups. The relative risk associated with treatment as compared with placebo was measured with the use of the risk ratio derived from the Cox model, with significance levels adjusted for multiple comparisons.[26] The median time to an end point was estimated on the basis of survival curves generated from the Cox model.

The secondary outcomes were examined with the use of survival analyses, analysis of variance, or analysis of covariance, as appropriate. Missing values were imputed by using the last observation carried forward. For each of these analyses, the rate of study completion was compared among the four groups. If significant differences were observed ($P \leq 0.1$), the time enrolled in the study was included as a covariate in the model.

Safety data were examined by using Fisher's exact test to compare the frequency of abnormal findings (e.g., adverse events or abnormalities in laboratory results or vital signs) among the study groups.

A safety-monitoring committee reviewed the safety data coded according to the study group or uncoded, as needed. The committee was responsible for recommending changes in the protocol or early termination of the study, if necessary. A preplanned interim analysis was conducted at the midpoint of the study, with prespecified rules for termination.[27] Log-rank tests were used for the unadjusted analysis, and the Cox model was used to adjust for age, score on the Mini–Mental State Examination, and sex. No significant treatment effects were observed in the interim analysis.

RESULTS

Table 1 shows the demographic and clinical characteristics of each study group at base line. There

TABLE 1. BASE-LINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF 341 PATIENTS WITH ALZHEIMER'S DISEASE RANDOMLY ASSIGNED TO RECEIVE PLACEBO, SELEGILINE, ALPHA-TOCOPHEROL, OR BOTH AGENTS.*

CHARACTERISTIC	PLACEBO (N=84)	SELEGILINE (N=87)	ALPHA-TOCOPHEROL (N=85)	SELEGILINE AND ALPHA-TOCOPHEROL (N=85)
Age (yr)	73.5±8.3	72.7±8.9	73.4±7.8	73.9±7.1
Education (yr)	12.2±3.1	12.4±3.7	12.6±3.3	12.7±3.3
Duration of illness (yr)	5.5±2.9	4.8±2.4	5.3±2.7	4.7±2.5
Female sex (% of patients)	65.5	67.8	65.9	60.0
Score on Mini–Mental State Examination†	13.3±4.9‡	12.7±5.0	11.3±5.7	12.9±5.7
Score on Blessed Dementia Scale§	6.1±2.1	6.3±1.9	6.6±2.1	6.4±2.3
Extrapyramidal signs (% of patients)	19.0	26.4	18.8	24.7
Clinical Dementia Rating¶	10.9±1.2	11.0±1.2	11.3±1.3	10.9±1.2

*Plus–minus values are means ±SD.

†Possible scores range from 0 (worst) to 30 (best).

‡$F = 2.37$; df = 3336; $P = 0.071$, for the comparison between the placebo group and the other three groups.

§Possible scores range from 0 (best) to 17 (worst).

¶Scores shown represent the total of the scores in six domains of the Clinical Dementia Rating.[17] Possible summary scores range from 0 (best) to 18 (worst).

was a trend toward a significant difference among the groups in the score on the Mini–Mental State Examination ($P = 0.071$), with the placebo group having the highest score and the alpha-tocopherol group having the lowest score. There were no significant differences in the other variables. In the Cox model, a higher score on the Mini–Mental State Examination was strongly associated with a delay in the primary outcome (risk ratio, 0.909 per unit increase in score; $P<0.001$) and was also associated with a delay in each of the individual outcomes.

Primary Outcome Measure

The results of unadjusted comparisons of selegiline with placebo (risk ratio, 0.72; $P = 0.087$), alpha-tocopherol with placebo (risk ratio, 0.70; $P = 0.077$), and combined treatment with placebo (risk ratio, 0.78; $P = 0.21$) were not statistically significant (Fig. 1A, 1B, and 1C). However, when the base-line score on the Mini–Mental State Examination was included as a covariate (Fig. 1D), a significant delay in the primary outcome was found with selegiline (risk ratio, 0.57; $P = 0.012$), alpha-tocopherol (risk ratio, 0.47; $P = 0.001$), and combination therapy (risk ratio, 0.69; $P = 0.049$). The estimated increase in median survival was 230 days for the patients receiving alpha-tocopherol, 215 days for those receiving selegiline, and 145 days for those receiving both, as compared with the patients receiving placebo (Table 2).

We also examined the effect of treatment on each of the individual end points in the primary outcome measure (Table 3). For the end point of institutionalization, the comparison of alpha-tocopherol with placebo showed a significant treatment effect (risk ratio, 0.42; $P = 0.003$). No statistically significant differences among the groups were observed for the other end points.

Secondary Outcome Measures

The results of the analyses of secondary outcome measures are presented in Table 4. In some cases, the cognitive data were not complete because of the development of advanced dementia. The mean time to the last score on the Mini–Mental State Examination was 15.6 months, and the scores did not differ significantly among the four groups. Changes from the base-line scores also did not differ significantly among the groups ($P = 0.83$).

The change in the performance on the cognitive portion of the Alzheimer's Disease Assessment Scale was calculated as the difference between the base-line score and the score at the last visit. The mean time to the last score was 12.4 months. The changes in the scores did not differ significantly among the four groups ($P = 0.17$). The use of the base-line score on the Mini–Mental State Examination and the time in the study as covariates did not change these results.

For the Blessed Dementia Scale, the mean time to

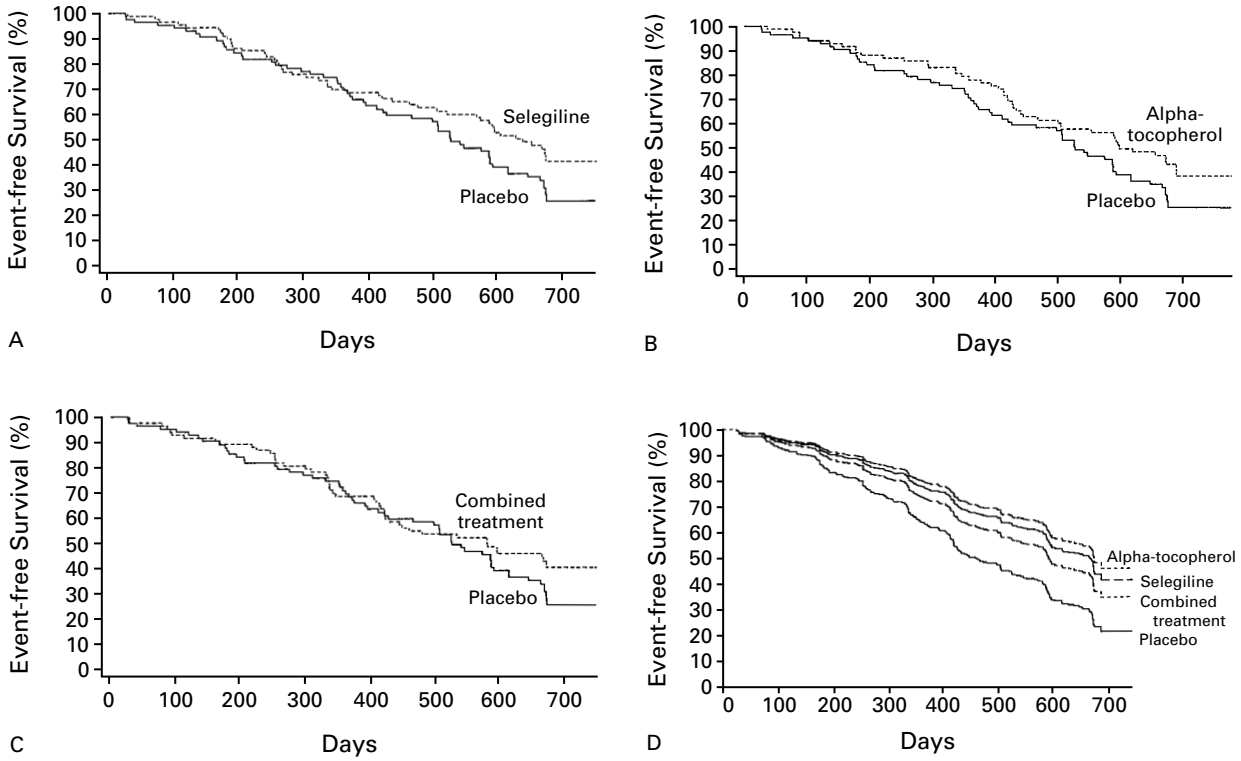

Figure 1. Event-free Survival of 341 Patients with Alzheimer's Disease Assigned to Treatment with Selegiline, Alpha-Tocopherol, Both, or Placebo.

Event-free survival was defined as survival until the occurrence of death, institutionalization, loss of the ability to perform the activities of daily living, or severe dementia (defined as a Clinical Dementia Rating of 3). Panels A, B, and C show Kaplan–Meier curves for the comparison of placebo with selegiline ($P=0.087$), alpha-tocopherol ($P=0.077$), and combined treatment ($P=0.21$), respectively. Panel D shows a Cox-model estimation for the comparison of the three treatments with placebo, with the base-line score on the Mini–Mental State Examination included as a covariate ($P=0.012$, 0.001, and 0.049, respectively).

the last observation was 20.0 months. The change in the score from base line to the last evaluation differed significantly among the groups ($P=0.004$), with the base-line score on the Mini–Mental State Examination included as a covariate. Pairwise post hoc comparisons showed significant differences between each treatment group and the placebo group, with a benefit associated with treatment.

At base line, 3 percent of the patients received the maximal rating of 3 for level of care. For the 331 patients who were not at level 3 at base line, similar proportions in the four groups received higher ratings at the last evaluation.

At base line, 3 percent of the patients had a maximal dependence level, defined as the need for assistance with moving, turning, eating, or using the toilet. For the 332 patients who were not at the maximal level at base line, the Cox model demonstrated a significant overall effect of treatment in maintaining a lower level of dependence ($P=0.039$). Patients treated with alpha-tocopherol alone or combined with selegiline required significantly less supervision than those receiving placebo ($P=0.021$ and 0.014, respectively).

Changes in the scores on the Behavioral Rating Scale for Dementia differed significantly among the four groups ($P=0.020$). The patients receiving combined therapy had a decrease in behavioral symptoms, whereas those receiving placebo had an increase in symptoms. The results of no other comparisons were significant.

Extrapyramidal signs were present at base line in 22 percent of the patients, with no significant differences among the four groups. There were no differences in the frequency of new extrapyramidal signs among the groups ($P=0.59$).

Safety Data

A total of 49 categories of adverse events were defined. There were significant differences among the groups in three categories: dental events, which were defined as any event that led to dental treatment

TABLE 2. PRIMARY OUTCOME AND MEDIAN SURVIVAL ACCORDING TO STUDY GROUP.*

PRIMARY OUTCOME AND SURVIVAL	PLACEBO (N=84)	SELEGILINE (N=87)	ALPHA-TOCOPHEROL (N=85)	SELEGILINE AND ALPHA-TOCOPHEROL (N=85)
Lost to follow-up — no. of patients (%)†	6 (7)	4 (5)	8 (9)	5 (6)
Primary outcome — no. of patients (%)	58 (69)	47 (54)	45 (53)	47 (55)
Unadjusted median survival (days)	526	628	597	581
Unadjusted difference in survival, treatment vs. placebo (days)	—	102	71	55
Estimated median survival (days)	440	655	670	585
Estimated difference in survival, treatment vs. placebo (days)	—	215	230	145

*Estimates of survival are derived from the Cox model, with adjustment for the base-line score on the Mini–Mental State Examination. Survival was defined as the time to the primary outcome.

†Patients lost to follow-up were those who did not reach an end point and did not complete the study.

TABLE 3. PERCENTAGE OF PATIENTS REACHING EACH END POINT, ACCORDING TO STUDY GROUP.

END POINT	PLACEBO	SELEGILINE	ALPHA-TOCOPHEROL	SELEGILINE AND ALPHA-TOCOPHEROL
	% of patients			
Loss of ability to perform activities of daily living	31	28	22	28
Clinical Dementia Rating of 3	51	43	48	47
Institutionalization	39	33	26	35
Death	12	10	12	7

($P=0.023$); falls ($P=0.005$); and syncopal episodes ($P=0.031$) (Table 5). The frequency of other adverse events, including cardiac, gastrointestinal, dermatologic, and psychiatric or other neurologic symptoms, did not differ significantly among the groups. Overall, there were no statistically significant differences among the groups in adverse-event categories after adjustment for multiple comparisons.[26] There were also no significant differences in vital signs, weight change, or laboratory values among the groups.

The death rate was 10.3 percent, which is similar to that reported in another cohort of patients with Alzheimer's disease of the same severity.[17] We also examined the cause of death and found no specific pattern associated with treatment.

Drug-Level Monitoring

Urine samples were available from 318 patients for analysis of amphetamine levels. The proportion of patients with positive tests for selegiline was 93 percent in the combined group, 98 percent in the selegiline group, 11 percent in the alpha-tocopherol group, and 13 percent in the placebo group. Serum samples were available from 332 patients. The proportion of patients with positive tests for alpha-tocopherol was 91 percent in the combined group, 93 percent in the alpha-tocopherol group, 9 percent in the selegiline group, and 12 percent in the placebo group.

DISCUSSION

In this double-blind, controlled study of patients with Alzheimer's disease, treatment with selegiline or alpha-tocopherol or both was beneficial in delaying the primary outcome of disease progression. The median time to the primary outcome was longer with each treatment than with placebo. There was a trend toward a delay in reaching each of the individual end points making up the primary outcome, with a significant delay in institutionalization in the alpha-tocopherol group. There were also significant delays in the deterioration of the performance of activities of daily living and the need for care. These findings should be of interest since, to date, no treatment for Alzheimer's disease has shown similar benefits with respect to these outcomes. The possibility that our findings reflect aberrations in the placebo group is unlikely, since the patients in this group reached the end points at the same rate as patients in other multicenter studies.[18]

Falls and syncope were more frequent in the treatment groups, especially the group receiving combined treatment, than in the placebo group. Although similar results have been reported with selegiline, there are no such reports with alpha-tocopherol, and the reason for the increased numbers of falls and syncopal episodes in the group receiving combined treatment is unclear. However, these events did not lead to the discontinuation of treatment, and we conclude that each agent alone may be relatively well tolerated by patients with Alzheimer's disease.

There were no demonstrable differences between the results in the group receiving combined treatment and either of the groups receiving individual treatment. There are several possible explanations for the lack of an additive effect of treatment. Perhaps both agents exert their effects through the same mechanism, with either agent providing a maximal benefit. Alternatively, each agent may work through an independent mechanism, but the disease may have been sufficiently severe that no additive benefit could be observed. Finally, one agent may interfere with the absorption or metabolism of the other, resulting in an effect that is not additive.

Our findings suggest that the use of selegiline or

alpha-tocopherol may delay clinically important functional deterioration in patients with Alzheimer's disease. One can only speculate about the mechanism underlying this effect. Selegiline may have enhanced the functioning of nigral neurons or enhanced their survival by inhibiting oxidative deamination. Alpha-tocopherol may have provided the same benefit, resulting in the inability to observe an additive effect in the group receiving combined treatment.

In our study, there was no improvement in cognitive test scores in any of the treatment groups. Our patients were more severely impaired than those described in other clinical trials,[28,29] and our observation period was long, with a large proportion of patients who did not complete the two years of testing. However, even when we controlled for the length of the observation period, treatment had no effect on cognitive scores. The observed changes in the scores on the cognitive portion of the Alzheimer's Disease Assessment Scale and the Mini–Mental State Examination are similar to those reported in other studies,[30] and our findings do not suggest that the patients had reached a maximal deficit. It is possible that other features of advanced disease (e.g., behavioral disturbances and functional impairments) make it difficult to assess the cognitive domain. Although cognitive measures have typically been the index of symptomatic improvement measured over a short interval, they may not be the best measures of disease progression, particularly in a cohort of patients with moderately severe Alzheimer's disease followed for a long interval. There was a benefit of treatment associated with the score on the Blessed Dementia Scale, which includes instrumental activities of daily living — those that require cognitive function. Perhaps functional and occupational measures of cognitive capacity are better indicators of disease progression than psychometric measures.

The role of selegiline and alpha-tocopherol in the treatment of neurodegenerative diseases is currently of great interest. Selegiline delays the onset of disability in patients with Parkinson's disease.[8] Previous trials of alpha-tocopherol have demonstrated no benefit in patients with Huntington's disease[31] or Parkinson's disease.[8] The neuronal populations involved in Alzheimer's disease are more sensitive to oxidative stress than those in other neurodegenerative diseases. Perhaps these neurons mediate the clinical end points described here. The outcome of improved function despite the absence of improved cognition raises the possibility that the effect we observed is a nonspecific health benefit to which our primary outcome was sensitive. For example, in elderly populations it has been suggested that antioxidants improve cardiovascular function[32] and the immune response[33] and also reduce the risk of cancer.[34] Although we found no differences in the frequency of these types of adverse events in our study groups, we have no biologic data to evaluate these possible effects. The small behavioral effect that we observed is unlikely to account for these results. Perhaps cognitive measures would be sensitive to changes at earlier stages of the disease. However, only randomized clinical trials can determine the usefulness of these agents in other populations.

Both selegiline and alpha-tocopherol delay functional deterioration, particularly as reflected by the need for institutionalization, and should be consid-

TABLE 4. SECONDARY OUTCOME MEASURES.

OUTCOME MEASURE*	PLACEBO	SELEGILINE	ALPHA-TOCOPHEROL	SELEGILINE AND ALPHA-TOCOPHEROL
Mini–Mental State Examination (mean change in score)	−4.6	−5.1	−4.6	−4.9
Alzheimer's Disease Assessment Scale (mean change in score)	6.7	8.3	8.3	6.5
Blessed Dementia Scale (mean change in score)	5.4	4.2†	4.0†	4.2†
Equivalent Institutional Service (% of patients receiving higher rating)	59	57	57	56
Dependence Scale (% of patients receiving higher score)	86	80	76‡	76‡
Behavior Rating Scale for Dementia (mean change in score)	8.9	5.4	4.4	−1.1§
Unified Parkinson's Disease Rating Scale (% of patients with new extrapyramidal signs)	57	61	58	52

*For the Mini–Mental State Examination, a lower number indicates worse performance. For all other measures, a higher number indicates worse performance.

†P=0.004 for the comparison with placebo.

‡P=0.039 for the comparison with placebo.

§P=0.020 for the comparison with placebo.

TABLE 5. FREQUENCY OF ADVERSE EVENTS ACCORDING TO STUDY GROUP.

ADVERSE EVENT	PLACEBO	SELEGILINE	ALPHA-TOCOPHEROL	SELEGILINE AND ALPHA-TOCOPHEROL	P VALUE*
	no. of patients (%)				
Dental event	0	6 (7)	1 (1)	1 (1)	0.023
Fall	4 (5)	8 (9)	12 (14)	19 (22)	0.005
Syncope	3 (4)	9 (10)	6 (7)	14 (16)	0.031

*P values are for the comparison of each treatment with placebo.

ered for use in patients with moderate dementia. Convenience and cost may play a part in treatment decisions, since both agents were effective. It should be noted that statistically significant results were seen in a model that included adjustment for the base-line differences among the groups in the score on the Mini–Mental State Examination. Although this type of adjustment was used in other studies of drugs to treat Alzheimer's disease,[28,29] it may limit the interpretation of these results. Replication of our findings would lend support to our data showing the efficacy of these agents. In addition, little is known about the efficacy of these compounds in other patients, such as those with mild cognitive impairment, early dementia, or the very late stages of Alzheimer's disease.

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APPENDIX

The following members of the Alzheimer's Disease Cooperative Study participated in this study: S. Vicari, Southern Illinois University, Springfield; D. Bennett, C. Forchetti, and A. Levin, Rush Institute on Aging, Chicago; C. Clark, University of Pennsylvania, Philadelphia; K. Davis, P. Aisen, D. Marin, and R. Mohs, Mount Sinai School of Medicine, New York; R. Doody, E. Lipscomb, and P. Schulz, Baylor College of Medicine, Houston; S. Ferris, E. Resnick, and T. McRae, New York University Medical Center, New York; N. Foster, N. Barbas, L. Bieliauskas, and L. Bluemlein, University of Michigan, Ann Arbor; J. Growdon, N. Simonian, M. Tennis, C. Burke, A. Markus, and K. Graefe, Massachusetts General Hospital, Boston; L. Harrell, University of Alabama at Birmingham, Birmingham; C. Kawas, H. Karagiozis, and A. Morrison, Johns Hopkins University, Baltimore; J. Kaye, Oregon Health Sciences University, Portland; D. Knopman, M. Prod'Homme, and L. Langley, University of Minnesota Hospital, Minneapolis; V. Kumar, University of Miami, Miami Beach, Fla.; R. Margolin and P. Brooks, Vanderbilt University, Nashville; J. Morris and E. Rubin, Washington University Medical Center, St. Louis; R. Petersen and L. Limbo, Mayo Clinic, Rochester, Minn.; E. Pfeiffer, University of South Florida Health Sciences Center, Tampa; M. Raskind and E. Peskind, Veterans Affairs Medical Center, Seattle; M. Sano, K. Marder, K. Bell, G. Dooneief, P. Schofield, M. Chun, A. Lawton, and J. Wilson, Columbia University, New York; F. Schmitt and W. Ashford, University of Kentucky, Lexington; L. Schneider, S. Pawluczyk, J. Olin, N. Taggart, and C. Ghoush, University of Southern California, Los Angeles; W. Strittmatter and S. Wyne, Duke University, Durham, N.C.; L. Thal, W. Samuel, J. Corey-Bloom, D. Galasko, D. Bower, and V. Rice, University of California at San Diego, La Jolla; P. Whitehouse, A. Lerner, K. Horner Fedor, P. Hedera, M. Patterson, M. Sanders, and C. Zadorozny, University Hospitals of Cleveland, Cleveland. Members of the data-monitoring and data-coordinating staff: J. Bochenek, L. Simon, B. White, S. Jin, J. Jeong, L. Berkman, J. Mackell, and M. Schittini. Members of the safety-monitoring committee: E. Jackson, P. Tariot, and T. Sunderland.

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